厚生労働科学研究費補助金

難治性疾患等政策研究事業（難治性疾患政策研究事業）
早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

令和 ５ 年度　総括・分担研究報書

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早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

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研究要旨

早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner症候群（以下 WS と略）、Hutchinson-Gilford Progeria 症候群（以下 HGPS と略）や Rothmund-Thomson 症候群（以下 RTS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため歳半ばで死亡し、国内推定患者数は約 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により診断基準改訂と世界初の WS 診療ガイドラインが作成され、平成 26 年度、重症度分類が作成され、平成 26 年5 月指定難病に指定された。平成 29 年度には診療ガイドライン、重症度分類を改訂し、令和 2 年には診療ガイドラインを英文誌に公表した。HGPS は 1～2 歳時に早老徴候が出現し、10 歳代でほぼ全例が死亡する重篤な小児疾患であり、平成 25 年度に施行した全国調査により、我が国で 6 名の患者が新規に同定され、平成 29 年度には世界初の HGPS 診断基準が作成され、令和元年 4 月指定難病に指定された。RTS は特徴的な皮膚所見が乳児期から認められ骨格異常や癌腫を合併する。平成 30 年に施行した全国調査により 10 名の患者を同定し、診断基準を改定した。

本研究は①WS 診断・診療ガイドラインの普及啓発と改訂、②その他の早老症研究（WS 類似疾患）、③HGPS、RTS の診療ガイドライン作成、④ 早老症の早期診断の実現と小児・成人を一体的に研究・診療できる体制の構築、⑤早老症レジストリを運用し、指定難病患者データベースの構築とそのフォローアップを行う。本研究班では、内科医・外科医・小児科医・臨床研究専門家の連携・融合による集学的な取り組みを通じて、小児から成人までの「早老症」の予後と QOL 改善を目指す。

A．研究目的

早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）、Hutchinson-Gilford Progeria 症候群（以下 HGPS と略）や Rothmund-Thomson 症候群（以下 RTS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡し、国内推定患者数は約 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により診断基準改訂と世界初の WS 診療ガイドラインが作成され、平成26年度、重症度分類が作成され、平成26年 5 月指定難病に指定された。平成 29 年度には診療ガイドライン、重症度分類を改訂し、令和 2 年には診療ガイドラインを英文誌に公表した。HGPS は 1～2 歳時に早老徴候が出現し、10 歳代でほぼ全例が死亡する重篤な小児疾患であり、平成 25 年度に施行した全国調査により、我が国で 6 名の患者が新規に同定され、平成 29 年度には世界初の HGPS 診断基準が作成され、令和元年 4 月指定難病に指定された。RTS は特徴的な皮膚所見が乳児期から認められ骨格異常や癌腫を合併する。平成 30年に施行した全国調査により 10 名の患者を同定し、診断基準を改定した。さらに早老症の実態を明らかにすべく難治性疾患実用化研究として推進されている早老症レジストリー研究と連携してきた。これらの研究を推進し、早老症の医療水準や患者QOL 向上に貢献することを本研究の目的とする。

B．研究方法

WS研究：①都道府県難病診療連携拠点病院を中心とした、難病医療支援センター、関連学会やナショナルセンター等と連携して診断基準や診療ガイドラインを啓発普及する。②WSの早期診断のための情報を収集するとともに、小児科と内科の連携により小児・成人を一体的に研究・診療できる体制を構築する。③早老症レジストリを運用してAMED「再生医療実現拠点ネットワークプログラム（疾患特異的iPS細胞の利活用促進・難病研究加速プログラム）」「老化メカニズムの解明・制御プロジェクト／個体・臓器老化研究拠点」厚労科研「指定難病の普及・啓発にむけた統合研究」を支援する。④ウェルナー症候群レジストリを運用し、引き続き患者登録及びフォローアップを行う。⑤ウェルナー症候群に対するニコチンアミドリボシドの安全性・有効性を検証するための前向き、単施設試験（責任研究者 千葉大学 横手幸太郎）を支援する。⑥本研究班において策定した診断基準に基づき、ウェルナー症候群患者の遺伝子診断を支援する。また、遺伝子診断の保険適応申請を支援する。

HGPS研究：①診療ガイドラインの作成へ向け、エビデンス収集を開始する。②関連学会において診療ガイドラインの承認を得る、③患者・家族会の設立を支援する。④小児科と内科の連携により小児・成人を一体的に研究・診療できる体制を構築する。

その他の早老症：①RTS の診療ガイドラインの作成へ向け、エビデンス収集を開始する。②WS 全国疫学調査の結果をもとに、aWS や WS 類似疾患の情報を収集する。

C．研究結果

WS研究：

Werner症候群に関する臨床的進歩、研究の普及・啓発活動をすべく、2023年度は以下のことを行った。

第66回日本糖尿病学会年次学術集会(2023.5月鹿児島)において、シンポジウム “糖尿病大血管合併症の最前線”にて「糖尿病と心腎連関」、と題して講演し、ウェルナー症候群における動脈硬化について啓発した。また、同学会の一般演題において「早老症Werner症候群の皮下脂肪における老化促進病態の解明」、「Werner症候群レジストリーを用いた糖尿病の有無における背景因子の検討」と題して発表した。IAGG Asia/Oceania Regional Congress 2023(2023年6月横浜)では”Pathogenesis of subcutaneous lipodystrophy in Werner syndrome” として一般演題を発表した。また、第65回日本老年医学会学術集会においては、3題の一般演題にて、いづれもウェルナー症候群の基礎研究、臨床研究を発表した。

また、7月9日内科学会地方会では、「希少難病を見過ごさないための診療アプローチ」（司会：越坂理也、ディスカッサー：谷口俊文）において、「遺伝的早老症ウェルナー症候群」（前澤善朗）、「早老症の見過ごされやすい症状」（窪田吉孝）として講演し、広く一般内科医を対象として啓発を行った。

また、本研究に派生して採択されたSICORP戦略的国際共同プログラム（SICORP）日・北欧共同研究「健康長寿の促進に向けた新規老化関連因子の探索と老化予測システムの開発」のミーティングの一環として2023.9月にオスロで行われたNorway-UK joint meeting on ageing and dementia. 2023 において、横手、加藤がシンポジストとして招聘され、講演した。また、ポスター演題を3題発表した。

加えて、2024年5月の日本小児科学会において、「遺伝性早老症とDown症候群」のセッションが予定され、ウェルナー症候群、ハッチンソンギルフォード症候群、ロズムンドトムソン症候群について本研究班の班員から、前澤、井原、松尾、金子がそれぞれ発表し、早老症の移行期医療のための重要な啓発の機会となる。

さらに、適切な医療の向上のため患者会と連携し、web患者会に複数回に渡って参加、(横手幸太郎、前澤善朗、越坂理也、加藤尚也）患者からの要望や疑問を拝聴し、意見交換した。また、レジストリや全国調査に協力いただいた施設と連携し、「ウェルナー症候群の診療経験のある医療機関」として、承諾を得てリスト化を行い、患者の医療機関選定の際に役立てるべくホームページに掲載した。また、患者会より要望のあった悪性腫瘍サーベイランス指針について論文化し、Geriatrics and Gerontology International(GGI)誌に投稿中である。さらにウェルナー症候群患者は、発症から診断まで16年の時間差があることが、レジストリ研究から判明している。ウェルナー症候群は両側白内障を初期症状とすることが多いため、早期診断のための眼科医に対する普及啓発文書「ウェルナー症候群全国疫学調査事務局からのお知らせ〜こんな患者さんいませんか〜」を日本眼科学会雑誌に掲載した。また、若年のウェルナー症候群疑い症例における遺伝子診断の適応についても提言をまとめ、HPでの公表と論文化を予定している。加えて、ウェルナー症候群患者の症候は、女性において男性よりも全ての症候が揃うのが遅いことがわかり、”Sex differences in symptom presentation and their impact on diagnostic accuracy in Werner syndrome”として, GGIに論文掲載された。

加えて、本研究より派生して採択された、下記のプログラムについても進捗が見られている。SICORP戦略的国際共同プログラム（SICORP）日・北欧共同研究「健康長寿の促進に向けた新規老化関連因子の探索と老化予測システムの開発」と連携し、ウェルナー症候群患者を対象に、老化を反映する代謝産物の同定と、老化予測システムのモデル化を行った。また、早老症疾患特異的iPS 細胞を用いた老化促進メカニズムの解

明を目指す研究（研究開発代表者　横手幸太郎）と連携し、根本治療として、エクソンスキッピング法を用いたWRN遺伝子の発現回復治療の開発に昨年度に引き続き取り組んでいる。また、ウェルナー症候群の病態解明基礎研究にも取り組み、その脂肪組織の慢性炎症について、Senescence-associated inflammation and inhibition of adipogenesis in subcutaneous fat in Werner syndromeとしてAging誌に発表した。加えて難治性疾患実用化研究事業として推進されている早老症レジストリ研究においても54名の症例が登録されている。横断解析動脈硬化性疾患の減少、腎機能の低下、悪性新生物の早期発症といった知見を得てRenal dysfunction, malignant neoplasms, atherosclerotic cardiovascular diseases, and sarcopenia as key outcomes observed in a three-year follow-up study using the Werner Syndrome RegistryとしてAging誌に発表した。また、潰瘍を有する患者と有さない患者の比較を行い、ピオグリタゾンの使用が潰瘍の軽減に有用である可能性などの新規知見を得ている。

また、Werner症候群レジストリおよび科学研究費補助金挑戦的研究・萌芽（日本学術振興会）の「老化モデル疾患を対象としたNAD前駆体による革新的治療および老化抑制機序の検討」と連携し、臨床試験を通じた新たな治療法の開発のため、ウェルナー症候群に対するニコチンアミド リボシドの安全性・有効性を検証するための前向き、単施設試験Prospective, single-center, cross-over trial to verify safety and effectiveness of nicotinamide riboside for patients with Werner syndrome (EMPOWER試験)を支援している。

HGPS 研究：
ファルネシル化酵素阻害剤Zokinvy™（lonafarnib: ロナファルニブ）の国内承認に向けて、国内代理店を通してPMDA及び厚生労働省へ各種申請を進めた結果、令和5年度末に承認された。さらに令和6年度の春には、保険診療としての治療開始が可能となった。また、国内承認後に速やかにロナファルニブを全国の患者に届けるため、新たに全国調査を行い、最新の日本人患者の疫学情報と臨床的特徴を明らかにした。以上の結果から、遺伝性早老症HGPSに対する治療薬ロナファルニブの厚労省承認を受け国内での治療が可能となり、さらにHGPSおよび*ZMPSTE24*遺伝子異常症の患者の把握により速やかな治療開始に貢献した。

その他の早老症：
ロスムンド・トムソン症候群は、多形皮膚萎縮症、骨格の異常を特徴とする常染色体潜性の遺伝形式をとる疾患である。我々は2010年と2020年にロスムンド・トムソン症候群の全国調査を行い本邦での特徴を報告した。本邦での患者数は2010年10症例、2020年8症例であった。ロスムンド・トムソン症候群は極めて稀な疾患であるためロスムンド・トムソン症候群の早期診断・早期治療介入を可能とするには、診療ガイドラインの策定が必要である。そこで、我々は全国調査による本邦の特徴を参考にした上でロスムンド・トムソン症候群の診療ガイドラインを作成した。作成した診療ガイドラインは日本小児遺伝学会の学会承認を得ることができた。さらに、医療関係者以外にロスムンド・トムソン症候群の理解を深めてもらうために、市民公開講座を開催し、患者会創設に繋げた。また、患者会と協力し疾患のリーフレットを作成した。これらの研究活動により、ロスムンド・トムソン症候群の認知度が高まり、適確な診断がなされ、多職種による定期的なフォローが早期から行われることにより患者のQOLの向上、生命予後の改善が期待される。

D．考察

ほぼ研究計画に沿って研究が行われた。本研究組織は、全国各地域の大学や国立研究センターに在籍する分担研究者と研究協力者によって構成される。これらのメンバーが WS、HGPS、RTSの症例集積を継続的に実施し、主要なエビデンスを収集、相互に協調しつつ診断基準や診療ガイドラインの作成・改訂や重症度分類の作成、検証を行い、さらにこれらを基盤として、より詳細な病態解明研究を行っている。また、臨床研究中核病院である千葉大学医学部附属病院の臨床試験部に設置された「早老症レジストリー」事務局において症例の登録とフォローアップが継続進行中であり、今回、WSレジストリとして２本目の論文を出版した。今後、長期的に臨床経過が詳細に観察され、早老症患者の自然史が明らかになることが期待される。

さらに本研究の成果（症例情報）をベースとして研究課題が採択されたAMED「再生医療実現拠点ネットワークプログラム（疾患特異的iPS細胞の利活用促進・難病研究加速プログラム）」（課題名：早老症疾患特異的 iPS細胞を用いた老化促進メカニズムの解明を目指す研究）および「老化メカニズムの解明・制御プロジェクト／個体・臓器老化研究拠点」（課題名：早老症に立脚したヒト老化病態の解明とその制御への応用）、SICORP戦略的国際共同プログラム（SICORP）日・北欧共同研究、など、多くの研究を支援し、2023年度で4本の英語論文出版を得ている。

本研究においては患者の声に耳を傾けることを重視し、WS患者会との連携から、患者向けパンフレットの作成や、悪性腫瘍スクリーニング指針の策定などを行いまた、patient public involvement (PPI)のプログラムであるRUDY JAPNとの連携へと新たな展開を試みている。HGPS, RTSにおいてもこれまでも患者向けハンドブックの日本語訳の作成や、患者会の組織など、患者ニーズに耳を傾けながら、研究を発展させてきた。このような活動から得られた診療

の指針は、患者の日常生活における QOL 向上に貢献するものと思われる。

HGPSは初の治療薬であるロナファルニブに期待が集まっている。2024年5月に国内承認され、今回の全国調査の結果が、適応症例に新薬が届くために重要な情報となった。また、国内においてもHGPSの患者さんが正しくピックアップされ、ロナファルニブの恩恵を受けることが期待される。また、新規に*ZMPSTE24*遺伝子異常症がHGPSの診断基準に改定追加されることから、このような患者についても把握が行われた意義は大きいと思われる。

また、RTSについても市民公開講座、患者会創設、リーフレットの作成など、幅広く活動している。作成したRTSガイドラインは日本小児遺伝学会の学会承認を得ており、普及啓発活動を展開している。患者との対話を重視し連携しつつ、診断基準の改定まで到達しており、本疾患は希少で臨床像の把握も困難であることから、このような活動と資料は本邦におけるRTS患者のために、またRTSに取り組む臨床医にとっても重要な貴重な情報源となっていると思われる。

今後も公開講座などを通じて国民へ啓発活動を行ってゆき、最終的に、小児から成人までの「早老症」の予後改善を目指してゆきたいと考える。

F．研究発表

1.論文発表

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３．ホームページ等

1. ウェルナー症候群日本語HP
https://www.m.chiba-u.jp/dept/clin-cellbiol/werner/

2. ウェルナー症候群英語HP
https://www.m.chiba-u.jp/dept/clin-cellbiol/werner/wernersyndrome/

3. ハッチンソン・ギルフォード症候群：日本語ホームページ
http://square.umin.ac.jp/hgps/

4. ハッチンソン・ギルフォード症候群：GeneReviews 日本語版
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5. ロズムンド・トムソン症候群
https://www.m.chiba-u.jp/dept/clin-cellbiol/files/6715/9763/8690/rothmund_thomson.pdf

G．知的財産権の出願・登録状況（予定を含む）

１．特許取得
なし

２．実用新案登録
なし

厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

ウェルナー症候群:
診療の質および患者 QOL を向上する全国研究

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研究要旨:早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳後半で死亡し、国内推定患者数は約 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により診断基準改訂と世界初の WS 診療ガイドラインが作成され、平成 26 年度、重症度分類が作成され、平成 26 年 5 月指定難病に指定された。平成 29 年度には診療ガイドライン、重症度分類を改訂し、令和 2 年には診療ガイドラインを英文誌に公表した。早老症の実態を明らかにすべく難治性疾患実用化研究として推進されている早老症レジストリー研究とも連携してきた。さらに診療ガイドラインの改定を行い、日本語版と英語版を作成し、英語版に関しては英文雑誌に掲載した。加えて、患者会との連携のもと、患者のニーズにあった啓発、情報提供の資材をさらに作成している。本研究では、これら一連の研究を広く周知する目的で、学会におけるシンポジウムの企画・発表、研究成果の学会誌への掲載、そして我が国を代表する内科学の教科書に記載しウェルナー症候群の普及・啓蒙活動を行った。

A. 研究目的

早老症あるいは早期老化症候群（progeroid syndrome、premature aging syndromes）では暦年齢に比較して加齢現象が促進して観察される。特定の早老徴候が特定の臓器に誇張された形で観察されることより、部分的早老症候群（segmental progeroid syndrome）とも呼ばれる。代表的な疾患としてウェルナー症候群（以下 WS と略）や Hutchinson-Gilford 症候群が挙げられる。それぞれ原因遺伝子は同定されているが、早老機序は必ずしも明らかではなく、根本的な治療法開発には至っていない。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡する早老症であり、国内推定患者数は 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治

療の標準化や世界初の WS 診療ガイドラインが作成され、平成 26 年度の政策研究事業により WS 重症度分類が作成され、平成 26 年 5 月指定難病に指定された。さらに難治性疾患実用化研究として推進されている早老症レジストリー研究と連携し、平成 29 年度には診療ガイドライン、重症度分類を改訂した。本研究の目的はこれまでの研究をさらに発展させ WS の診療の質および患者 QOL 向上に貢献することである。

B． 研究方法

1. これまでの早老症に関する臨床的進歩、研究の普及・啓発活動を行っている。

（倫理面への配慮）

本研究では個人情報を収集するため、個人情報保護法、文部科学省・厚生労働省・経済産業省：ヒトゲノム・遺伝子解析研究に関する倫理指針、文部科学省・厚生労働省：疫学研究に関する倫理指針、厚生労働省：臨床研究に関する倫理指針経済産業省：情報システムの信頼性向上に関するガイドライン、民間部門における電子計算機処理に係る個人情報の保護に関するガイドラインなどを順守して研究計画の立案・遂行を行う。調査・研究の実施に際しては、各施設の倫理委員会に諮り、許可を申請する。患者の血液検体解析においては、事前に文書で本人に説明と同意を得ることとし、不参加の場合でも何らの不便･不都合とならないことを伝える。解析にあたっても患者のプライバシーに配慮し、臨床経過が個人と結びつかないようデータを管理した。

C． 研究結果

Werner 症候群に関する臨床的進歩、研究の普及・啓発活動をすべく、2023 年度は以下のことを行った。

第 66 回日本糖尿病学会年次学術集会(2023.5 月鹿児島）において、シンポジウム “糖尿病大血管合併症の最前線”にて「糖尿病と心腎連関」、と題して講演し、ウェルナー症候群における動脈硬化について啓発した。また、同学会の一般演題において「早老症 Werner 症候群の皮下脂肪における老化促進病態の解明」、「Werner 症候群レジストリーを用いた糖尿病の有無における背景因子の検討」と題して発表した。IAGG Asia/Oceania Regional Congress 2023(2023 年 6 月横浜)では”Pathogenesis of subcutaneous lipodystrophy in Werner syndrome”として一般演題を発表した。また、第 65 回日本老年医学会学術集会においては、3 題の一般演題にて、いづれもウェルナー症候群の基礎研究、臨床研究を発表した。

また、7 月 9 日内科学会地方会では、「希少難病を見過ごさないための診療アプローチ」（司会：越坂理也、ディスカッサー：谷口俊文）において、「遺伝的早老症ウェルナー症候群」（前澤善朗）、「早老症の見過ごされやすい症状」（窪田吉孝）として講演し、広く一般内科医を対象として啓発を行った。

また、本研究に派生して採択された SICORP 戦略的国際共同プログラム（SICORP）日・北欧共同研究「健康長寿の促進に向けた新規老化関連因子の探索と老化予測システムの開発」のミーティングの一環として 2023.9 月にオスロで行われた Norway-UK joint meeting on ageing and dementia. 2023 において、横手、加藤がシンポジストとして招聘され、講演した。また、ポスター演題を 3 題発表した。

加えて、2024 年 5 月の日本小児科学会において、「遺伝性早老症と Down 症候群」のセッションが予定され、ウェルナー症候群、ハッチンソンギルフォード症候群、ロズムンドトムソン症候群について本研究班の班員から、前澤、井原、松尾、金子がそれぞれ発表し、早老症の移行期医療のための重要な啓発の機会となる。

さらに、適切な医療の向上のため患者会と連携し、web 患者会に複数回に渡って参加、（横手幸太郎、前澤善朗、越坂理也、加藤尚也）患者からの要望や疑問を拝聴し、意見交換した。

このような患者会との連携から、下記の情報提供や資材の作成、並びに研究を行なった。まず、レジ

ストリや全国調査に協力いただいた施設と連携し、「ウェルナー症候群の診療経験のある医療機関」として、承諾を得てリスト化を行い、患者の医療機関選定の際に役立てるべくホームページに掲載した。また、患者会より要望のあった悪性腫瘍サーベイランス指針について論文化し、Geriatrics and Gerontology International(GGI)誌に投稿中である。さらにウェルナー症候群患者は、発症から診断まで16年の時間差があることが、レジストリ研究から判明している。ウェルナー症候群は両側白内障を初期症状とすることが多いため、早期診断のための眼科医に対する普及啓発文書「ウェルナー症候群全国疫学調査事務局からのお知らせ～こんな患者さんいませんか～」を日本眼科学会雑誌に掲載した。また、若年のウェルナー症候群疑い症例における遺伝子診断の適応についても提言をまとめ、HP での公表と論文化を予定している。加えて、ウェルナー症候群患者の症候は、女性において男性よりも全ての症候が揃うのが遅いことがわかり、”Sex differences in symptom presentation and their impact on diagnostic accuracy in Werner syndrome”として, GGI に論文掲載された。

加えて、本研究より派生して採択された、下記のプログラムについても進捗が見られている。前述のSICORP 戦略的国際共同プログラムでは、ウェルナー症候群患者を対象に、老化を反映する代謝産物の同定と、老化予測システムのモデル化を行った。また、早老症疾患特異的 iPS 細胞を用いた老化促進メカニズムの解明を目指す研究（研究開発代表者横手幸太郎）と連携し、根本治療として、エクソンスキッピング法を用いた WRN 遺伝子の発現回復治療の開発に昨年度に引き続き取り組んでいる。また、ウェルナー症候群の病態解明基礎研究にも取り組み、その脂肪組織の慢性炎症について、Senescence-associated inflammation and inhibition of adipogenesis in subcutaneous fat in Werner syndrome として Aging 誌に発表した。加えて難治性疾患実用化研究事業として推進されている早老症レジストリ研究においても54名の症例が登録されている。横断解析動脈硬化性疾患の減少、腎機能の低下、悪性新生物の早期発症といった知見を得て Renal dysfunction, malignant neoplasms, atherosclerotic cardiovascular diseases, and sarcopenia as key outcomes observed in a three-year follow-up study using the Werner Syndrome Registry として Aging 誌に発表した。また、潰瘍を有する患者と有さない患者の比較を行い、ピオグリタゾンの使用が潰瘍の軽減に有用である可能性などの新規知見を得ている。

また、Werner 症候群レジストリおよび科学研究費補助金挑戦的研究・萌芽（日本学術振興会）の「老化モデル疾患を対象とした NAD 前駆体による革新的治療および老化抑制機序の検討」と連携し、臨床試験を通じた新たな治療法の開発のため、ウェルナー症候群に対するニコチンアミド リボシドの安全性・有効性を検証するための前向き、単施設試験 Prospective, single-center, cross-over trial to verify safety and effectiveness of nicotinamide riboside for patients with Werner syndrome (EMPOWER 試験)を支援している。

D. 考察

2009 年 厚生労働省科学研究費補助金 難治性疾患研究事業では、我が国における WS の現状を調査すべく、 2009 年年 9 月には一次アンケート調査を、2009 年 10 月には一次アンケートで明らかとなった症例に対する二次アンケート調査を行った。そしてこれらの調査で明らかになった臨床的特徴をもとにして、診断基準の改訂が行われた。2012 年 2 月 19 日には東京国際フォーラムにて「遺伝性早老症ウェルナー症候群のこれまでの研究の歩みとこらからの展望」とのタイトルで研究報告会が行われたが、この会では患者・家族の会も同時に行われ、その当時の最新の研究成果を研究者のみならず患者・家族会でも共有した。この年には我が国におけるウェルナー症候群の臨床経験をもとにして世界で初めて「ウェルナー症候群の

診療ガイドライン 2012 年版」が発表された。2015 年には WS の重症度分類を作成し発表した。そして、2015 年 7 月 1 日、WS は指定難病に選定された。

その後、2016 年には 2 回目の全国調査が施行され、 2020 年にはレジストリー研究の一部が報告されている。また大阪大学の中神らは創修復作用と抗菌活性の両方の特性をもつ SR-0379 液を難治性潰瘍に対する外用薬として開発し、この薬剤の効果が WS においても検証された。その結果、SR-0379 はプラセボに対して有意に潰瘍サイズを縮小（22.9% vs. 0.1%）させたことが報告されている。今後のウェルナー症候群の難治性潰瘍治療に貢献することを期待したい。

また最近の WS の臨床的特徴を検討すべく、2009 年の全国 2 次調査の結果と、2020 年のレジストリー研究の結果が比較検討された。その結果、難治性皮膚科潰瘍、狭心症、心筋梗塞、悪性腫瘍の併存率が減少していることが報告されている。狭心症、心筋梗塞に関しては診断を受けた症例の脂質、血圧、血糖管理の成果が奏功している可能性がある。内服薬の比較でもスタチンは両年ともに 65％以上に、ARB は 42.1%、35.3％処方されていた。血糖降下薬に関しては両年で使用トレンドが異なってきているが、SGLT2 阻害剤、GLP-1 受容体作動薬といった一般の糖尿病患者において心血管イベント抑制作用が報告されている薬剤も登場してきており、WS における適応やその効果に関して今後の解析が必要と思われる。興味深いことに、近年のレジストリ解析において、ピオグリタゾン内服中の患者は潰瘍が少ないことがわかり、今後治療薬選択において考慮すべき要素となる可能性がある。

また、今回の解析では、WS 患者において動脈硬化性疾患が大きく減少し、主要な死因が悪性腫瘍となった。中でも、上皮性癌よりも、非上皮性肉腫が死因となることが多く、主要サーベイランスの方法構築が必要である。また、腎機能低下は一般老化と比較して十倍急速であることも判明し、今まで注目されていなかった WS の腎機能低下に今後注目していく必要がある。

さらに、今回は診療経験のある医療機関の HP への掲載、悪性腫瘍サーベイランス指針の提唱、眼科学会への啓発、そして若年者 WS に対する遺伝子診断の指針案の策定を行なっており、それぞれ患者側、医療者側に役立つ指針となると考える。

このような知見の発信、並びに英語化されたパンフレットやホームページを介して、日本国内のみならず世界中の WS の治療が標準化され、患者の生命予後や QOL 向上に寄与することを期待したい。

E． 結論

一般的に老化を進行させる要因として遺伝因子と環境因子が挙げられるが、WS においては遺伝要因がその早老機序に関与することは疑いの余地はない。一方、WS 患者の平均寿命は以前の報告に比し延長しており、WS をより早期に診断し、より早期から合併する代謝性疾患や下肢潰瘍の管理を行うことは寿命延長や QOL の向上の観点から意義は大きい。WS は日本に多いとはいえ、推定 2000 症例であり、希少疾患である。WS の発症年齢が 26.1±9.5 年であるのに対し、診断年齢は 42.5±8.6 年と報告されており、適切な診断まで実に 16 年の歳月を要している。このギャップを埋めることは喫緊の課題といえ、このために今回の眼科学会への啓発と、若年者に対する遺伝子診断の指針は、重要な指針となると思われる。また、今回明らかになった急速な腎機能低下と悪性腫瘍、特に間葉系腫瘍の高率な合併は今後の治療ストラテジーの改善のために重要な要素となると思われる。

また本研究班ではウェルナー症候群に限らず、Hutchinson-Gilford 症候群や Rothmund-Thomson 症候群の臨床研究が行われている。2018 年 2 月 16 日～18 日には、千葉県のかずさアカデミアパークにて「国際シンポジウム・早老症と関連疾患 2018」が開催され多くの臨床医、研究者による意見

交換が行われた。このような活動を通じて早老症全体の ADL、QOL の向上や予後が改善することを今後も期待したい。

F． 健康危惧情報

特になし。

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H．知的財産権の出願・登録状況

（予定を含む。）

1．特許取得

無し

2．実用新案登録

無し

3．その他

無し

厚生労働科学研究費補助金（難治性疾患等政策研究事業）
分担研究報告書

ハッチンソン・ギルフォード症候群の新規治療薬ロナファルニブの国内承認に向けた取り組みと全国調査（詳細調査）

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研究要旨： ハッチンソン・ギルフォード症候群(Hutchinson-Gilford progeria syndrome; HGPS)は遺伝性早老症の中でも症状が特に重篤な希少疾患である。ファルネシル化酵素阻害剤 Zokinvy™ (lonafarnib：ロナファルニブ)の国内承認に向けて、国内代理店とともに PMDA と厚生労働省に各種の申請を進めた結果、令和 5 年度末に承認され令和 6 年度春には治療開始が可能となった。国内承認後に速やかにロナファルニブを全国の患者さんに届けるために、過去 10 年で発症した HGPS,HGPS 疑い患者、それ以外のラミノパチーの患者について全国調査（2 次詳細調査）を実施した。

A．研究目的

ハッチンソン・ギルフォード症候群(Hutchinson-Gilford progeria syndrome; HGPS)は、遺伝性早老症の中でも最も症状が重篤な疾患であり、出生後から重度の成長障害、脱毛、老化顔貌、皮下脂肪の減少、動脈硬化性疾患の合併症により平均寿命は 14.6 歳と報告されている。国内で 10 例程度、全世界でも 350～400 人の患者が報告されている超希少疾患である。*LMNA* 遺伝子の特定の病的バリアントにより産生される異常ラミン A タンパク質「プロジェリン」が病因である。

本研究班では、アメリカ合衆国 FDA で承認されたファルネシル化酵素化タンパク質阻害剤 Zokinvy™ (lonafarnib:ロナファルニブ)の日本国内の患者への治療承認に向けて、米国 Eiger BioPharmaceuticals 社の日本代理店（AnGes 社）と協議を継続してきた。

一方、本研究班で実施した前回の全国患者の疫学調査から約 10 年が経過した。新規に発症した HGPS,HGPS 疑い患者、それ以外のラミノパチーの患者さんに対し、国内承認後に速やかにロナファルニブを届けるため昨年度に全国疫学調査（一次調査）を行った。本年度は「HGPS 等の疾患の診療経験」があり「二次調査への協力が可能」と一次調査で回答のあった計 15 施設に対し、多機関共同臨床研究の承認後、2 次詳細調査を行った。

B．研究方法

（１）ロナファルニブの国内承認に向けた協議

ロナファルニブの国内承認に向け、国内代理店 AnGes 社と本班は情報を共有し協議を継続している。国内の薬事承認、保険承認、薬価収載（14 日処方制限解除申請を含む)、指定難病の診断基準の改訂などを並行して進めた。

（２）全国患者疫学調査（２次調査）

臨床研究課題名： ハッチンソン・ギルフォード・プロジェリア症候群（HGPS)等患者実態全国調査（２次調査）について、大分大学倫理審査委員会の承認（2646-D12）の後、Creative Survey 社のオンライン調査等を行った。その結果、HGPS 5 名、*ZMPSTE24* 遺伝子異常症 3 名を確認した。その中で 7 名が新規治療薬ロナファルニブの適応患者であることが明らかになった。また過去に診療経験ありと回答された施設から 4 名の HGPS 症例を確認した。

Ｃ．研究結果

（１）HGPS の概要

10 年前の調査時の 1 症例も含めて合計 10 例の HGPS の概要をまとめた。性別は男女各 5 例で、調査時点の年齢の中央値は 12 歳、生存中５例、死亡症例は 5 例であった。診断時年齢は中央値 1 歳、死亡時年齢の中央値 15 歳と既報と同様であり、また死亡者の直接的な死因は心不全２例、不整脈１例、腎不全１例だった。遺伝型は、典型的バリアント(c.1824C>T)が 7 例、非典型的バリアント(c.1762T>C と c.1968+1G>A)が 2 例、臨床診断例が１例であった。調査した臨床症状は、診断基準の皮膚・骨・顔面頭部の変化、成長障害、また合併症として糖脂質代謝、高血圧、脳卒中、心疾患、骨粗しょう症、二次性徴の有無などであり、特に皮膚、骨格、顔面頭部、合併症の４項目については 1 歳時の出現頻度は 2～8 割と徴候により差異があったが、10 歳以降にはほぼ 100%の徴候が出現していた。

（２）*ZMPSTE24* 遺伝子異常症の概要

ZMPSTE24 遺伝子異常症 2 例は姉妹例（現在 20 歳と 24 歳）で管理中の同一施設から報告された。診断時の年齢は生後１か月と 3 か月と乳児期であり、*ZMPSTE24* 遺伝子異常症についても HGPS と同様の臨床的特徴に関して調査した。その結果、1 歳時には２例とも皮膚の変化と早老様顔貌、10 歳以降には診断基準の徴候すべてが出現していた。成長曲線については、HGPS と *ZMPSTE24* 遺伝子異常の重度成長障害は酷似しており乳児期早期は成長障害が目立たず１歳頃から大きく曲線から下方に外れた成長障害を示すことが明らかになった。

（３）HGPS 診断基準等改訂とゾキンヴィ薬事承認

厚生労働省から指定難病の改訂について問い合せに従い、概要と診断基準の改訂を行った。診断基準の改定案については日本小児遺伝学会（黒澤理事長）の承認を受けた（令和 6 年 1 月 30 日）。

令和 5 年 12 月 8 日に開催された厚生労働省の薬事・食品衛生審議会医薬品 第一部会にて、ゾキンヴィ（ロナファルニブ）の薬事承認について審議の後に了承された。さらにゾキンヴィの 14 日処方制限解除要望書を日本小児遺伝学会（黒澤健司理事長）から提出していただいた。その結果、令和６年４月 10 日の中央社会保険医療協議会(中医協）において薬価が承認された（50 mgカプセル 91,796.40 円、75 mgカプセル 136,544.00 円）。また DPC 対象からの除外、また 14 日処方制限の解除についても承認された。これにより 50mg および 75mg ともに 30 カプセルが包装されたボトル単位で長期処方が可能となり、その後、ゾキンヴィの発売開始に向けて準備が進められている。

Ｄ.展望

HGPS, HGPS 疑い患者, それ以外のラミノパチー患者の二次調査を通して本症候群の最新の疫学情報を明らかにした。今後、すべての患者にロナファルニブ治療の選択肢を提案する予定である。そのためには内服治療を開始する前の患者さんへの説明用パンフレットや医療者向けの手引書を作成するとともに、医療者のみならず一般市民への疾患啓発活動を進める必要がある。さらに治療開始後の患者さんの長期治療成績調査につい

てはAnGes社とともに実施準備を進めている。

Ｅ．結論

遺伝性早老症の中でも症状が特に重篤な希少疾患 HGPS に対する治療薬ロナファルニブの国内国内承認を受けた。また我が国の過去 10 年で発症したHGPS,HGPS疑い患者、それ以外のラミノパチーの患者について全国調査（２次詳細調査）を行い、疫学情報ならびに臨床的特徴を明らかにした。

Ｆ．健康危険情報

なし

G.研究発表

１．論文発表

なし

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３．ホームページ等

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http://square.umin.ac.jp/hgps/

2) ハッチンソン・ギルフォード症候群：GeneReviews 日本語版

http://grj.umin.jp/grj/hgps.htm

H．知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

ロスムンド・トムソン症候群のリーフレット作成

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研究要旨:ロスムンド・トムソン症候群は、多形皮膚萎縮症、骨格の異常を特徴とする常染色体潜性の遺伝形式をとる疾患である。我々は 2010 年と 2020 年にロスムンド・トムソン症候群の全国調査を行い本邦での特徴を報告した。本邦では 10 名前後の患者数であり、ロスムンド・トムソン症候群は極めてまれな疾患であることが改めて明らかになった。医療関係者・一般の人々におけるロスムンド・トムソン症候群の認知度は高くない。患者のケア、教育にかかわる人々の理解不足により、様々な困りごとに直面することも想定される。そこで一般の人々にロスムンド・トムソン症候群について、理解を促すため患者会と協力しリーフレットの作成を行った。リーフレットには疾患の概要、日常生活で気をつけていることなどを記載した。リーフレットの普及を通じて、ロスムンド・トムソン症候群の理解度を高めることで、患者の QOL の向上が期待される。

A.　研究目的

本研究の目的は、本邦でのロスムンド・トムソン症候群の実態を明らかにし、患者の QOL の向上、生命予後の改善を図ることである。本邦における実態を明らかにするため2010年と2020年に2回のアンケート調査を実施した。以前報告したように、本邦での患者数は2010年10症例、2020年8症例と非常に少なかった。

ロスムンド・トムソン症候群は稀少疾患ではあるため、一般の人々のみならず医療関係者もロスムンド・トムソン症候群に対する認知度は低い。患者のケア、教育にかかわる人々の理解不足により、患者が様々な困りごとに直面する場面も想定される。そこで一般の人々にロスムンド・トムソン症候群について、理解を促すため患者会と協力しリーフレットの作成を行った。

B.　研究方法

患者会創設への支援

患者会創設の最初の取り組みとして市民公開講座を 2022 年 11 月 25 日に Zoom を用いた Web 形式にて開催した。参加者の選定は学術論文や医師間のネットワークを活用した。主治医から患者、患者保護者に市民公開講座の概要について説明し、参加の意向を尋ねた。ロスムンド・トムソン症候群小児 2 名、バレー・ジェラルド症候群の小児 1 名、保護者 4 名、医師 3 名が参加した。市民公開講座の中で、日本ではロスムンド・トムソン症候群の患者会が存在していないこと、患者会活動の重要性を保護者に説明した。その後、参加者らにより患者会が創設された。市民公開講座終了後下記の質問、意見があった。

・皮膚の症状に対して保湿、UV ケアは具体的にどこまですればよいのか。

・学校での UV 遮蔽のシールについて、学校が対応してくれない場合がある。

・難聴があるがロスムンド・トムソン症候群には多いのか。

リーフレット作成

患者会の保護者から、リーフレット作成の希望が出された。疾患の概要や日常的に気を付けていることをわかりやすく記載することとした。対象は患者

の学校関係者、患者のケアを行う人が想定した。

（倫理面への配慮）

臨床情報を収集する場合は、連結可能匿名化した。「ロスムンド・トムソン症候群の全国疫学調査」として岐阜県総合医療センターの倫理委員会の承認を得た。

C. 研究結果

ロスムンド・トムソン症候群のリーフレットを作成した（添付）。

疾患の概要として、骨と皮膚の病気であること、骨肉腫や皮膚がんが発症しやすいことを記載した。生活の中で気を付けていることとして、紫外線の対策をしていること、紫外線カットフィルムを貼るなどの環境設定を依頼する場合があることを記載した。本リーフレットは、ロスムンド・トムソン症候群家族会ホームページ(https://rts-family.wixsite.com/my-site)に掲載され、希望者は自由に使用可能となっている。

D. 考察

ロスムンド・トムソン症候群は極めてまれな疾患であり、医療関係者であってもその認知度は高くない。一般の人々はさらに低いことは容易に予想される。このような状況で、患者会の創設、リーフレッツとの作成により、疾患について一般の人々に広報していくことは患者の生活の質の向上に寄与すると考えられる。実際、患者会の参加者には、全国調査では把握できていなかった患者も存在しており、本邦における全体像の解明にも重要である。さらに、患者会やリーフレットが、ロスムンド・トムソン症候群における骨肉腫、皮膚がんの定期的な観察の意義について情報提供することで、患者の生命予後の向上が期待される。

E. 結論

患者会と協働してリーフレットを作成した。リーフレットの普及を通じて、ロスムンド・トムソン症候群の理解度を高めることで、患者のQOLの向上が期待される。

F. 健康危惧情報

特になし。

G. 研究発表

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別冊日本臨牀「血液症候群（第3版）II 」2023年10月 pp309-314

3) 金子英雄
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ASHG annual meeting 2023 Walter E. Washington Convention Center (Washington DC) Nov. 1-5, 2023

H. 知的財産権の出願・登録状況（予定を含む。）

１．特許取得
無し

２．実用新案登録
無し

３．その他
無し

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
大西秀典	DNA修復障害	日本免疫不全・自己炎症学会	原発性免疫不全症候群　診療の手引き	診断と治療社	東京	2023	41－48

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kaneko H, Kawase C, Seki J, Ikawa Y, Yachie A, Funato M.	Intellectual disability and abnormal cortical neuron phenotypes in patients with Bloom syndrome.	J Hum Genet	68	321－327	2023
金子英雄	ブルーム（Bloom）症候群	別冊日本臨牀血液症候群（第3版）	II	304－308	2023
金子英雄	Good症候群(免疫不全症を伴う胸腺腫)	別冊日本臨牀血液症候群（第3版）	II	309－314	2023
茂木精一郎	Werner症候群	皮膚科	5	57-63	2024
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ARTICLE

Intellectual disability and abnormal cortical neuron phenotypes in patients with Bloom syndrome

Hideo Kaneko[1,2]✉, Chizuru Kawase[2], Junko Seki[2], Yasuhiro Ikawa[3], Akihiro Yachie[4] and Michinori Funato[2]

Bloom syndrome (BS) is a rare autosomal recessive disorder characterized by genomic instability that leads to various complications, including cancer. Given the low prevalence of BS in Japan, we conducted a nationwide survey. We recruited eight patients with BS, three of whom exhibited intellectual disability. The 631delCAA mutation in the *BLM* gene was detected in 9 out of 16 alleles. To investigate neuronal development in patients with BS, we generated induced pluripotent stem cells derived from one of these patients (BS-iPSCs). We examined the phenotypes of the induced cortical neurons derived from the generated BS-iPSCs using a previously reported protocol; the generated BS-iPSCs showed an approximately 10-times higher frequency of sister-chromatid exchange (SCE) than the control iPSCs. Immunocytochemistry revealed shorter axons and higher proliferative potential in BS-iPSC-derived cortical neurons compared with control iPSCs. To our knowledge, our study is the first to clarify the abnormality of the cortical neuron phenotypes derived from patients with BS. Our findings may help identify the pathogenesis of neuronal differentiation in BS and aid in the development of novel therapeutic agents.

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INTRODUCTION

Bloom syndrome (BS) is an autosomal recessive disease caused by loss-of-function mutations in *BLM*, a subfamily of DExH boxes containing DNA and RNA helicases [1]. The absence of a functional BLM protein causes chromosome instability, excessive homologous recombination, and a greatly increased number of sister-chromatid exchanges (SCE), which have been used for diagnosing BS, because SCE was considered to be a characteristic feature of BS [2, 3]. BLM helicases constitute a multiprotein complex called the BTRR (BLM-TOP3A- a- RMI2) complex, which also includes topoisomerase III alpha (TOP3A) and RecQ-mediated genome instability protein 1 (RMI1) and 2 (RMI2) [4–6]. Recently, homozygous frameshift mutations in TOP3A and RMI1 as well as loss of the RMI2 gene as a result of a large homozygous deletion have been associated with a BS phenotype, including the elevated frequency of SCE [7, 8].

BS is characterized by dermatologic complications, growth deficiency, immune deficiency, reduced glucose tolerance, a significantly increased risk of early-onset cancer and the development of multiple cancers, which is a major medical concern for BS [9].

Some individuals with BS exhibit intellectual disabilities [10, 11]. Single-cell transcription profiles in patients with BS reveal significant deregulation of genes that cause inherited forms of primary microcephaly associated with intellectual disability [12]. Although the hypomorphic *BLM* mouse model exhibits tumor formation similar to that associated with BS and may be a preclinical model for BS [13, 14], only one BS-iPSC line has been established [15]; no human cell model of BS for studying cortical neurons has been reported. Owing to the rarity of BS, the actual condition of patients with BS has not been elucidated. In the current study, we initially investigated the clinical features of patients with BS, those with intellectual disabilities, via a nationwide survey in Japan. Finally, we derived induced pluripotent stem cells (iPSCs) from one patient, and thereon differentiated into cortical neurons to analyze their phenotype.

MATERIAL AND METHODS

Investigation of patients with BS in Japan

Following the administration of the first questionnaire in 2010, a second questionnaire was administered. In the survey, 515, 515, and 377 first questionnaires were sent to the relevant specialist departments of training hospitals for pediatrics, dermatology, and hospitals with a cancer center, respectively. The first 15 questionnaires were returned as no destination was found. After the first questionnaire, 12 answers were returned from attending physicians for patients with suspected BS. Eight of the 12 patients in this study were recruited as patients with BS if they exhibited one or more of the following inclusion criteria: short stature; skin lesions such as sun-sensitive erythema, pigmentation or café-au-lait spots; immunodeficiency; together with either a confirmed elevated frequency of SCE or *BLM* gene mutation. We sent a second questionnaire to attending physicians for eight patients with BS. The contents of the questionnaire were as follows: sex; age; dead or alive; family history; consanguineous marriage; height and body weight; initial symptoms; chromosomal abnormality; SCEs; analysis of *BLM* gene mutation; white blood cell count; T cell count; B cell count; serum IgG, IgM, IgA, and IgE levels; antibiotic prophylaxis; gamma globulin replacement; and hematopoietic cell transplantation. In addition, we asked about the presence or absence of the following diseases: (1) Skin disease, (2) Malignancy, (3) Autoimmune disease, (4) Muscle/Bone/Joint disease, (5) Allergy, (6) Neurological disease, (7) Intellectual disability/central nervous

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system malformation: IQ or DQ, (8) Cardiovascular disease, (9) Respiratory disease, (10) Kidney/urinary disease, (11) Gastrointestinal disease, (12) Liver/biliary/pancreatic disease, (13) Eye disease, (14) Otolaryngological disease, and (15) Metabolic and endocrine diseases.

Establishment of BS-iPSCs

Initially, a dermal fibroblast cell line from a patient with BS (Case 3) was generated in our laboratory. Informed consent was obtained from the patient. These fibroblasts were cultured in a growth medium containing Dulbecco's modified Eagle medium (DMEM)/F12 1:1 (Thermo Fisher Scientific, Rockford, IL, United States), 10% fetal bovine serum (Thermo Fisher Scientific), and 500 U/mL penicillin/streptomycin (Thermo Fisher Scientific), and were maintained in 5% CO_2 at 37 °C and passaged every seven days. Thereafter, iPSCs were generated via electroporation with the episomal vector reprogramming factors (OCT3/4, SOX2, KLF4, LIN28, L-MYC, and p53 shRNA) [16, 17]; the procedure was performed using a Nucleofector II Device (Lonza, Basel, Switzerland). We used iPSCs derived from a control individual as wild-type (WT) iPSCs; which was the 201B7 line [18].

Cortical neuron differentiation

In the first stage, we used a serum-free floating culture of embryoid body (EB)-like aggregates via the quick reaggregation (SFEBq) method, as previously described [19]. We treated 5000 single iPSCs with 2 μM dorsomorphin (Sigma-Aldrich, St. Louis, MO) and 10 μM SB431542 (SB; Cayman Chemicals, San Diego, CA) in a differentiation medium, based on a Dulbecco's modified Eagle's medium (DMEM)/F12 (Life Technologies), 5% knockout serum replacement (Life Technologies), and 500 U/ml PS for the first 2 days. After two days the medium was refreshed, using the same media formulation, and this was repeated every 2–3 days. Seven days later, EB aggregates were plated onto Matrigel-coated 96-well plates (Becton, Dickinson and Company, Franklin Lakes, NJ) and treated with 2 μM dorsomorphin and 10 μM SB in the first differentiation medium for an additional 7 days. After induction, the neural precursor cells were cultured in a second differentiation medium containing 10 ng/mL brain-derived neurotrophic factor (BDNF; R&D Systems, Minneapolis, MN), 10 ng/mL glial cell line-derived neurotrophic factor (GDNF; R&D Systems), 1 μM cyclic adenosine monophosphate (cAMP; Wako), and 200 ng/mL ascorbic acid (AA; Sigma-Aldrich). The medium was changed every 2–3 days.

Karyotyping and SCE assays

Karyotyping via chromosomal G-band analysis and SCE assays of BS-iPSCs was performed by the Nihon Gene Research Laboratories (Miyagi-ken, Japan, http://www.ngrl-japan.com) and Chromosome Science Labo Inc. (Sapporo, Japan, http://www.chromoscience.jp).

Immunocytochemistry

After washing the plated cells with PBS, they were fixed in 4% paraformaldehyde (Nacalai Tesque, Kyoto, Japan) for 20 min at 4 °C and then washed again with PBS. The cells were then blocked against nonspecific labeling with 5% donkey serum and 0.1% Triton X-100 (Nacalai Tesque) in PBS for 30 min at 4 °C. Cells were washed with PBS and incubated with primary antibodies overnight at 4 °C, followed by labeling with the appropriate fluorescent dye-labeled secondary antibody. The nuclei were stained with Hoechst 33342 (Life Technologies). The primary antibodies used in this study are listed in Supplementary Table 1. The secondary Alexa Fluor-labeled antibodies included: 594 donkey anti-rabbit, 594 donkey anti-goat, 594 donkey anti-mouse, 488 donkey anti-mouse, 488 donkey anti-rabbit, and 488 donkey anti-goat IgGs (Life Technologies, secondary antibody dilution was 1:1000).

Statistical analysis

SCE data are presented as the mean ± SD. Data related to cortical neurons are presented as the mean ± SEM. Statistical significance was evaluated using a two-tailed Student's *t*-test or two-way analysis of variance, followed by a two-tailed Student's *t*-test using the Statistical Package for the Social Sciences 16.0 J (SPSS Japan, Inc., Tokyo, Japan).

RESULTS

Nationwide survey of BS in Japan

In the survey, 427, 342, and 136 replies were obtained from the relevant specialist departments of training hospitals for pediatrics,

Table 1. Clinical features and gene mutations of BLM in Bloom syndrome investigated by a nationwide survey in Japan

Case No	sex	age	height (age)	BW (age)	skin lesion	intellectual disability	malignancy (age)	miscellaneous	IgG	IgA	IgM	SCE	BLM mutation
1	M	26 (alive)	139 cm (25)	29 Kg (25)	—	—	B cell lymphoma (8)		461	103	21	+	631delCAA/ND
2	F	13 (alive)	125 cm (13)	24 Kg (13)	café au lait spot	+	Burkitt lymphoma (13)	DM (type II)	600	66	27	+	631delCAA/735delACTG
3	F	24 (alive)	140 cm (20)	32 Kg (20)	—	—	—	bronchial asthma	711	110	33	+	631delCAA/631delCAA
4	M	7 (dead)	N.D.	N.D.	depigmentation	+	Wilms tumor (5), myelodysplastic disorder (5)	—	1690	39	27	+	1610insA/ND
5	F	16 (alive)	116 cm (9), 142 cm(16)	20 Kg (9), 42 Kg (16)	sun-sensitive erythema, pigmentation	+	—	ASD 、DM (type II)、urinary stone	700	137	43	+	A2475C/T2979C
6	F	28 (dead)	140 cm (26)	37 Kg (26)	—	ND	lymphoma (13), breast cancer (26)	DM, hepatic disorder	ND	ND	ND	+	631delCAA/1610insA
7	M	23 (dead)	143 cm (21)	43 Kg (21)	sun-sensitive erythema	—	B cell lymphoma (23)	DM (type I)	1166	233	28	+	631delCAA/631delCAA
8	F	40 (alive)	144 cm (19)	45 Kg (19)	sun-sensitive erythema	—	B cell lymphoma (25)	—	770	199	16	+	631delCAA/631delCAA

Case 7 and case 8 were siblings. The unit of IgG, IgA, IgM was mg/dL. Serum Ig levels in Japanese healthy individuals were as follows. Average (±standard deviation), 7 years-old: IgG; 1170 (775-1767), IgA 186 (104-331), IgM 112 (55-227), 13 years-old: IgG; 1319 (846-2009), IgA 266 (180-393), IgM 123 (53-284), over 15 years-old: IgG; 1312 (821-2099), IgA 251 (133-475), IgM 108 (44-264) [29]
DM diabetes mellitus, *ASD* atrial septal defect, -: not affected, SCE+: elevated frequency of sister chromatid exchanges, *ND* not dated

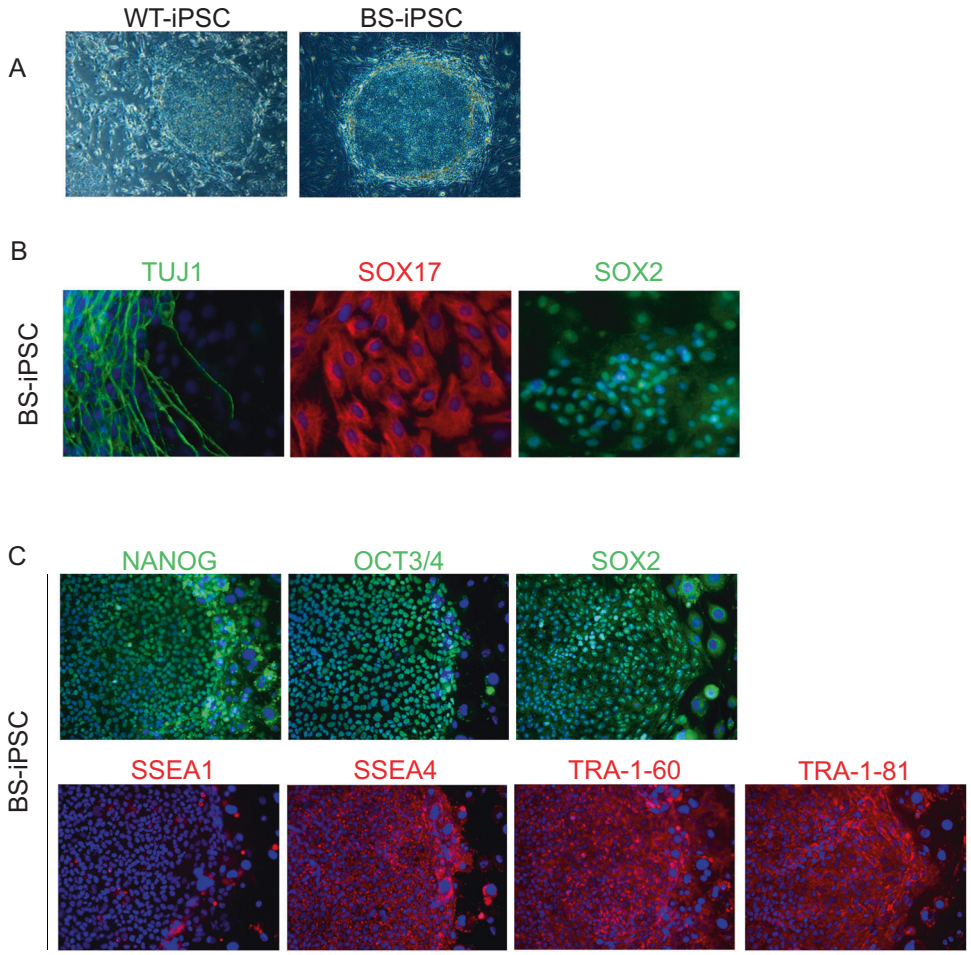

Fig. 1 Establishment of induced pluripotent stem cells (iPSCs) derived from patients with Bloom syndrome (BS). **A** Newly generated iPSCs fully reprogrammed from the fibroblasts of a patient with BS. Embryoid bodies formation of BS-iPSCs. Scale bar = 200 μm. **B** Expression of TUJ1, SOX17, and SOX2 in BS-iPSCs. **C** Expression of ectoderm, endoderm, mesoderm, and pluripotent markers including OCT3/4, NANOG, SOX2, SSEA4, TRA-1-60, and TRA-1-81. SSEA1 was the negative control. Scale bars = 100 μm

dermatology, and hospitals with a cancer center respectively. In the first questionnaire, twelve answers from attending physicians for suspected patients with BS were returned. Eight of the twelve patients in this study were recruited as patients with BS according to the criteria as described in "Material and Methods".

Table 1 presents the clinical features of this study from second questionnaires as documented by the attending physicians. Clinical features of Case 6 were not described in detail. Three patients died. Five of the eight patients had skin lesions, such as sun-sensitive erythema. Three of the seven patients had intellectual disabilities, and there were three cases of malignant B-cell lymphoma. Additionally, diabetes mellitus was observed in three patients.

No obvious susceptibility to infection was reported in any patient. All patients had low serum IgM levels (<50 mg/dL) and elevated frequencies of SCE. The *BLM* gene was investigated in eight patients, and the 631delCAA mutation of the *BLM* gene was detected in 9 of the 16 alleles.

Establishment of iPSCs derived from patients with BS (BS-iPSCs)

We established BS-iPSCs from a patient with homozygous 631delCAA *BLM* (Case 3). Dermal fibroblasts derived from a patient with BS (BS-FbCs) were generated. For the first time, we generated iPSCs derived from BS-FbCs using episomal vector reprogramming factors (*OCT3/4*, *SOX2*, *KLF4*, *LIN28*, *L-MYC*, and *p53 shRNA*) [17]. We confirmed the pluripotency of BS-iPSCs using embryoid body formation (Fig. 1A), which stained the ectoderm, endoderm, and mesoderm with markers, anti-β-III tubulin (TUJ1), SOX17, and SOX2, respectively (Fig. 1B). Thereafter, we examined whether the generated BS-iPSCs had characteristics similar to those of human ES cells. We performed immunostaining using undifferentiated markers and confirmed that OCT3/4, SOX2, and NANOG were expressed in the nuclei of the generated BS-iPSC; in contrast, SSEA4, TRA-1-60, and TRA-1-81 were all expressed in the cytoplasm (Fig. 1C). The generated iPSCs did not express SSEA1, a mouse undifferentiated marker (Fig. 1C). BS-iPSCs may have the potential to acquire additional chromosomal abnormalities due to genomic instability. Therefore, we compared the chromosomal profiles of the cultured BS-iPSCs using karyotype analysis. The chromosomal profiles of BS-iPSCs showed mosaicism with the following karyotypes: 18 of 20 cells had normal karyotype 46, XY, one cell was 46, XY with a deletion in 8q, and one cell was 46, XY with a deletion in 8q together with reciprocal translocations between 1p and 14q, and 4p and 7q.

SCE in peripheral blood and iPSCs derived from a healthy control and BS patient

BS is characterized by genomic instability, while gene translocation events such as SCEs have been observed in patients with BS. Therefore, to confirm the high SCE frequency in BS-iPSCs and peripheral blood, we compared the SCE frequency of peripheral blood and iPSCs of control individuals with that of a patient with

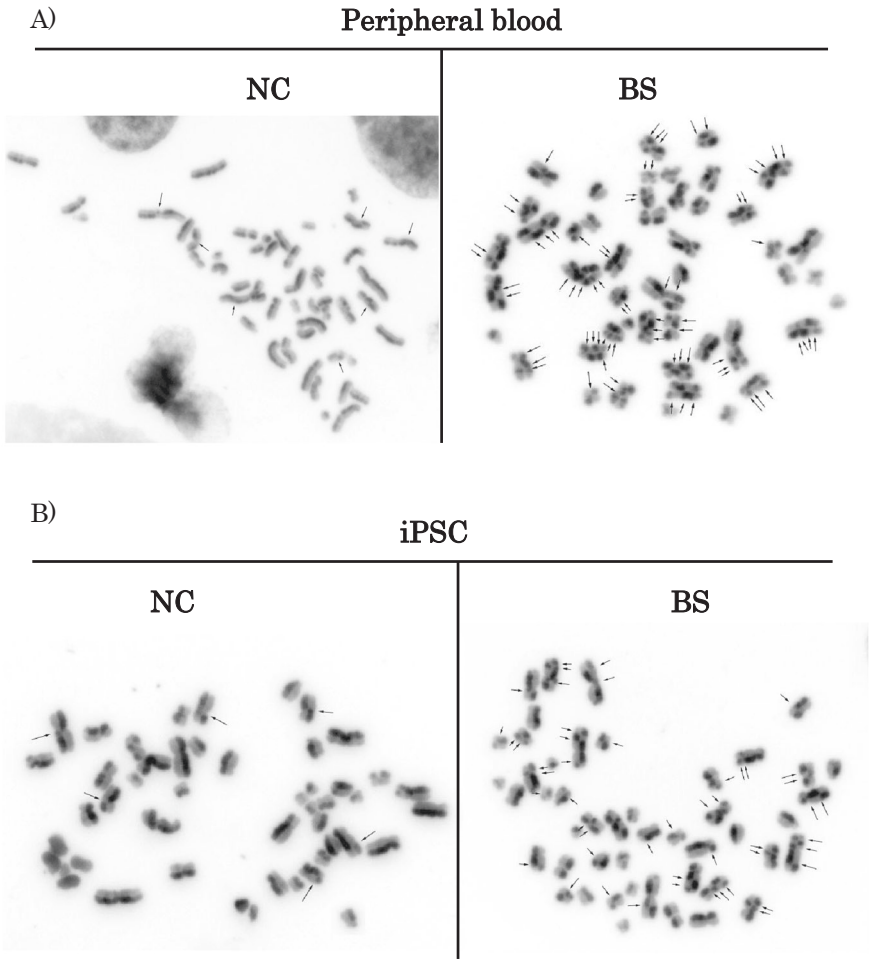

Fig. 2 Sister-chromatid exchange (SCE) of the peripheral blood and induced pluripotent stem cells (iPSCs) derived from patients with Bloom syndrome (BS). The regions of SCE were indicated by arrows. **A** The SCE of BS peripheral blood showed a 10-times higher frequency than that of the normal control. **B** The SCE of BS-iPSC showed a 10-times higher frequency than that of the normal control. The mean frequency and standard deviation of SCE in normal iPSCs and BS-iPSCs were 5.4 ± 2.2 and 57.8 ± 14.2, respectively ($n = 20$)

BS. The mean frequency and standard deviation of SCE in normal iPS and BS-iPS cells were 5.4 ± 2.2 and 57.8 ± 14.2, respectively. Our results show that the SCE frequency of the peripheral blood (Fig. 2A) and BS-iPSCs (Fig. 2B) of patients with BS were ten times higher than that of normal controls, suggesting that the generated BS-iPSCs reflected the genome instability of BS.

Axon elongation and proliferation of cortical neurons derived from WT- or BS-iPSCs

Cortical neurons were induced from BS-iPSCs, using a previously reported protocol (Fig. 3A) [19]. To investigate whether any differences could be observed, such as dendrite and axon development of cortical neurons derived from WT- and BS-iPSCs, we performed co-immunostaining using TUJ1, which is a dendritic marker protein, and anti-TBR1. BS-iPSCs showed no changes in TBR1-positive cortical neuron differentiation in WT- or BS-iPSCs (WT-iPSCs:77.58 ± 6.403%; BS-iPSCs:73.7 ± 3.44%) (Fig. 3B, C). Cortical neurons derived from BS-iPSCs showed shortened axons in our culture system (Fig. 3B, D). Mutations in *BLM* are expected to cause abnormal cell proliferation. Therefore, to investigate whether cortical neurons derived from BS-iPSCs have high proliferation potential, we performed immunostaining using anti-Ki-67 (a marker protein of proliferative cells). The results showed that Ki-67-positive cells were increased in cortical neurons derived from BS-iPSCs at day 72, but there was no change at day 50 (Fig. 3E, F).

DISCUSSION

We conducted a national survey to elucidate the clinical features of patients with BS in Japan. Consistent with a previous report, no obvious susceptibility to infection was reported in every patient [20], but all patients showed a serum IgM level of <50 mg/dL. As we previously reported, the 631delCAA mutation in the *BLM* gene is relatively common in Japan [21]. Four of the twelve patients did not meet the criteria for BS. One patient without SCE elevation was identified as AMeD syndrome (designated as N1037) [22].

One minor observation was that three of the seven patients showed intellectual disabilities. The attending physicians of the recruited patients with BS were asked about the presence or absence of intellectual disability, including IQ or DQ; though these were not documented in any of the three patients. Therefore, we were unable to determine details on intellectual disability. This is a major limitation of this study. Intellectual disability was caused by various etiologies such as mental retardation or autism spectrum disorder. Microcephaly, a complication of BS [23], also caused intellectual disability. We intend to clarify the characteristics of intellectual disability in BS in detail in future studies. To focus on BS-associated intellectual disability, we generated iPSCs derived from a patient with BS recruited in a nationwide survey.

We demonstrated that BS-FbCs could be reprogrammed into iPSCs using Yamanaka factors, and the resulting iPSCs showed undifferentiated states and the potential to differentiate into three germ layers. These results indicate that the generated BS-iPSCs

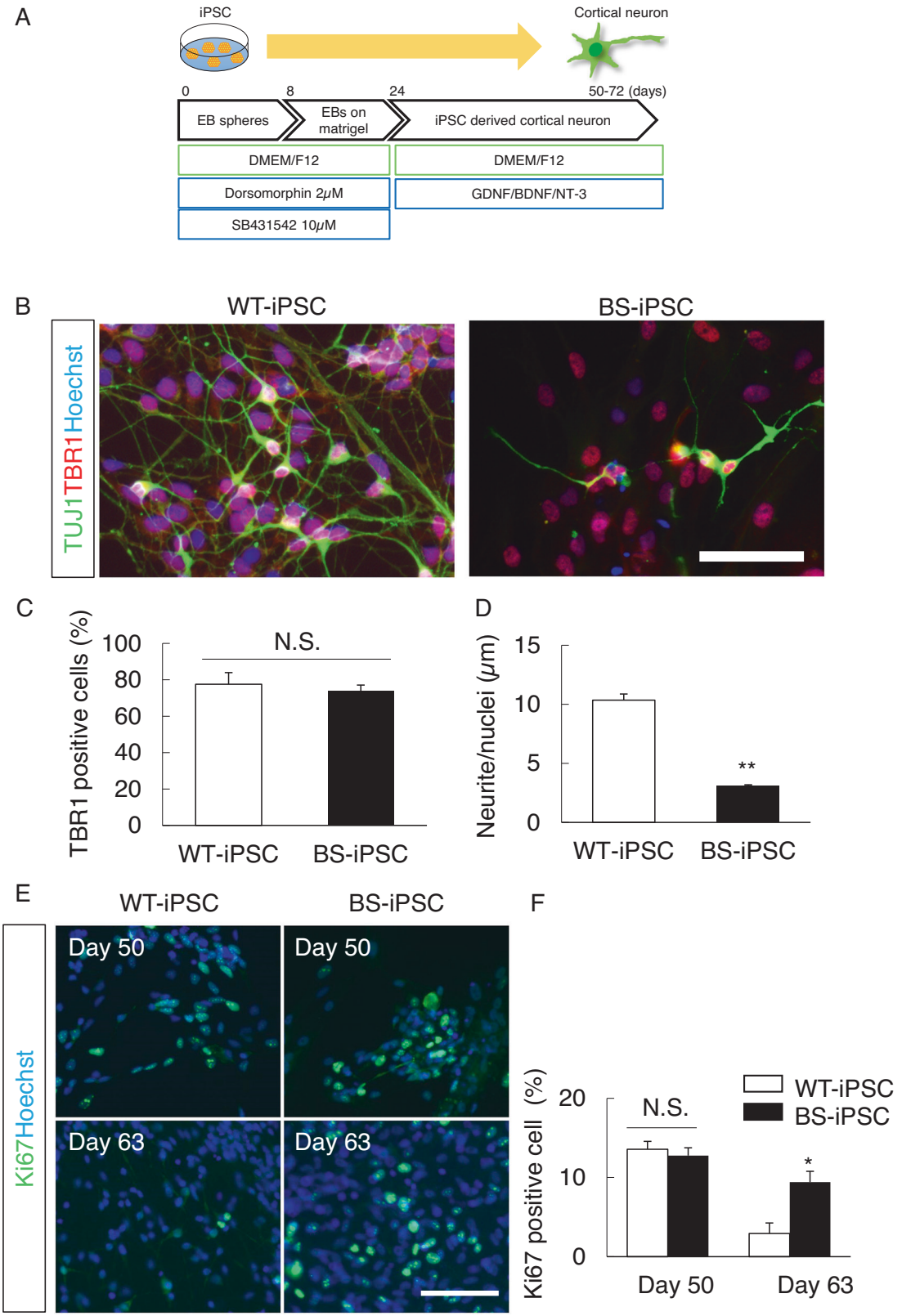

Fig. 3 Cortical neurons from induced pluripotent stem cells derived from patients with Bloom syndrome (BS-iPSCs). **A** Protocol for the induction of cortical neurons from BS-iPSCs (15). **B** Typical image of neurite length in cortical neurons derived from wild type (WT)- or BS-iPSCs. Scale bar = 100 μm. **C** The ratio of TBR1-positive cells in WT- or BS-iPSCs. **D** Quantitative analysis of neurite length and the TBR1 + cell rate. The neurite length of BS-iPSC-derived cortical neurons (TBR1+) was significantly shorter than that of induced iPSCs derived from WT ($n = 3$). **E** Representative image of Ki67+ cells from WT- or BS-iPSC-derived culture systems. **F** Quantitative analysis of Ki67+ cells in WT- or BS-iPSCs. The Ki67+ cell rate increased on day 63, although it did not change on day 50 ($n = 5$–6 or 3). $^{**}P < 0.01$. $^{*}P < 0.05$ versus WT-iPSCs (Student's *t*-test)

had ES-like features. A high frequency of SCE showed the hyperrecombinability of BS-iPSCs, which indicates genomic instability. Finally, we induced cortical neurons from the BS-iPSC. Most induced neuronal cells express TBR1, which is specifically expressed in the olfactory bulb, cerebral cortex, hippocampus, and amygdala [24–27], thus indicating that the generated TBR1-positive cortical neurons were induced with high efficiency. Furthermore, the generated cortical neurons derived from BS-iPSCs showed shorter axons and greater proliferation than those observed in cells derived from WT-iPSCs, suggesting that the *BLM* mutation drives the proliferation of immature neurons which fail to differentiate into mature cortical neurons. These findings provide evidence of intellectual disability found in some patients with BS. However, it is difficult to conclude whether the defects in cortical neurons derived from BS-iPSC, such as shortened axons and upregulated proliferation, are due to *BLM* mutations or chromosomal abnormalities observed in BS-iPSC. Only one iPSC cell line from each of BS and WT have been compared, and therefore gross generalizations cannot be made about the role played by BLM in neuronal differentiation.

It was previously reported that cerebellar Purkinje cells showed positive BLM immunoreactivity at 21 weeks of gestation, which transiently increased at 40 weeks. Further, neurons in the brain pons showed immunoreactivity during the early embryonic stages [28]. Therefore, BLM may be involved in the development of the central nervous system. The present study's data suggests that the BLM mutation at the fetal stage drives the proliferation of immature neurons which fail to differentiate into mature cortical neurons. Further investigation will be needed to determine whether control iPS cell-derived neurons that have a CRISPR-Cas9-induced nonsense mutation in the *BLM* gene, which may minimize chromosomal aberrations induced by the *BLM* gene mutation, show neuronal abnormalities as described above.

In conclusion, we established a human stem cell model system using BS-iPSCs and elucidated the phenotypes of cortical neurons derived from these cells. Consequently, we will be able to identify some aspects of the BS pathomechanism. These in vitro BS models may be useful for identifying novel therapeutic agents for the treatment of BS.

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AUTHOR CONTRIBUTIONS

Research design: MF, CK, YI, AY, and HK. Experiments, data acquisition, and data analysis: CK and HK. Manuscript writing: HK.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The generation and pathological analysis (including human gene analysis) of patient-derived iPSCs in this study were approved by the Ethical Review Committee of the National Hospital Organization, Nagara Medical Center (approval no. 26-15). Established human stem cells were handled according to revisions of the guidelines for clinical research using human stem cells by the Ministry of Health, Labour and Welfare of Japan. Written informed consent was obtained from the Bloom syndrome patient for the publication of this report. The 201B7 line was provided by Dr. K. Osafune (Kyoto University).

ADDITIONAL INFORMATION

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Research Paper

Renal dysfunction, malignant neoplasms, atherosclerotic cardiovascular diseases, and sarcopenia as key outcomes observed in a three-year follow-up study using the Werner Syndrome Registry

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ABSTRACT

Werner syndrome is an adult-onset progeria syndrome that results in various complications. This study aimed to clarify the profile and secular variation of the disease. Fifty-one patients were enrolled and registered in the Werner Syndrome Registry. Their data were collected annually following registration. A cross-sectional analysis at registration and a longitudinal analysis between the baseline and each subsequent year was performed. Pearson's chi-squared and Wilcoxon signed-rank tests were used. Malignant neoplasms were observed from the fifth decade of life (mean onset: 49.7 years) and were observed in approximately 30% of patients during the 3-year survey period. Regarding renal function, the mean estimated glomerular filtration rate calculated from serum creatinine (eGFRcre) and eGFRcys, which were calculated from cystatin C in the first year, were 98.3 and 83.2 mL/min/1.73 m^2, respectively, and differed depending on the index used. In longitudinal analysis, the average eGFRcre for the first and fourth years was 74.8 and 63.4 mL/min/1.73 m^2, showing a rapid decline. Secular changes in Werner syndrome in multiple patients were identified. The prevalence of malignant neoplasms is high, and renal function may decline rapidly. It is, therefore, necessary to carry out active and detailed examinations and pay attention to the type and dose of the drugs used.

INTRODUCTION

Werner syndrome is an autosomal recessive adult-onset progeroid disorder that affects approximately 700-2,000 individuals in Japan [1–4]. Patients with Werner syndrome present with various aging phenotypes from a young age. Graying and/or loss of hair presents in their third decade of life; bilateral cataracts and diabetes, around their fourth decade of life; and atherosclerotic diseases and malignant neoplasms, around their fifth decade of life [5]. These patients also develop a high proportion of skin ulcers, often requiring amputation of the lower extremities. Although it was previously reported that patients with Werner syndrome die at 46 years of age on average [6], recent evidence indicates the average age of death is 59 years [7]. In Werner syndrome, quality of life (QOL) and activities of daily living (ADL) decline due to the various symptoms [8].

Since it is a rare disease, there is often a long period between the disease onset and the diagnosis [9]. Therefore, early detection and therapeutic intervention are important. Recently, the number of long-term survivors has increased due to therapeutic advances; however, new complications have also been observed. Although detailed and long-term involvement in medical care is essential for maintaining QOL and ADL, few reports have followed the changes over time in patients with Werner syndrome.

The Werner Syndrome Registry was established in 2017 to investigate the disease, recruit participants for clinical trials, and provide information to patients and physicians. In this report, the updated cross-sectional and longitudinal analyses of the Werner Syndrome Registry database were performed to reveal the current status and natural course in patients with Werner syndrome.

RESULTS

Werner Syndrome Registry cross-sectional analysis

Twelve facilities and fifty-one diagnosed patients were enrolled in the registry. Table 1 shows the patients' characteristics; the percentage of baseline major signs, clinical symptoms, and comorbidities in patients with Werner syndrome; the drugs administered for diabetes, dyslipidemia, and hypertension; and the blood examination results at the point of enrollment to the registry. The patients' mean registered age was 49.0 ± 7.2 years. Although the mean age of onset, inferred from the interviews or medical histories, was 25.8 ± 9.2 years, the mean age at diagnosis was 41.8 ± 8.2 years. Patients with Werner syndrome were lower in height, weight, and body mass index (BMI) than the average Japanese adults [10, 11]. Despite having a low BMI, the mean waist circumference was 77.2 ± 11.1 cm, and the mean visceral fat area measured by computed tomography was 97.5 ± 57.5 cm^2. The mean skeletal muscle index (SMI) on dual-energy X-ray absorptiometry was 5.36 ± 1.61 kg/m^2 for men and 3.99 ± 0.98 kg/m^2 for women, the grip strength (in the right hand) was 22.8 ± 8.6 kg for men and 12.9 ± 5.5 kg for women, and the average gait speed was 0.96 ± 0.56 m/sec. The grip strength and SMI met the diagnostic criteria for sarcopenia. Approximately 30% of patients' parents had consanguineous marriages.

Regarding comorbidities, the malignant neoplasm was found in about 25% of the patients. The specific types identified were as follows: breast cancer, thyroid cancer (follicular and papillary), colon cancer, bladder cancer,

Table 1. Patients' characteristics at baseline.

	N[a]	% (*n* patients with this characteristic)
Major signs		
Graying and/or loss of hair	51	98.0 (50)
Bilateral cataracts	51	100 (51)
Skin changes	51	98.0 (50)
Intractable skin ulcers	51	66.7 (34)
Soft tissue calcification	49	93.9 (46)
Bird-like face	51	92.2 (47)
High-pitched voice	51	82.4 (42)
Clinical symptoms		
Diabetes, IGT	51	68.6 (35)
Dyslipidemia	51	66.7 (34)
Hypertension	48	39.6 (19)
Fatty liver	49	59.2 (29)
Cerebral bleeding	51	0 (0)
Cerebral infarction	51	0 (0)
AP or MI	51	2.0 (1)
PAD	51	11.8 (6)
Malignant neoplasm	51	25.5 (13)
Amputation	51	11.8 (6)
Medications		
(1) For diabetes		
DPP-4 inhibitor	35	34.3 (12)
Biguanide	35	34.3 (12)
Thiazolidine	35	42.9 (15)
Alpha GI	35	5.7 (2)
Sulfonylurea	35	8.6 (3)
Glinide	35	0 (0)
SGLT2 inhibitor	35	2.9 (1)
GLP-1 analog	35	5.7 (2)
Insulin	35	14.3 (5)
(2) For dyslipidemia		
Statin	34	58.8 (20)
Fibrate	34	2.9 (1)
Ezetimibe	34	0 (0)
EPA	34	14.7 (5)
Ion exchange resin	34	0 (0)
Nicotinic acids	34	14.7 (5)
(3) For hypertension, among others		
Ca blocker	19	47.4 (9)
ARB	19	36.8 (7)
ACE inhibitor	19	0 (0)
Alpha1 blocker	19	0 (0)
Beta blocker	19	10.5 (2)
Diuretics	19	0 (0)
Eplerenone	19	0 (0)
Nitrate	48	0 (0)
Aspirin	48	4.2 (2)
Antiplatelet	47	10.6 (5)
Warfarin	48	0 (0)
Anticoagulant	47	2.1 (1)

	Total		Male		Female	
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD
Patients' backgrounds						
Registered age (years)	51	49.0 ± 7.2	27	48.3 ± 7.1	24	49.7 ± 7.5
Onset age (years)	41	25.8 ± 9.2	21	28.0 ± 8.1	20	23.4 ± 9.9
Diagnosed age (years)	50	41.8 ± 8.2	26	41.8 ± 6.0	24	41.8 ± 10.3
Consanguineous marriage (%)	14/48	29.2	7/24	29.2	7/24	29.2
Physical findings/function						
Height (cm)	51	154.2 ± 10.5	27	160.1 ± 8.2	24	147.6 ± 8.7
Average 40s Japanese height (cm)				171.5 ± 5.8		158.1 ± 5.4
Body weight (kg)	51	43.7 ± 9.6	27	49.6 ± 8.6	24	37.1 ± 5.5
Average 40s Japanese body weight (kg)				72.8 ± 12.8		55.6 ± 10.0
BMI (kg/m^2)	51	18.3 ± 3.1	27	19.4 ± 3.2	24	17.1 ± 2.5
Average 40s Japanese BMI (kg/m^2)				24.7 ± 4.0		22.3 ± 4.0

Systolic blood pressure (mmHg)	45	123 ± 19	23	128 ± 19	22	118 ± 18
Diastolic blood pressure (mmHg)	45	69 ± 13	23	73 ± 11	22	65 ± 13
Pulse (/min)	43	87 ± 14	22	88 ± 14	21	85 ± 13
Waist circumference (cm)	30	77.2 ± 11.1	17	80.2 ± 11.3	13	73.2 ± 9.9
Visceral fat area (cm^2)	14	97.5 ± 57.5	6	117.3 ± 63.6	8	82.7 ± 51.7
Skeletal muscle mass index (kg/m^2)	18	4.60 ± 1.44	8	5.36 ± 1.61	10	3.99 ± 0.98
Grip strength (right) (kg)	32	18.1 ± 8.8	17	22.8 ± 8.6	15	12.9 ± 5.5
Grip strength (left) (kg)	32	16.6 ± 7.8	17	21.0 ± 7.4	15	11.5 ± 4.6
Walking speed (m/sec)	16	0.96 ± 0.56	8	1.03 ± 0.60	8	0.88 ± 0.55
Blood examinations						
WBC (/μL)	50	7504 ± 2268	27	7486 ± 2605	23	7525 ± 1855
RBC ($x10^4$/μL)	50	414 ± 85	27	429 ± 70	23	397 ± 99
Hb (g/dL)	50	12.6 ± 2.1	27	13.2 ± 2.1	23	12.0 ± 1.9
Plt ($x10^4$/μL)	50	28.6 ± 9.1	27	26.0 ± 7.2	23	31.7 ± 10.2
AST (U/L)	51	31.6 ± 17.5	27	34.9 ± 19.6	24	27.8 ± 14.4
ALT (U/L)	51	41.2 ± 32.9	27	48.6 ± 38.2	24	33.0 ± 23.9
γGTP (U/L)	49	98.3 ± 103.6	27	95.1 ± 96.4	22	102.2 ± 114.1
LDH (U/L)	48	223 ± 161	27	234 ± 208	21	210 ± 65
ALP (U/L)	45	272 ± 173	26	273 ± 149	19	271 ± 205
ChE (U/L)	35	368 ± 98	18	374 ± 114	17	361 ± 82
T-Bil (mg/dL)	44	0.55 ± 0.25	25	0.57 ± 0.26	19	0.52 ± 0.24
TP (g/dL)	47	7.77 ± 0.57	26	7.78 ± 0.51	21	7.74 ± 0.65
Alb (g/dL)	48	4.25 ± 0.72	25	4.32 ± 0.84	23	4.17 ± 0.59
UA (mg/dL)	46	5.39 ± 1.32	25	5.59 ± 1.24	21	5.15 ± 1.40
BUN (mg/dL)	48	16.4 ± 7.4	27	16.4 ± 8.0	21	16.3 ± 6.7
Cre (mg/dL)	50	0.77 ± 0.86	27	0.96 ± 1.13	23	0.54 ± 0.19
eGFRcre ($mL/min/1.73\ m^2$)	50	98.3 ± 36.3	27	92.3 ± 28.5	23	105.3 ± 43.3
BSA-uncorrected eGFRcre (mL/min)	50	77.8 ± 27.0	27	79.6 ± 24.8	23	75.5 ± 29.8
eGFRcys ($mL/min/1.73\ m^2$)	15	83.2 ± 29.5	10	86.1 ± 30.3	5	77.4 ± 30.3
Na (mEq/L)	48	140 ± 3	26	139 ± 3	22	140 ± 3
K (mEq/L)	48	4.27 ± 0.39	26	4.26 ± 0.43	22	4.27 ± 0.36
Cl (mEq/L)	47	104 ± 3	25	104 ± 3	22	104 ± 4
TC (mg/dL)	43	193 ± 32	25	196 ± 33	18	189 ± 31
TG (mg/dL)	49	161 ± 96	26	178 ± 98	23	143 ± 92
LDL-C (direct) (mg/dL)	39	119 ± 27	20	121 ± 28	19	117 ± 26
HDL-C (mg/dL)	46	57 ± 21	23	56 ± 20	23	59 ± 21
HbA1c (%)	46	6.42 ± 1.25	23	6.29 ± 0.98	23	6.55 ± 1.49
FPG (mg/dL)	21	118 ± 29	10	123 ± 36	11	112 ± 21
PPG (mg/dL)	24	142 ± 55	13	151 ± 47	11	132 ± 63

[a]*N* denotes the number of patients who had data. Regarding medications for diabetes, dyslipidemia, and hypertension, N means the patients with diabetes, dyslipidemia, and hypertension. Abbreviations: IGT: Impaired glucose tolerance; AP: Angina pectoris; MI: Myocardial infarction; PAD: peripheral artery disease; DPP-4: Dipeptidyl peptidase-4; alpha GI: alpha glucosidase inhibitor; SGLT2: Sodium-glucose cotransporter-2; GLP-1: Glucagon-like peptide-1; EPA: Eicosapentaenoic acid; Ca: Calcium; ARB: Angiotensin- II receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: body mass index; SMI: skeletal muscle mass index; WBC: white blood cell; RBC: red blood cell; Hgb: hemoglobin; Plt: platelet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ChE: cholinesterase; T-Bil: total bilirubin; TP: total protein; Alb: albumin; UA: uric acid; BUN: blood urea nitrogen; Cre: creatinine; BSA: body surface are; eGFR: estimated glomerular filtration rate; Na: natrium; K: potassium; Cl: chlorine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; SD: standard deviation.

lung cancer, meningioma, malignant melanoma, undifferentiated polymorphic sarcoma, osteosarcoma, and soft tissue sarcoma.

Regarding the drugs, the most commonly used drug for diabetes mellitus was thiazolidine in 42.9% (15/35), followed by dipeptidyl peptidase-4 inhibitor (DPP4i) and metformin in 34.3% (12/35) of the patients with diabetes. Approximately 58.8% (20/34) of the patients with dyslipidemia were administered a statin. As for hypertension, calcium channel blockers followed by angiotensin II receptor blockers (ARBs) were the two most common types of drugs administered.

Regarding the blood examination, the gamma-glutamyl transpeptidase (γGTP) level was twice higher than the upper normal limit (for males 13-64, females 9-32 U/L). As for lipid profile, the mean low-density lipoprotein cholesterol (LDL-C) level was 121 ± 28 mg/dL for men and the mean triglyceride (TG) level was 161 ± 96 mg/dL, which were both slightly higher values than the normal range (for patients with diabetes, LDL-C

120 mg/dL, TG 150 mg/dL). Concerning the glucose profile, the mean glycated hemoglobin (HbA1c) was 6.42 ± 1.25%, the mean fasting plasma glucose was 118 ± 29 mg/dL, and the mean postprandial plasma glucose was 142 ± 55 mg/dL, which were all values within the target range (HbA1c 6.5%, fasting plasma glucose 126 mg/dL, postprandial plasma glucose 200 mg/dL). As for renal function, while the estimated glomerular filtration rate calculated from serum creatinine (eGFRcre) was 98.3 ± 36.3 mL/min/1.73 m^2, the body surface area (BSA)-uncorrected eGFRcre was 77.8 ± 27.0 mL/min. The GFR calculated from cystatin C (eGFRcys) was 83.2 ± 29.5 mL/min/1.73 m^2. Dissociation was observed between eGFRcre, BSA-uncorrected eGFRcre, and eGFRcys (P = 0.0017).

Werner Syndrome Registry longitudinal analysis

Table 2 shows the comparison between the point of registration and one year later. Although there were no significant changes in physical examination findings compared to the baseline regarding major signs, the proportion of patients with intractable skin ulcers tended to increase (62.5% vs. 75.0%, P = 0.350). Regarding comorbidities, the percentage of patients with malignant neoplasms tended to increase (20.8% vs. 25.0%, P = 1.000); four patients died from malignant neoplasms (lung cancer and undifferentiated polymorphic sarcoma, osteosarcoma, soft tissue sarcoma, and malignant melanoma), and one patient died from renal failure.

Blood examinations showed significant decreases in the white blood cell count (7266/μL vs. 6300/μL, P = 0.003), γGTP (96.6 mg/dL vs. 61.3 mg/dL, P = 0.010), and total bilirubin (T-Bil; 0.57 mg/dL vs. 0.43 mg/dL, P = 0.043). Significant decreases in total cholesterol (TC; 187.4 mg/dL vs. 164.1 mg/dL, P = 0.021), LDL-C (118.4 mg/dL vs. 97.5 mg/dL, P = 0.033), and HbA1c (6.43% vs. 6.08%, P = 0.030) were also observed.

Table 3 shows the comparison between the point of registration and two years later. Due to the difference in patients' enrolled period, the number of observed patients decreased by the end of the study. The mean body weight decreased significantly (44.4 kg vs. 43.0 kg, P = 0.029). One patient died from brainstem hemorrhage caused by a myelodysplastic syndrome with overt acute myeloid leukemia infiltration to the central nervous system.

The blood examination showed that glucose and lipid metabolism were controlled within the target range, and T-Bil decreased (0.55 mg/dL vs. 0.34 mg/dL, P = 0.039), while a new increase in the mean serum potassium was observed (4.33 mEq/L vs. 5.48 mEq/L, P = 0.022). Regarding therapeutic drugs, metformin tended to increase, while thiazolidine tended to decrease in association with diabetes, and the use of ARBs as antihypertensive drugs were discontinued in two patients using them.

Table 4 shows the comparison between the point of registration and three years later. A significant decrease in renal function was observed over time. At the point of registration, the mean eGFRcre was 74.8 mL/min/1.73/m^2, and the mean BSA-uncorrected eGFRcre was 59.3 mL/min, whereas three years later, the mean eGFRcre was 63.4 mL/min/1.73 m^2 (P = 0.078) and the mean BSA-uncorrected eGFRcre was 50.2 mL/min (P = 0.047), which correlated to a decrease of approximately 3 mL/min (/1.73 m^2) per a year on average.

The results of the survey covering the entire period regarding malignant neoplasms, renal function, and aspiration pneumonia are described below.

Regarding malignant neoplasms, the morbidity due to malignant neoplasms at baseline was 25.5% (out of 51 patients) and 31.4% in the entire survey period. Table 5 shows the type of malignant neoplasms and the age of onset. The breakdown of the malignant neoplasm types revealed epithelial neoplasms in eight patients (15.7%), non-epithelial in four patients (7.8%), and both in three patients (5.9%). Multiple neoplasms were found in 3/51 (5.9%) of all the patients enrolled, and 3/16 (18.8%) of the patients with malignant neoplasms.

Regarding renal function, Figure 1 shows the age group and the mean renal function during the entire survey period. Of the three indices of renal function, there was a discrepancy between eGFRcre and BSA-uncorrected eGFRcre/eGFRcys. The mean eGFRcre, BSA-uncorrected eGFRcre, and eGFRcys for each age decile were as follows: 30s, 129.9/108.5/121.6; 40s, 93.7/74.5/69.0; 50s, 88.2/72.8/79.8; and 60s, 50.2/36.9/33.1.

Many patients with Werner syndrome have painful leg ulcers and frequently use non-steroidal anti-inflammatory drugs (NSAIDs). Frequent use of NSAIDs is connected with an observed decrease in renal function. Table 6 shows that in the relationship between the presence of leg ulcers and renal function, renal function tended to be low in patients with leg ulcers, and eGFRcre, BSA-uncorrected eGFRcre, and eGFRcys were as follows: patients with leg ulcers, 91.5 ± 30.5 mL/min/1.73 m^2 vs. without leg ulcers, 112.9 ± 43.9 mL/min/1.73 m^2, P = 0.121; 73.7 ± 25.2 mL/min vs. 86.3 ± 29.4 mL/min, P = 0.228; and 77.0 ± 27.5 mL/min/1.73 m^2 vs. 100.1 ± 32.2 mL/min/1.73 m^2, P = 0.240, respectively. In relation to

Table 2. Comparison between the point of registration and one year later.

	N	% (*n* patients with this characteristic)		*P*-value
		at registration	one year later	
Major signs				
Graying and/or loss of hair	24	100 (24)	100 (24)	–
Bilateral cataracts	24	100 (24)	100 (24)	–
Skin changes	24	95.8 (23)	95.8 (23)	1.000
Intractable skin ulcers	24	62.5 (15)	75.0 (18)	0.350
Soft tissue calcification	22	86.4 (19)	90.9 (20)	0.635
Bird-like face	24	83.3 (20)	87.5 (21)	0.683
High-pitched voice	24	83.3 (20)	83.3 (20)	1.000
Clinical symptoms				
Diabetes, IGT	24	70.8 (17)	79.2 (19)	0.505
Dyslipidemia	24	79.2 (19)	83.3 (20)	0.712
Hypertension	22	45.5 (10)	36.4 (8)	0.540
Fatty liver	22	54.5 (12)	50.0 (11)	0.763
AP or MI	24	4.2 (1)	8.3 (2)	0.551
PAD	24	4.2 (1)	4.2 (1)	1.000
Malignant neoplasm	24	20.8 (5)	25.0 (6)	1.000
Medications				
(1) For diabetes				
DPP-4 inhibitor	23	21.7 (5)	26.1 (6)	0.730
Biguanide	23	26.1 (6)	34.8 (8)	0.522
Thiazolidine	23	34.8 (8)	30.4 (7)	0.753
Alpha GI	24	8.3 (2)	4.2 (1)	0.551
Sulfonylurea	24	8.3 (2)	4.2 (1)	0.551
SGLT2 inhibitor	24	4.2 (1)	0 (0)	0.312
GLP-1 analog	24	4.2 (1)	8.3 (2)	0.551
Insulin	24	12.5 (3)	12.5 (3)	1.000
(2) For dyslipidemia				
Statin	23	21.7 (5)	26.1 (6)	0.730
Fibrate	23	26.1 (6)	34.8 (8)	0.522
Ezetimibe	23	34.8 (8)	30.4 (7)	0.753
EPA	24	8.3 (2)	4.2 (1)	0.551
Ion exchange resin	24	8.3 (2)	4.2 (1)	0.551
(3) For hypertension and others				
Ca blocker	24	20.8 (5)	20.8 (5)	1.000
ARB	24	12.5 (3)	8.3 (2)	0.637
Beta blocker	24	8.3 (2)	8.3 (2)	1.000
Diuretics	24	0 (0)	4.2 (1)	0.312
Aspirin	24	4.2 (1)	4.2 (1)	1.000
Antiplatelet	23	8.7 (2)	13.0 (3)	0.636
Anticoagulant	23	4.3 (1)	4.3 (1)	1.000
	N	Mean ± SD		*P*-value
		at registration	one year later	
Physical findings/function				
Body weight (kg)	21	45.1 ±9.7	44.9 ± 10.0	0.383
BMI (kg/m^2)	21	18.4 ± 2.8	18.0 ± 2.9	0.279
Systolic blood pressure (mmHg)	19	124.0 ± 16.7	127.0± 18.0	0.628
Diastolic blood pressure (mmHg)	19	72.3 ± 9.5	73.7 ± 11.3	0.571
Pulse (/min)	13	87.1 ± 14.3	88.7 ± 13.4	0.570
Waist circumference (cm)	8	80.3 ± 15.6	79.4 ± 15.3	0.500
Mean grip strength (right) (kg)	8	18.6 ± 7.8	19.6 ± 7.9	0.469
Mean grip strength (left) (kg)	7	17.3 ± 7.4	17.4 ± 6.9	1.000
Blood examinations				
WBC (/μL)	19	7266 ± 1838	6300 ± 1988	0.003
RBC (x10^4/μL)	19	455.2 ± 60.1	435.2 ± 75.4	0.447
Hb (g/dL)	19	13.42 ± 1.88	13.05 ± 2.27	0.574
Plt (x10^4/μL)	19	28.3 ± 6.8	26.5 ± 9.9	0.050
AST (U/L)	20	30.3 ± 12.2	30.7 ± 13.4	0.958
ALT (U/L)	20	44.4 ± 29.2	37 ± 25.5	0.383
γGTP (U/L)	20	96.6 ± 141.9	61.3 ± 80.3	0.010
LDH (U/L)	18	195.9 ± 36.7	191.7 ± 39.6	0.827
ALP (U/L)	17	269.9 ± 197.8	207.9 ± 67.4	0.289
ChE (U/L)	16	395.1 ± 78.0	376.9 ± 71.6	0.323
T-Bil (mg/dL)	13	0.57 ± 0.14	0.43 ± 0.25	0.043
TP (g/dL)	19	8.02 ± 0.51	7.84 ± 0.49	0.172

Alb (g/dL)	18	4.54 ± 0.58	4.47 ± 0.48	0.510
UA (mg/dL)	18	5.37 ± 1.42	5.23 ± 1.36	0.641
BUN (mg/dL)	20	17.2 ± 7.5	16.5 ± 6.9	0.595
Cre (mg/dL)	20	0.775 ± 0.284	0.801 ± 0.293	0.157
eGFRcre (mL/min/1.73 m^2)	20	85.4 ± 24.1	82.8 ± 27.6	0.408
BSA-uncorrected eGFRcre (mL/min)	17	70.8 ± 23.2	69.4 ± 26.6	0.109
Na (mEq/L)	20	139.7 ± 1.3	140 ± 1.7	0.486
K (mEq/L)	20	4.39 ± 0.31	4.37 ± 0.39	0.624
Cl (mEq/L)	20	104.5 ± 2.2	104.9 ± 2.7	0.123
TC (mg/dL)	16	187.4 ± 29.1	164.1 ± 26.2	0.021
TG (mg/dL)	19	172.3 ± 93.2	153 ± 74.4	0.390
LDL-C (direct) (mg/dL)	13	118.4 ± 28.5	97.5 ± 20.4	0.033
HDL-C (mg/dL)	18	54.0 ± 10.6	56.1 ± 13.1	0.424
HbA1c (%)	18	6.43 ± 0.84	6.08 ± 0.63	0.030
FPG (mg/dL)	5	115.4 ± 40.1	105.4 ± 10.5	0.625
PPG (mg/dL)	8	142.9 ± 29.9	152.4 ± 38.7	0.641

Abbreviations: IGT: Impaired glucose tolerance; AP: Angina pectoris; MI: Myocardial infarction; PAD: peripheral artery disease; DPP-4: Dipeptidyl peptidase-4; alpha GI: alpha glucosidase inhibitor; SGLT2: Sodium-glucose cotransporter-2; GLP-1: Glucagon-like peptide-1; EPA: Eicosapentaenoic acid; Ca: Calcium; ARB: Angiotensin- II receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: body mass index; SMI: skeletal muscle mass index; WBC: white blood cell; RBC: red blood cell; Hgb: hemoglobin; Plt: platelet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ChE: cholinesterase; T-Bil: total bilirubin; TP: total protein; Alb: albumin; UA: uric acid; BUN: blood urea nitrogen; Cre: creatinine; BSA: body surface are; eGFR: estimated glomerular filtration rate; Na: natrium; K: potassium; Cl: chlorine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; SD: standard deviation.

Table 3. Comparison between the point of registration and two years later.

	N	% (*n* patients with this characteristic)		*P*-value
		at registration	two years later	
Major signs				
Graying and/or loss of hair	20	100 (20)	100 (20)	–
Bilateral cataracts	20	100 (20)	100 (20)	–
Skin changes	20	95 (19)	100 (20)	0.311
Intractable skin ulcers	20	60 (12)	75 (15)	0.311
Soft tissue calcification	20	85 (17)	85 (17)	1.000
Bird-like face	20	85 (17)	80 (16)	0.677
High-pitched voice	20	80 (16)	80 (16)	1.000
Clinical symptoms				
Diabetes, IGT	20	75 (15)	80 (16)	0.705
Dyslipidemia	20	75 (15)	80 (16)	0.705
Hypertension	19	42.1 (8)	42.1 (8)	1.000
Fatty liver	19	47.4 (9)	52.6 (10)	1.000
Cerebral bleeding	20	0 (0)	5 (1)	0.311
Cerebral infarction	20	0 (0)	5 (1)	0.311
AP or MI	20	5 (1)	5 (1)	1.000
PAD	20	0 (0)	5 (1)	0.311
Malignant neoplasm	20	25.0 (5)	35.0 (7)	0.731
Medications				
(1) For diabetes				
DPP-4 inhibitor	19	31.6 (6)	26.3 (5)	1.000
Biguanide	19	21.1 (4)	36..8 (7)	0.476
Thiazolidine	19	47.4 (9)	31.6 (6)	0.508
Alpha GI	19	5.3 (1)	0 (0)	1.000
Sulfonylurea	19	10.5 (2)	5.3 (1)	1.000
GLP-1 analog	19	5.3 (1)	10.5 (2)	1.000
Insulin	19	15.8 (3)	15.8 (3)	1.000
(2) For dyslipidemia				

Statin	19	63.2 (12)	52.6 (10)	0.743
Fibrate	19	5.3 (1)	10.5 (2)	1.000
EPA	19	5.3 (1)	5.3 (1)	1.000
Nicotinic acids	19	10.5 (2)	5.3 (1)	1.000
(3) For hypertension, and others				
Ca blocker	19	21.1 (4)	31.6 (6)	0.714
ARB	19	15.8 (3)	5.3 (1)	0.604
Beta blocker	19	10.5 (2)	10.5 (2)	1.000
Aspirin	19	5.3 (1)	5.3 (1)	1.000
Antiplatelet	18	5.6 (1)	5.6 (1)	1.000
Anticoagulant	18	5.6 (1)	0 (0)	1.000

	N	**Mean ± SD**		***P*-value**
		at registration	**two years later**	
Physical findings/function				
Body weight (kg)	19	44.4 ±9.5	43.0 ± 10.3	0.029
BMI (kg/m^2)	18	18.0 ± 2.9	17.5 ± 3.3	0.056
Systolic blood pressure (mmHg)	15	123.9 ± 15.9	119.1± 17.3	0.482
Diastolic blood pressure (mmHg)	15	72.5 ± 10.4	70.3 ± 8.9	0.270
Pulse (/min)	6	84.7 ± 17.3	81.5 ± 17.2	0.719
Waist circumference (cm)	6	74.6 ± 11.0	74.9 ± 10.2	0.625
Mean grip strength (right) (kg)	5	16.5 ± 6.9	15.0 ± 4.1	0.438
Mean grip strength (left) (kg)	4	13.5 ± 6.5	12.1 ± 3.1	0.625
Blood examinations				
WBC (/μL)	16	6859 ± 1696	7186 ± 2261	0.836
RBC (x10^4/μL)	16	442.6 ± 52.8	412.6 ± 89.3	0.298
Hb (g/dL)	16	13.05 ± 1.79	12.66 ± 2.85	0.850
Plt (x10^4/μL)	16	28.33 ± 6.64	64.53 ± 106.3	0.744
AST (U/L)	17	26.4 ± 9.6	28.3 ± 9.9	0.551
ALT (U/L)	17	35.8 ± 27.4	31.6 ± 20.8	0.923
γGTP (U/L)	16	82.4 ± 129.3	71.1 ± 78.4	0.536
LDH (U/L)	14	195.9 ± 39.6	202.4 ± 46.6	0.366
ALP (U/L)	13	248.8 ± 215.0	205.0 ± 111.2	0.906
ChE (U/L)	12	374.7 ± 70.8	373.8 ± 90.5	0.733
T-Bil (mg/dL)	9	0.55 ± 0.16	0.34 ± 0.29	0.039
TP (g/dL)	16	7.96 ± 0.54	7.78 ± 0.61	0.774
Alb (g/dL)	15	4.44 ± 0.59	4.27 ± 0.68	0.668
UA (mg/dL)	15	5.38 ± 1.45	4.72 ± 0.88	0.089
BUN (mg/dL)	16	17.7 ± 8.0	17.2 ± 6.7	0.657
Cre (mg/dL)	17	0.766 ± 0.311	0.788 ± 0.386	0.451
eGFRcre (mL/min/1.73 m^2)	17	84.5 ± 25.6	87.6 ± 41.6	0.644
BSA-uncorrected eGFRcre (mL/min)	15	68.5 ± 22.8	70.6 ± 33.6	0.639
Na (mEq/L)	16	139.7 ± 1.4	138.8 ± 3.6	0.461
K (mEq/L)	16	4.33 ± 0.33	5.48 ± 3.65	0.022
Cl (mEq/L)	16	104.7 ± 2.2	97.9 ± 26.2	0.892
TC (mg/dL)	12	182.0 ± 23.6	173.6 ± 26.5	0.531
TG (mg/dL)	15	146.1 ± 79.1	141.2 ± 53.4	0.836
LDL-C (direct) (mg/dL)	11	113.2 ± 27.9	101.4 ± 27.3	0.182
HDL-C (mg/dL)	14	57.1 ± 10.7	55.2 ± 11.1	0.726
HbA1c (%)	16	6.26 ± 0.65	6.31 ± 1.02	0.550
PPG (mg/dL)	7	137.0 ± 26.9	148.1 ± 34.3	0.375

Abbreviations: IGT: Impaired glucose tolerance; AP: Angina pectoris; MI: Myocardial infarction; PAD: peripheral artery disease; DPP-4: Dipeptidyl peptidase-4; alpha GI: alpha glucosidase inhibitor; SGLT2: Sodium-glucose cotransporter-2; GLP-1: Glucagon-like peptide-1; EPA: Eicosapentaenoic acid; Ca: Calcium; ARB: Angiotensin- II receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: body mass index; SMI: skeletal muscle mass index; WBC: white blood cell; RBC: red blood cell; Hgb, hemoglobin; Plt: platelet; AST, aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ChE: cholinesterase; T-Bil: total bilirubin; TP: total

protein; Alb: albumin; UA: uric acid; BUN: blood urea nitrogen; Cre: creatinine; BSA: body surface are; eGFR: estimated glomerular filtration rate; Na: natrium; K: potassium; Cl: chlorine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; SD: standard deviation.

Table 4. Comparison between the point of registration and three years later.

	N	% (*n* patients with this characteristic)		*P*-value
		at registration	three years later	
Major signs				
Graying and/or loss of hair	9	100 (9)	100 (9)	–
Bilateral cataracts	9	100 (9)	100 (9)	–
Skin changes	9	88.9 (8)	100 (9)	1.000
Intractable skin ulcers	9	66.7 (6)	77.8 (7)	1.000
Soft tissue calcification	9	100 (9)	100 (9)	-
Bird-like face	9	77.8 (7)	77.8 (7)	1.000
High-pitched voice	9	77.8 (7)	88.9 (8)	1.000
Clinical symptoms				
Diabetes, IGT	9	55.6 (5)	66.7 (6)	1.000
Dyslipidemia	9	66.7 (6)	77.8 (7)	1.000
Hypertension	8	50.0 (4)	62.5 (5)	1.000
Fatty liver	9	55.6 (5)	66.7 (6)	1.000
PAD	9	0 (0)	11.1 (1)	1.000
Malignant neoplasm	9	44.4 (4)	44.4 (4)	1.000
Medications				
(1) For diabetes				
DPP-4 inhibitor	9	22.2 (2)	33.3 (3)	1.000
Biguanide	9	11.1 (1)	22.2 (2)	1.000
Thiazolidine	9	22.2 (2)	11.1 (1)	1.000
GLP-1 analog	9	11.1 (1)	11.1 (1)	1.000
Insulin	9	11.1 (1)	11.1 (1)	1.000
(2) For dyslipidemia				
Statin	9	55.6 (5)	55.6 (5)	1.000
Fibrate	9	11.1 (1)	11.1 (1)	1.000
EPA	9	11.1 (1)	11.1 (1)	1.000
Nicotinic acids	9	22.2 (2)	11.1 (1)	1.000
(3) For hypertension and others				
Ca blocker	8	37.5 (3)	50.0 (4)	1.000
ARB	8	12.5 (1)	0 (0)	1.000
Beta blocker	8	12.5 (1)	12.5 (1)	1.000
Antiplatelet	8	12.5 (1)	12.5 (1)	1.000
Anticoagulant	8	12.5 (1)	0 (0)	1.000
	N	Mean ± SD		*P*-value
		at registration	three years later	
Physical findings/function				
Body weight (kg)	7	45.29 ±4.62	44.30 ± 4.57	0.281
BMI (kg/m^2)	3	18.06 ± 1.43	17.35 ± 1.69	0.500
Systolic blood pressure (mmHg)	5	132.8 ± 21.6	138.4± 15.8	0.625
Diastolic blood pressure (mmHg)	5	74.0 ± 10.77	76.6 ± 12.54	0.875
Pulse (/min)	4	92.5 ± 12.0	93.5 ± 22.2	0.875
Blood examinations				
WBC (/μL)	6	7517 ± 1699	8550 ± 2671	0.313
RBC (x10^4/μL)	6	424.8 ± 69.7	394.7 ± 63.2	0.156
Hb (g/dL)	6	12.05 ± 2.02	12.15 ± 1.82	0.688
Plt (x10^4/μL)	6	29.23 ± 5.44	33.27 ± 7.01	0.156

AST (U/L)	7	24.7 ± 4.2	24.3 ± 9.6	1.000
ALT (U/L)	8	28.6 ± 14.5	27.8 ± 17.4	0.734
γGTP (U/L)	8	43.5 ± 32.3	58.4 ± 55.9	0.398
LDH (U/L)	7	195.9 ± 39.9	194.9 ± 26.5	0.563
ALP (U/L)	6	204.5 ± 100.9	241.2 ± 69.4	0.156
ChE (U/L)	6	374.2 ± 98.0	376.0 ± 102.2	1.000
TP (g/dL)	7	7.94 ± 0.20	8.14 ± 0.59	0.641
Alb (g/dL)	7	4.34 ± 0.69	4.36 ± 0.29	1.000
UA (mg/dL)	8	5.56 ± 1.40	4.91 ± 1.03	0.109
BUN (mg/dL)	7	23.1 ± 9.1	25.6 ± 12.3	0.438
Cre (mg/dL)	7	0.904 ± 0.425	1.133 ± 0.747	0.078
eGFRcre (mL/min/1.73 m^2)	7	74.8 ± 33.5	63.4 ± 31.9	0.078
BSA-uncorrected eGFRcre (mL/min)	7	59.3 ± 25.2	50.2 ± 26.9	0.047
Na (mEq/L)	7	139.3 ± 1.6	139.7 ± 2.0	0.531
K (mEq/L)	7	4.51 ± 0.37	4.96 ± 0.82	0.141
Cl (mEq/L)	7	104.6 ± 2.9	105.0 ± 3.8	0.922
TC (mg/dL)	6	179.8 ± 16.7	189.7 ± 25.9	0.563
TG (mg/dL)	7	114.1 ± 25.8	126.6 ± 55.6	0.578
LDL-C (direct) (mg/dL)	4	115.0 ± 17.9	103.3 ± 11.9	0.375
HDL-C (mg/dL)	6	52.3 ± 8.8	54.2 ± 8.9	0.375
HbA1c (%)	7	6.20 ± 0.70	6.17 ± 0.91	0.875
PPG (mg/dL)	3	144.0 ± 24.8	139.0 ± 11.1	1.000

Abbreviations: IGT: Impaired glucose tolerance; AP: Angina pectoris; MI: Myocardial infarction; PAD: peripheral artery disease; DPP-4: Dipeptidyl peptidase-4; alpha GI: alpha glucosidase inhibitor; SGLT2: Sodium-glucose cotransporter-2; GLP-1: Glucagon-like peptide-1; EPA: Eicosapentaenoic acid; Ca: Calcium; ARB: Angiotensin- II receptor blocker; ACE: Angiotensin-converting enzyme inhibitor; BMI: body mass index; SMI: skeletal muscle mass index; WBC: white blood cell; RBC: red blood cell; Hgb: hemoglobin; Plt: platelet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ChE: cholinesterase; T-Bil: total bilirubin; TP: total protein; Alb: albumin; UA: uric acid; BUN: blood urea nitrogen; Cre: creatinine; BSA: body surface are; eGFR: estimated glomerular filtration rate; Na: natrium; K: potassium; Cl: chlorine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; SD: standard deviation.

Table 5. Type of malignant neoplasms and age of onset.

Patient No.	Age of onset (years)	Type of malignant neoplasm	Age during reporting or die (years)	Status
1	32	Bladder cancer	61	Alive
2	36	Breast cancer	44	Alive
3	42	Colon cancer	56	Alive
4	48, 49	Papillary thyroid cancer, meningioma[a]	49	Alive
5	48	Myelodysplastic syndrome[a], acute myeloid leukemia[a]	48	Dead
6	50	Papillary thyroid cancer	50	Alive
7	52	Lung adenocarcinoma	53	Alive
8	52	Breast cancer	55	Alive
9	56	Melanoma[a]	58	Dead
10	57, 60, 64	Meningioma[a], breast cancer, lung cancer	65	Alive
11	Unknown	Osteosarcoma[a]	45	Dead
12	Unknown	Thyroid follicular carcinoma	53	Alive
13	Unknown, unknown	Lung cancer, undifferentiated pleomorphic sarcoma[a]	55	Dead
14	Unknown	Soft tissue sarcoma[a]	56	Dead
15	Unknown	Lung adenocarcinoma	64	Alive
16	Unknown	Unknown	64	Dead

[a]Shows non-epithelial neoplasm.

Table 6. Relationship between renal function and the presence of leg ulcers/the usage of NSAIDs.

	N	Patients with ulcer (mean ± SD)	*N*	Patients without ulcer (mean ± SD)	*P*-value
eGFR (mL/min/1.73 m^2)	34	91.5 ± 30.5	16	112.9 ± 43.9	0.121
BSA-uncorrected eGFRcre (mL/min)	34	73.7 ± 25.2	16	86.3 ± 29.4	0.228
eGFRcys (mL/min/1.73 m^2)	11	77.0 ± 27.5	4	100.1 ± 32.2	0.240
	N	Patients with NSAIDs (mean ± SD)	*N*	Patients without NSAIDs (mean ± SD)	*P*-value
eGFR (mL/min/1.73 m^2)	9	94.0 ± 28.7	41	99.2 ± 38.0	0.830
BSA-uncorrected eGFRcre (mL/min)	9	74.5 ± 26.3	41	78.5 ± 27.4	0.910
eGFRcys (mL/min/1.73 m^2)	3	75.0 ± 9.2	12	85.2 ± 32.7	0.471

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; eGFR: estimated glomerular filtration rate; BSA: body surface area.

the usage of NSAIDs, there was no difference in renal function between the users and non-users, as follows: NSAIDs user 94.0 ± 28.7 mL/min/1.73 m^2 vs. non-user 99.2 ± 38.0 mL/min/1.73 m^2, P = 0.830; 74.5 ± 26.3 mL/min vs. 78.5 ± 27.4 mL/min, P = 0.910, and 75.0 ± 9.2 mL/min/1.73 m^2 vs. 85.2 ± 32.7 mL/min/1.73 m^2, P = 0.471, respectively.

Two patients (4.9%) were hospitalized with aspiration pneumonia; the age at onset was 67 years and 63 years, respectively.

During the four-year follow-up, deaths could be confirmed in six patients, of whom five died from malignant neoplasms and one from renal failure. The average age of death was 54.2 years (52.4 years for malignant neoplasms and 63.0 years for renal failure).

DISCUSSION

Data from the registry described in this study revealed the occurrence of changes over time for up to four years after registration in patients with Werner syndrome in Japan. Notably, a novel finding was that the index of renal function may greatly deviate from the actual state of renal function and that the rate of decline in renal function may be rapid. Although there were case reports regarding declining renal function in a patient with

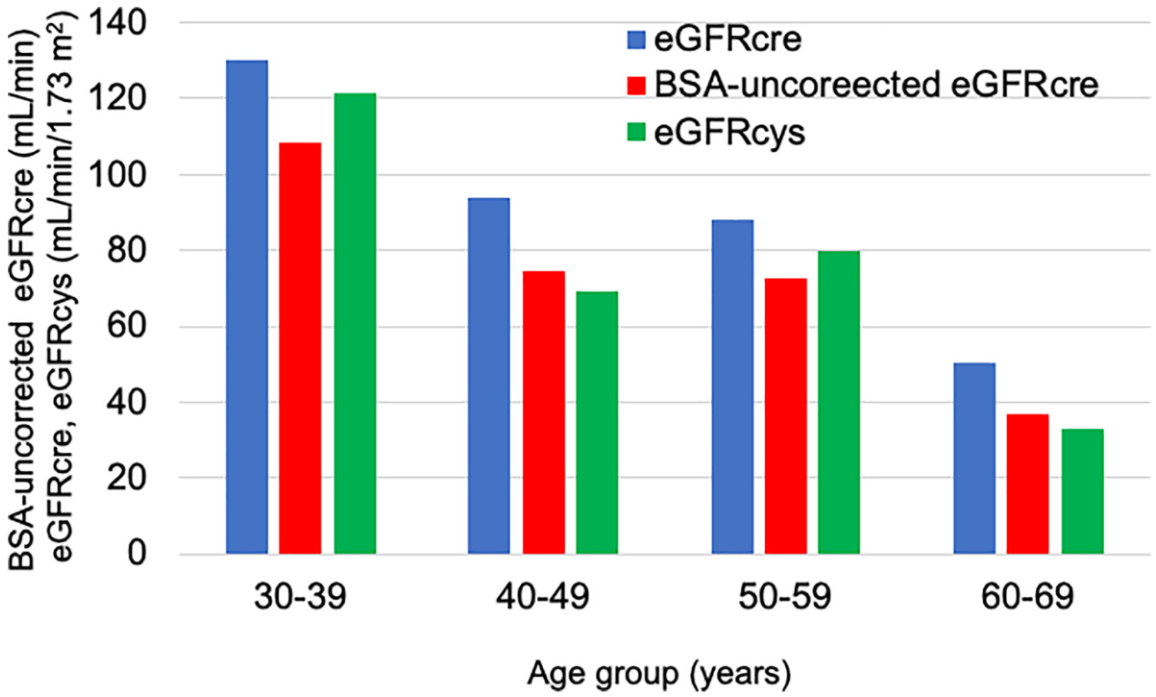


Figure 1. Average renal function in each age group over the entire survey period. The blue bar shows the eGFRcre. The red bar shows the BSA-uncorrected eGFRcre. The green bar shows the eGFRcys.

Werner syndrome [12–15], there was no report with a large sample size and long-term follow-up. Moreover, it was clarified that the morbidity due to malignant neoplasms is higher than that of the general population, the age of onset is younger, and both epithelial and non-epithelial neoplasms exist in similar ratios. In addition, aspiration pneumonia was observed in patients in their sixties.

The life expectancy of patients with Werner syndrome is extending [7] due to improvements in understanding the pathology of Werner syndrome and the development of medical treatments for diabetes and dyslipidemia [9]. Therefore, longer-term, more detailed follow-ups and medical interventions are needed. Atherosclerotic cardiovascular diseases (ASCVD), malignant neoplasms, sarcopenia, and leg ulcers were mentioned as the main pathological conditions affecting the prognosis of patients with Werner syndrome. The medical intervention seems to be effective for improving life quality [16–18]. Each important comorbidity is now discussed as follows.

Malignant neoplasms

In this study, the morbidity due to malignant neoplasms at baseline was 25.5% (13/51 patients). The morbidity due to malignant neoplasms in patients with Werner syndrome is increasing, and aging is a possible contributing factor [19]. In other words, patients with Werner syndrome are no longer dying from cardiovascular diseases at a young age; therefore, the morbidity due to malignant neoplasms may be increasing as a result.

Moreover, the ratio of epithelial neoplasms to non-epithelial neoplasms is generally approximately 10:1, while patients with Werner syndrome have very high morbidity associated with non-epithelial neoplasms [19, 20]. Similarly, the ratio of epithelial neoplasms to non-epithelial neoplasms was 12:7 for the entire study period.

Although the prevalence of epithelial neoplasms has been reported to be significantly higher in patients with diabetes compared to patients without diabetes [19], Lauper et al. reported no association between diabetes and epithelial or non-epithelial neoplasms [21]. In our study, the prevalence of epithelial neoplasms in patients with diabetes was 18.9%, and that in patients without diabetes was 28.6%.

Furthermore, reportedly, the age of onset for malignant neoplasm was low in patients with Werner syndrome, with the predominant onset age for malignant neoplasms being 25–65 years. In particular, the morbidity due to non-epithelial neoplasms, in other words, those of mesenchymal origin (sarcoma), is particularly high (20%) in patients with Werner syndrome before the age of 41 years [22]. In other reports, the average age of malignant neoplasm onset was 47.2 years for epithelial neoplasms, 45.2 years for non-epithelial neoplasms, and 45.8 years for all malignant neoplasms [19]. Figure 2 shows the percentage of malignant neoplasms by onset in each age group. Epithelial neoplasms developed at a younger age, and the incidence of non-epithelial neoplasms increased during the late 40s. The average age of onset was 48.4 years for epithelial neoplasms, 52.5 years for non-epithelial neoplasms, and 49.7 years for all malignant neoplasms. Therefore, the age of onset of non-epithelial neoplasms is higher than in previous reports as well. This may be due to the fact that the patients' lifespan has been prolonged by cardiovascular disease prevention and epithelial neoplasm treatment.

The table in Figure 2 shows the age-specific incidence risk of malignant neoplasms in the general population in Japan. Since the probability of malignant neoplasms in the 30s and 60s of the general population is 1.2–21.6%, the morbidity due to malignant neoplasms is higher in the same age group of patients with Werner syndrome. Malignant neoplasms onset is approximately 10 years earlier in patients with Werner syndrome than in the general population [23].

A high percentage of multiple neoplasms is also characteristic of patients with Werner syndrome. In other reports, there were multiple neoplasms in 5.3% of all patients and 15–20% of patients with malignant neoplasms [19, 24]. A similar tendency was observed in this study.

Reportedly, two-thirds of neoplasms in the Werner syndrome population were thyroid neoplasms, malignant melanomas, meningiomas, soft tissue sarcomas, leukemia and preleukemic conditions, and osteosarcoma and bone neoplasms; in our study, half of the patients with malignant neoplasms had these neoplasms, and the incidence of breast and lung cancers in the epithelial neoplasm group was also high [25]. Regarding osteosarcoma, X-ray screening of long bones may be useful. Therefore, screening of these neoplasms should be prioritized.

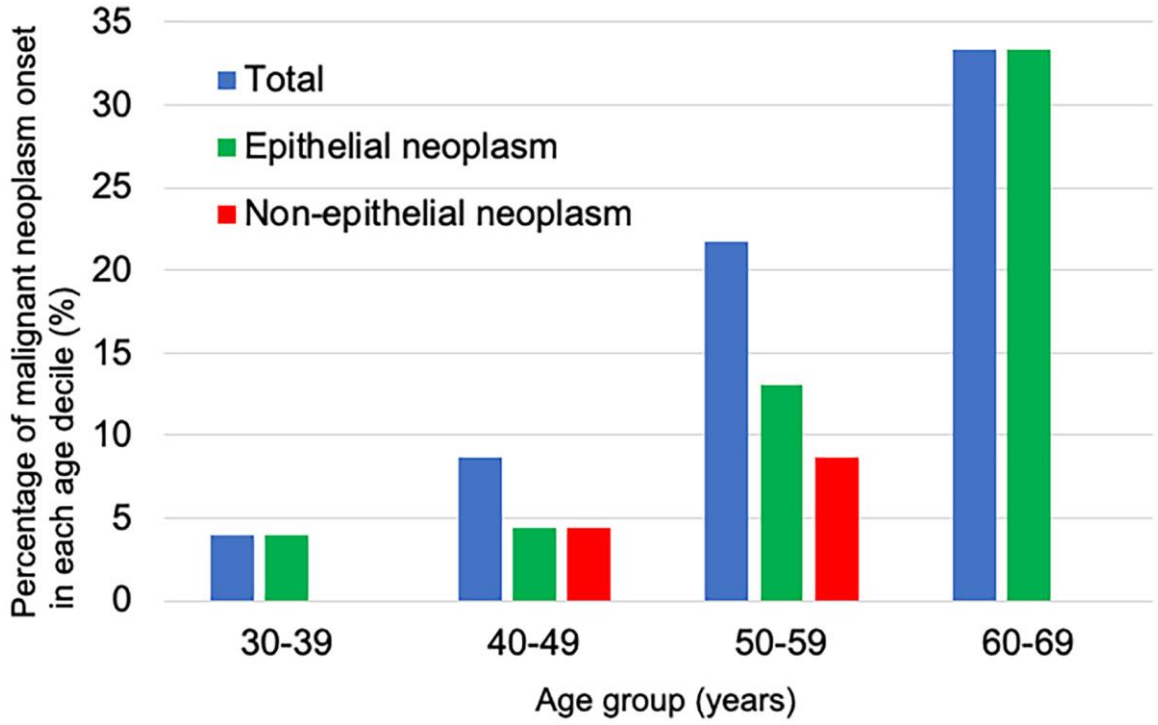
Currently, the main cause of death in patients with Werner syndrome is malignant neoplasms development, and malignant neoplasms greatly influence prognosis; therefore, early detection and treatment by regular screening from a younger age are both very important to ameliorate their prognosis.

There are some cautions to be considered regarding cancer treatment for patients with Werner syndrome.

Reportedly, a patient with a heterozygous mutation in the WRN gene and a retroperitoneal liposarcoma had dramatic renal and hematological toxicity after cytotoxic chemotherapy [26]. For patients with a WRN mutation, close monitoring of the hematologic profile and renal function is needed to avoid severe toxicities. Furthermore, it was reported that radiotherapy is contraindicated in most homozygous patients with recessive radiosensitivity syndromes, including Werner syndrome [27]. Therefore, safer and more effective new cancer treatments for patients with Werner syndrome are needed.

Recently, the mechanism of high morbidity and treatment strategies for malignant neoplasm in patients with Werner syndrome have been getting clear. The Werner syndrome ATP-dependent helicase (WRN) is a RecQ enzyme involved in the maintenance of genome integrity. WRN is associated with Werner syndrome and a predisposition to multiple cancers, such as multiple myeloma [28], myelodysplastic syndrome/ acute myeloid leukemia [29], colorectal cancer [30], breast cancer [31], and ovarian cancer [32]. WRN contributes to chromosomal stability for survival in both normal and cancer cells [33]. WRN is also required for DNA damage repair and the survival of cancer cells with microsatellite instability (MSI) [34]. WRN depletion induces double-strand DNA breaks and promotes apoptosis and cell cycle arrest selectively in MSI models. Loss of WRN leads to synthetic lethality in mismatch repair-deficient/high MSI cells [35].

Genome-wide screening studies have reported that WRN inhibition induces massive chromosome disruption [36] and synthetic lethality in cancer cells with high MSI [37, 38]. The development possibility of novel therapeutic agents that target WRN for MSI-associated cancers by pharmacological inhibition of WRN helicase function has been reported [35, 36, 38]. Reportedly, exposure to small-molecule compounds,



Age-specific incidence risk of malignant neoplasms in the general population in Japan based on reference 20.

	0-39 years	0-49 years	0-59 years	0-69 years	0-79 years
Male (%)	1.2	2.8	7.8	21.6	43.0
Female (%)	2.3	6.2	12.3	21.1	32.7

Figure 2. Percentage of malignant neoplasms onset in each age decile in the patients with Werner syndrome. The blue bar shows the percentage of total malignant neoplasms in each age group. The green bar shows the percentage of epithelial neoplasms in each age group. The red bar shows the percentage of non-epithelial neoplasms in each age group. Patients with thyroid follicular cancer, osteosarcoma, lung cancer/undifferentiated polymorphic sarcoma, and soft tissue sarcoma were excluded because the exact age of onset was unknown.

such as NSC 19630 (N-(1-(4-((4-methoxyphenyl) amino) quinazolin-6-yl) ethyl)-3-(pyridin-3-yl) acryl-amide) and NSC 617145 (5-(4-chlorophenyl)-4-(4-methylphenyl)-4,5-dihydro-1H-imidazol-2-amine N-(4-methylphenyl) sulfonylacetamide), which inhibits WRN helicase activity, sensitizes cancer cells to DNA-damaging agents [39] and DNA cross-linking agents [40]. Sublethal dosage of small-molecule compounds and the chemotherapy drug act synergistically to inhibit cell proliferation and induce DNA damage in cancer cells. These studies are still in progress and thus the results are highly awaited.

Renal function

According to the renal function index, the discrepancy was observed in patients with Werner syndrome. It may be because patients with Werner syndrome have a smaller body size and less muscle mass than those without Werner syndrome.

The calculation of eGFRcre (mL/min/1.73 m^2) requires the serum creatinine level, age, and sex. The calculation of BSA-uncorrected eGFRcre (mL/min) requires five items: serum creatinine level, age, sex, height, and weight. In other words, it considers the physique. The calculation of eGFRcys (mL/min/1.73 m^2) requires three items: serum cystatin C level, age, and sex. Therefore, it is not affected by muscle mass.

Since creatinine is easily affected by muscle mass, diet, and exercise, eGFRcre is often higher in older adults with less muscle mass, and discrepancies are likely to be observed. The situation is similar to that in patients with Werner syndrome. Therefore, in the patients with Werner syndrome, it is considered that eGFRcre dissociates from BSA-uncorrected eGFRcre and eGFRcys.

It can be observed from Figure 1 that the eGFRcys/eGFRcre ratios are <1.0. Reportedly, the presence of low eGFRcys/eGFRcre ratios (<1.0) is associated with sarcopenia [41]. In Figure 1, the eGFRcys/eGFRcre ratio is also low in non-elderly people, which may reflect that patients with Werner syndrome are small and have low muscle mass even at a young age. Therefore, there are concerns due to the dissociation of the renal function indices. Side effects may likely occur when using medicines such as antibiotics and NSAIDs for patients with poor renal function. For patients with extremely small body size and decreased renal function, the use of BSA-uncorrected eGFRcre or eGFRcys is preferable to eGFRcre. It is important to carefully consider which renal function index to use before deciding the amount of medicine to be used.

The other problem is that when there is a worse eGFRcys than eGFRcre, it is associated with a higher risk of death and end-stage renal disease [42, 43]. Therefore, it is necessary to carefully follow the course of a patient's renal function.

Renal function (eGFRcre, BSA-uncorrected eGFRcre) tended to decrease over three years, and BSA-uncorrected eGFRcre showed a significant decrease. The average rate of decline in BSA-uncorrected eGFRcre in the patients with Werner syndrome was 9.1 mL/min for three years, that is, approximately 3 mL/min in a year. In addition, as Figure 1 shows, the decrease in renal function is remarkable in the 30s and after the 50s. The average rate of decline in eGFR for general Japanese people aged 40 and above is 0.36 mL/min/1.73 m^2 (males 40–49 years: 0.35 mL/min/1.73 m^2; 50–59 years: 0.31 mL/min/1.73 m^2; 60–69 years: 0.37 mL/min/1.73 m^2; 70–79 years: 0.42 mL/min/1.73 m^2; females 40–49 years: 0.41 mL/min/1.73 m^2; 50–59 years: 0.31 mL/min/1.73 m^2; 60–69 years: 0.32 mL/min/1.73 m^2; and 70–79 years: 0.39 mL/min/1.73 m^2) [44]. Therefore, this suggests that the rate of renal function decline was faster than that of the general population of the same age.

While the management of diabetes and hypertension was appropriate, the use of analgesics such as NSAIDs was considered one of the reasons that the rate of renal function decline was rapid. Approximately 70% of patients with Werner syndrome develop painful intractable ulcers, and NSAIDs are frequently used. Although there was no relationship between leg ulcers or NSAIDs and renal function in this three-year follow-up, various factors, such as the presence of peripheral angiopathy, also affect the results; therefore, it may be necessary to pay attention to the dose of NSAIDs in patients with painful intractable ulcers. The use of NSAIDs in older adults is often noted, and similar caution is needed in patients with Werner syndrome, even the non-elderly, whose renal dysfunction cannot be predicted by eGFRcre alone. For other medicines, such as antibiotics, anti-cancer drugs, and ARBs, it is also necessary to care about drug-induced renal damage or side effects due to overdose.

Atherosclerotic cardiovascular diseases and metabolic diseases

ASCVDs, such as myocardial infarction, angina pectoris, and atherothrombotic cerebral infarction, were not common during the study period. The reduction of ASCVD appears to be extending the life expectancy of patients with Werner syndrome. This is presumed to be associated with the improved management of metabolic diseases such as diabetes, dyslipidemia, and hyper-tension. Regarding diabetes treatments, similar to findings in a previous report [9], pioglitazone, metformin,

and insulin sensitizers were often used. While, longitudinally, the percentage of metformin use has increased more than that of pioglitazone, suggesting that the negative effects of pioglitazone on osteoporosis may be considered. Among those with dyslipidemia, statins were used in 58.8% of patients. Although the baseline data were generally within the control target range over four years, the LDL-C level decreased more from baseline, suggesting suitable interventions took place. Hypertriglyceridemia should also be noted. It was reported that a 29-year-old patient with Werner syndrome and hypertriglyceridemia (triglyceride level of 3900 mg/dL) had advanced three-vessel disease requiring coronary artery bypass graft surgery [45]. Therefore, in addition to statins, management of hypertriglyceridemia may also be needed. Regarding antihypertensive medications, the use of ARBs decreased in patients over the four years, and eventually, there were no patients using ARBs. Hyperkalemia was cited as one of the reasons for medication discontinuation, suggesting a relationship with impaired renal function. Although metabolic diseases were sufficiently controlled overall, as life expectancy prolongs, appropriate medications must be selected to address potential side effects. Moreover, patients with severe aortic stenosis [46, 47] and heart failure due to impaired coronary microcirculation with no coronary artery stenosis have been reported [48]. Therefore, a comprehensive evaluation of arteriosclerosis in patients with Werner syndrome is still needed.

Sarcopenia

The sarcopenia diagnostic criteria by the Asian Working Group for Sarcopenia 2019 [49] has three indicators, of them, the following three indicators were used in this survey: 1) grip strength (male/female) <28 kg/<18 kg, 2) walking speed <1.0 m/s, and 3) SMI dual-energy X-ray absorptiometry <7.0 kg/m^2 (male) and <5.4 kg/m^2 (female), SMI bioimpedance, <7.0 kg/m^2 (male) and <5.7 kg/m^2 (female). As Table 1 shows, the mean values of grip strength and SMI in the present registry met the criteria of 1) and 3), and sarcopenia was suspected. The patients with Werner syndrome tended to have sarcopenia obesity (visceral fat increase despite low BMI). It was reported that sarcopenia tended to appear before visceral fat accumulation [50]. Moreover, over the years, body weight, BMI, and grip strength tended to decrease in this study. The adipogenic and chondrogenic differentiation capacity was significantly decreased in the foot fibroblasts of patients when Werner syndrome *in vitro*. It may partially explain the underlying mechanism of sarcopenia in patients with Werner syndrome [51]. The presence of sarcopenia may be related not only to QOL reduction but also to renal function evaluation, as aforementioned, suggesting that sarcopenia prevention is needed. Measures such as leucine intake [52, 53] and strength training [54, 55], which have general preventive effects on sarcopenia, should be considered. Ghrelin receptor agonist has been shown to increase body weight, muscle mass, and appetite in patients with cancer cachexia [56, 57]. These findings suggest that ghrelin receptor agonist also may be effective in patients with Werner syndrome, in whom skeletal muscle mass is significantly reduced.

Other complications associated with aging

As lifespans prolong, complications such as aspiration pneumonia, which are often seen in late older adults, are increasing. Two patients with aspiration pneumonia were reported in this survey. They were aged in their 60s and were thus younger than the average age group that generally experienced aspiration pneumonia. Vaccinations to prevent pneumonia in those aged in their early 60s and oral care may be useful preventive measures. Further, the use of benzodiazepine should be avoided.

This study is limited because the evaluated registry does not cover all patients with Werner syndrome in Japan. However, almost half of the patients confirmed in a previous national survey registered; therefore, the clinical evidence was established based on a highly universal (and the largest) database of Werner syndrome in Japan.

Although the overall prognosis of patients with Werner syndrome is improving, new opportunities for early diagnosis and treatment intervention are still needed. It has been suggested that the inclusion of the WRN gene in genetic analyses for early-onset diabetes, lipodystrophy, or dyslipidemia may offer an opportunity to diagnose patients with Werner syndrome long before the presentation of the full spectrum of symptoms and complications, enabling earlier interventions, including malignant neoplasm screenings and prevention of diseases listed in the clinical criteria [58]. Recently, novel senescent markers, ATP6V0D1 and RTN4, were shown to be increased in cells derived from patients with Werner syndrome, raising a possibility that they may serve as markers of disease progression [59]. Similarly, ribonuclease H2 subunit A (RNaseH2A) was shown to be downregulated in Werner syndrome cells as well as selected cancer cells [60]. Therefore, it may also be used as a diagnosis and severity marker. It was reported that patients with Werner syndrome have thinning of the retinal nerve fiber layer, ganglion cell complex, and choroidal thickness and the loss of visual field [61]. It may be useful for early diagnosis to have retinal and choroidal check-ups with the optical coherence tomography images when patients present with juvenile cataracts of unknown cause. For early detection of complications, genetic testing for

complications, such as malignant neoplasms, may also be useful, when Werner syndrome is diagnosed. Early detection makes it possible to reduce risk factors such as smoking and to do early prevention and treatment.

Regarding renal protection, renin-angiotensin system inhibitors are hard to use, since many patients stopped their usage due to hyperkalemia. Additionally, sodium-glucose cotransporter 2 inhibitors are also difficult to use due to concern of sarcopenia in patients with Werner syndrome. However, a mineralocorticoid receptor antagonist, finerenone, may be a good candidate, since it is less likely to cause hyperkalemia.

Regarding intractable skin ulcers, treatment with a functional peptide SR-0379 was found to be safe, well-tolerated, and effective for leg ulcers in patients with Werner syndrome in clinical trials [62, 63].

Reportedly, p38 inhibitors reduced the accelerated cell senescence in primary fibroblasts from patients with Werner syndrome [64]. It is believed that in the near future, p38 inhibitors may be used in *in vivo* studies. Nicotinamide adenine dinucleotide (NAD) is important for the activation of sirtuin, a type of protein involved in regulating cellular processes including the aging and death of cells. NAD levels decrease in patients with Werner syndrome [65], therefore supplementation with NAD precursors may be effective. A clinical trial with nicotinamide riboside, a precursor of NAD, which may be effective for intractable ulcers, sarcopenia, and ASCVD, is investigating the safety and efficacy in patients with Werner syndrome [66]. Using state-of-the-art technologies, such as genome, transcriptome, and epigenome analyses [67], study of the generation of iPS cells from patients with Werner syndrome and the correction of the WRN gene by the CRISPR/Cas9-mediated methods [68] will create new treatments for patients with Werner syndrome.

In conclusion, this study clarified secular changes in multiple patients with Werner syndrome. The morbidity due to malignant neoplasms is high even in those of young age; therefore, it is necessary to carry out active and detailed screening examinations for malignant neoplasms. Renal function declines rapidly; therefore, evaluation based on BSA-uncorrected eGFRcre or eGFRcys and attention to the type and amount of drugs used are needed.

MATERIALS AND METHODS

Werner Syndrome Registry (patient registration system)

To reveal the disease profile and prognosis and to seek suitable medical intervention methods, the Werner Syndrome Registry was established. Based on the results of a nationwide primary survey, the patients were recruited to the registry from facilities with patients definitively diagnosed with Werner syndrome according to the diagnostic criteria [20].

The study complied with the ethical rules for human experimentation as specified in the Declaration of Helsinki. The study received approval from the Ethics Board of Chiba University on 27th July 2016 (approval number: 278) and from the Ethics Board of Kyoto University on 29th January 2020 (approval number: R2370). The study was registered at the UMIN Clinical Trial Registry (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034058) on 3rd November 2017 (ID: UMIN000029812). Written informed consent was obtained from patients before registration.

The key inclusion criteria for the registry were as follows: 1) patients with confirmed Werner syndrome based on the diagnostic criteria [20], and 2) patients who provided written informed consent prior to their participation in the registry. There were no exclusion criteria. The registry data included patient background (age at the time of onset, diagnosis, and registration; height, weight, BMI, abdominal circumference, and presence of consanguineous marriage), characteristic major signs and clinical symptoms, comorbidities (diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, fatty liver, cerebrovascular diseases, cardiovascular diseases, peripheral artery disease, foot amputation, and malignant neoplasms), the pattern of gene mutation, blood examination (blood cell count, biochemistry, liver and renal functions, and glucose and lipid profiles), visceral fat area, SMI, physical function (grip strength and walking speed), and treatment content. Renal function was evaluated using the following three indices: eGFRcre, BSA-uncorrected eGFRcre, and eGFRcys.

The calculation formula of each eGFR index was as follows:

(1) eGFRcre (mL/min/1.73 m^2)

Male: eGFRcre (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287}$

Female: eGFRcre (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$

(2) BSA-uncorrected eGFRcre (mL/min) = eGFRcre × (BSA/1.73)

BSA can be calculated using the Du Bois method. BSA (m^2) = Height $(cm)^{0.725}$ × Weight $(kg)^{0.425}$ × 0.007184.

(3) eGFRcys (mL/min/1.73 m^2)

Male: eGFRcys (mL/min/1.73 m^2) = {104 × $CysC^{-1.019}$ × 0.996^{Age}} −8

Female: eGFRcys (mL/min/1.73 m^2) = {104 × $CysC^{-1.019}$ × 0.996^{Age} × 0.929} −8

The datasheets were collected from the facilities annually. The collected data were subsequently inputted into the registration system Fountayn (previously named DATATRACK ONE) (NTT DATA, Tokyo, Japan) [9].

Cross-sectional analysis and longitudinal analysis

The data were extracted on May 12, 2022. Data obtained at the registration time of each patient were analyzed through a cross-sectional analysis study model. For longitudinal analysis of the data in the Werner Syndrome Registry, the data at the time of initial registration and after one, two, and three years were compared in the patients with such data. For continuous variables, the paired t-test was used for items with a normal distribution, and the Wilcoxon signed-rank test was used for items with a non-normal distribution. For binary variables, Pearson's chi-squared test was used for items with 20 patients and more, and Fisher's exact test was used for items with less than 20 patients included. All data were analyzed with JMP pro 15 (SAS Institute, Cary, NC, USA). A *p*-value less than 0.05 was considered statistically significant.

The prevalence of malignant neoplasms and aspiration pneumonia was also investigated for the entire period from registration to three years later. Regarding malignant neoplasms, the presence or absence of malignant neoplasms, categorization of epithelial or non-epithelial neoplasms, and type of neoplasms were investigated.

Moreover, the association between renal function and leg ulcers/NSAIDs was also investigated. The relationship between renal function (eGFRcre, BSA-uncorrected eGFRcre, and eGFRcys) and both the presence or absence of leg ulcers and the use of NSAIDs were investigated using the baseline data.

AUTHOR CONTRIBUTIONS

MKoshizaka, MS, YMaeda, HKaneko, HKato, YMaezawa, MT, and KYokote managed the project. MKoshizaka, MS, YMaeda, HKato, YM, JK, KYoshinaga, MI, AS, SM, HN, YY, ST, AT, KS, YT, YS, KHashimoto, TYoshimura, AK, DS, NO, TYoshida, KW, MKuzuya, and KYokote recruited the patients and carried out examinations. MKoshizaka, YMaeda and MS analyzed data. YMaeda and MKoshizaka drafted the manuscript. MKoshizaka, YMaeda, MS, HKaneko, HKato, YMaezawa, JO, and KYokote edited and revised the manuscript. KYokote acted as the "principal investigator." All authors contributed significantly, read, and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

ETHICAL STATEMENT AND CONSENT

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Research Paper

Senescence-associated inflammation and inhibition of adipogenesis in subcutaneous fat in Werner syndrome

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ABSTRACT

Werner syndrome (WS) is a hereditary premature aging disorder characterized by visceral fat accumulation and subcutaneous lipoatrophy, resulting in severe insulin resistance. However, its underlying mechanism remains unclear. In this study, we show that senescence-associated inflammation and suppressed adipogenesis play a role in subcutaneous adipose tissue reduction and dysfunction in WS. Clinical data from four Japanese patients with WS revealed significant associations between the decrease of areas of subcutaneous fat and increased insulin resistance measured by the glucose clamp. Adipose-derived stem cells from the stromal vascular fraction derived from WS subcutaneous adipose tissues (WSVF) showed early replicative senescence and a significant increase in the expression of senescence-associated secretory phenotype (SASP) markers. Additionally, adipogenesis and insulin signaling were suppressed in WSVF, and the expression of adipogenesis suppressor genes and SASP-related genes was increased. Rapamycin, an inhibitor of the mammalian target of

rapamycin (mTOR), alleviated premature cellular senescence, rescued the decrease in insulin signaling, and extended the lifespan of WS model of *C. elegans*. To the best of our knowledge, this study is the first to reveal the critical role of cellular senescence in subcutaneous lipoatrophy and severe insulin resistance in WS, highlighting the therapeutic potential of rapamycin for this disease.

INTRODUCTION

Werner syndrome (WS) is a rare monogenic premature aging disorder caused by *WRN*, a gene that encodes a RecQ-type DNA helicase which is involved in DNA replication and repair [1]. The first symptoms of WS-associated premature aging appear after puberty [2] and include age-related diseases such as diabetes mellitus, dyslipidemia, cardiovascular diseases, and malignant neoplasms [3, 4]. Therefore, research on WS is important as it can provide insights into the pathogenesis and development of treatments not only for WS but also for general age-related diseases [5].

Visceral fat accumulation induces diabetes and other metabolic diseases [6]. Moreover, obesity induces chronic inflammation, leading to insulin resistance [7–9]. However, the role of subcutaneous fat in insulin resistance remains unclear. Lipodystrophy, characterized by the loss of adipose tissues, is often accompanied and aggravated by insulin-resistant diabetes mellitus [10]. WS is characterized by the accumulation of visceral fat and loss of subcutaneous fat (lipodystrophy) in the extremities [11] and is often associated with insulin-resistant diabetes [12], which suggests an association between subcutaneous fat atrophy and insulin resistance. However, the pathogenesis of subcutaneous fat atrophy in WS is not clear. Therefore, this study aimed to reveal the pathogenesis of subcutaneous fat atrophy in the extremities of patients with WS.

RESULTS

A decrease in subcutaneous fat is associated with aggravated insulin resistance in patients with WS

In this study, the hyperinsulinemic-euglycemic clamp technique was used to assess insulin resistance in four patients with WS attending our hospital. The characteristics of the four patients are listed in Table 1. Two of the four patients were female, and the median age of the patients was 46 years old (Table 1). The median values of the body mass index (BMI) and skeletal muscle mass index (SMI) were 19.5 and 4.7, respectively, indicating sarcopenia with a relatively small body weight (Table 1). Moreover, we assessed visceral and subcutaneous fat areas using abdominal computed tomography (CT), which showed visceral fat area (VFA) accumulation and a low percentage of the subcutaneous fat area (SFA) (Table 1). The median value of glucose infusion rate (GIR) was 3.8 mg/kg/min, indicating insulin resistance (normal range > 6.0 mg/kg/min; Table 1). Additionally, to investigate the association between lipodystrophy and insulin resistance, we compared subcutaneous fat area/total fat area (SFA/TFA) to the GIR and found a significant positive correlation (R^2 = 0.95, p = 0.024; Figure 1). These results suggest that subcutaneous fat loss in patients with WS may be associated with aggravated insulin resistance.

The stromal vascular fraction of patients with WS exhibits premature cellular senescence with increased expression of senescence-associated inflammatory genes

Next, we assessed adipose-derived stem cells from the stromal vascular fraction (SVF) obtained from subcutaneous adipose tissues of a patient with WS *in vitro*. The SVF derived from the subcutaneous fat of a 64-year-old healthy individual (HSVF) was compared to that of a 47-year-old patient with WS (WSVF), and both individuals were women. Analysis of the cell growth curve showed that WSVF exhibited premature cell proliferation arrest (Figure 2A). WSVF cells also exhibited senescence-like morphology with enlarged and flattened cell shape at an early passage (population doubling level: PDL 10; Figure 2B). Additionally, quantitative polymerase chain reaction (qPCR) analysis revealed that the telomere length was significantly shortened in WSVF (p < 0.0001; Figure 2C). The number of senescence-associated β-galactosidase (SA-β-gal) positive cells was increased in WSVF compared to HSVF (indicated by black arrows, Figure 2D). Furthermore, WSVF showed increased expression levels of senescence-associated inflammatory cytokines, SASP genes, such as *IL6* (p < 0.001) and *CXCL8* (p < 0.0001). The expression of *CDKN1A* (p < 0.0001) and *CDKN2A* (p < 0.001), major cyclin-dependent kinase inhibitors, also increased in WSVF compared to HSVF (Figure 2E). These results indicate that the SVF of patients with WS exhibits premature cellular senescence with increased expression levels of SASP genes.

WSFV exhibits distinct gene expression

To investigate the gene expression and pathways involved in cellular senescence in WSVF, we performed a transcriptome analysis of WSVF and HSVF. We analyzed the data using k-means clustering and

Table 1. Characteristics of the four patients with WS in our study.

Case	Normal range	#1	#2	#3	#4	Median
Age [years old]		48	44	44	64	46
Sex		Man	Woman	Man	Woman	
BMI [kg/m^2]		19.6	20.3	19.4	15.1	19.5
SMI [kg/m^2]	M: > 6.87 F: > 5.46	4.7	5.7	4.6	2.7	4.7
TFA [cm^2]		238.0	248.8	329.0	191.3	243.4
VFA [cm^2]	< 100	108.9	128.3	205.8	97.4	118.6
SFA [cm^2]		129.2	120.6	123.2	93.9	121.9
V/S ratio		0.84	1.06	1.67	1.04	1.05
S/T ratio		0.54	0.48	0.37	0.49	0.49
GIR [mg/kg/min]	> 6	4.9	4.1	1.7	3.5	3.8

conducted a pathway analysis using gene ontology (GO) biological processes. The top 2000 genes with the largest changes in expression were analyzed; 821 genes were upregulated and 1179 genes were downregulated in WSVF compared to HSVF (Figure 3A, 3B). Pathway analysis using GO biological processes revealed that genes related to cell adhesion and cell structure were upregulated in WSVF whereas those related to chromosome organization and segregation, nuclear division, and cell cycle were downregulated (Figure 3B). These results were consistent with premature cellular senescence.

Adipogenesis is suppressed in WS

We subsequently performed adipogenesis experiments to evaluate the adipogenic potential of WSVF. The protocol for adipogenic differentiation is shown in Figure 4A. During adipogenesis, the number of cells with lipid droplets increased in HSVF (Figure 4A). Oil Red O staining showed that the stained areas were reduced in WSVF on both days 9 and 15 (Figure 4B). Moreover, quantification of the Oil Red O-stained area showed that the number of cells positive for Oil Red O staining was significantly decreased in WSVF compared to that in HSVF on both days 9 and 15, indicating suppressed adipogenesis in WSVF ($p < 0.01$; Figure 4C). During adipogenesis, WSVF exhibited decreased expression levels of *PPARG* ($p < 0.0001$) and *FABP4* ($p < 0.0001$), adipogenesis-related genes, and *ADIPOQ* ($p < 0.001$) and *LEP* ($p < 0.01$) compared to HSVF (Figure 4D). In contrast, WSVF exhibited increased expression levels of *TIMP1* ($p < 0.01$) and *YAP1* ($p < 0.05$), which are suppressors of adipogenesis [13, 14] but decreased expression levels of *NAMPT* ($p < 0.001$), which is a gene related to mitochondrial function, compared to HSVF (Figure 4D). Furthermore, during adipogenesis, the expression levels of the inflammatory molecules SASP, such as *IL6* ($p < 0.001$), *CXCL8* ($p < 0.01$), and *IL1B* ($p < 0.05$), and those of senescence-related cell cycle regulators, such as *CDKN1A* ($p < 0.01$) and *CDKN2A* ($p < 0.01$), were increased in WSVF compared to HSVF (Figure 4D). Interestingly, *TCF21*, whose expression is usually increased in visceral fat [15, 16], was also increased ($p < 0.01$) in WSVF compared to HSVF (Figure 4D). These results suggest that adipogenesis is suppressed and inflammatory genes are increased in WS.

Insulin signaling is suppressed in WS

We investigated insulin-related pathways in WSVF using western blotting. After stimulation with insulin, the protein expression levels of p-Akt compared to Akt in WSVF were lower than those in HSVF (Figure 5A). The p-Akt/Akt ratio was reduced to 68.6% in WSVF compared to that in HSVF (Figure 5B). IRS1 and PI3K

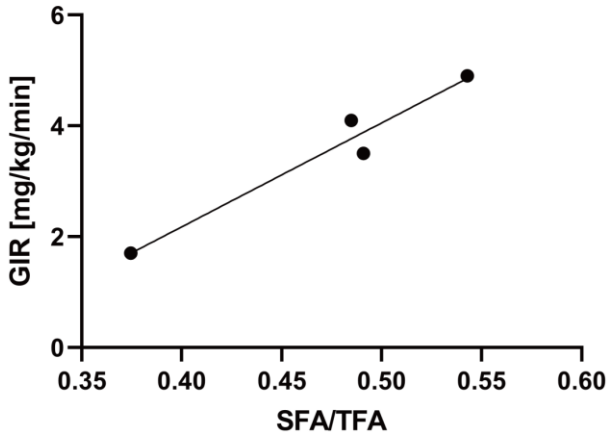

Figure 1. The SFA/TFA ratio is correlated with the GIR. Four patients with WS patients were included. The correlation coefficient between the SFA/TFA and GIR; $R^2 = 0.95$, $p = 0.024$; for statistical analysis, simple linear regression analysis was performed. WS: Werner syndrome; TFA: total fat area; SFA: subcutaneous fat area; GIR: glucose infusion rate.

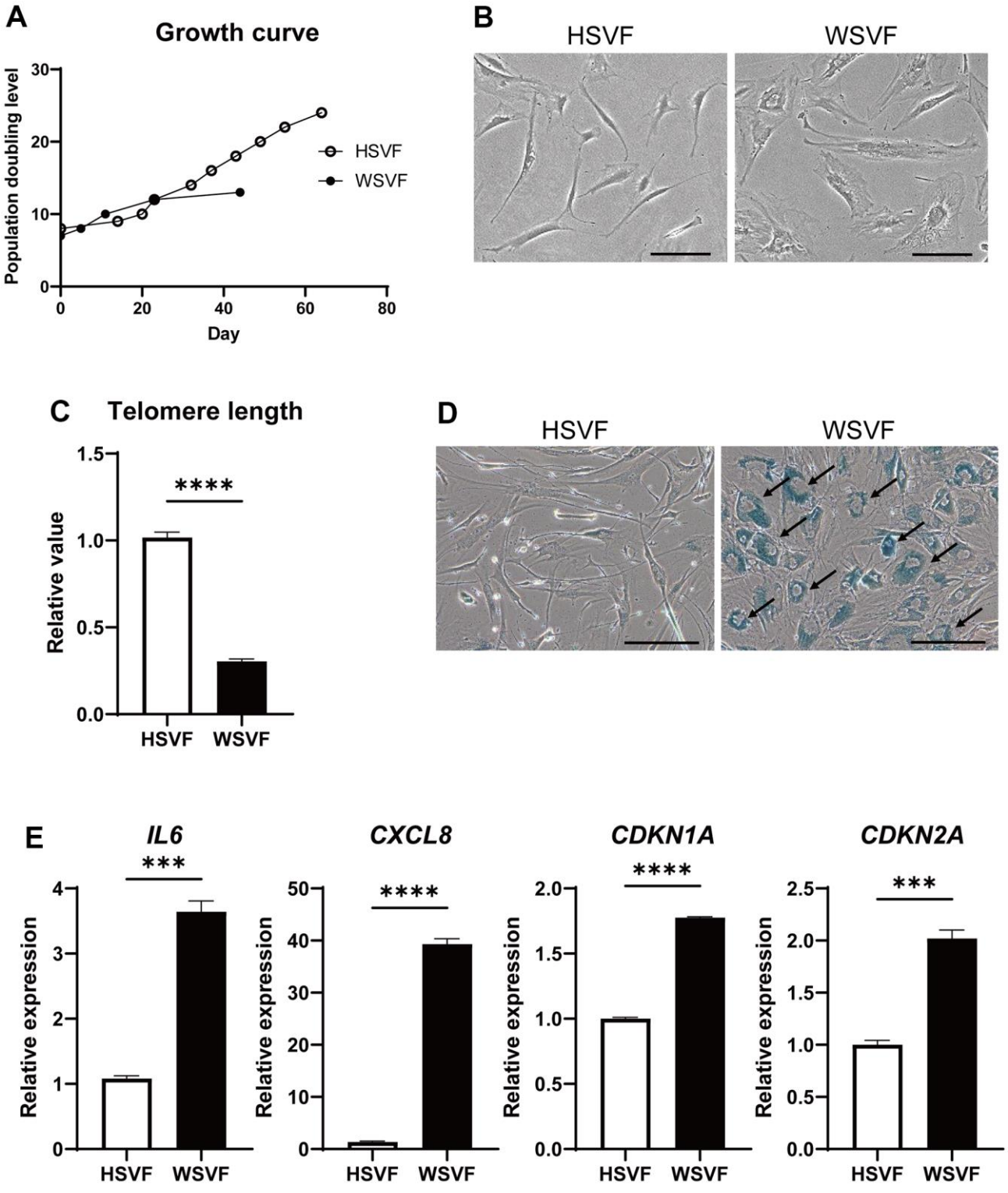

Figure 2. WSVF exhibits cellular senescence and increased expression levels of inflammatory genes. (**A**) Growth curves of SVF derived from a healthy individual and a patient with WS. (**B**) Comparison of the morphological features of the SVFs. Scale bar, 300 μm. (**C**) Quantification of the telomere length analyzed by quantitative real-time polymerase chain reaction. Data are presented as means ± S.E.M. of three technical replicates. For statistical analysis, student t-test was performed (****$p < 0.0001$). (**D**) Representative images of SA-β-gal staining of SVF. Black arrows indicate SA-β-gal-positive cells. Scale bar, 300 μm. (**E**) Quantitative real-time polymerase chain reaction of the relative expression of senescence-related genes. Data are presented as means ± S.E.M. of three technical replicates. For statistical analysis, student t-test was performed (ns, not significant; ***$p < 0.001$; ****$p < 0.0001$). WS: Werner syndrome; SVF: stromal vascular fraction; SA-β-gal: senescence-associated β-galactosidase.

were decreased in WSVF (Supplementary Figure 3). Moreover, similar results were obtained for WS fibroblasts where the p-Akt/Akt ratio was reduced in WS fibroblasts compared to that in normal fibroblasts (Supplementary Figures 1, 2). These *in vitro* results suggest aggravated insulin resistance in WS.

Rapamycin ameliorates cellular senescence in SVF and extends the life span of *WRN*-knockout *Caenorhabditis elegans*

Rapamycin extends the lifespan of many species by inhibiting the mTOR pathway [17]. Therefore, we used rapamycin as an agent to inhibit cellular senescence. Treatment with rapamycin prolonged the final PDL attained in both HSVF and WSVF (Figure 6A). Moreover, rapamycin rescued the altered morphology of WSVF from swollen and flattened senescent cells to spindle-shaped cells (Figure 6B). In addition, treatment with rapamycin resulted in a significant decrease in SA-β-gal-positive or senescent cells in both HSVF and WSVF ($p < 0.0001$; Figure 6C, 6D).

To investigate the effect of rapamycin on autophagy, we investigated LC3 using western blotting and found that LC3-II/LC3-I [18] expression levels were increased in WSVF (Figure 6E, 6F), suggesting that autophagosome excessively accumulates in WSVF. Treatment with rapamycin further increased LC3-II/I ratio in WSVF. The mTOR and S6K phosphorylation were decreased with the addition of rapamycin in SVF, confirming the general effect of rapamycin (Supplementary Figure 3).

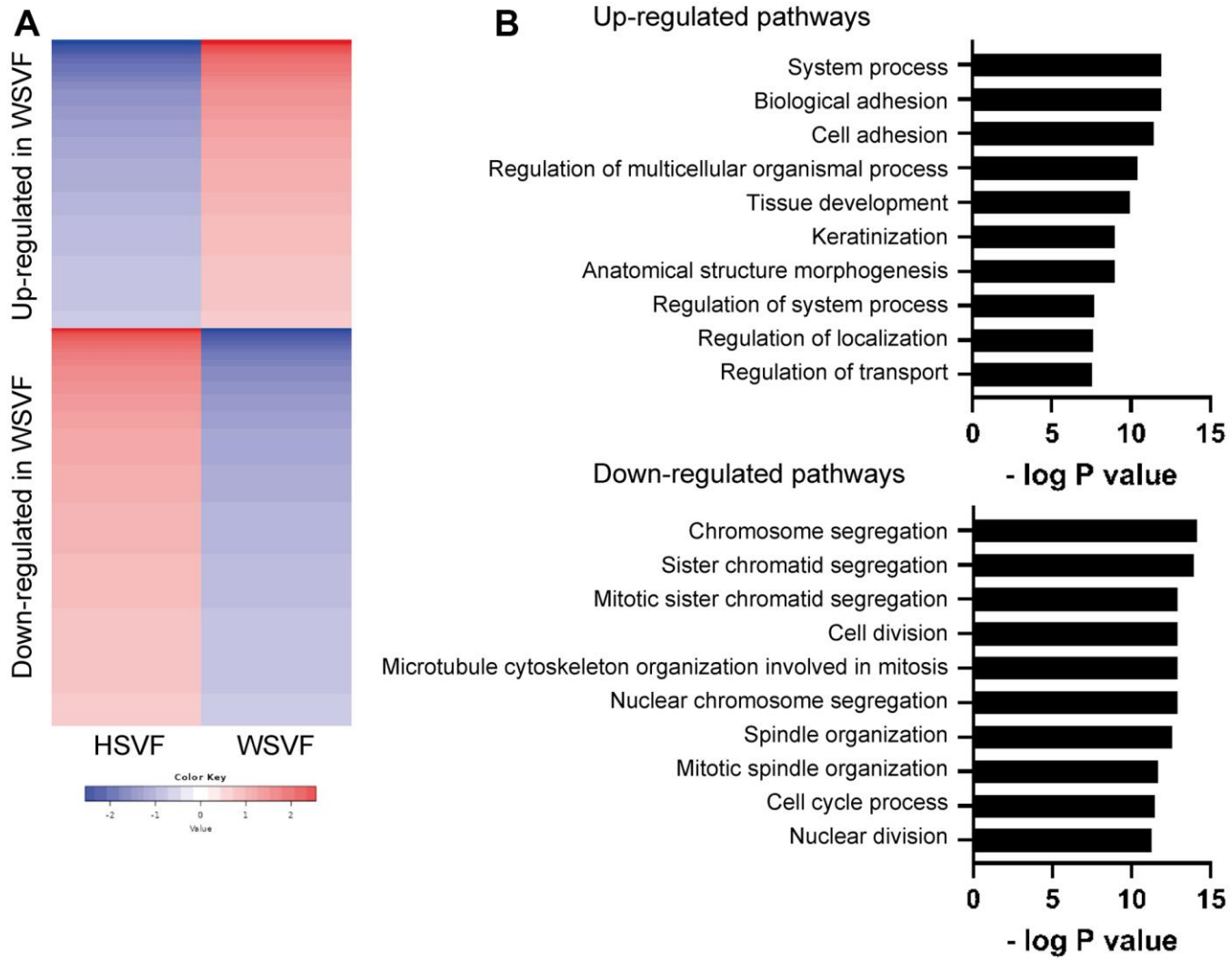

Figure 3. Transcriptome analysis reveals distinct gene expression in WSVF. (**A**) k-means clustering of HSVF and WSVF. (**B**) List of the top ten gene ontology terms and corresponding p values related to Figure 3A. Pathway analysis of the top 2000 transcriptome using GO biological process. WS: Werner syndrome; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy individual; WSVF: SVF derived from a patient with WS.

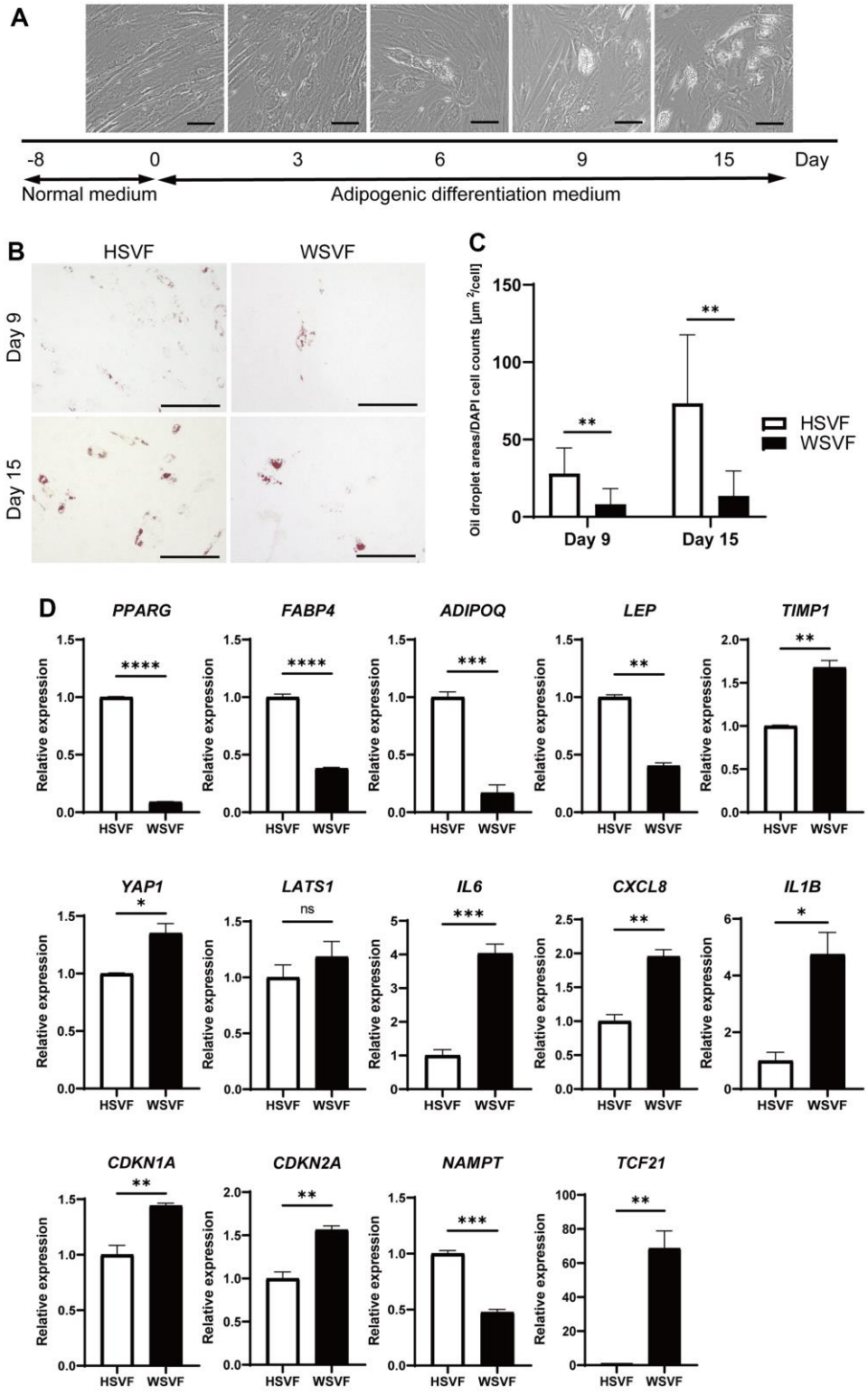

Figure 4. Adipogenesis is suppressed in WS. (**A**) Schematic illustration of the adipogenesis experiment. Representative images on days 0, 3, 6, 9, and 15. Scale bar, 100 μm. (**B**) Representative images of Oil Red O staining on days 9 and 15 after adipogenesis in HSVF and WSVF. Scale bar, 300 μm. (**C**) Quantification of the oil droplet area based on DAPI cell counts. Data are presented as means ± S.E.M. from nine different microscopic views. For statistical analysis, student t-test was performed (**$p < 0.01$). (**D**) Quantitative real-time polymerase chain reaction of the relative gene expression during adipogenesis of three technical replicates. For statistical analysis, student t-test was performed (ns, not significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). WS: Werner syndrome; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy patient; WSVF: SVF derived from a patient with WS.

Rapamycin also restored the p-Akt (S473)/Akt ratio from 55.1% to 191.2% and p-Akt (T308)/Akt ratio from 45.0% to 387.2% in WSVF compared to HSVF under stimulation with insulin (Figure 6G–6I). Moreover, similar results were obtained for WS fibroblasts (Supplementary Figure 2). Furthermore, *in vivo*, 1 μM ($p < 0.01$) and 10 μM ($p < 0.05$) of rapamycin significantly prolonged the life span of *WRN*-knockout *C. elegans* (gk99) (Figure 6J). Moreover, the expression of *daf-16*, a gene repressed by mammalian target of rapamycin complex 1 (mTORC1), increased in gk99 treated with 1 μM and 10 μM of rapamycin on days 4 and 11 ($p < 0.01$) (Figure 6K, 6L). These results suggest that rapamycin rescues cellular senescence and insulin resistance in WSVF, and extends the lifespan of the WS model *in vivo*.

DISCUSSION

The present study revealed for the first time, that a decrease in subcutaneous fat mass to total fat mass ratio was associated with aggravated insulin resistance in patients with WS. We revealed that SVF derived from subcutaneous fat tissues of patients with WS exhibited premature cellular senescence, accompanied by elevated SASP and suppression of adipogenic differentiation *in vitro*. Furthermore, we demonstrated that rapamycin rescues cellular senescence in WSVF and extended the life span of *WRN*-knockout *C. elegans* (gk99) *in vivo*.

Adipose tissue is an insulin-sensitive organ that is important for metabolic homeostasis [19]. Lipodystrophy causes atrophy of the subcutaneous fat in the extremities and is accompanied by severe insulin-resistant diabetes [10]. Patients with WS develop sarcopenic obesity, in which visceral fat accumulates, subcutaneous tissue atrophies, and skeletal muscle loss progresses at a young age [20]. These patients tend to have high blood insulin levels before the onset of diabetes and higher insulin resistance than their peers [12]. Hutchinson-Gilford progeria syndrome, a hereditary premature aging syndrome similar to WS, is also characterized by lipodystrophy in the extremities [21]. Additionally, the general older adult population also exhibits subcutaneous tissue and skeletal muscle loss with age, as well as aggravated insulin resistance [22, 23]. The present study suggests that subcutaneous fat loss, which progresses with age, plays a major role in insulin resistance.

The association between subcutaneous fat atrophy in the extremities and aging is unknown. In the present study, our results suggest that cellular senescence-induced SASP leads to suppressed adipogenesis, ultimately playing a role in subcutaneous fat mass loss. Cellular senescence has been previously demonstrated in fibroblasts derived from patients with WS [24] and in mesenchymal stem cells derived from *WRN*-knockout embryonic stem (ES) cells [25]. In this study, we demonstrated for the first time that cellular senescence also occurs in SVF derived from the subcutaneous fat of patients with WS. Senescent cells secrete inflammatory cytokines and SASPs [26–28], which induce chronic inflammation, promote aging, and contribute to the progression of age-related diseases [29, 30]. Cellular senescence suppresses adipogenesis [31], and SASP acts on adipogenic progenitor cells to inhibit adipogenesis [32], suggesting that WSVF may inhibit its adipogenic differentiation by the autocrine effect of its secreted SASP. Additionally, SVF homogenizes into adipose-derived stem cells by passaging culture [33]; therefore, the cellular senescence of WSVF may reflect aging at the stem cell level. In this study, we observed upregulated

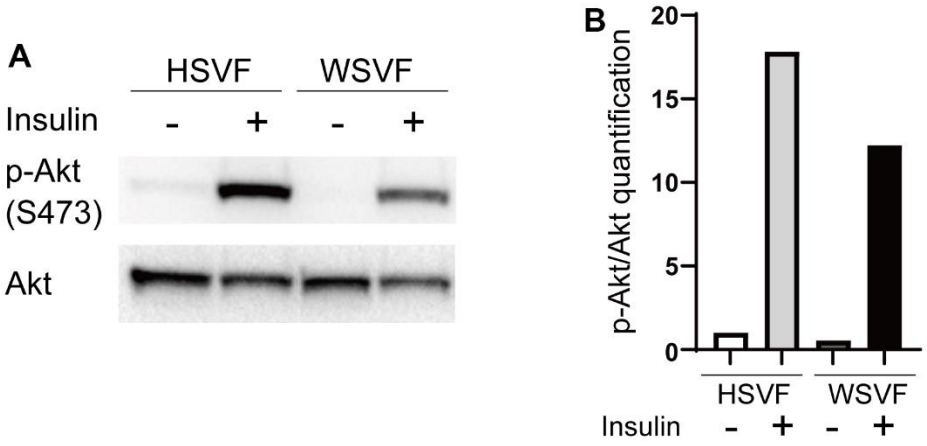

Figure 5. Insulin signaling is decreased in WS. (**A**) Western blotting of p-Akt (S473) and Akt for HSVF and WSVF. (**B**) Quantitative analysis of p-Akt/Akt. WS: Werner syndrome; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy patient; WSVF: SVF derived from a patient with WS.

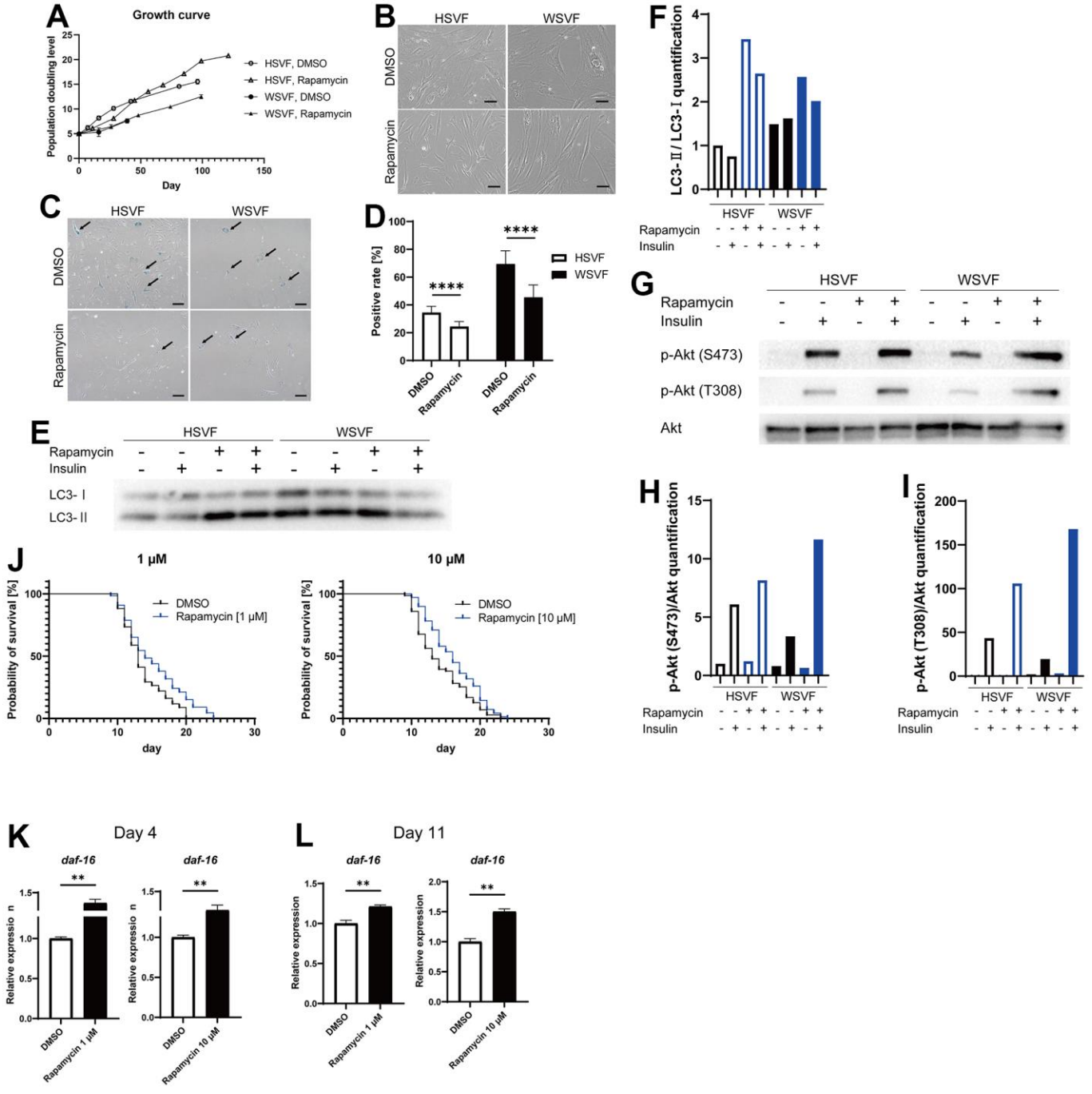

Figure 6. Rapamycin alleviates cellular senescence in SVF. (**A**) Growth curves of HSVF and WSVF treated with rapamycin. (**B**) Morphological changes of the SVFs treated with rapamycin. Scale bar, 100 μm. (**C**) Representative images of SA-β-gal staining of the SVFs treated with rapamycin. Black arrows indicate SA-β-gal-positive cells. Scale bar, 100 μm. (**D**) Quantification of SA-β-gal-positive cells. Data are presented as means ± S.E.M. from nine different microscopic views. For statistical analysis, student t-test was performed (****$p < 0.0001$). (**E**) Western blotting of the protein expression of LC3-I and LC3-II in HSVF and WSVF. (**F**) Quantification of (**E**). (**G**) Western blotting of p-Akt (S473), p-Akt (T308), and Akt in HSVF and WSVF treated with rapamycin. (**H**) Quantitative analysis of p-Akt (S473)/Akt. (**I**) Quantitative analysis of p-Akt (T308)/Akt. (**J**) Survival probability of *WRN*-knockout *C. elegans* (gk99) treated with 1 μM and 10 μM of rapamycin. For statistical analysis, log-rank (Mantel-Cox) test was performed; **$p < 0.01$ compared with DMSO in 1 μM of rapamycin, *$p < 0.05$ compared with DMSO in 10 μM of rapamycin. (**K**, **L**) Quantitative real-time polymerase chain reaction of the relative expression of *daf-16* on days 4 and 11 in gk99 treated with 1 μM and 10 μM of rapamycin. Data are presented as means ± S.E.M. of three technical replicates. For statistical analysis, student t-test was performed (**$p < 0.01$). WS: Werner syndrome; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy patient; WSVF: SVF derived from a patient with WS; SA-β-gal: senescence-associated β-galactosidase; mTORC1: mammalian target of rapamycin complex 1.

expression levels of *YAP1* and *TIMP1*, which are known to suppress adipogenesis [13, 14]. Telomere dysfunction activates YAP and induces inflammation [34]. Moreover, nucleotide excision repair-deficient mice develop adipose loss due to chronic inflammation [35], and *WRN*-deficient ES cells exhibit suppressed adipogenesis [36]. Collectively, these findings suggest that SASP induced by a defective DNA damage response suppresses subcutaneous fat differentiation in the extremities, causing lipodystrophy in WS.

A decrease in the quality of the remaining subcutaneous adipocytes might occur in patients with WS. Cellular senescence leads to insulin resistance in adipocytes [37], and suppression of senescent cells accumulated in adipose tissues by blocking TP53 improves insulin resistance [38]. In the present study, we observed reduced insulin signaling in both WF fibroblasts and WSVF, which is consistent with a previous study reporting reduced insulin signaling in WS fibroblasts [39]. We also observed decreased expression of adipokine genes such as leptin and adiponectin. Leptin is decreased in lipoatrophy, and leptin supplementation improves insulin resistance [40]. A recent case report reported the efficacy of leptin supplementation in WS [41]. In addition, subcutaneous fat has been reported to increase with improved glucose tolerance when troglitazone is administered to patients with type 2 diabetes [42]. Pioglitazone also improves insulin resistance, fat distribution, and adipokine abnormalities in WS [43, 44] and Cockayne syndrome, another form of premature aging [45]. Therefore, in addition to the control of subcutaneous fat mass, improvement of the quality or function of subcutaneous adipocytes is important to treat insulin resistance in WS (Figure 7).

The mTOR pathway is one of the pathways involved in the molecular pathogenesis of premature aging [46]. Rapamycin has been reported to extend the lifespan of various organisms by inhibiting the mTOR pathway [17, 47, 48], and its effectiveness has also been demonstrated in *WRN*-deficient human fibroblasts [49]. The previous report also showed that rapamycin treatment reduced the accumulation of DNA damage due to the clearance of damaged proteins in WRN-deficient human fibroblasts [49]. Our results may suggest that autophagosome excessively accumulates in WSVF and that treatment with rapamycin alleviates this state. We also revealed for the first time that rapamycin extends the lifespan of *WRN*-knockout *C. elegans* (gk99), demonstrating its potential therapeutic application in WS. *daf-16* is a gene corresponding to human *FOXO*, which is repressed by mTORC1. *daf-16* is activated by rapamycin which suppresses mTORC1. Activated *daf-16* is involved in life span extension [50]. In this study, the gene expression of *daf-16* was upregulated in gk99 treated with 1 μM and 10 μM of rapamycin on days 4 and 11, supporting that treatment with rapamycin contributed to the prolongation of the lifespan in WS model of *C. elegans*. Additionally, rapamycin not only alleviates senescence but also improves adipogenic differentiation [51, 52] and insulin

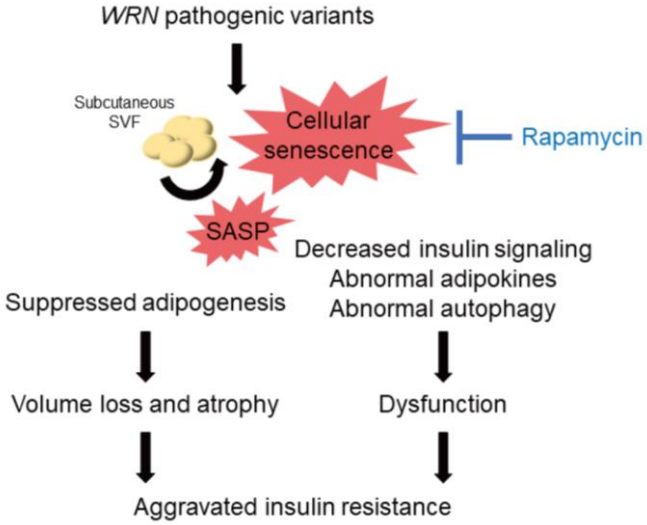

Figure 7. Schematic illustration of the lipodystrophy and insulin resistance exhibited by patients with WS. The genomic repair defect caused by pathogenic variants of the *WRN* gene leads to chronic inflammation and cellular senescence, resulting in inhibition of adipogenesis and dysfunction of adipocytes, leading to subcutaneous fat mass and quality loss, which in turn leads to subcutaneous fat atrophy and insulin resistance in patients with WS. WS: Werner syndrome; SVF: stromal vascular fraction; SASP: senescence-associated secretory phenotypes.

resistance [53]. Therefore, regulation of the mTOR pathway is a promising therapeutic target for cellular senescence, subcutaneous fat atrophy, and dysfunction in WS (Figure 7).

The Akt-mediated insulin signaling pathway and the mTOR pathway may be depicted as a series of pathways, but they may be complexly related by interactive cross-talk and feedback effects [54–56]. While there is a report that rapamycin extended the life span of *C. elegans* by activating daf-16 [50], some reports indicates that rapamycin increases insulin signaling [57–59], and the increased insulin signaling may assumingly suppress *daf-16* and its orthologs [56]. Moreover, a previous report suggested that rapamycin directly activates lysosomal function independent of mTOR [60]. It is speculated that rapamycin may have multiple points of effect on multiple pathways via mTOR inhibition or in mTOR-independent manner.

This study has several limitations. First, although WS is a rare disease, the number of cases in which insulin resistance was assessed using glucose clamping was limited. Moreover, WSVF was difficult to obtain, which restricted the amount of data and experiments that could be performed. However, only factors with robust changes of 2-fold or more were analyzed using RNA-seq. Future studies using patient-derived iPS-driven differentiated adipocytes are needed to validate our results. Moreover, visceral adipose-derived SVF was not analyzed because of the unavailability of samples. Further studies comparing visceral fat-derived SVF and subcutaneous SVF are needed to reveal the cause of insulin-resistant diabetes in WS to determine the phenotypic differences based on the regions of the adipose tissue.

MATERIALS AND METHODS

Clinical patient data and hyperinsulinemic-euglycemic clamp test

Physical examination, fat distribution, and insulin resistance were evaluated in four patients with WS. Physical examination included BMI and SMI. Abdominal CT was used to assess fat distribution, including visceral, and subcutaneous fat areas. The hyperinsulinemic-euglycemic clamp test was used to assess insulin resistance. The insulin infusion rate was maintained at 1.25 mU/kg/min, and the glucose infusion rate was measured.

Establishment of SVF and cell culture

Subcutaneous adipose tissue was obtained from one healthy individual (a 64-year-old woman) and one patient with WS (a 47-year-old woman). The adipose tissue derived from the patient with WS was transplanted from the abdominal subcutaneous fat to the lower extremities, and the remainder was used for this study. The adipose tissue derived from the healthy individual was used for fat reduction surgery, and the remainder was used in this study. SVF was isolated and established from adipose tissues. Cell culture was performed with DMEM (043-30085, Wako Pure Chemical, Osaka, Japan) supplemented with 10% fetal bovine serum (FBS, 10270106; Gibco, Thermo Fisher Scientific, Waltham, MA, USA) and antibiotic-antimycotic (15240062, Gibco) in humidified 5% CO_2 air. Collagen-type I-coated cell culture plates (4810-010; AGC TECHNO GLASS Co., Ltd., Shizuoka, Japan) were used. The medium was changed every two days. When sub-confluency was reached, cells were passaged at a 1:4 split ratio until growth arrest, and population doubling level was calculated as previously described [24].

Quantitative polymerase chain reaction

RNA was extracted and reverse-transcribed as previously described [61]. TaqMan Gene Expression Assays for IL6 (Hs00174131_m1), CXCL8 (Hs00174103_m1), CDKN1A (Hs00355782_m1), CDKN2A (Hs00923894_m1), FABP4 (Hs01086177_m1), CEBPA (Hs00269972_s1), ADIPOQ (Hs00605917_m1), LEP (Hs00174877_m1), TIMP1 (Hs00171558_m1), YAP1 (Hs00902712_g1), LATS1 (Hs01125524_m1), IL1B (Hs01555410_m1), NFKB1 (Hs00765730_m1), NAMPT (Hs00237184_m1), TCF21 (Hs00162646_m1), daf-16 (Ce02422838_m1), GAPDH (Hs02786624_g1), and rps-23 (Ce02465854_g1) were purchased from Applied Biosystems (Thermo Fisher Scientific). Quantification was performed using the Ct method with GAPDH and rps-23 as an internal control. Telomere length analysis was performed by qPCR using SYBR Green PCR Master Mix (Applied Biosystems).

SA-β-gal staining

The Senescence β-Galactosidase Activity Assay Kit (fluorescence, plate-based; #23833; Cell Signaling Technology, Danvers, MA, USA) was used for SAβgal staining according to the manufacturer's protocol. Cells were stained overnight at 37° C in a room CO_2 incubator air. The cells were washed with phosphate-buffered saline (PBS) (−) and stained with Hoechst 33342 (H342; Dojindo, Kumamoto, Japan). Imaging and quantification of stains were performed using a BZ-X700 microscope (Keyence, Osaka, Japan).

Transcriptomic analysis

For transcriptomic analysis, mRNA was extracted from the SVF at PDL 10. RNA sequencing was

performed at the Kazusa DNA Research Institute. The obtained CSV file data were analyzed using iDEP (http://bioinformatics.sdstate.edu/idep/) as previously described [62]. Gene clustering was performed by analyzing the top 2,000 genes with variable expression using k-means.

Adipose differentiation and Oil Red O staining

SVF was cultured in DMEM (043-30085, Wako) supplemented with 10% FBS (10270106, Gibco) and antibiotic-antimycotic (15240062, Gibco) to full confluency. The day the medium was changed to adipogenic differentiation medium (A10070-01, StemPro® Adipogenesis Differentiation Kit; Gibco) was designated day 0. SVF at PDL 10 was used. Oil Red O staining (Sigma-Aldrich, St. Louis, MO, USA) was performed on days 9 and 15 of cell differentiation. The staining was quantified using a BZ-X700 microscope (Keyence).

Western blotting

Cultured cells were collected in Laemmli buffer, heated to 95° C, and proteins were extracted. Western blotting was performed according to standard protocols, and images were captured using ChemiDoc (Bio-Rad Laboratories, Hercules, CA, USA). Primary antibodies against GAPDH (D16H11, XP® Rabbit mAb, CST, #5174), phospho-Akt (Ser473, D9E XP® Rabbit mAb, CST, #4060), Akt (Antibody Rabbit, CST, #9272), LC3A/B (Antibody Rabbit, CST, #4108), phospho-Akt (Thr308, C31E5E Rabbit mAb, CST, #2965), IRS-1 (Antibody Rabbit, CST, #2382), PI3 Kinase p85 (19H8, Rabbit mAb, CST, #4257), phospho-mTOR (Ser2448, Antibody Rabbit, CST, #2971), mTOR (Antibody Rabbit, CST, #2972), phospho-p70 S6 Kinase (Thr421/Ser424, Antibody Rabbit, CST, #9204), and p70 S6 Kinase (49D7, Rabbit mAb, CST, #2708) were purchased from Cell Signaling Technology. The primary antibodies were diluted to 1:1000. GAPDH and Ponceau-S staining solutions (BCL-PSS-01, Beacle, Inc., Kyoto, Japan) were used as the internal standards.

The secondary antibody, anti-rabbit IgG, HRP-linked whole antibody donkey (#NA934), was purchased from GE Healthcare (Chicago, IL, USA) and diluted to 1:2500. Band quantification was performed using ImageJ Macro, Band/Peak Quantification Tool (https://dx.doi.org/10.17504/protocols.io.7vghn3w).

Insulin stimulation experiments

The SVF of PDL 7 was used for the insulin stimulation experiments. Serum starvation was performed for 24 h, followed by insulin stimulation for 15 min. The cells were immediately washed twice with PBS on ice and then collected in Laemmli buffer heated to 95° C.

Treatment with rapamycin

Rapamycin (100 nM; LC Laboratories, Woburn, MA, USA) with DMSO (Wako Pure Chemicals) as the solvent was added to DMEM (043-30085, Wako Pure Chemicals) supplemented with 10% FBS (10270106, Gibco) and antibiotic-antimycotic (15240062, Gibco). The control was a medium supplemented with DMSO diluted to the equivalent concentration. The medium was changed every two days. Cells were subjected to SAβgal staining and RNA analysis using the methods described above.

Life span of *C. elegans* treated with rapamycin

WRN-knockout *C. elegans*, wrn-1 (gk99), was provided as a gift from Dr. Bohr (Biomedical Research Center, Lab. of Molecular Gerontology, National Institute of Aging, Baltimore, MD, USA) [63]. Gk99 was maintained at 23° C as previously described [64].

Age-synchronized nematodes were prepared as previously described [65]. Nematodes were placed on nematode growth media (NGM) plates seeded with *Escherichia coli* OP50 previously described protocols [50]. The day of hatching was set as day 1, and 100 μM 5-fluoro-2′-deoxyuridine (FudR) was added on days 3 and 4, which corresponded to the L4 stage to suppress reproductive function. Rapamycin (LC Laboratories) dissolved in DMSO (Wako Pure Chemicals) was added to the nematode culture medium at final concentrations of 1 μM and 10 μM, and nematodes were reared from day 1, according to previously described protocols [50]. The control plates contained an equivalent concentration of DMSO. The probability of survival of approximately 60 nematodes in a rapamycin-supplemented medium was compared to that of 60 nematodes in the equivalent DMSO-supplemented medium.

Abbreviations

WS: Werner syndrome; BMI: body mass index; SMI: skeletal muscle mass index; TFA: total fat area; VFA: Visceral fat area; SFA: subcutaneous fat area; V/S ratio: VFA/SFA ratio; S/T ratio: SFA/TFA ratio; GIR: glucose infusion rate; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy individual; WSVF: SVF derived from a patient with WS; SASP: senescence-associated secretory phenotype; mTOR: mammalian target of rapamycin; CT: computed tomography; PDL: population doubling level; SA-β-gal: senescence-associated β-galactosidase; GO: gene ontology; NF: fibroblasts from a normal individual; WF: fibroblasts

from a patient with WS; mTORC1: mammalian target of rapamycin complex 1; ES cells: embryonic stem cells; NGM: nematode growth media.

AUTHOR CONTRIBUTIONS

D. Sawada, H. Kato, D.K., Y. Maezawa, and K.Y. designed the study. D. Sawada, H. Kato, H. Kaneko, and Y. Maezawa analyzed the data, and wrote the manuscript; D. Sawada, H. Kato, H. Kaneko, S.F., T.M., A.T-W, and R.N. performed the experiments; D. Sawada, and H. Kaneko created the figures and table; H. Kaneko, D.K., A. Takasaki, K.I., and M.K. conducted the euglycemic hyperinsulinemic glucose clamp experiments; Y.E. conducted transcriptome analysis; T.M., M.K., K.A., A. Yamaguchi, N.T., Y. Maeda, T.O., A.H., K.I., S.I., M.S., T.K., A.I., Y.O., N.T., K.E., K.F., T.T., T.S., and H.H. discussed the data; H. Kato, H. Kaneko, D.K., T.M., M.K, H.O., Y.K., N.M., and Y. Maezawa performed the sampling from patients; all authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL STATEMENT AND CONSENT

Written informed consent was obtained from the study participants to conduct and publish this study, which was approved by the Institutional Ethics Review Board of the Chiba University Graduate School of Medicine (IRB-1145 [1029]).

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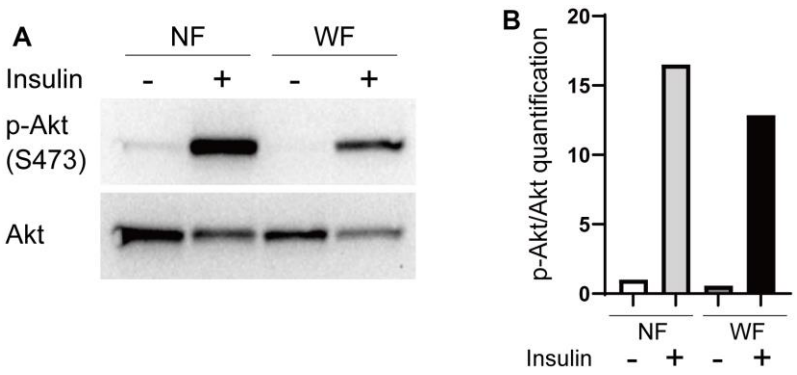
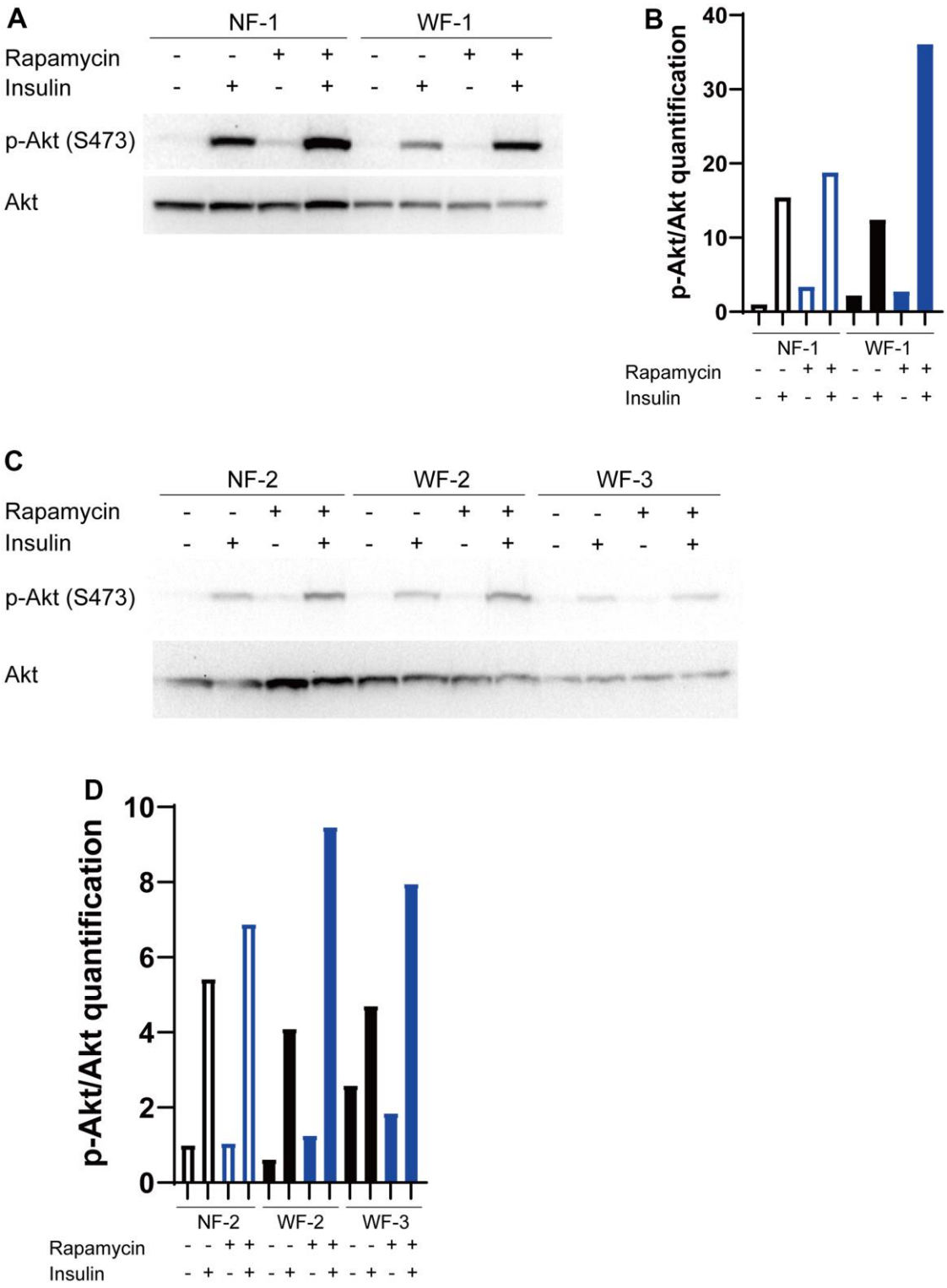
SUPPLEMENTARY MATERIALS

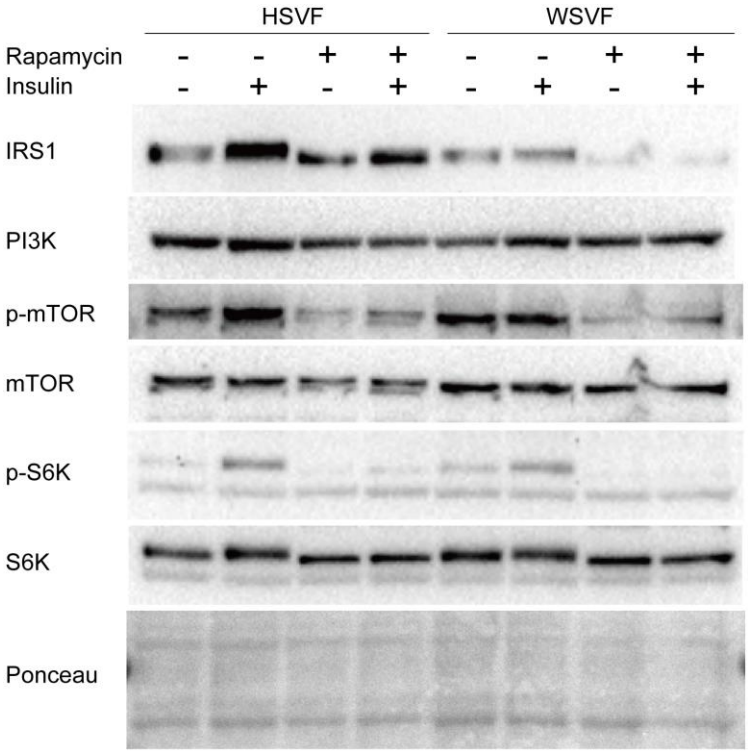
Supplementary Figures



Supplementary Figure 1. Insulin signaling is decreased in WF. (**A**) Western blotting of p-Akt (S473) and Akt in NF and WF. (**B**) Quantitative analysis of p-Akt/Akt. NF: fibroblasts from a normal individual; WF: fibroblasts from a patient with WS; WS: Werner syndrome.



Supplementary Figure 2. Rapamycin alleviates decreased insulin signaling in WF. (**A**) Western blotting of p-Akt (S473) and Akt in NF-1 and WF-1 treated with rapamycin. (**B**) Quantitative analysis of p-Akt/Akt in NF-1 and WF-1. (**C**) Western blotting of p-Akt (S473) and Akt in NF-2, WF-2, and WF-3 treated with rapamycin. (**D**) Quantitative analysis of p-Akt/Akt in NF-2, WF-2, and WF-3. NF: fibroblasts from a normal individual; WF: fibroblasts from a patient with WS; WS: Werner syndrome.



Supplementary Figure 3. Western blotting of IRS1, PI3K, p-mTOR, mTOR, p-S6K, and S6K for HSVF and WSVF. WS: Werner syndrome; SVF: stromal vascular fraction; HSVF: SVF derived from a healthy patient; WSVF: SVF derived from a patient with WS.

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ORIGINAL ARTICLE

BIOLOGY

Sex differences in symptom presentation and their impact on diagnostic accuracy in Werner syndrome

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Aim: Whether sex differences exist in hereditary progeroid syndromes remains unclear. In this study, we investigated sex differences in patients with Werner syndrome (WS), a model of human aging, using patient data at the time of diagnosis.

Methods: The presence of six cardinal signs in the diagnostic criteria was retrospectively evaluated.

Results: We found that the percentage of patients with all cardinal signs was higher in males than in females (54.2% vs. 21.2%). By the age of 40 years, 57.1% of male patients with WS presented with all the cardinal signs, whereas none of the female patients developed all of them. In particular, the frequency of having a high-pitched, hoarse voice, a characteristic of WS, was lower in female patients. The positive and negative predictive values for clinical diagnosis were 100% for males and females, indicating the helpfulness of diagnostic criteria regardless of sex. More female patients than male (86.7% vs. 64%) required genetic testing for their diagnosis because their clinical symptoms were insufficient, suggesting the importance of genetic testing for females even if they do not show typical symptoms of WS. Finally, the frequency of abnormal voice was lower in patients with WS harboring the c.3139-1G > C homozygous mutation.

Conclusion: These results indicate, for the first time, that there are sex differences in the phenotypes of hereditary progeroid syndromes. The analysis of this mechanism in this human model of aging may lead to the elucidation of sex differences in the various symptoms of normal human aging. **Geriatr Gerontol Int 2024; 24: 161–167**.

Keywords: abnormal voice, clinical diagnosis, diagnostic criteria, sex differences, Werner syndrome.

Introduction

As the world population ages, the interest in age-related diseases is growing. In recent years, it has become evident that age-related diseases such as atherosclerotic, metabolic, and neurodegenerative diseases exhibit sex differences.[1,2] Sex differences in life expectancy and healthy life expectancy have been recognized worldwide.[3]

Werner syndrome (WS) is a typical progeroid syndrome in which various signs of aging appear after puberty. It has attracted attention as a model of human aging. It is inherited as an autosomal recessive trait, and various aging phenomena, such as gray hair, bilateral cataracts, diabetes, arteriosclerosis, and skin ulcers, develop at an early age. The number of patients with WS in Japan is estimated to be 700–2000, and 60% of the world's patients have been reported in Japan. The syndrome is caused by a mutation in the *WRN* gene, which encodes a RecQ helicase on chromosome 8. The pathogenesis of this syndrome involves reduced DNA damage repair, telomere shortening, chronic inflammation, mitochondrial dysfunction, and epigenetic changes.[4–6] However, it remains unclear whether sex differences are observed in WS.

The main "cardinal" signs of WS are progeroid changes in the hair; bilateral cataracts; skin changes; intractable skin ulcers; calcification of the Achilles tendon; a birdlike face; and a high-pitched, hoarse voice. According to the 2012 Japanese WS Diagnostic Criteria, the syndrome can be diagnosed on the basis of clinical symptoms alone when all six "cardinal" signs are present. When some of the six signs are not present, a genetic diagnosis is required (Table 1).[7] However, whether sex differences exist in the frequency and timing of these aging symptoms remains unclear. Moreover, the usefulness of these diagnostic criteria and whether they are useful for both male and female patients have not been verified. Recently, the recognition of WS has increased, and the life expectancy of patients has increased from 40 to 59 years.[8,9] Accordingly,

Table 1 Diagnostic criteria for Werner syndrome 2012

I. Cardinal signs and symptoms (onset occurring after the age of 10 years until 40 years)	
1. Progeroid changes of hair	Gray hair, baldness, etc.
2. Cataract	Bilateral
3. Changes of skin, intractable skin ulcers	Atrophic skin, tight skin, clavus, callus
4. Soft-tissue calcification	Achilles tendon, etc.
5. Birdlike face	
6. Abnormal voice	High-pitched, squeaky, hoarse voice
II. Other signs and symptoms	
1. Abnormal glucose and/or lipid metabolism	
2. Deformation and abnormality of the bone	Osteoporosis, etc.
3. Malignant tumors	Nonepithelial tumors
4. Parental consanguinity	
5. Premature atherosclerosis	Angina pectoris, myocardial infarction
6. Hypogonadism	
7. Short stature and low body weight	
III. Genetic testing	

Addendum: Mental retardation is seldom observed in patients with Werner syndrome, and their cognitive function is often appropriate for their age. Confirmed: Presence of all cardinal signs or confirmation of biallelic *WRN* mutations and at least three cardinal signs. Suspected: Presence of both I-1 (progeroid changes in hair) and I-2 (cataracts) in conjunction with at least two signs or symptoms other than I or II.

it is assumed that the age and symptoms of patients are more diverse than when the diagnostic criteria were established.

Therefore, we investigated whether there are sex differences in the aging progression of WS by examining the positivity ratio and timing of the appearance of the cardinal signs. We also investigated the validity of the current diagnostic criteria in both male and female patients.

Methods

We evaluated the clinical symptoms described in the referral letters of patients whose primary physicians suspected WS and requested genetic diagnosis at Chiba University Hospital. A total of 170 patients whose requests were received from 2009 to January 2022 were included, and a genetic diagnosis was performed for all patients. Clinical manifestations, especially the cardinal signs of WS and age, were evaluated on the basis of the time when the genetic diagnosis was performed. Clinical symptoms were independently reviewed by two physicians with experience in treating patients with WS. We excluded 78 patients for whom the clinical classification could not be determined because of insufficient information about symptoms in the referral letters. Ultimately, we analyzed the symptoms and genetic results of 92 patients.

Analysis was performed using Pearson's chi-squared test, and a P-value of <0.05 was considered statistically significant. This study was approved by the Ethics Committee of Chiba University Hospital (approval no. 1145 on October 21, 2021) and conducted in accordance with the Declaration of Helsinki.

Results

Of the 170 patients with suspected WS who were referred to our hospital between 2009 and 2022, 92 with detailed clinical data available were included. Of the 92 patients in the study, 48 (52.2%) were men and 44 (47.8%) were women. They had a median age at genetic diagnosis of 44.5 years (interquartile range [IQR], 40–51 years), with a median age at genetic diagnosis for men of 43.5 years (IQR, 39.8–50 years) and 45.5 years (IQR, 40–52.3 years) for women. The patients were divided into three categories according to the clinical components of the diagnostic criteria. The "definite" category included patients with all the cardinal signs. The "probable" category included those with three cardinal signs or those who had hair changes and cataracts plus at least two more signs. The "excluded" category consisted of patients who did not meet the criteria for the first two categories. All the patients with positive genetic test results were diagnosed with WS.

First, we examined the categories of clinical diagnoses according to the sex of the patients who had a positive genetic test. The proportion of clinically definite was 19 of 35 (54.2%) men and 7 of 33 (21.2%) women, indicating that male patients with WS were significantly more likely to have all the cardinal signs than female patients ($\chi^2[1] = 7.867$; $P = 0.0050$; $\varphi = 0.340$; Fig. 1a). When comparing patients with WS who were aged < 40 years, 4 of 7 (57.1%) men were definite, whereas none of the six women were definite ($\chi^2[1] = 4.952$; $P = 0.026$; $\varphi = 0.617$; Fig. 1b). Furthermore, we evaluated the age distribution of definite and probable male and female patients (Fig. 1c). The histogram shows that male patients with WS tend to develop all the cardinal signs in their 40th year, whereas many female patients lacked some of the cardinal signs and were categorized as probable until their 50s. These results suggest that men with WS are more likely to develop all the cardinal signs earlier than women.

We examined the positivity ratio (number of patients with clinical symptoms/number of patients who underwent the examination) and inspection ratio (number of patients who underwent the examination/total number of patients) for each cardinal sign in patients with WS (Table 2). The positivity ratio for abnormal voice was as low as 73.2% among the patients with definite WS and only 50% for clinically probable patients. In addition, the positivity ratio for abnormal voice was lower in female patients (15/26 [57.7%]) than in male patients (26/30 [86.7%]; $\chi^2[1] = 5.963$; $P = 0.015$; $\varphi = 0.326$). The positivity ratio of abnormal voice in male patients in their 20s, 30s, and 40s was 100%, 100%, and 92.3%, respectively. In comparison, the positivity ratio for female patients in their 20s, 30s, and 40s was 0%, 50%, and 69.2%, respectively ($\chi^2[1] = 4.690$; $P = 0.016$; $\varphi = 0.685$; Fig. 2a; Table S1.). Comparison of male and female patients aged <40 years showed that seven of seven male patients and only one of three female patients were positive for abnormal voice (Fig. 2b). Thus, female patients with WS showed delayed development of abnormal voice.

To validate the accuracy of diagnostic criteria for both sexes, we compared the categories of clinical diagnoses, with a positive genetic test as a confirmed diagnosis (Table 3). Of the 26 patients categorized as definite, all 26 were confirmed to have WS on genetic testing. For the 11 excluded patients, the genetic test was negative in all, demonstrating remarkable concordance between the clinical category and genetic test. Two of the excluded patients had a non-Werner genetic progeroid disease. One patient had atypical WS with generalized lipodystrophy and a de novo heterozygous *LMNA* p.T10I mutation.[10] One patient harbored a *POLD1* mutation. Both patients were diagnosed as non-WS because of the absence of cataracts.

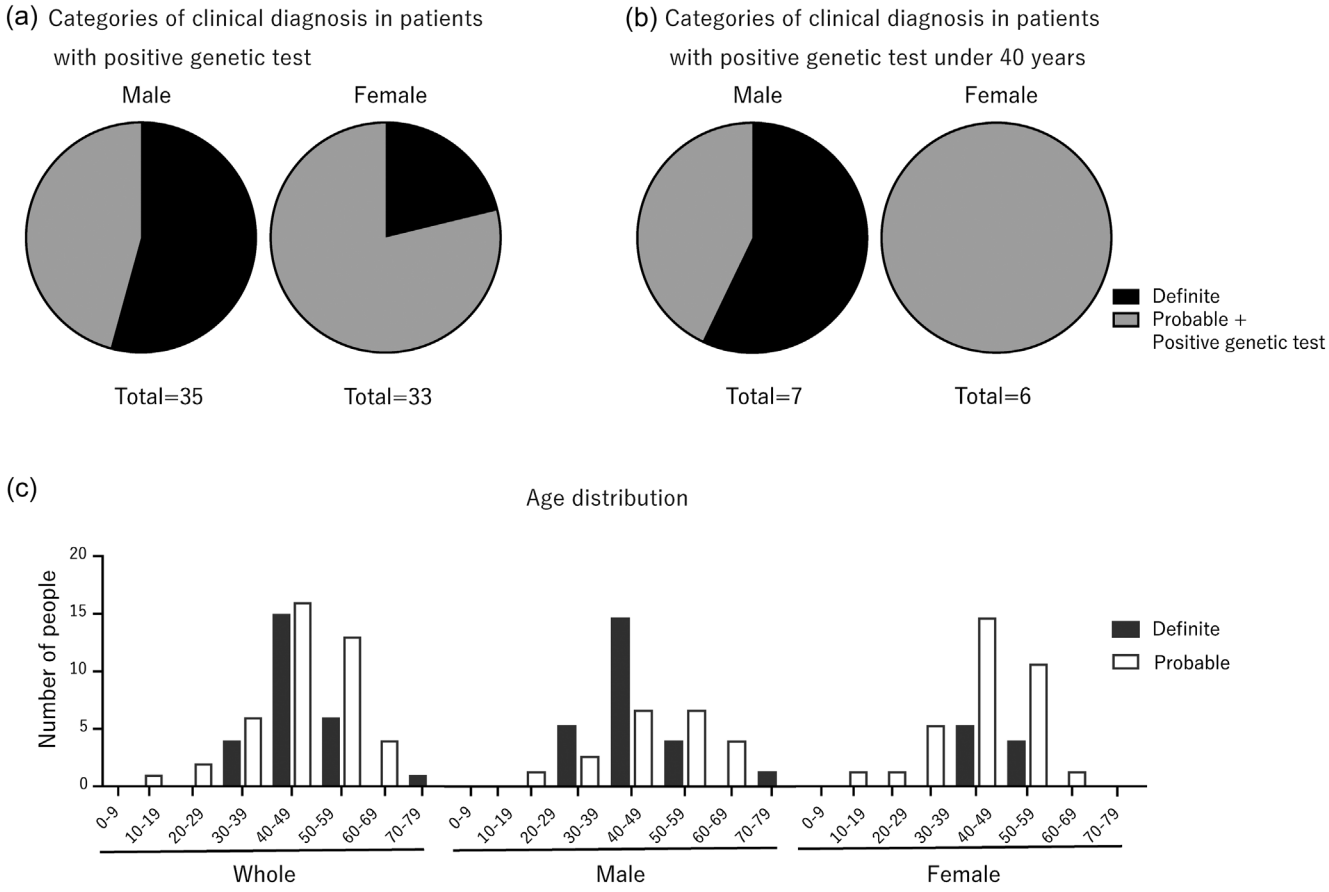

Figure 1 (a) Categories of clinical diagnosis in patients with positive genetic test. (b) Categories of clinical diagnosis in patients with positive genetic test <40 years of age. (c) Age distribution of definite and probable patients by sex in genetically positive patients.

Table 2 Positivity ratios and inspection ratios for each cardinal sign of genetic test-positive patients

		Progeroid changes of hair	Cataracts	Changes of skin, intractable skin ulcers	Achilles tendon calcification	Birdlike face	Abnormal voice
Overall	Positivity ratio	98.4 (60/61)	98.5 (64/65)	94 (63/67)	96.4 (53/55)	93.1 (54/58)	73.2 (42/56)
	Inspection ratio	89.7 (61/68)	95.6 (65/68)	98.5 (67/68)	80.9 (55/68)	85.3 (58/68)	82.4 (56/68)
Probable	Positivity ratio	97.1 (34/35)	97.4 (38/39)	88.1 (37/42)	78.1 (25/32)	87.5 (28/32)	50 (15/30)
	Inspection ratio	83.7 (36/43)	92.9 (39/42)	97.6 (41/42)	76.2 (32/42)	76.2 (32/42)	71.4 (30/42)
Male	Positivity ratio	96.9 (31/32)	100 (34/34)	94.1 (32/34)	96.6 (28/29)	96.7 (29/30)	86.7 (26/30)
	Inspection ratio	91.4 (32/35)	97.1 (34/35)	97.1 (34/35)	82.9 (29/35)	85.7 (30/35)	85.7 (30/35)
Female	Positivity ratio	100 (29/29)	96.8 (30/31)	93.9 (31/33)	96.2 (25/26)	89.3 (25/28)	57.7 (15/26)
	Inspection ratio	87.9 (29/33)	93.9 (31/33)	100 (33/33)	78.8 (26/33)	84.8 (28/33)	78.8 (26/33)

Positivity ratio % (number of patients with clinical symptoms/number of patients who underwent the examination).

Inspection ratio % (number of patients who underwent the examination/total number of patients).

Of the 55 clinically probable patients, 42 (76.4%) were positive on genetic testing (Table 3A). When examined by sex, the positive and negative predictive values for "definite" and "excluded" by clinical symptoms were 100.0% for both men and women (Table 3B,C). Among the probable patients, the positivity ratio of the genetic test was 64.0% in men (16/25 patients) and 86.7% in women (26/30 patients) (Table 3B,C) ($\chi^2[1] = 3.882$; $P = 0.049$; $\varphi = 0.071$). Given that the current diagnostic criteria were revised in 2012, we selected 81 patients who were diagnosed after establishment of the current diagnosis and examined the validity of the diagnostic criteria (Table S2A–C). We found positive and negative predictive values were 100%, even when restricted from 2012 to 2022.

An abnormal voice and a "birdlike face" can be a subjective sign. Therefore, we examined the accuracy of the diagnoses when either an abnormal voice (Table S3A) or a birdlike face (Table S3B) was deleted from the cardinal signs and when both were deleted (Table S3C). First, when the abnormal voice was

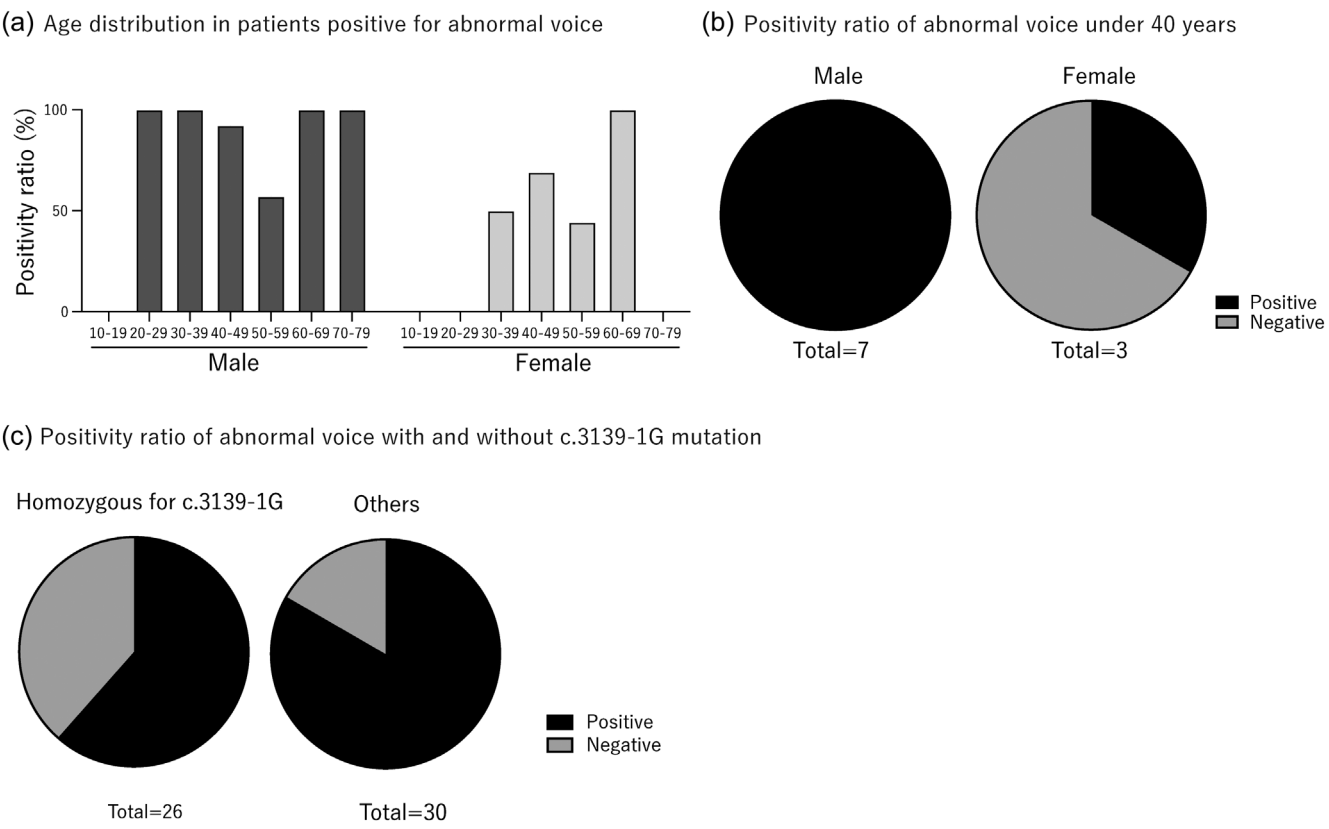

Figure 2 (a) Age distribution in patients positive for abnormal voice. (b) Positivity ratio of abnormal voice <40 years. (c) Positivity ratio of abnormal voice with and without the c.3139-1G mutation homozygous for c.3139-1G.

deleted from the cardinal signs, the positive predictive value was 100%; however, the negative predictive value was reduced to 91.7%. Similarly, when the birdlike face was deleted, the positive predictive value was 100%, but the negative predictive value was reduced to 85.7%. Finally, when both were deleted, the positive predictive value was 100%, and the negative predictive value was reduced to 78.9% (Table S3A–C). These results indicate the necessity of including the birdlike face and abnormal voice for the accuracy of the criteria.

Finally, we examined other factors that affect the frequency of abnormal voices and found that the site of the gene mutation was associated with its presence. More than 80 *WRN* mutations have been reported, of which c.3139-1G > C is the most frequent in Japanese patients with WS.[11] In this study, of the 68 patients with a positive genetic test, clinical data on abnormal voice were available for 56. We analyzed the association between homozygosity for the c.3139-1G > C mutation and the presence of an abnormal voice. The results showed that patients homozygous for c.3139-1G > C exhibited an abnormal voice less frequently ($\chi^2[1] = 5.482$; $P = 0.019$; $\chi = 0.313$) (Fig. 2c), and the proportion of homozygosity did not differ between sexes ($\chi^2[1] = 0.249$; $P = 0.618$; $\chi = 0.067$). The actual number of patients is shown in Table S4. Therefore, the site of the genetic mutation influences the occurrence of abnormal voices.

Discussion

In this study, we demonstrated that the main symptoms of WS appear earlier and more frequently in males. In addition, we showed that the characteristic high-pitched, hoarse voice is less frequent in women, especially in patients with the c.3139-1G > C homozygous founder mutation. This is the first report of sex differences in hereditary progeroid syndromes caused by a single gene mutation and provides a new perspective on the similarities between general aging and genetic progeroid syndromes. We also revealed, for the first time, that the phenotype of WS differs depending on genetic mutations. This provides new insight into the partial functionality of the WRN mutant protein, contrary to the conventional view that the symptoms of WS are the same regardless of the genetic mutation.

As average life expectancy increases, interest in sex differences in longevity and age-related diseases, such as metabolic syndrome and atherosclerosis, is increasing.[12,13] However, Goto *et al.*, in their 1966 to 2004 study of 1019 Japanese patients with WS, reported an average life expectancy of 51.9 years for women compared to 53.6 years for men, with no sex difference.[14] However, in that study, most patients were diagnosed only clinically, and a genetic confirmation was not obtained.[14] There have been no reports concerning sex differences in other progeroid syndromes, including Hutchinson–Gilford progeria and Cockayne syndromes.[15,16] This study shows, for the first time, the sex differences in hereditary progeroid syndromes using patient data with a genetically confirmed diagnosis.

In general, women live longer than men. Mitochondrial dysfunction and shortened telomeres have been reported as hallmarks of aging,[17] and women have longer telomeres and greater amounts of mitochondrial DNA.[18] In addition, postmenopausal women who receive estrogen supplementation have lower epigenetic age and reduced cardiac disease and total mortality.[19] Furthermore,

Table 3 Definite cutoff.

A. Results of genetic testing for each clinical diagnosis group				
			Positive	Negative
Clinical symptoms		Definite	26	0
		Probable	42	13
		Excluded	0	11
			Positive predictive value	Negative predictive value
Definite cutoff	(%)		100	36.4
	Number of patients		26/26	13 + 11/42 + 13 + 11
Probable cutoff	(%)		84	100
	Number of patients		26 + 42/24 + 42 + 13	11/11
B. Results of genetic testing for each male clinical diagnosis group				
			Positive	Negative
Clinical symptoms		Definite	19	0
		Probable	16	9
		Excluded	0	4
			Positive predictive value (%)	Negative predictive value (%)
Definite cutoff	(%)		100	44.8
	Number of patients		19/19	9 + 4/16 + 9 + 4
Probable cutoff	(%)		79.5	100
	Number of patients		19 + 16/19 + 16 + 9	4/4
C. Results of genetic testing for each female clinical diagnosis group				
			Positive	Negative
Clinical symptoms		Definite	7	0
		Probable	26	4
		Excluded	0	7
			Positive predictive value (%)	Negative predictive value (%)
Definite cutoff	(%)		100	29.7
	Number of patients		7/7	4 + 7/26 + 4 + 7
Probable cutoff	(%)		89.2	100
	Number of patients		7 + 26/7 + 26 + 4	7/7

When the cutoff is set between "Definite" and "Probable," positive predictive value includes Definite, and negative predictive value includes Probable and "Excluded." Probable cutoff: When the cutoff is set between Probable and Excluded, positive predictive value includes Definite and Probable, and negative predictive value includes Excluded.

telomere length and epigenetic age correlate with cardiovascular disease and metabolic disease.[20,21] Thus, in women, there are estrogen-dependent and -independent, cellular, and individual suppression mechanisms on aging. Telomere shortening, mitochondrial dysfunction, and increased epigenomic age are also critical in WS. The presence of premature menopause in patients with WS suggests that the protective effect of estrogen is lost in the 30s. On the other hand, delayed symptoms in the current study suggest a protective effect on aging that persists even after menopause.

Estrogen potentially has a protective effect on hair loss, skin atrophy, and cataracts.[22,23] Estrogen levels affect subcutaneous fat deposition in women, and visceral fat accumulation and insulin resistance occur more frequently in men.[24,25] The frequency of cardiovascular disease is low in women before menopause.[26,27] Age-related decrease in estimated glomerular filtration rate is greater in men.[28–30] Refractory skin ulcers are often observed in patients with WS, and a microarray study of skin wound healing in older men reported that 76% of the identified aging-related genes were estrogen regulated.[31] At the molecular level, age-related reductions in double-strand break repair and increased telomere uncapping, which are also characteristic of WS, are more severe in postmenopausal women than in men.[32,33] These findings suggest that estrogen may contribute to delayed aging symptoms of WS in women. However, the effect of estrogen on birdlike face and abnormal voice may not be likely because it is specific to WS.

Interestingly, WRN expression is upregulated following estrogen administration,[34] suggesting that *WRN* upregulation by estrogen contributes to double-strand break repair and telomere maintenance in women. However, Imura *et al.* reported that follicle-stimulating hormone and luteinizing hormone are elevated in patients with WS in their 30s and 40s, suggesting primary hypogonadism at an early age. Serum testosterone levels were lower than in age-matched controls, and testicular biopsies showed pronounced atrophy. Therefore, it may be difficult to attribute the delay of WS manifestations in women only to sex hormones.[35] Various factors, including chromosome structure, mitochondrial genetic format, and mitochondrial DNA content, also influence sex differences in aging other than estrogen.[36,37] Taken together, these results suggest that estrogen-independent mechanisms may also be involved.

A high-pitched, hoarse voice is a characteristic clinical finding of WS.[38] In normal aging, the voice tends to become hoarse as vocal cord atrophy progresses.[39] While men acquire a high-pitched voice due to the hardening of the vocal muscles by aging, women acquire a low-pitched voice due to edema and thickening of the vocal folds caused by a decrease in the female hormones.[40] Therefore, the less frequent high-pitched voices in women with WS are consistent with age-related changes. Also, our data (Fig. 2) suggest that abnormal voice increases with age, and it occurs the latest among the various manifestations of WS. Among the cardinal signs, high-pitched, hoarse voices and birdlike faces are specific to WS rather than normal aging, yet they still appear according to age.

In this study, the positive and negative predictive values for the definite and excluded categories were 100% for both sexes, suggesting that these diagnostic criteria are helpful regardless of sex. On the other hand, the positivity ratio of genetic diagnosis in the probable category was 76.4%, suggesting the importance of genetic diagnosis when clinical symptoms are insufficient. In addition, more female patients required genetic testing, indicating the importance of genetic testing in females even if they do not show typical symptoms. These criteria could not detect atypical WS or *POLD1* mutations, suggesting that an additional strategy is required to detect rare non-Werner progeroid patients.

This study had some limitations. First, this was a retrospective cohort study; therefore, a prospective study is needed to confirm these results. Additionally, the number of participating patients was small because WS is a rare disease. Moreover, the present study focused only on the occurrence of the six cardinal signs because it is based on the information in the referral letter for request of genetic diagnosis; we could not describe the detailed clinical data such as comorbidities, body composition, or onset and progression of diabetes or atherosclerosis.

In conclusion, this study, for the first time, showed that sex differences exist in WS symptoms. In addition, sex differences were found for occurrence of abnormal voices in the cardinal signs and were influenced by genotype. Further detailed studies are required to clarify whether the sex differences observed in this study are specific to WS or applicable to general aging.

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Disclosure statement

All authors declare no conflicts of interest and nothing to disclose.

Author contributions

H. Kaneko, A.T.Y., H. Kato, M.K., and K.Y. managed the project. H. Kaneko, A.T.Y., H. Kato, M.S., Y. Maeda, M.K., and M.T. recruited the patients. H. Kaneko, H. Kato, M.K., A.T.W., R.N., S.F., K.A., and N.T. collected the data. H. Kaneko, H. Kato, M.K., D.S., T.M., A.H., K.I., S.I., and T.K. analyzed the data. H. Kato and Y. Maezawa directed this research. H. Kaneko, H. Kato, and Y. Maezawa wrote the manuscript. All authors read and discussed the manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Supplementary Table S1. Inspection and positivity ratios for abnormal voices in male patients with positive genetic test results.

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English

第66回 日本糖尿病学会年次学術集会

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第9回肝臓と糖尿病・代謝研究会

Cookie 研究会 ポスター >

第66回日本糖尿病学会年次学術集会は、5月11日（木）～13日（土）の3日間、現地鹿児島にて、ならびにライブ配信を通し大変多くの方にご参加いただき盛会のうちに終了いたしました。
また6月1日(木)より行っておりましたオンデマンド配信につきましても、6月30日（金）をもって終了いたしました。改めて、皆様方のご支援・ご協力に深く感謝申し上げます。

新着情報

一覧

2023.08.01	【糖尿病専門医】更新単位反映状況に関するご案内
2023.05.12	第 13 回若手研究奨励賞（YIA）/ 第 7 回医療スタッフ優秀演題賞 受賞者を更新致しました。 鹿児島の耳寄り＆お得情報を再度更新致しました。
2023.05.11	Special Lecture 1・2 (同時通訳)のご視聴方法を、プログラムに更新致しました。
2023.05.10	ツイッターを更新致しました。
2023.05.09	LIVE 配信視聴利用方法、オンライン配信プログラムを更新致しました。 取得可能単位情報を更新致しました。
2023.05.09	トップページを更新致しました。
2023.05.08	鹿児島の耳寄り＆お得情報を更新致しました。
2023.04.28	Web抄録検索Webアプリを更新致しました。
2023.04.25	オンデマンド配信プログラム内容を更新致しました。必ずご確認下さい。

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Ⅰ－56－2　Imeglimin が 2 型糖尿病モデルマウスのミトコンドリア，インスリン顆粒へ与える影響
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横浜市立大学大学院医学研究科発生成育小児医療学　**西山　邦幸，他**

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済生会宇都宮病院内科（糖尿病・内分泌内科）　**齋藤　聡，他**

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佐賀大学医学部付属病院肝臓・糖尿病・内分泌内科　**吉富　裕加，他**

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奈良県総合医療センター消化器内科/奈良県総合医療センター糖尿病内分泌内科　**尾﨑　邦彰，他**

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第 3 日　5 月 13 日（土）　デジタルポスター会場 2　かごしま県民交流センター　3F　中研修室 1

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新松戸中央総合病院糖尿病・内分泌代謝内科　**伊藤　新，他**

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ポスター 64

その他の糖尿病 2　9：20〜10：10　座長　岐阜大学大学院医学系研究科総合診療科・総合内科学　森　一郎

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P－64－2　当院におけるエンホルツマブ ベドチン投与時の血糖コントロールへの影響
広島赤十字・原爆病院内分泌・代謝内科　**藤原　典子，他**

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国立病院機構姫路医療センター内科　**畑尾満佐子**

Ⅰ－56－1 膵β細胞においてオートファジーフラックスを制御する新規化合物の同定と創薬への応用

伊藤　南[1]，西田　友哉[1]，青山　周平[1]，金井　晶子[1]，植本　響政[1]，
岩本　達也[1]，鵜澤　博嗣[1]，飯田　雅[1]，小島　宏達[2]，綿田　裕孝[1]
順天堂大学大学院医学研究科代謝内分泌内科学[1]，東京大学大学院薬学系研究科附属創薬機構[2]

オートファジーは細胞内恒常性維持に重要な役割を担い，糖尿病に伴う膵β細胞機能不全にも深く関与することが知られている．したがって，その制御により糖尿病の発症や進展に介入できる可能性がある．そこで本研究では，オートファジー活性の指標であるオートファジーフラックスを評価可能なpHluroin-LC3-mCherryプローブを発現するMIN6細胞に対し，低分子化合物ライブラリーを用いてスクリーニングを実施した．このプローブによる一次スクリーニングに続き，カウンタースクリーニングや用量反応性による二次スクリーニングを行い，オートファジーフラックスを活性化する化合物を同定した．最後に，これらの化合物が脂肪毒性モデルによる膵β細胞オートファジー不全を改善することを明らかにした．今後は作用機構解明や糖尿病モデルでの有効性の検討を進め，創薬へと結実させる．

Ⅰ－56－2 Imeglminが2型糖尿病モデルマウスのミトコンドリア，インスリン顆粒へ与える影響

真田　淳平，小畑　淳史，伏見　佳朗，岩本　秀幸，岩本侑一郎，
片倉　幸乃，木村　友彦，下田　将司，中西　修平，宗　友厚，
加来　浩平，金藤　秀明
川崎医科大学糖尿病・代謝・内分泌内科学

【目的】2型糖尿病モデルマウスの膵β細胞へのImeglimin（Ime）の影響を検討する．【方法】db/db，KK-Ayマウスに対しImeを4週間投与し，電子顕微鏡で膵β細胞内のミトコンドリア，インスリン顆粒を観察した．尿中8-OHdGで酸化ストレスの評価，TUNEL染色，realtime PCRでアポトーシス等の評価を行った．【結果】電子顕微鏡ではIme群はインスリン顆粒数が維持され，良質な顆粒の割合が増加した．ミトコンドリア形態はControl群では膨化しクリステ構造が崩壊していたが，Ime群では膨化やクリステ構造の崩壊が軽減された．尿中8-OHdGはIme群で低下し，TUNEL陽性細胞の減少やアポトーシス・炎症マーカーの発現量の減少がIme群でみられた．【結語】Imeは膵β細胞のアポトーシスを抑制するなど有益な効果を有した．

Ⅰ－56－3 肥満糖尿病db/dbマウスにおけるimeglminとmetforminの併用による膵β細胞保護効果の検討

西山　邦幸[1,2,3]，小野　正人[2]，都野　貴寛[1,2]，井上　亮太[1,2]，渥美　拓士[1]，
寺内　康夫[2]，伊藤　秀一[3]，白川　純[1,2]
群馬大学生体調節研究所代謝疾患医科学分野[1]，横浜市立大学大学院医学系研究科分子内分泌・糖尿病内科学[2]，横浜市立大学大学院医学研究科発生成育小児医療学[3]

肥満・糖尿病モデルであるdb/dbマウス（db/db）への非投与，imeglimin，metforminの単独および併用投与，db/+マウスの5群でそれぞれ5-7週間投与し解析した．db/dbの4群内では随時血糖値，体重，耐糖能およびインスリン抵抗性に差を認めなかった．db/dbへの併用投与により膵β細胞量の増加，膵β細胞増殖の促進および膵β細胞アポトーシス抑制を認めた．各群の単離膵島の遺伝子発現解析では併用投与群で非投与群と比べて504分子の有意な発現低下，GSEAにて細胞増殖や細胞死の負の制御などへの関与が示唆された．db/db単離膵島への両薬剤の併用添加により，膵β細胞アポトーシスは有意に減少し，細胞死に関連する分子の発現が抑制された．以上よりimeglminとmetforminは相加的に膵β細胞保護作用を示すことが示唆された．

Ⅰ－56－4 膵β細胞におけるUFMylationの病態生理学的意義の検討

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植本　響政[1]，和栗　聡[2]，小松　雅明[3]，綿田　裕孝[1]
順天堂大学大学院医学研究科代謝内分泌内科学講座[1]，福島県立医科大学医学部解剖・組織学講座[2]，順天堂大学大学院医学研究科器官・細胞生理学講座[3]

タンパク翻訳後修飾であるUFMylationは，細胞内恒常性維持機構の制御を通じた生体機能調節に関与し，その異常に伴う疾患との関連も明らかにされている．そこで我々は，UFMylationが膵β細胞の恒常性維持に重要な役割を担うという仮説を検証した．膵β細胞特異的Ufm1 KOマウス（UFM1-β KO）を作製しUFMylationを膵β細胞において欠損させたところ，通常食投与下において耐糖能が低下することを見出した．一方，組織学的な検討ではUFM1-β KO膵島の構造的な脆弱性が示唆され，膵β細胞死の増加と膵β細胞数の減少が認められた．さらに，電子顕微鏡による検討では小胞体腔拡大や変形が観察された．これらの結果から，UFMylationが膵β細胞の恒常性の維持に寄与し，その破綻は膵β細胞機能不全をもたらすことが示唆された．

Ⅰ－56－5 FGF21アナログの膵β細胞生存に対する効果

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白川　純[1,2]
横浜市立大学大学院医学研究科分子内分泌・糖尿病内科学[1]，群馬大学生体調節研究所代謝疾患医科学分野[2]

FGF21アナログPF-05231023（FGF21a）の膵β細胞への影響を解析した．マウス膵島におけるFGFR1-4およびβ-Klothoの発現を確認した．FGF21aの添加は，マウス膵島のグルコース応答性インスリン分泌や膵β細胞増殖に変化を与えず，高グルコースによる膵β細胞アポトーシスを32%有意に抑制した．FGF受容体阻害薬（TAS-120）により，FGF21aによる膵β細胞アポトーシス改善は抑制された．ヒト膵島においてもFGF21aにより，グルコース誘導性膵β細胞アポトーシスは24%の有意な改善を認めた．FGF21a添加マウス膵島の遺伝子発現解析にて，Apelin-APJ systemやautophagyの経路の関与が示唆された．Thapsigarginやパルミチン酸を添加したマウス膵島においてもFGF21aは膵β細胞アポトーシスを抑制した．以上より，FGF21はFGF受容体を介して高血糖や小胞体ストレスによる膵β細胞アポトーシスを抑制する可能性が示唆された．

Ⅰ－57－1 健康寿命の長い女性の血清アディポネクチン（APN）は高い：車椅子不使用で独歩，自宅で独居の85-96歳の女性における検討

本田　まり[1,2]，猪川(淡)聡美[3,4]，梶(坪井)彩加[3,5]，北岡かおり[3,7]，武内　海歌[3]，
矢野めぐむ[3,6]，鞍田　三貴[3,8]，鹿住　敏[2,3,9]，福尾　恵介[2,3,8]
神戸女子大学健康福祉学部健康スポーツ栄養学科[1]，武庫川女子大学生活習慣病オープン・リサーチ・センター[2]，武庫川女子大学栄養科学研究所[3]，愛媛大学大学院農学研究科地域健康栄養学分野[4]，大阪市立十三市民病院栄養部[5]，大阪公立大学大学院医学研究科分子生体医学講座病態生理学[6]，滋賀医科大学NCD疫学研究センター最先端疫学部門[7]，武庫川女子大学食物栄養科学部食物栄養学科[8]，一般財団法人甲南会甲南加古川病院内科糖尿病外来[9]

【目的】健康寿命の長い女性の特性を調べた．【方法】対象は独居で独歩の前期高齢95名（65-74歳），後期高齢176名（75-84歳），超高齢51名（85-96歳）．【結果】APN（μg/mL）は前期と後期で差はなかったが超高齢で高かった（順に13.9±6.9，15.1±7.7，18.7±8.6）．加齢に伴って貧血頻度（ヘモグロビン＜12g/dL）は増加した（順に10，23，39%，共にp<0.001）．APNは貧血の有無で前期（無：13.8，有：14.6）と後期（順に14.6，16.9）では差はなかったが超高齢の貧血では高かった（無：16.0，有：22.8，p=0.005）．【考察】超高齢のAPN高値は過剰なアポトーシス細胞の除去に対する，貧血の超高齢におけるAPN高値は過剰なエリフトーシスに対するAPNの反応性増加の可能性が示唆された．

Ⅰ－57－2 早老症Werner症候群のインスリン抵抗性と皮下脂肪における老化促進病態の検討

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船山真一郎[1]，南塚　拓也[1]，越坂　理也[1]，塩浜　直[2]，高谷　具純[2]，
濱田　洋通[2]，横手幸太郎[1]
千葉大学大学院医学研究院内分泌代謝・血液・老年内科学[1]，千葉大学大学院医学研究院小児病態学[2]

【背景】代表的な遺伝性早老症であるWerner症候群（WS）は，四肢の皮下脂肪萎縮とインスリン抵抗性糖尿病を合併する．WSの皮下脂肪萎縮の病態解明を目的とした．

【材料と方法】4名のWS患者の皮下脂肪面積とインスリン抵抗性をグルコースクランプ法で比較検討した．WS患者由来皮下脂肪組織（WSVF）を健常者と比較解析し，*WRN* knockout線虫（gk99）のrapamycinの効果を検討した．

【結果】WS患者の皮下脂肪割合減少はインスリン抵抗性亢進と相関した．WSVFは早期細胞老化，脂肪分化抑制を呈し，インスリンシグナルの低下を認めた．RapamycinはWSVF，gk99の寿命延長効果を示した．

【考察】WSではSVFの細胞老化が促進し，皮下脂肪量の減少と慢性炎症を認め，インスリン抵抗性亢進に関わることが示唆された．

Ⅰ－57－3 イメグリミンは脂肪細胞に作用し，Fibroblast Growth Factor 21の産生・分泌を促進する

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【背景・目的】新規経口糖尿病治療薬イメグリミンには骨格筋や肝臓に対する膵外作用が示唆されているが，その詳細は明らかではない．これまでに我々はイメグリミンが脂肪細胞の糖取り込み促進作用およびComplexI阻害作用を有することを見いだしており，今回はイメグリミンのアディポサイトカイン分泌への影響を検討した．【方法・結果】3T3-L1脂肪細胞にイメグリミンを作用させ検討を行ったところ，培地のFibroblast Growth Factor 21（FGF21）濃度や細胞内FGF21 mRNA発現量は増加した．また，イメグリミンによるFGF21 mRNA発現量の増加はAMPK阻害剤Compound CやPI3K阻害剤LY294002によって減弱した．【考案】イメグリミンは脂肪細胞に対してFGF21の産生・分泌を増加させ，その機序として細胞内シグナル伝達分子であるAMPKやPI3Kの関与が示唆された．

P−62−3 SGLT2阻害薬内服中にケトアシドーシスを発症し入院を要した3例の検討

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江口　和人，井上　知紗，真木加奈子，竹下　敦郎，岡野　優子，西濵　康太，
上村　　明，安間　太郎，鈴木　俊成，古田　範子，矢野　　裕
三重大学医学部附属病院糖尿病・内分泌内科

症例1：43歳男性．2型糖尿病．複数の経口薬（ルセオグリフロジン5mg/日）で加療．腹痛，嘔吐出現も休薬せず．入院時血糖（BS）100mg/dL，尿ケトン（UK）3+，pH 7.249．症例2：44歳女性．1型糖尿病．強化インスリン療法とダパグリフロジン5mg/日併用．嘔気，倦怠感，BS 47mg/dLで入院．翌日腹痛悪化．BS 366 mg/dL，UK 3+，pH 6.976．日常的な糖質制限が判明．症例3：57歳男性．2型糖尿病．インスリンとエンパグリフロジン25mg/日併用．X-6日前に腹痛，嘔吐で近医に入院しスライディングで対応．X-3日前に食事，経口薬を再開．X日に嘔吐，意識障害が出現し転院．BS 421mg/dL，UK 3+，pH 6.702．精査で内因性インスリン分泌低下，持効型インスリンの中止，SGLT2阻害薬再開が関与の可能性．考察：SGLT2阻害薬使用時は，内因性インスリン分泌能の評価，sick day時の休薬指導，過度に糖質制限しない等注意を要する．

P−62−4 当院で経験したSGLT-2阻害薬による正常血糖糖尿病ケトアシドーシスの4症例

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松尾　英城[1]，中谷　敏也[3]
奈良県総合医療センター消化器内科[1]，奈良県総合医療センター糖尿病内分泌内科[2]，大和高田市立病院消化器内科[3]

【症例】
症例1：26歳女性．13歳時に1型糖尿病と診断されたが，アドヒアランスは不良だった．SGLT-2阻害薬が開始されたが，食事量減少に伴い消化管症状が出現し，euDKAと診断した．
症例2：43歳女性．健診でHbA1c10%が指摘された．SGLT-2阻害薬が開始され，糖質制限食を開始した．開始10日程度で消化管症状が出現し，euDKAと診断した．
症例3：79歳男性．糖尿病に対してSLGT-2阻害薬を内服していた．消化器外科に腹腔鏡下腫瘍摘出術が施行されたが，術前に内服中止がされておらず，術中にeuDKAを発症した．
症例4：54歳男性．糖尿病に対してSGLT-2阻害薬の内服および糖質制限食を開始した．10日程度で消化管症状が出現し，euDKAと診断した
【考察】
SGLT-2阻害薬は処方数が増加しており，十分な情報提供と患者教育が重要であると考えらえた．

P−62−5 SGLT2阻害薬トホグリフロジン（Tofo）10mgの有用性の検討

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○方法
食事療法，経口薬，GLP-1，インスリン投与中の2型糖尿病に対して，Tofo10mgを初回投与した．このうち10mgを12か月投与した10例（A群）と，途中20mgに増量した12例（B群）において，比較検討した．
○結果
A群とB群では投与前のHbA1cに有意差を認めないが，B群では深夜勤務の症例が有意に多かった．年齢はA群（70±10.3歳）がB群（62.0±11.3歳）より高齢で，体重はA群（76.1±11.3kg）がB群（68.7±7.4kg）より増加傾向であった．Tofo10mgを12か月投与後，体重はA群-3.96kg，B群-2.4kgと有意に減少した．HbA1cはA群-1.4%と有意に低下したが，B群は改善しなかった．またA群では肝機能が有意に改善したが，B群では改善しなかった．eGFRは両群とも有意な低下を認めなかった．
○結語
Tofo10mgは初期投与量として有用であり，一部の症例は20mgと同等の改善効果を示す．

P−62−6 著明高血糖に対するSGLT2阻害薬（SGLT2i）の有効性と安全性

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長野市民病院内分泌・代謝内科[1]，長野赤十字病院糖尿病・内分泌内科[2]，宮本内科クリニック[3]

【背景】インスリン非依存的に血糖降下作用を示すSGLT2iは，糖毒性によりインスリン分泌不全を来たした高血糖状態においても血糖改善作用が期待できる．【方法】SGLT2iを単剤投与した79名のうちHbA1c 12%以上の8名（男性6名）について，投与前後の血糖値，HbA1c，CPR，総ケトン体，体重を12週間にわたり解析した．【結果】HbA1cは平均値で13.8→6.72%，血糖値は357.5→132.2 mg/dLと著明に改善した．CPRは2.84→5.25 ng/mL，総ケトン体は831.8→124.0 μmol/Lと改善した．体重は72.6→71.9 kgと変化を認めなかった．【考察】インピーダンス法での細胞外液量に変化なく脱水の助長を認めなかった．ケトン体はSGLT2i投与により減少していた．インスリン非依存的に血糖値を改善するSGLT2iは，インスリン作用不足によりケトン体が上昇するような著明な高血糖状態においても非常に有効な治療選択となる．

P−62−7 当院におけるダパグリフロジンの導入状況および安全性に関する検討

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目的：ダパグリフロジン（DAPA）新規導入例の背景・適応疾患，および導入後の有害事象・中止例等について調査する．
方法：2020年7月～2022年8月の間，入院中にDAPA10mgを新規導入した82例（男性59例，女性23例，平均年齢70.8±13.7歳）を対象に後ろ向きに検討．
結果：DAPA適応疾患は重複も含め糖尿病48例，心不全40例，腎臓病51例であり，3疾患の内の2疾患合併29例，3疾患合併16例であった．有害事象は28例に30件，中止症例15例であり，主要なものは脱水・腎機能悪化18件（中止7例），尿路感染症8件（中止3例）であった．脱水・腎機能悪化は複数疾患合併症例に多く，尿路感染症は8件の内7件が糖尿病を有する患者であった．
結語：複数疾患合併症例も45例（54.9%）と多く，そのことが脱水・腎機能悪化のリスクとなっていた．尿路感染症では糖尿病がリスクとなる傾向であった．

P−63−1 Werner症候群レジストリーを用いた糖尿病の有無における背景因子の検討

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正司　真弓，前澤　善朗，横手幸太郎
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【目的】Werner症候群（WS）は遺伝性早老症であり，インスリン抵抗性を主体とした糖尿病を高率に合併する．糖尿病がない例も約3割で認められ，糖尿病の有無に関連する背景因子を検討した．【方法】2016年から2022年にWSレジストリーに登録された51名のWS患者を糖尿病の有無で2群に分け，背景因子を解析した．【結果】糖尿病群は非糖尿病群と比較して有意に高齢，内臓脂肪の蓄積を認め，HDL-Cが低く，AST，ALTが高い傾向であった．また糖尿病群で筋肉量は有意に多く，閉塞性動脈硬化症（ASO）は糖尿病群で少ない傾向であった．【考察】WSにおいて糖尿病の有無は健常者と同様に年齢や内臓脂肪蓄積との関係性が認められた．ASOの合併は糖尿病の有無によらず，WSにおける細胞老化や慢性炎症の関与が示唆された．

P−63−2 褐色細胞腫・パラガングリオーマにおける耐糖能異常の特徴

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姜　　知佳[1]，小川　達雄[1]，有安　宏之[1]，小谷　仁人[1]，井上　達秀[1]
静岡県立総合病院糖尿病・内分泌代謝センター[1]，静岡県立総合病院遺伝診療科[2]

【背景と目的】褐色細胞腫・パラガングリオーマ（PPGL）において，約半数に耐糖能異常を認めることが知られている．しかし，耐糖能異常の合併率，機序については依然として議論の余地がある．
【方法】PPGLと診断された38症例を対象に，糖尿病（DM群）と非糖尿病（non-DM群）の2群に分け，患者背景（年齢，BMI，性別，血中および尿中カテコラミン（CA），尿中CA代謝産物，腫瘍径）との関連性を検討した．
【結果】38例のうち12例（31.6%）に糖尿病を認めた．2群の患者背景の比較では，DM群で有意に血中・尿中アドレナリン（A）が高値，腫瘍径が大きかった．（それぞれp=0.041，p=0.033，p=0.023）．
【結語】PPGLの耐糖能異常には，血中・尿中A上昇が関与すると考えられた．腫瘍径については交絡因子の可能性もあり今後の検討を要する．

P−63−3 動悸及び腰背部痛を契機に褐色細胞腫と診断された糖尿病の1例

奥野　沙織，浦田　晴可，石井　晴香，原　　宏幸，上田　莉子，
丸岡あずさ，高橋　一久，浮田千津子，塩島　一朗，豊田　長興
関西医科大学附属病院第二内科

【症例】56歳，男性【現病歴】35歳より高血圧，52歳で糖尿病と診断．X年6月頃から血糖コントロールが悪化した．8月，動悸，発汗，腰背部痛が出現し，近医を受診．CTにて右副腎腫瘍（5cm）を認め紹介受診となった．当院受診時，低血圧を認めた．補液にて改善するも，その後，177/122mmHgまで上昇．褐色細胞腫のクリーゼが疑われ，緊急入院となった．尿中アドレナリン，ノルアドレナリンなどの24時間排泄量が正常上限の約10倍以上高値を認め，褐色細胞腫と診断．入院後～第7病日まで，レギチーンの投与開始．ドキサゾシンを少量より開始し，16mg/日の投与にて血圧は概ね良好にコントロールできるようになった．一方，血糖コントロールも改善した．【考察】ドキサゾシンの投与が，血糖コントロールの改善に寄与した可能性が考えられた．

第33回日本老年学会総会

オンデマンド視聴
配信期間は2023年7月3日（月）正午～7月31日（月）正午までとなります。

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第33回日本老年学会総会として参加登録はおこなっておりませんので、ご注意ください。

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- 第65回日本老年社会科学会大会
- 第46回日本基礎老化学会大会
- 第34回日本老年歯科医学会学術大会

大会事務局

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医学系研究科老年病学
事務局長　小川 純人

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第 1 日　ノース 2 階　第 12 会場（G217）
一般演題 口述発表 O3-1―O3-7, O8-1―O10-6

9：00～10：24（O3-1―O3-7）AI/ICT/先進技術　　座長：東　浩太郎（東京大学医学部附属病院老年病科）

O3-1. ICT ネットワークを用いた医療介護連携による高齢慢性心不全重症化予防の取り組み ……
（名寄市立総合病院循環器内科）酒井博司，井澤和眞，豊嶋更紗，岩田周耕，中川敬太，尾野稔侑，小尾基記

O3-2. 1 枚の腰椎正面 X 線画像のみから腰椎及び大腿骨近位部の骨密度推定値を演算する AI 骨粗鬆症診断補助システム ……
（東京大学医学部附属病院関節機能再建学講座[1]，同 22 世紀医療センターロコモ予防学講座[2]，同大学院医学系研究科整形外科学[3]，同大学院医学系研究科老年病学[4]）茂呂　徹[1]，吉村典子[2]，齋藤琢[3]，大野久美子[3]，飯高世子[2]，小川純人[4]，田中　栄[2]

O3-3. アイトラッキング式認知機能評価法における正解関心領域外の視線情報と認知機能障害の関連 ……
（大阪大学大学院医学系研究科臨床遺伝子治療学[1]，大阪精神医療センターこころの科学リサーチセンター[2]，大阪大学大学院医学系研究科老年・総合内科学[3]，同保健学専攻老年看護学[4]）杉原七海[1]，武田朱公[1]，大山　茜[2]，中嶋恒男[3]，伊藤祐規[1]，三木国熙[1]，鷹見洋一[3]，竹屋　泰[4]，樂木宏実[3]，森下竜一[1]

O3-4. スマートシューズを用いた歩行機能の加齢性変化の検討 ……
（横浜市立大学附属病院救急科[1]，株式会社 MTG[2]）三澤菜穂[1]，西井基継[1]，酒井和也[1]，白井智之[2]，竹谷恵美[2]，川出周平[2]，竹内一郎[1]

O3-5. 人工知能を用いた CT 画像における加齢性胸腺萎縮の解析 ……
（総合病院国保旭中央病院内科[1]，慶應義塾大学大学院理工学研究科[2]，総合病院国保旭中央病院 PET 画像診断センター[3]，慶應義塾大学医学部衛生学公衆衛生学教室[4]，総合病院国保旭中央病院放射線科[5]，慶應義塾大学理工学部機械工学科[6]，総合病院国保旭中央病院アレルギー膠原病内科[7]）岡村勇輝[1]，遠藤克浩[2]，鳥井原彰[3]，福田一成[1]，佐藤泰憲[4]，磯貝　純[5]，泰岡顕治[6]，加々美新一郎[7]

O3-6. 高齢者施設向け体調変動検知システムの開発 ……
（パナソニックホールディングス株式会社）塩谷真帆，山口勝久

O3-7. IoT 機器から取得される歩行データに着目した高齢者の状態変化検知 ……
（コニカミノルタ株式会社[1]，介護老人保健施設竜間之郷[2]）橘　和佳[1]，坂本優衣[1]，河本　望[1]，寄崎恵美子[1]，岡田真和[1]，大河内二郎[2]

14：20～15：44（O8-1―O8-7）基礎老化・早老症　　座長：東　浩太郎（東京大学医学部附属病院老年病科）

O8-1. 遺伝性早老症 Werner 症候群の皮下脂肪萎縮の病態解明 ……
（千葉大学大学院医学研究院内分泌代謝・血液・老年内科学）澤田大輔，加藤尚也，金子ひより，木下大輔，船山真一郎，青野和人，南塚拓也，越坂理也，前澤善朗，横手幸太郎

O8-2. 早老症 Werner 症候群レジストリを用いた糖尿病の有無における背景因子の検討 ……
（千葉大学大学院医学研究院内分泌代謝・血液・老年内科学）青野和人，越坂理也，金子ひより，前田祐香里，加藤尚也，正司真弓，前澤善朗，横手幸太郎

O8-3. ウェルナー症候群の症状呈示における性差と診断精度への影響 ……
（千葉大学大学院医学研究院内分泌代謝・血液・老年内科学）金子ひより，前澤善朗，塚越彩乃，青野和人，船山真一郎，澤田大輔，加藤尚也，越坂理也，横手幸太郎

ん妄発症など様々な因子が予後不良のリスク因子として報告されているが，食事摂取不良もまた，同様にリスク因子として指摘されている．しかし，具体的な食事量と予後の関連を検討した研究は少なく，今回退院後3か月後に生存している患者と死亡した患者での入院中の食事摂取状況について検討を行った．【方法】2019年10月1日から2020年7月31日までに当院老年内科に入院した65歳以上の高齢者の，退院前3日間の1日食事摂取量の平均を算出し，退院後3ヶ月時点での死亡率との関連を検討した．退院3か月後の死亡を目的変数とし，年齢，性別，退院前3日間の実測体重当たりの1日平均摂取カロリーを説明変数とした多重ロジスティック回帰分析により，オッズ比（OR）を算出した．【結果】100例（男性33例）の解析を行った．年齢の中央値は85（四分位範囲：82-88）歳であった．退院3ヶ月後時点での死亡は10例（10%）であった．多重ロジスティック回帰分析の結果，実測体重当たりの平均摂取カロリー（OR：0.903, 95%信頼区間：0.826-0.987）が退院3ヶ月後死亡の有意な関連因子となった．【結論】当院老年内科の患者は一般集団と比較してより高齢な集団であるが，その中でも入院中の食事摂取量が中長期的な予後に関連することが示唆された．食事量と長期予後の関連について，具体的なエネルギー量まで言及した研究は少なく，今後一般内科病棟における，より適切な食事の提供につなげられる可能性がある．

一般演題

O7-5

高齢者救急病院における CCU 選定救急搬送患者の傾向

東京都健康長寿医療センター総合内科・高齢診療科[1]，同救急診療部[2]，同循環器内科[3]
大川庭熙[1]，坪光雄介[2]，藤本　肇[3]

【目的】コロナ下では救急外来や病床がひっ迫しており，特に高齢者救急医療に甚大な影響を与えている．当院は高齢者救急病院でありながら，東京都CCUネットワークに加盟し，循環器救急症例を積極的に受け入れている．当院にCCUネットワーク経由で搬送となった患者の傾向を分析し，都心部における高齢者救急病院の役割と機能を明確にすることは重要と考えられる．【方法】当院において，直近1年間（2021年11月1日～2022年10月31日）のCCUネットワーク経由に搬送された136例について患者背景，転帰などの傾向を調査した．【結果】136人中，男性79例（65±17歳），女性57例（77±17歳）であった．入院した患者は61　%（82人，うちCCU入院54人，一般内科病棟入院　28人），入院せず帰宅となった患者　37%（51人），転院搬送患者2%（3人）であった．診断名はCCU入院群：急性心不全（39%），心筋梗塞（24%），大動脈解離（17%），不整脈（11%），狭心症（3%），大動脈瘤（2%），肺塞栓（2%）であり，内科入院群：慢性腎臓病（24%），肺炎（17%），COVID-19（14%），胆石・胆管炎（7%），整形疾患（7%），帰宅群：不整脈16%・狭心症12%・心不全6%，整形疾患（肋骨・圧迫骨折等）6%，薬剤性（過降圧・副作用等）4%，起立性低血圧・反射性失神4%，認知症4%，神経症4%などであった．入院期間についてはCCU群：22±20日，内科群22±18日と両群に差はなかった．【結論】当院ではCCU選定で搬送された救急患者には非循環器系疾患患者も多く含まれていた．高齢患者は多様な病態を呈するため，救急要請された患者は積極的に受け入れたうえで，診断・入院の要否を適切に判断することが重要である．

O7-6

認知症ケアチーム加算対象入院患者における臨床的特徴

藤田医科大学医学部認知症・高齢診療科
芳野　弘，武地　一

【目的】2016年4月の診療報酬改定において「認知症ケア加算」が創設された．当院においても多職種による認知症ケアチームの活動を行っている．対象患者（認知症自立度III以上）では入院関連機能障害，せん妄，転倒のリスクが予想される．今回，認知症ケアチーム加算対象の患者の入院時の臨床上の特徴やどのような関連因子があるか検討した．【方法】2019年4月1日から2021年3月31日までに認知症ケアチームが介入した患者を対象にカルテを後方視的に調査した．対象患者：入院患者569名．評価項目：平均年齢，性別，入院時疾患，併存症の有無，血液検査，入院前の状況等．統計解析はSPSSにて2群間の連続変数の比較はt検定，カテゴリー変数は$\chi 2$検定を行った．最も多い入院時疾患の有無を従属変数として関連する投入変数に対し多変量解析を行った．【結果】平均年齢83.4±6.8歳，入院時疾患：感染症188名(33.0%)，併存症：認知症355名(62.4%)，糖尿病：134名（23.5%），高血圧322名（56.4%），alb　3.15±0.68 g/dl, CRP　4.94±7.06mg/dl. 入院前自宅293名(51.5%)，入院前施設入所　220名(38.7%)．入院時疾患は感染症が最も多く，感染症の有無で群間比較をした．感染症　VS　非感染症：BMI 19.0 ±3.7　VS　20.4±4.1（P<0.01），alb 2.1±0.7　VS　3.3±0.6g/dl（P<0.01），入院前施設入所51.7　VS　32.5%（P<0.01）．入院時疾患で感染症を従属変数，各項目を投入変数として多変量解析を行いBMI(P=0.013)，alb（P<0.01），入院前施設入所（P<0.01）が関連因子（P<0.05）となった．【結論】認知症ケアチーム加算対象患者は感染症が多く，低栄養状態が認められる傾向にあり，入院前は施設入所が高頻度であった．入院中に対象患者を評価しその背景を精査することは各疾患の増悪を軽減する可能性がある．

O8-1

遺伝性早老症 Werner 症候群の皮下脂肪萎縮の病態解明

千葉大学大学院医学研究院内分泌代謝・血液・老年内科学
澤田大輔，加藤尚也，金子ひより，木下大輔，船山真一郎，
青野和人，南塚拓也，越坂理也，前澤善朗，横手幸太郎

【目的】Werner症候群（WS）はRecQ型DNAヘリカーゼをコードする *WRN* の遺伝子変異に起因する代表的な遺伝性早老症である．その病態解明は本疾患の治療法開発にとどまらず，ヒトの一般老化の理解にも資することが期待される．WSは内臓脂肪蓄積と皮下脂肪萎縮を示し，重度のインスリン抵抗性をきたすが，そのメカニズムは不明である．WSの皮下脂肪萎縮の病態解明を目的とした．【方法】当院4名のWS患者を対象に，腹部CTによる脂肪面積とグルコースクランプ法によるインスリン抵抗性を比較した．また，WS患者由来皮下脂肪組織からstromal　vascular　fraction（SVF）を分離し（WSVF），健常SVF（HSVF）と比較した．WSVFの老化表現型解析，網羅的遺伝子発現解析，脂肪分化誘導実験，mammalian target of rapamycin（mTOR）阻害剤であるrapamycin添加実験を行い，さらに *WRN* knockout線虫（gk99）へのrapamycinの効果を評価した．【結果】WS患者はサルコペニア肥満を呈し，WS患者の皮下脂肪割合減少はインスリン抵抗性亢進と有意に相関した（$R^2 = 0.95$, $p = 0.024$）．WSVFは早期細胞増殖停止，形態の扁平肥大化，テロメア長の有意な短縮（$p < 0.0001$）を示し，SA-β-gal染色では老化陽性細胞が増加し，老化関連炎症因子（SASP）の発現が有意に増加した．RNA sequence解析により，細胞分裂や染色体制御に関連する遺伝子発現の減少が認められ，早期細胞老化が示唆された．また，WSVFでは脂肪分化能の減弱（$p < 0.01$），脂肪分化抑制遺伝子とSASPの発現上昇，アディポカインの発現低下，インスリンシグナルの抑制，オートファジーの過剰亢進を認めた．さらに，rapamycinの添加は早期細胞老化，インスリンシグナル低下を改善し，*WRN* knockout線虫の寿命を有意に延長した（$p < 0.01$）．Rapamycinを添加した *WRN*　knockout線虫では *daf-16* の有意な発現上昇があり（$p < 0.01$），寿命延長にmTOR経路の関与が示唆された．【結論】WSの皮下脂肪萎縮と重度のインスリン抵抗性に細胞老化が関わることを明らかにし，mTOR経路を標的としたWSの治療の有用性を示した．

O8-2

早老症 Werner 症候群レジストリを用いた糖尿病の有無における背景因子の検討

千葉大学大学院医学研究院内分泌代謝・血液・老年内科学
青野和人，越坂理也，金子ひより，前田祐香里，加藤尚也，
正司真弓，前澤善朗，横手幸太郎

【目的】Werner症候群（WS）は *WRN* を原因遺伝子とする遺伝性早老症であり，思春期以降に老化徴候や動脈硬化，悪性腫瘍などが早発する．サルコペニアが多いにも関わらず，インスリン抵抗性を主体とした糖尿病が特徴的である．　WSにおける糖尿病の有無の背景を明

らかにした.【方法】WSレジストリに登録された51名のWS患者を糖尿病の有無で2群に分け，糖尿病の有無と関連する背景因子に関し，Welch検定を用いて解析した.【結果】糖尿病群（35名）は非糖尿病群（16名）と比較して有意に高齢で（51.1±5.1 vs 45.7±8.1歳，P=0.003），内臓脂肪蓄積（112.6±53.7 vs 42.2±29.5cm^2，P=0.045）を認めた．糖尿病群で筋肉量は有意に多く（12.3±3.5 vs 8.0±2.3kg，P=0.037），骨格筋指数（SMI）が高い傾向（4.9±0.4 vs 3.7±0.6kg/m^2，P=0.077）であったが，握力や歩行速度に差は見られなかった．閉塞性動脈硬化症（ASO）は糖尿病群で少ない傾向であったが，悪性腫瘍の有無は同等であった．*WRN*の変異部位では，mutation4ホモ接合体群でそれ以外の変異に比し糖尿病が少ない傾向であった（57.1 vs 81.3%，P=0.151）．【結論】WSにおいて糖尿病の有無は非WS患者と同様に年齢や内臓脂肪蓄積との関係性が認められた．筋肉量やSMIが糖尿病群で多いがサルコペニアの指標となる握力や歩行速度に差がみられず，筋肉量によらず相対的な内臓脂肪蓄積が糖尿病の有無に大きく関係していると考えられた．またASOは糖尿病群で少ない傾向にあり，WSにおける細胞老化や慢性炎症が動脈硬化に直接関与していると考えられた．*WRN*の遺伝子変異部位により糖尿病が発症しにくい傾向もあり，遺伝学的検査が予後予測や疾患予防に有用な可能性が示唆された．

O8-3

ウェルナー症候群の症状呈示における性差と診断精度への影響

千葉大学大学院医学研究院内分泌代謝・血液・老年内科学
金子ひより，前澤善朗，塚越彩乃，青野和人，船山真一郎，
澤田大輔，加藤尚也，越坂理也，横手幸太郎

【目的】超高齢社会の到来により，糖尿病，動脈硬化症などの加齢関連疾患の性差が注目されている．一方，単一の遺伝子変異によって引き起こされる遺伝性早老症にも性差が存在するかどうかはまだ不明である．本研究では，ヒトの老化のモデルであるウェルナー症候群（WS）の症状の性差を，診断時の患者データを用いて検討した.【方法】2009年12月から2022年1月までに主治医がWSを疑い，当院に紹介した170例のうち診断に必要な臨床症状が得られた92例について診断時の解析を行った．全例で遺伝子診断が実施されていた．診断基準の6つの主要徴候の有無から，全ての主要徴候を有する群，3つの主要徴候の存在，または毛髪変化と白内障に加え，すべての徴候から少なくとも2つ以上の徴候を有する群，上記以外の3群に分類し，臨床症状の性差，性差に基づく診断基準の妥当性を検討した.【結果】92人中，48人が男性，44人が女性で，平均年齢は男性43.4±11.9歳，女性44.8±12.2歳であった．すべての主要徴候を認めた割合は，女性より男性で多く認めた（男性39.6%，女性15.9%）．また，主要徴候をすべて満たしていなくても，初めて遺伝子診断で診断されたのは女性の方が多かった（男性33.3%，女性59.1%）．さらに，WSの主要徴候のひとつである高調性嗄声の頻度は，女性で低いことがわかった．最後に，性差に基づく診断基準の妥当性を確認した．臨床症状による確定診断，除外診断の陽性・陰性予測値は，男女共に100%であった.【結論】女性は男性と比較しすべての主要徴候が揃いにくく，初めて遺伝子診断で診断されたのは女性の方が多いことから，女性にはより積極的な遺伝子診断が推奨されることも示唆された．臨床症状による確定，除外診断は男女共に100%であり，診断基準が男女に有用であることが示された．各臨床症状の出現頻度の性差の検討はWSの病態解明の足がかりになり得る．

O8-4

脂質代謝酵素PNPLA7は骨格筋のミトコンドリア機能維持に重要である

東京大学大学院医学系研究科加齢医学講座[1]，同疾患生命工学センター[2]
松本昇也[1]，武富芳隆[2]，小川純人[1]，秋下雅弘[1]，村上　誠[2]

【目的】加齢に伴って骨格筋の機能は低下する．主要な膜リン脂質であるホスファチジルコリン（PC）の合成に関わるコリンキナーゼβ（CHKB）や，PCの分解に関わるリン脂質代謝酵素iPLA$_2\gamma$の変異や欠損が，いずれも骨格筋におけるミトコンドリアの変性や筋障害を起こすことが報告されている．膜リン脂質は絶えず新陳代謝を繰り返すことにより筋細胞の膜環境を一定に保つことが想定されるものの，この分子機構は未解明である．本研究では，筋細胞における脂質代謝酵素群の包括的発現解析を契機に，リゾホスホリパーゼPNPLA7の機能に着目し，筋細胞の膜リン脂質の新陳代謝の機序を解明することを目的とした.【方法】*Pnpla7*の全身性又は筋特異的欠損マウスの表現型を解析するとともに，遺伝子発現や代謝物の網羅的解析を行った.【結果】PNPLA7は筋細胞に高発現しており，その欠損によりリゾリン脂質の分解が妨げられた．*Pnpla7*全身性及び筋特異的欠損マウスは，10週齢から血中クレアチンキナーゼの上昇を認め，半年齢で中心核をもつ筋線維が出現し，加齢に伴い筋持久力の低下が顕著化した．半年齢の欠損マウスの骨格筋では，ミトコンドリアの形態異常，脂肪酸β酸化の関連分子や遅筋特異的遺伝子の発現低下，TCA回路の低下を示唆する代謝物の変動が認められた．これらの所見に先立ち，欠損マウスではミトコンドリア特有のリン脂質であるカルジオリピンの減少，ドコサヘキサエン酸を含有するPCの減少とリノール酸やアラキドン酸を含有するPCの代償的増加など，骨格筋リン脂質の組成が大きく変動した．以上のことから，PCの分解と新規合成はPNPLA7により結ばれ，この膜リン脂質の新陳代謝が骨格筋の恒常性の維持に重要であると考えられた.【結論】PNPLA7は膜リン脂質の分解と新規合成を結ぶ新陳代謝に関わり，骨格筋の恒常性およびミトコンドリア機能の維持に重要な役割を担うこと，本経路の機能不全はミトコンドリアの変性と筋障害をもたらすことが示唆された．

O8-5

腹部大動脈瘤に対する人参養栄湯の抑制作用：マウスモデルを用いた検討

東京大学大学院医学系研究科加齢医学講座[1]，同高齢社会総合研究機構[2]
七尾道子[1]，孫　輔卿[2]，宋　沢涵[1]，豊島弘一[1]，大浦美弥[1]，
小室　絢[1]，小川純人[1]，秋下雅弘[1]

【目的】腹部大動脈瘤（Abdominal Aortic Aneurysm：AAA）は加齢性血管疾患であり，高血圧，動脈硬化，喫煙，男性が危険因子として知られている．最近，我々は男性ホルモンであるテストステロンが大動脈瘤形成と病変部の炎症を抑制することを動物実験で明らかにした．しかし，テストステロン補充による治療法は副作用などを考えるとまだ課題が多い．一方，補剤として処方される人参養栄湯（NYT）は人参，黄耆，当帰など性ホルモン様の作用を持つ生薬が多く含まれており，血管保護作用を有することが報告されている．本研究ではNYTのAAA瘤に対する抑制効果を明らかにするために，AAA誘導モデル動物を用いてNYTの作用およびその機序を検討した.【方法】NYTを普通食餌に混ぜ（最終割合5%），雄性C57BL6マウス（8週齢）に8週間食べさせた後，AAA［塩化カルシウム液（0.5mol/L，15分）の局所塗布とアンジオテンシンIIの浸透圧ポンプによる持続投与］を誘導した．さらに4週後，大動脈瘤形成への影響（大動脈径，組織学的解析）を検討した．また，大動脈でのMatrixmetalloproteinase（MMP）-2,9や炎症性サイトカインの発現をreal time PCR，Western blotを用いて検討した.【結果】8週間のNYT投与はAAA群での瘤形成を有意に抑制した．組織学的検討において，AAA群の瘤病変に認められた中膜の破壊およびF4/80陽性マクロファージの浸潤がNYT投与により抑制された．同時に，AAA群で上昇した大動脈F4/80，IL-1β発現に対してNYTが抑制的にはたらくことが明らかになった.【結論】雄性マウスにおいて，漢方薬NYTがAAA形成を抑制することが分かった．その機序としてはテストステロンと同様に大動脈瘤部の炎症抑制が示唆された．今後，詳細な炎症抑制機序およびアンドロゲン受容体の関与などを解明することで，NYTが老化基盤である炎症を抑制し，加齢性血管疾患およびフレイルの予防・治療策になりうる可能性を検証する．

O8-6

老化関連疾患としての肺気腫におけるLTBP-4の肺組織保護効果の検討

Yokohama, Japan

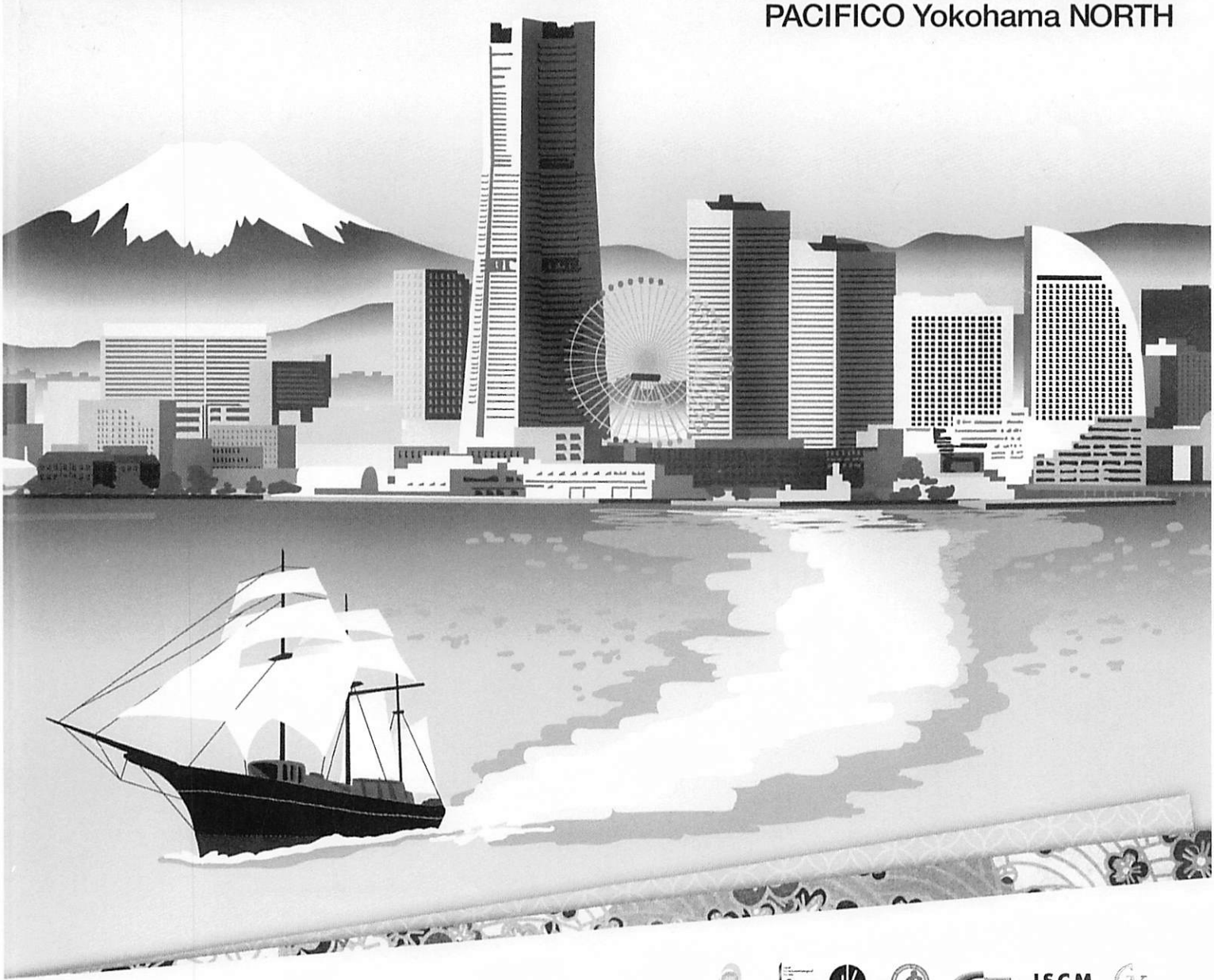
IAGG 2023 YOKOHAMA

IAGG Asia/Oceania Regional Congress 2023

PROGRAM BOOK

For Enhanced Wellbeing in Later Life through Innovation and Wisdom Sharing

June 12-14, 2023
PACIFICO Yokohama NORTH



P10-15-500 **Clinical and radiological outcomes of total hip arthroplasty in octogenarian patients using a three-dimensional porous titanium cup**

Taizo Kaneko, Hiroshi Hamaji, Kentaro Hayakawa, Fumiaki Tokimura, Tsuyoshi Miyazaki

P10-16-521 **Severe Orthostatic Hypotension after Acute Levodopa Challenge in Patients with Early Multiple System Atrophy**

Pan Jing, Pro Chan Piu*

P10-17-527 **Role of endoplasmic reticulum stress on accelerated aging in the progeroid Werner syndrome**

Hiyori Kaneko*, Hisaya Kato, Yoshiro Maezawa, Yasuo Ouchi, Naoya Takayama, Atsushi Iwama, Koji Eto, Koutaro Yokote

P10-18-561 **Analysis of traditional medicine concept: Qi deficiency and Qi depression scores – Relationship with the factors evaluated in Brain Doc test**

Atsushi Nagai*, A Garu, Masahiro Takamura, Yukie Kanai, Kosuke Asayama, Satoshi Asayama

P10-20-611 **Combined effect of depressive symptoms and low dietary diversity on incident disability in community-dwelling older adults with sarcopenia**

Yuto Kiuchi*, Takehiko Doi, Kota Tsutsumimoto, Sho Nakakubo, Satoshi Kurita, Kazuhei Nishimoto, Hyuma Makizako, Hiroyuki Shimada

P10-21-615 **Development of a secure dashboard to monitor progress of data collection efforts for stepped wedge cluster randomised trial using REDCap API**

Noriko Sato*, Kenji Fujita, Timothy Chen

P10-22-643 **Caring for our wisdom bearers: Pacific Mātua (Elder) care**

Siautu Alefaio*, Tracie Mafile'o, Sione Vaka, Kotalo Leau

P10-24-840 **The effect of pharmacotherapy on the changes of social networks in outpatients visiting frailty clinic**

Sho Hasegawa*, Fumihiro Mizokami, Yuji Hayakawa, Yasumoto Matsui

P10-25-917 **The atrophy rate of ventral striatum is greater in spinocerebellar ataxia type 2 patients than in healthy controls**

Kenjiro Nakayama*, Kiyotaka Nemoto, Tetsuaki Arai

P10-26-956 **Delivering care through Telemedicine during the COVID-19 pandemic reduce the risk of unplanned hospital visit, a study from a large medical school in Thailand**

Unchana Sura-amonrattana, Chairat Permpikul, Varalak Srinonprasert*

P10-27-1036 **The effectiveness of long-term periodical pharmaceutical care to manage drug-related problems in community-dwelling older adults in Taiwan –A cluster randomized controlled trial**

Chen-Yu Wang*, Shau-Huai Fu

The NYO3 5th NO-Age/AD meeting and the 1st Norway-UK joint meeting on ageing and dementia

18-19 Sep. 2023

On-line zoom with free registration here https://uio.zoom.us/webinar/register/WN_XBxzUlSqTEOGwnYawHH7BQ

Room: Domus Medica, Auditorium L-200

Address: Sognsvannsveien 9, 0372 Oslo, Norway

Organizers:
Evandro F. Fang (Oslo, Norway)
Lynne Cox (Oxford, UK)
Richard Siow (KCL, UK)

Special co-organizers
Linda Dahlberg (British Embassy Oslo)
He-Ling Wang (Oslo, Norway)

More details

SCAN ME

Poto_EFF

Introduction

Ageing is emerging as a ‘pandemic’ worldwide, including in Norway and the UK. The increase in numbers of people reaching old age brings formidable healthcare and socioeconomic pressure globally. Dementia is one of the most common age- predisposed diseases, putting substantial pressure on the family and society as a whole. Scientists have shown that if we can slow down the ageing process, we may be able to reduce the chances of getting different diseases, including dementia, while we are ageing. In response to the ‘ageing pandemic’, collaborative work among stakeholders and countries is in urgent demand.

Both Norway and the UK are in the forefront of agieng and dementia research, and there is a great opportunity to boost the collaborations between the two countries. Correspondingly, UK Research and Innovation (UKRI) and Research Council of Norway (RCN) have signed a Money Follows Cooperation agreement to reduce barriers to cross-border collaboration. This 1st joint meeting will nourish research collaborations, initiate new joint grant opportunities, and propose ideas for preparation of the impending aging burden; our final goal is to nurture an environment conducive to healthy aging in Norway, the UK, and beyond.

The Events

Associate Prof. Evandro Fang (coordinator of the NO-Age and NO-AD networks; UiO and Ahus), Prof. Richard Siow (director of the ageing research at KCL, London, UK), Prof. Lynne Cox (coordinator of the ageing research networks at Oxford, Oriel, Oxford, UK) welcome you to attend a two-day event in Olso entitled 'The 5th NYO3 NO- Age/AD meeting and the 1st Norway-UK joint meeting on ageing and dementia'.

The event will cover the broad topics of ageing and dementia (especially Alzheimer's and Parkinson's diseases) at molecular, individual, and societal levels. Please see the programme for details. In addition, there will be an open-to-the-public event at Domus Bibliotheca from 19:00-21:00 on the 18th Sep 2023. For the evening event, our confirmed speakers are Dame Linda Partridge DBE FMedSci FRS, Biological Secretary and Vice-President, The Royal Society (UK), and Prof. Ole Petter Ottersen, Neuroscientist and former president/rector of UiO (Norway) and the Karolinska Institute (Sweden), among others.

Registration is not required and attendance at all events will be free of charge.

On-line attendance
https://uio.zoom.us/webinar/register/WN_XBxzUlSqTEOGwnYawHH7BQ)

The NYO3 5th NO-Age/AD meeting cum the 1st Norway-UK joint meeting on ageing and dementia

18-19 Sep. 2023

Venue: Domus Medica, Auditorium L-200 (Address: Sognsvannsveien 9, 0372 Oslo), University of Oslo, Norway

Organizers: Evandro F. Fang (Oslo, Norway), Lynne Cox (Oxford, UK), Richard Siow (KCL, UK)

On-site and zoom (zoom registration). All welcome, registration free and mandatory (see page 1)

Vilhelm Bohr
Copenhagen, DK

Ole Petter Ottersen
UiO, Norway

Lene J. Rasmussen
Copenhagen, DK

Linda H. Bergersen
UiO, Norway

Sofie Lautrup
UiO, Norway

Jon Storm-Mathisen
UiO, Norway

Hilde Nilsen
UiO, Norway

Geir Selbæk
UiO, Norway

Ioannis Sotiropoulos
Athenes, Greece

Linda Partridge
UCL, UK

Janna Saija Saarela
UiO, Norway

Koutaro Yokote
Chiba, Japan

Hisaya Kato
Chiba, Japan

Per Nilsson
Karolinska, Sweden

Katerina Veverova
Charles U., CZ

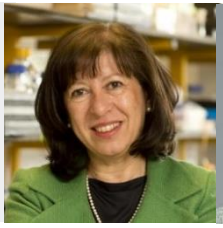
Dag Årsland
KCl/Stavanger

Miguel G. Borda
Stavanger, Norway

Konstantinos Palikaras
Athenes, Greece

Evandro F. Fang
UiO/Ahus, Norway

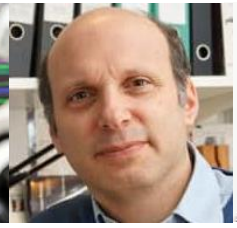
M. Scheibye-Knudsen
CU, Denmark



Maria G. Spillantini
Cambridge, UK

Kristina Xiao Liang
UiB, Norway

Chris I. De Zeeuw
ErasmusMC, Netherlands



David C. Rubinsztein
Cambridge, UK

Tormod Fladby
UiO, Norway

Martin Vyhnálek
Charles U., CZ

Anne Simonsen
UiO, Norway

Lynne Cox
Oxford, UK

Richard Siow
KCL, UK

Nektarios Tavernarakis
U. Crete, Greece

Leiv Otto Watne
AHUS, Norway

He-Ling Wang
UiO, Norway

Stathis Gonos
Athens, Greece

Guobing Chen
Ji-nan U, China

NO-Age NO-AD

Pictures: designated institutions

Day 1 (18 Sep. 2023)	Mechanisms of ageing and dementia	
08:00-08:15 Oslo time	Opening by • UiO vice Rector Prof. Per Morten Sandset • Clare Filshie, Deputy Head of Mission, The British Embassy, Oslo • Dr. Øystein Lund, Counsellor for Research and Education, Royal Norwegian Embassy in London	
PART 1: Mechanisms of ageing and dementia. Chairs: David Rubinsztein (from 08:15) and Ole Petter Ottersen (from 10:45)		
08:15-09:00 Oslo time	Linda Partridge (UCL)	Ageing: a gut feeling
09:00-09:30 Oslo time	Linda Bergersen (UiO)	Exercise in neuroprotection
09:30-10:00 Oslo time	Richard Siow (KCL)	Healthy brain ageing – from cell to society
10:00-10:15 Oslo time	Break	
10:15-10:45 Oslo time	Lynne Cox (Oxford)	Developing therapeutics to treat cell senescence
10:45-11:15 Oslo time	Lene J. Rasmussen (Copenhagen)	FOXO-regulated OSER1 reduces oxidative stress and extends lifespan in multiple species
11:15-11:35	Konstantinos Palikaras (Athens)	The yin and yang of mitophagy in neuronal physiology
11:35-11:55	Ioannis Sotiropoulos	Exosomes & Chronic Stress: key players in progression and diagnosis of AD brain pathology
11:55-12:30 Oslo time	A summary of the ageing and neuroscience activities in Norway and the UK Talks from Sponsors	Prof. Jon Storm-Mathisen to introduce the Norwegian ageing and neuroscience activities Prof. David Rubinsztein to introduce the UK neuroscience activities Prof. Lynne Cox to introduce the UK ageing activities Talks from sponsors
12:30-13:30 Oslo time	Lunch	
PART 2: Mechanisms of ageing and dementia. Chairs: Lynne Cox and Jon Storm-Mathisen		
13:30-14:15 Oslo time	Maria G. Spillantini (Cambridge)	Tau, microglia, and neurodegeneration (tentative)
14:15-14:45 Oslo time	Chris I. De Zeeuw (ErasmusMC)	A linkage between cerebellum and AD? (tentative)
14:45-15:15 Oslo time	Leiv Otto Watne	Delirium and AD (tentative)
15:15-15:30 Oslo time	Break	
15:30-16:00 Oslo time	Katerina Veverova, Martin Vyhnalek (Charles)	Alterations of human CSF and serum-based mitophagy biomarkers patients from Czech Brain Aging Study (CBAS)
16:00-16:15 Oslo time	Kristian Xiao Liang (UiB)	iPSC models for neurodegenerative disease (tentative)
16:15-16:30 Oslo time	He-Ling Wang	The synergistic role of physical excise and NAD^+ in treating AD
16:30-17:15 Oslo time	Nektarios Tavernarakis (Crete)	Autophagy and ageing (tentative)
19:00-21:00	Evening event: Domus Bibliotheca (Karl Johans gate 47, 0162 Oslo, Norway), room booked Key speakers: Ole Petter Ottersen, Linda Partridge	

Panel debate on anti-ageing strategies and a happy ageing society

19:00-21:00 CEST, 18th Sep. 2023

Address: Domus Bibliotheca (Karl Johans gate 47, 0162 Oslo, Norway)

Day 1 (18 Sep. 2023) Evening event	
18.30-19.00	Light dinner at Domus Bibliotheca for speakers only
18.50	Doors open to the audience
19.00	Opening of event by Sofie Lautrup (moderator) Welcome in Norwegian and English
19.10	**Section 1: Ageing Science** Panel members: Linda Partridge, Vilhelm A. Bohr, Maria G. Spillantini, David Rubinsztein, Nektarios Tavernarakis, Richard Siow, Katina Handeland
19.55	Coffee-break and networking
20.10	**Section 2: Ageing Society** Panel members: Ole Petter Ottesen, Lynne Cox, Evandro Fei Fang, Geir Selbæk, Erik Borge Skei, Jon Storm-Mathisen
20.50	Ending remarks by Sofie Lautrup
21.00	Evening event closes

Practical information:

During each section Sofie Lautrup will be the moderator of discussion and ensure to keep the time schedule. The last 15 min of each section will be Q&As from the audience.

A photographer will document the event (please let us know if you do not want photos to be taken of you) Dress-code: Semiformal/formal (audience casual)

Section 1: Ageing Research. Topics: why studying ageing, Popular topics in ageing science, ethical considerations, animal models and humans and more.

Section 2: Ageing Society. Topics: How are we preparing for an ageing society? How is it going? How are interactions between scientists and politicians and clinicians? And the general population?

Day 2 (19 Sep. 2023) **Mechanisms of ageing and dementia**		
08:10-08:15 Oslo time	Coffee	
PART 1: Mechanisms of ageing (Chairs: Linda Partridge and Richard Siow)		
08:15-09:00 Oslo time	Vilhelm Bohr (Copenhagen)	DNA damage signaling to mitochondria in neurodegeneration and aging
09:00-09:30 Oslo time	Koutaro Yokote (Chiba)	Werner syndrome: a model of accelerated aging in human
09:30-10:00 Oslo time	Janna Saija Saarela (UiO)	SNP and ageing (tentative)
10:00-10:30 Oslo time	Hilde Nilsen (UiO and OUS)	DNA damage response as a driver of progressive neurodegenerative diseases – from mechanisms to clinical intervention.
10:30-10:45 Oslo time	Break	
10:45-11:15 Oslo time	Stathis Gonos (Athens)	Proteasome activation delays aging and progression of neurodegenerative diseases (tentative)
11:15-11:45 Oslo time	Morten Scheibye-Knudsen (Copenhagen)	DNA repair and AI in healthy ageing (tentative)
11:45-12:15 Oslo time	Guobing Chen (Ji-nan U.)	Immune ageing and its application on ageing related diseases (tentative)
12:15-12:30 Oslo time	Hisaya Kato (Chiba)	NAD+-based clinical trials in Werner syndrome (tentative)
12:30-13:30 Oslo time	Lunch	
PART 2: Targeting ageing at population and societal levels (Chairs: Maria Spillantini and Vilhelm Bohr)		
13:30-14:00 Oslo time	Geir Selbæk (UiO)	Lifetime risk factors of dementia in the Ageing in Trøndelag cohort study
14:00-14:30 Oslo time	Tormod Fladby (AHUS and UiO)	AD biomarkers (tentative)
14:30-15:00 Oslo time	Per Nilsson (Karolinska)	Autophagy and Alzheimer's disease (tentative)
15:00-15:30 Oslo time	Anne Simonsen	Mitophagy and disease (tentative)
15:30-15:45 Oslo time	Break	
15:45-16:15 Oslo time	Dag Årsland (KCl/Stavanger)	Dementia treatment
16:15-16:30 Oslo time	Miguel G. Borda (Stavanger)	The Crossroads of Dementia, Neurodegeneration, frailty, and sarcopenia
16:30-16:45 Oslo time	Sofie Lautrup (UiO)	Spatiotemporal quantification of mitophagy in AD brain samples (tentative)
16:45-17:30 Oslo time	David C. Rubinsztein (Cambridge)	Autophagy and neurodegenerative disease (tentative)
17:45	Departure/Dinner	

Organizers

Evandro F. Fang
UiO/Ahus, Norway

Dr. Evandro Fei Fang is a molecular gerontologist whose research focuses on understanding the molecular mechanisms of human ageing and age-related diseases. His team uses bench-top knowledge to guide the development of novel interventional strategies towards human ageing, with a final goal of improving the quality of life in all older people. After finishing his PhD at the Chinese Universtiy of Hong Kong, he completed a 6-year postdoc with Prof. Vilhelm Bohr on molecular gerontology and Prof. Mark Mattson on neuronal resilience in Alzheimer's disease at the National Institute on Ageing, Baltimore; he opened his lab in Oslo in the fall of 2017. He is the founding (co)coordinator of the Norwegian Centre on Healthy Ageing network (NO-Age, www.noage100.com), the Norwegian National anti-Alzheimer's disease Network (NO-AD, www.noad100.com), and the Hong Kong-Nordic Research Network.

Lynne Cox
Oxford, UK

Lynne Cox heads the lab of Ageing and Cell Senescence at the University of Oxford. She studied at the University of Cambridge (MA, PhD) and held a Royal Society of Edinburgh fellowship at the University of Dundee, developing initial IP for spin-out Cyclacel. She has served on the UK's All Party Parliamentary Group for Longevity, co-authoring 'Health of the Nation – a strategy for healthier longer lives' launched in 2020 by the UK Secretary of State for Health and Social Care. She is a recipient of the US Glenn Award for research on ageing, and the British Society for Research on Ageing Lord Cohen medal for contributions to ageing science. She co-chairs the European Geriatric Medicine Society Ageing Biology group, co-directs the UK Ageing Research Networks (https://www.ukanet.org.uk/) and is Program Director of Dynamic Resilience, a $60m global healthy longevity program funded by Wellcome Leap and Temasek Trust (https://wellcomeleap.org/dr/).

Richard Siow
KCL, UK

Richard is a graduate of King's College London (BSc Nutrition, PhD Cardiovascular Physiology) and followed his degrees with postdoctoral research in the Department of Medicine, University of Cambridge. Since 2015 he has been the Director of Ageing Research at King's (ARK), a cross-university consortium of researchers taking a multidisciplinary approach to better understand the mechanisms of ageing, improving health-span and the social and economic impact of ageing. He is currently a visiting senior academic in the Department of Physiology, Anatomy and Genetics, University of Oxford. He is the Secretary General of the European Society of Preventive Medicine. His research team focuses on the role of nutrigenomics and ageing on redox signalling in cardiovascular and cerebrovascular health and disease. He has numerous international collaborations including University of Oxford, University of Zurich, National University of Singapore, Harvard Medical School, Charité Berlin, Technical University of Dresden and University of Tsukuba.

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University of Oxford

David C. Rubinsztein
Cambridge, UK

David Rubinsztein FRS FMedSci is Professor of Molecular Neurogenetics and a UK Dementia Research Institute Group Leader at the University of Cambridge. His research is focused in the field of autophagy, particularly in the context of neurodegenerative diseases. His laboratory pioneered the strategy of autophagy upregulation as a possible therapeutic approach in various neurodegenerative diseases, and has identified drugs and novel pathways that may be exploited for this objective. He has made contributions that reveal the relevance of autophagy defects as a disease mechanism and to the basic cell biology of this important catabolic process.

Ole Petter Ottersen
UiO, Norway

Ole Petter Ottersen is a highly accomplished professor of medicine at UiO, holding numerous leadership roles throughout his career. He has been involved in various academic and research initiatives, both nationally and internationally, and has contributed significantly to the field of neuroscience. With extensive teaching experience, Ottersen has prioritized study quality, internationalization, innovation, and communication. He has received prestigious awards and holds honorary doctorates from esteemed institutions. His scholarly work has made a significant impact, with a high citation count and an h-factor of 113.

Linda Partridge
UCL, UK

Professor Dame Linda Partridge DBE FRS is a renowned geneticist and the founding Director of the Max Planck Institute for Biology of Ageing. Her groundbreaking research focuses on aging, lifespan extension, and age-related disorders like Alzheimer's and Parkinson's. Linda's work has applications in developing treatments for these diseases and promoting healthy aging. She studies the evolution of aging rates, mechanisms of lifespan extension in model organisms, and the role of nutrient-sensing pathways. Currently, she focuses on pharmacological treatments for improving health during aging.

Linda H. Bergersen
UiO, Norway

The research group of Dr. Linda Bergersen investigates the role of lactate in pathogenic brain as we age. Dr. Bergersen obtained her PhD from the University of Oslo, and she is now a professor at the University of Oslo, holding multiple roles, including Head of Electron Microscopy Laboratory and Leader of the Brain and Muscle Energy Group, Institute of Oral Biology (IOB), Department of Oral Biology (UiO), Professor in Physiology at the Faculty of Dentistry (UiO), and Professor of Neurobiology of Aging at the Center of Healthy Aging (CEHA), University of Copenhagen, Denmark.

Lene J. Rasmussen
Copenhagen, DK

Dr. Rasmussen’s research focuses on understanding a central challenge of modern biomedicine, namely the genetic origins of complex diseases and the contribution of environmental factors. Her particular research interests include the role of deoxynucleoside kinases in maintaining genomic integrity, interaction between dNTP pools and mitochondrial function, basic research into aging, the molecular mechanisms underlying mitochondrial-mediated mutagenesis, and identification of proteins involved in maintaining integrity of the mitochondrial genome.

Ioannis Sotiropoulos
Athenes, Greece

Dr. Ioannis Sotiropoulos is a researcher and group leader at the Institute of Biosciences & Applications, NCSR "Demokritos", Greece. His research work focuses on understanding the orchestrating role of environmental risk factors (e.g., chronic, lifetime stress) on the onset of Alzheimer´s disease (AD) with a specific focus on the relationship between AD and depression, a stress-related disorder. Combining cell-, animal- and human-based studies, Dr. Sotiropoulos' innovative work aims to clarify the diverse factors that regulate the cellular role of Tau as a key molecule of neuroplasticity and neuropathology while his recent work focuses on exosomes as both mediators of brain pathology and potent biomarkers. He has received different prizes & awards including the Hirnliga Alzheimer Award 2009, AD/PD Young Faculty 2014 Award, Jerome Lejeune 2017 Award, Janssen Innovation Award 2017, Alzheimer Association Award for Best Mentor in Neuroscience 2021.

Konstantinos Palikaras
Athenes, Greece

Konstantinos Palikaras is Assistant Professor of Experimental Physiology at the Medical School of the National and Kapodistrian University of Athens, in Athens, Greece. His research focuses on studies of autophagy, mitophagy, and cellular homeostasis investigating the role of energy metabolism in neuronal physiology and survival. His main interests are the molecular mechanisms of necrotic and mitophagic cell death and their interplay between cellular metabolism and ageing, and the development of novel genetic tools for biomedical research. For his scientific accomplishments, Konstantinos Palikaras has received several notable scientific prizes including the “Fotis Kafatos” Award for excellence in biology from Hellenic Society of Bioscientists and ERC Starting Grant (2022) among others. He is also a member of Genetics Society of America (GSA), the Hellenic Society of Biochemistry and Molecular Biology (HSBMB), the Hellenic Society for Neuroscience (HSfN) and the Hellenic Initiative Against Alzheimer’s Disease (HIAAD).

Jon Storm-Mathisen
UiO, Norway

Jon Storm-Mathisen is a Norwegian brain researcher and is professor emeritus of medicine at the University of Oslo. Retiring officially in 2011, Storm-Mathisen was previously deputy head of the Center for Molecular Biology and Neuroscience. He received the Anders Jahres medical prize in 2006 for his pioneering research on signaling substances in the brain. He received UiO's research prize in 2004. He was also awarded the Nansen Medal and the Lundbeck Prize, and elected member of the Norwegian Academy of Science and Letters. He chaired the inaugural Kavli Prize Committee for Neuroscience.

Maria G. Spillantini
Cambridge, UK

Maria Grazia Spillantini is Professor of Molecular Neurology at the University of Cambridge. She received a Laurea in Biological Sciences from the University of Florence. In 1987 she obtained a PhD in Molecular Biology from Cambridge University. In 1996 she moved to the Department of Clinical Neurosciences at Cambridge. With her collaborators, she identified alpha-synuclein as the major component of the filaments that form the Lewy bodies in PD and described one of the first mutations in the MAPT gene causing FTDP-17T. She has received the Potamkin Prize of the American Academy of Neurology, the Cotzias Prize of the Spanish Neurological Society and the Jay Van Andel Award for achievements in PD. She is Fellow of the Academy of Medical Sciences, and of the Royal Society, and has received a Knighthood from the President of Italy.

Chris I. De Zeeuw
ErasmusMC, Netherlands

Chris I. De Zeeuw is Chairman of the Department of Neuroscience at Erasmus MC in Rotterdam, Vice-Director of the Netherlands Institute for Neuroscience in Amsterdam, and Director of Neurasmus BV. Soon after receiving the Fellowship Award from de Royal Dutch Academy of Sciences (KNAW) he became visiting professor at NYU Med School in New York. When he returned to the Netherlands he became Professor and Chair of the department that he founded in Rotterdam around the turn of the new millennium. He has been Principal Coordinator of the EU Robotics program (SENSOPAC) and President of Neuro-Bsik Mouse- and Pharma-Phenomics consortia. De Zeeuw has received over 100 grants, including the PIONIER Award from ZonMw and the ERC advanced grant. In 2006 he received the Beatrix Award for Brain Research from her Majesty the Queen, in 2014 he became elected member of the Dutch Academy of Arts & Science, and in 2018 he received the international Casella Prize for Physiology.

Leiv Otto Watne
AHUS, Norway

Professor Leiv Otto Watne is a geriatrician at the Department of Geriatric Medicine, Akershus University Hospital, Norway. He is the President of the European Delirium Association and the leader of Oslo Delirium Research Group. The group has carried out pharmacological and non-pharmacological intervention studies, as well as studies on delirium pathophysiology and epidemiology. The group has comprehensive experience in sampling biological and clinical data from patient cohorts. Their biobank of CSF and blood samples from delirious patients is a valuable source of information on pathophysiological mechanisms in delirium.

Katerina Cechova
Charles U., CZ

Dr. Katerina Veverova (Cechova) is a cognitive neuroscientist at the Second Faculty of Medicine, Charles University in Prague and University Hospital Motol. In 2021, she completed her Ph.D. focusing on BDNF as a marker of prediction, follow-up, and intervention in neurodegenerative diseases in the Czech Brain Aging Study (www.cbas.cz). She is an Assistant Professor at the Department of Psychology, Charles University, and deputy chairperson of the Neuropsychological section of the Czech-Moravian Psychological Society. Currently, her main research interest is the interaction of biofluid biomarkers of Alzheimer's disease and cognition, with a particular focus on mitophagy as a promising molecular mechanism underlying the pathogenesis of AD (www.mitophagyeu.cz).

Martin Vyhnálek
Charles U., CZ

Associate Professor Martin Vyhnálek is a cognitive neurologist based in Motol University Hospital, Charles University in Prague, Czech Republic. After his medical studies, he completed a degree in clinical neuropsychology at Montpellier University in France. After returning to Prague, he co-founded the Czech Brain Aging Study – the only Czech longitudinal, observational study on aging and dementia. He is responsible for neuropsychological core and biobanking. His research focuses mainly on early cognitive and neuropsychiatric markers of neurodegeneration and the role of subjective cognitive complaints in early AD diagnostics.

Kristina Xiao Liang
UiB, Norway

Dr. Kristina Xiao Liang is the Principal Investigator and Group Leader of the Mitochondrial Stem Cell Group at the University of Bergen (UiB) Faculty of Medicine. She is an expert in using stem cell models, especially induced pluripotent stem cells (iPSCs), to identify mechanisms underlying mitochondrial diseases and to develop iPSC-based platforms to test therapeutics. Her research group is based in the UiB's Department of Clinical Medicine (K1) and is part of Neuro-SysMed, the Center of Excellence for Clinical Research in Neurological Diseases, Department of Neurology, Haukland University Hospital. Her research group has established the capabilities and facilities required for iPSC reprogramming and differentiation, enabling the study of neuronal cells from patients and healthy controls. The group has also recently developed 3D brain organoids to study disease mechanisms and test treatments, including NR.

He-Ling Wang
UiO, Norway

He-Ling Wang is a DPhil candidate in the Evandro Fang Laboratory at the University of Oslo, Norway. She holds a Bachelor's degree in Medicine and a Master's degree in Oral Medicine from Jilin University, China. During her Master programme, she completed a one-year internship program at Okayama University, Japan, where she received training in microbiota. In the Fang laboratory, she is studying three major research topics: 1) mechanistic studies of Alzheimer's disease (AD) with a particular emphasis on roles of reduced NAD+ and compromised autophagy/mitophagy in AD progression; b) investigating potential synergistic benefits of exercise plus NAD+ in slowing AD; and c) conducting research on the connection between malfunctioned and imbalanced microbiota profile and AD. Her final goal is to identify effective and publicly accessible therapeutic interventions.

Nektarios Tavernarakis
U. Crete, Greece

Nektarios Tavernarakis is Professor of Molecular Systems Biology at the Medical School of the University of Crete, Chairman of the Board of Directors at the Foundation for Research and Technology-Hellas, and Research Director at the Institute of Molecular Biology and Biotechnology, in Heraklion, Greece, where he is heading the Neurogenetics and Ageing laboratory. He is the Founder and first Director of the Graduate Program on BioInformatics at the University of Crete, Chairman of the European Institute of Innovation and Technology (EIT) Governing Board, and has served as Vice President of the Scientific Council of the European Research Council (ERC), and Director of IMBB. He is a member of AAAS, EMBO, Leopoldina, EASA, Academia Europaea, the European Academy of Sciences (EurASc) and the Academy of Athens. He earned his Ph.D. degree at the University of Crete and trained as a postdoctoral researcher at Rutgers University in New Jersey, USA. His work focuses on the molecular mechanisms of necrotic cell death and neurodegeneration, the interplay between cellular metabolism and ageing, the mechanisms of sensory transduction and integration by the nervous system, and the development of novel genetic tools for biomedical research.

Vilhelm Bohr
Copenhagen, DK

Prof. Bohr's main contributions to science have been in the area of DNA repair. He has worked on many aspects of DNA damage and its processing in mammalian cells. He developed a widely used method for the analysis of DNA repair in individual genes and found that active genes are preferentially repaired. This observation was a major advance in the clarification of the tight interaction between DNA repair and transcription, a process termed transcription-coupled repair. In recent years numerous papers from his laboratory have focused on mechanisms of DNA damage processing, particularly on nucleotide excision repair and transcription coupling. A main interest now is to elucidate how these processes change in relation to aging.

Koutaro Yokote
Chiba, Japan

Koutaro Yokote, a graduate of Chiba University, is a physician scientist in the field of Endocrinology, Diabetology, and Geriatrics. He received Ph.D from Uppsala University for the study of PDGF receptor signaling, under Dr. Carl-Henrik Heldin the former Chairman of the Nobel Foundation. Dr. Yokote developed interest in pathogenesis of atherosclerosis in relation to aging, which led to studies of the progeroid Werner syndrome in Japan. He organized the Werner syndrome registry in Japan and played a central role in establishing management guidelines for the syndrome. He is engaged in both clinical and basic studies on Werner syndrome, with a belief that the efforts would facilitate not only the research of the specific disease, but also the understanding of common age-related disorders such as atherosclerosis and diabetes. He has published more than 360 papers in peer-review journals including NEJM and Nature, and is currently the president of Japan Society for the Study of Obesity.

Janna Saija Saarela
UiO, Norway

The Saarela group’s research focuses on improving the understanding of biological pathways and pathogenic mechanisms behind rare and common immune diseases. They especially focus on primary immune deficiencies and multiple sclerosis and utilising the new knowledge to the benefit of the patients. They use rare immune diseases as models for autoimmunity and focus on identifying novel causative genes for the rare disorders in the founder population of Finns and study the functional consequences of the identified gene defects.

Hilde Nilsen
UiO, Norway

Hilde Loge Nilsen is a researcher and professor at the University of Oslo. Her work focuses on studying DNA and RNA quality control mechanisms in human disease, particularly in relation to cancer, aging, and neurodegenerative disorders. With extensive experience and notable contributions in the field, Nilsen investigates the role of DNA repair enzymes and their impact on preventing mutations and maintaining cellular function. Her research also highlights the involvement of DNA repair proteins in RNA quality control. Nilsen's work aims to advance our understanding of tumorigenesis, age-related diseases, and the intricate interplay between DNA and RNA maintenance.

Stathis Gonos
Athens, Greece

Stathis Gonos graduated from the University of Athens, Greece, and obtained his Ph.D. at the University of Glasgow and was a Docent at the Orebro University Medical School, Sweden. He worked at the Ludwig Institute for Cancer Research/University College in London and at the National Hellenic Research Foundation/ICB. Since 2021, he has been the General Director of the Hellenic Pasteur Institute. His research focuses on the genetic and environmental factors that are linked to human aging and longevity. He has published more than 150 research articles and holds patents that have resulted in the development of novel anti-aging products. Dr. Gonos has been a "Senior expert'' for the EU in "Human development and the aging process" and is a past member of the Executive Committee of International Union of Biochemistry and Molecular Biology (IUBMB). He is Editor-in-Chief of “Mechanisms of Ageing & Development” and “IUBMB Life”.

M. Scheibye-Knudsen
CU, Denmark

Dr. Scheibye-Knudsen’s lab focuses on trying to understand the cellular and organismal consequences of DNA damage in ageing with the aim of developing interventions to treat this damage, and thus ageing. His team discovered that DNA damage leads to changes in certain metabolites and that replenishment of these molecules may alter the rate of ageing in model organisms. These findings suggest that normal ageing and age-associated diseases may be amenable to similar interventions. The hope is to develop interventions that will allow everyone to live healthier, happier and more productive lives.

Guobing Chen
Ji-nan U, China

Guobing Chen is Professor of Immunology, Director of Institute of Geriatric Immunology and Deputy Dean of the School of Medicine, Jinan University in China. His group is working on how the immune system changes during aging, to identify the biomarkers of immune aging, explore the immunological factors relevant to geriatric diseases, such as infectious, autoimmune and neurodegenerative diseases, and finally to develop the efficient treatment to prevent aging and aging related diseases.

Hisaya Kato
Chiba, Japan

Dr. Hisaya Kato is committed to revealing the mechanisms of aging through the study of the progeroid Werner syndrome. He has developed disease-specific induced pluripotent stem (iPS) cells and gene repair methods using CRISPR/Cas9, along with techniques for inducing differentiation into mesenchymal stem cells and adipocytes. Dr. Kato is also engaged in omics analysis using patient-derived fibroblasts and liquid biopsy samples. Additionally, he is involved in the EMPOWER clinical trial, which examines the effects of nicotinamide riboside on Werner syndrome patients.

Geir Selbæk
UiO, Norway

Geir Selbæk is a professor at the University of Oslo and research director at the Norwegian Centre for Ageing and Health. He is a medical doctor (1991), and psychiatrist (2001). He completed his PhD on neuropsychiatric symptoms and medication use in nursing home patients with dementia in 2008. He leads the Norwegian registry for persons with cognitive symptoms, at present including 24,000 persons from 47 outpatient departments in Norway. He is also leader of the population-based study of cognition in old age, HUNT4 70+, including 12,000 persons 70 years of age or older, and the 4-year follow-up study of this cohort, Ageing in Trøndelag. He is a member of the Lancet Commission on Dementia Prevention, Treatment and Care. His research covers several aspects of ageing, with a particular focus on cognitive impairment and dementia.

Tormod Fladby
UiO, Norway

Tormod Fladby is a professor of neurology at the University of Oslo Institute of Clinical Medicine, and leader of the neurology clinic at Akershus University Hospital, and previous leader of the Norwegian Forum for Neuropsychiatry. In 2017, he won the prestigious Norwegian National Association for Public Health's Dementia research prize. He was an initiator of the Norwegian Neuropsychiatric Association, and previous chairman of the Nansen Neuroscience Federation. His main research focuses on Alzheimer's disease (AD), by far the most common cause of dementia, where he has undertaken studies looking into biomarkers of disease within blood and spinal fluid.

Per Nilsson
Karolinska, Sweden

Per Nilsson's group focuses on the role of autophagy in Aβ metabolism and neurodegeneration in Alzheimer's disease, analysing the mechanism of autophagy in the metabolism of Aβ using state of the art AD mouse models; using genetic tools, we inhibit autophagy in different neuronal cells. Intriguingly, we have found that when autophagy is deleted in nerve cells, the extracellular Aβ plaques decrease and Aβ instead accumulates intracellularly. This activates neurodegenerative processes which could be linked to the neurodegeneration taking place in the AD brain. This neurodegeneration is currently being investigated using different genetic and omics approaches.

Anne Simonsen
UiO, Norway

Dysfunctional autophagy is linked to several pathophysiological conditions, including cancer and neurodegenerative disorders. The main focus of the "Simonsen Lab" is to characterize of the molecular mechanisms involved in cargo sequestration and autophagosome biogenesis during non-selective and selective types of autophagy with a long-term goal to identify novel targets for diagnosis or treatment of human disease. Work in our laboratory is focused on identification of novel lipid-binding proteins involved in different types of autophagy and elucidation of their function in autophagy and link to disease. To address these challenges, we use a combination of cell biological, biochemical, imaging, genomic and computational approaches, as well as disease-related model systems.

Dag Årsland
KCL/Stavanger

Prof. Dag Årsland is a Professor and Department Head at the Department of Old Age Psychiatry, Institute of Psychiatry, Psychology , and Neuroscience at King's College London. His research takes in a wide range of topics within neuropsychiatry, including Parkinson's disease and dementia with Lewy bodies; he has been a member of many international collaborations in these areas. He was key in the development of the "Parkinson-spectrum Memory Clinic" for patients with Parkinson's and Lewy body dementia at the South London and Maudsley NHS Foundation Trust. Professor Årsland is a prolific author, and a popular lecturer in his field at international scientific conferences.

Miguel G. Borda
Stavanger, Norway

Miguel is a medical doctor specialising in geriatric medicine (2019). He received both his medical and specialty degrees from Pontificia Universidad Javeriana in Colombia and completed a Master's degree in Movement Disorders at the Universidad de Murcia in Spain. He has a Doctorate in Health Sciences from the University of Stavanger in Norway, where his thesis focuses on clinical and neuroimaging prognostic markers in Alzheimer's Disease and Lewy Body Dementia, with a particular emphasis on the role of muscle status and nutrition. His main research interests centre around dementia, particularly Lewy body dementia, and the systemic interactions between dementia and the body, specifically the role of muscle. He also has a special interest in nutrition, sarcopenia, frailty, functional capacity, fatty acids, and interventions to promote cognitive health and healthy aging.

Sofie Lautrup
UiO, Norway

Dr. Sofie Lautrup is a researcher and senior postdoc in the Evandro Fang lab at the Univerity of Oslo. She studied the connections between the DNA base excision repair (BER) and cognitive capacity during brain ageing (Aging Cell 2023) with Professor Tinna Stevnsner at Aarhus University, Denmark. She also worked in the laboratory of Dr. Vilhelm A. Bohr at the National Institute on Aging (NIA), Baltimore, USA during her PhD, whereby she focused on the NAD+ precursor Nicotinamide Riboside (NR) as an Alzheimer's Disease (AD) therapeutic (PNAS, 2018). In the Fang lab, she is studying how NAD+ affects both normal and premature ageing using spatial-OMICS and staining to map the spatio-temporal changes of mitophagy and beyond in the human aging and disease brain.

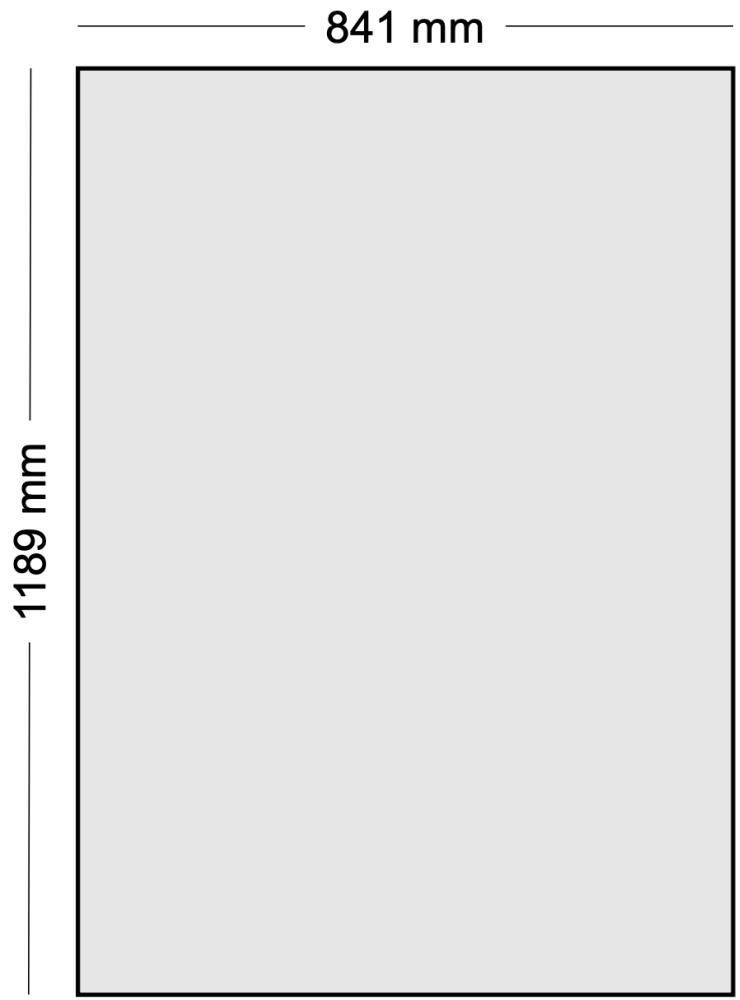
Erik Borge Skei
Ahus, Norway

Erik Borge Skei is the Director of the medical division at Akershus University hospital in Norway since 2019, which consists of 17 departments including geriatrics. He was previously the clinical director at the Children- and youth clinic at Ahus. He is a medical doctor with specialties in pediatrics and children's diseases. Erik Borge Skei has been greatly involved in Norwegian policies as the former deputy chairman of the Oslo Left party, chairman and deputy chairmen of different departments in the Oslo municipality.

Katina Handeland
Aker Biomarine, Norway

Dr Katina Handeland is Director of Research & Development and Human Nutrition at Aker BioMarine in Oslo, Norway. Aker Biomarine is a biotech innovator and Antarctic krill-harvesting company, with the dedication of improving human and planetary health. Handeland is working on both design and follow-up of the pre-clinical and clinical trials for the human health portfolio, studying the biological effects of krill and its benefits. Katina Handeland holds a Ph.D. in Nutrition from the University of Bergen, and she has extensive experience with innovation projects for medical nutrition and is currently serving as the President of the Board for the Norwegian Nutrition Society.

Poster



How to format your poster:

- ❑ Size: Posters should be no larger than A0 size (841 x 1189 mm), in portrait format

- ❑ On main area of the poster, include a reproduction of your abstract with the following headings (which should be in 40 pt font):
  - Introduction
  - Methods
  - Results
  - Conclusions
  - References
  - Discussion (optional)

- ❑ Recommended fonts are Arial, Calibri, Century Gothic, Geneva, ad Helvetica (San serif fonts)

Acknowledgements

The NO-Age and NO-AD Seminar Series

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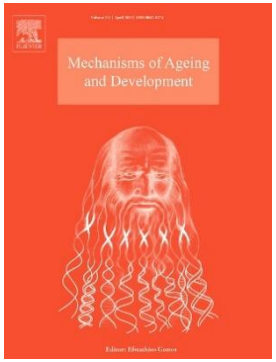

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Acknowledgement

The **Validation of specific mitophagy biomarkers across Alzheimer's disease continuum** benefits from a € 1 404 000 grant from Iceland, Liechtenstein and Norway through the EEA Grants and the Technology Agency of the Czech Republic within the KAPPA Programme.

Iceland Liechtenstein Norway grants

Programme Kappa

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見過ごされやすい症状から見つかる早老症ウェルナー症候群

思春期以降に急速に老化が進行する遺伝的早老症ウェルナー（Werner）症候群は、本邦で約2000人の患者数と推定される希少難病です。外見の老化のみならず、サルコペニアや糖尿病、脂質異常症、動脈硬化性疾患、悪性腫瘍を高率で合併し、下肢や肘の難治性皮膚潰瘍を伴います。診断に難渋し発病から診断まで平均16年を要するという報告もあります。本セミナーでは、「遺伝的早老症ウェルナー症候群」と「見過ごされやすい症状」を早老症ウェルナー症候群診療に精通した内科医と形成外科医の先生方から、講義いただきます。また、司会者、企画担当者を加えて質疑応答を行います。総合内科専門医だけでなく、認定内科医、あるいは臨床研修医などすべての方々が参加可能になっておりますので、奮ってご参加ください。

開催日	2023年7月9日(日) 10時30分～11時30分
開催形式	ハイブリッド開催(現地参加とweb開催の併用)
現地会場	**日本都市センター 3階コスモスホール** 千代田区平河町2-4-1 TEL：03-3265-8211
企画	専門医部会関東支部
世話人	千葉大学予防医学センター/糖尿病・代謝・内分泌内科　越坂　理也 千葉大学医学部附属病院感染症内科・感染制御部　谷口　俊文 東京大学医学部附属病院消化器内科　佐藤　雅哉
参加費	無料
会場参加	**直接会場で受付を行ってください。(事前参加登録は不要です)** ※ご来場の際は下記リンクから「企画参加同意書」を入手しご持参ください ➔ **支部企画にご参加されるみなさまへ**
web参加	**第688回関東地方会**への事前参加登録が必要になります。 ※お住まいの地域に関係なくご参加いただけます。
認定更新単位設定	**【認定内科医・総合内科専門医】2単位** ※視聴時間は任意といたしますが、60分以上のご参加をお願いいたします。 ➔ 入退場時間記録について

	【内科専門医】[出席単位]：なし　[視聴単位]：1時間1単位 ※視聴時間が問われます ➔ 「内科専門医」資格の認定と更新についてのご案内
注意事項	**単位がパーソナルウェブに反映まで1か月程度かかります** 参加状況確認後、事務局にて自動付与いたします。別途申請等を行う必要はありません。 **単位付与は当日の視聴記録(アクセスログ)に基づき行われます。** 視聴記録が確認できない場合は単位付与できませんのでご注意ください。

プログラム

テーマ『希少難病を見過ごさないための診療アプローチ』

司会

千葉大学予防医学センター/糖尿病・代謝・内分泌内科　越坂　理也

プログラム

1. はじめに

東京大学医学部附属病院消化器内科　佐藤　雅哉

2. 講演『遺伝的早老症ウェルナー症候群』

千葉大学医学部附属病院糖尿病・代謝・内分泌内科　前澤　善朗

3. 講演『早老症の見過ごされやすい症状』

千葉大学医学部附属病院形成外科学　窪田　吉孝

4. ディスカッションおよび質疑応答

ディスカッサー：千葉大学感染制御部・感染症内科　谷口　俊文

東京大学医学部附属病院消化器内科　佐藤　雅哉

詳細

日付:

2023年7月9日

会場

日本都市センター(ハイブリッド開催)

千代田区平河町２－４－１ + Google マップ

電話:

03-3265-8211

ウェルナー症候群患者さんの診療経験のある医療機関（順不同）

2023年10月

東北	福島県立医科大学会津医療センター	糖尿病代謝・腎臓内科学
関東	千葉大学医学部附属病院	糖尿病・代謝・内分泌内科
	千葉大学医学部附属病院	形成外科
	国際医療福祉大学成田病院	糖尿病・代謝・内分泌内科
	群馬大学医学部附属病院	皮膚科
	慶応義塾大学病院	皮膚科
	佐野厚生総合病院	皮膚科
	成田赤十字病院	糖尿病・内分泌代謝科
	公立昭和病院	皮膚科
	横浜市立大学附属病院	遺伝子診療科
中部	名古屋大学医学部附属病院	老年内科
	名鉄病院	老年内科
	名古屋市立大学病院	内分泌・糖尿病内科
	愛知医科大学病院	糖尿病内科／糖尿病センター
	伊那中央病院	皮膚科
	国立病院機構　金沢医療センター	内分泌代謝内科
	国立病院機構　金沢医療センター	皮膚科
	地域医療機能推進機構　中京病院	皮膚科 膠原病リウマチセンター
	名南病院	内科
近畿	大阪大学医学部附属病院	老年・高血圧内科
	大阪大学医学部附属病院	皮膚科
	奈良県立医科大学附属病院	整形外科
	神戸大学医学部附属病院	皮膚科
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	天理よろづ相談所病院	内分泌内科
	鈴鹿中央総合病院	消化器内科
	福知山市民病院	整形外科
	住友病院	皮膚科
中国	川崎医科大学高齢者医療センター	高齢者総合診療科
	岡山大学病院	皮膚科
	岡山大学病院	総合内科・総合診療科
九州	九州大学病院	内分泌代謝・糖尿病内科
	佐賀大学医学部附属病院	形成外科
	恵愛会　大分中村病院	形成外科
	一般財団法人杏仁会　江南病院	糖尿病・内分泌内科
	佐賀県医療センター好生館	糖尿病代謝内科
	大分大学医学部附属病院	小児科学講座
	大分大学医学部附属病院	内分泌糖尿病内科
	熊本大学病院	糖尿病・代謝・内分泌内科

（ウェルナー症候群の患者様は受診される際には、可能であれば事前に当該病院の外来に電話などでご連絡いただけますと、診療がよりスムーズに進みます。）

Title: New recommendations for cancer screening and surveillance in patients with Werner syndrome

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Keywords

Werner syndrome, *WRN*, cancer screening, cancer surveillance, non-epithelial tumor

Werner syndrome (WS) is an autosomal recessive premature aging disorder caused by mutations in the *WRN* gene. It is characterized by the development of age-related diseases, such as juvenile bilateral cataracts, gray hair, hair loss, insulin-resistant diabetes mellitus, atherosclerosis, and cancer after adolescence. The leading causes of death in patients with WS are coronary heart disease and cancer. Due to improvements in the management of diabetes and dyslipidemia, deaths from atherosclerotic disease have decreased dramatically, and life expectancy has increased to 59 years.[1]

The average age of cancer onset has increased in patients with WS, from 36.9 years in 1966 to 49.7 years in 2023.[2,3] However, since the average age at the onset of cancer is younger in patients with WS than in healthy individuals, early detection and treatment are critical.[3]

In patients with WS, the morbidity of non-epithelial tumors, such as malignant melanoma, meningioma, soft tissue sarcomas, osteosarcomas, and hematologic tumors (myelodysplastic syndrome and multiple myeloma), is higher than that in the general population, and the frequency of multiple primary cancers is higher.[2,4,5] The ratio of epithelial to non-epithelial tumors is 1:1.5 in patients with WS, compared with 10:1 in the general population.[3] However, recent reports indicate that the incidence of epithelial tumors, such as thyroid, lung, and breast cancers, is increasing, and the ratio of epithelial to non-epithelial tumors is 1.6:1. This change may reflect the increased life expectancy of patients with WS. [2]

Guidelines of cancer screening in patients with WS are insufficient. Ultrasound screening for thyroid cancer and annual full-body skin examinations are recommended for malignant melanomas.[6] The most common types of malignant melanoma in patients with WS are acral lentiginous melanoma and mucosal melanoma, particularly in nasal mucosa, palms, and soles.[4] Neurological evaluations of signs and symptoms are also important to screen for intracranial tumors.[7]

Recently, we have received many inquiries regarding cancer screening and treatment in patients with WS. Based on the types of cancers commonly observed in patients with WS and the specific problems with screening tests, we proposed a strategy for cancer screening and surveillance in patients with WS, as shown in Table 1.

In general, recommendations for cancer screening in Japan include radiography or endoscopy for gastric cancer, fecal occult blood tests for colorectal cancer, radiography or sputum cytology for lung cancer, mammography and palpation for breast cancer, and cytology or human papillomavirus (HPV) tests for cervical cancer. World Health Organization also strongly recommends HPV tests for cervical cancer.[8] However, because WS is caused by a defect in the WRN protein, which is involved in DNA metabolism, radiation that can cause DNA damage may be carcinogenic. WS cells are susceptible to X-ray-induced chromosomal aberrations; therefore, excessive irradiation should be avoided.[9] Interview and physical examination should

also be performed assuming non-epithelial tumors, which are more common in WS.

For cancer screening in young-onset progeria syndromes, such as Bloom syndrome, characterized by abnormal DNA repair mechanisms arise from mutations in the *BLM* gene, ultrasound and MRI are preferred over X-rays and CT scans.[10] Blood cell counts to screen for hematologic tumors and routine skin examinations with minimal UV exposure to screen for skin cancers are also recommended. The benefits of routine screening for osteosarcoma have yet to be established, and imaging should be considered as necessary, with attention to signs and symptoms. Therefore, the proposed cancer screening for WS includes the use of ultrasound and MRI, rather than X-rays.

Patients with WS can receive chemotherapy and surgery, similar to other patients with cancer. Treatments for cancer are advancing, and early detection may prolong survival. Although we have recommendations for cancer screening in WS for the first time, there is a lack of information on the effectiveness of the screening program, including the age of initiation, the appropriateness of the intervals, and the cost-effectiveness. Therefore, further studies are warranted.

We expect that the newly proposed malignancy screening strategy will improve the quality of life and prognosis of patients with WS.

Authors' contributions

Y.M., H. Kato, and K.Y. managed the project. Y.M. and K.A. drafted and revised the manuscript. K.A., Y.M., H.Kato., H.Kaneko., Y.K., T.T., T.O., S.M., H.N., A.T., K.W., M.T., M.K., K.Y. critically reviewed the manuscript. All the authors contributed to reviewed and approved the final manuscript.

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Conflict of Interest disclosure

The authors declare no conflict of interest.

Ethics approval statement

The study adhered to the tenets of the Declaration of Helsinki. The study received approval from the Ethics Board of Chiba University on 27th July 2016 (approval number: 278) and from the Ethics Board of Kyoto University on 29th January 2020 (approval number: R2370). Written informed consent was obtained from patients before enrollment.

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Table 1. Recommendations for Cancer Screening and Surveillance in Patients with Werner Syndrome (2024)

Cancer type	Frequency	Screening type	Interval/timing	Notes
Thyroid cancer	High	Palpation, ultrasound	Annual	
Lung cancer	Less	Chest X-ray	Annual	Avoid smoking
Breast cancer	Less	Breast ultrasound	Every 2 years	Avoid excessive alcohol intake
Meningioma	High	Interviews for headache, dizziness, and neurological symptoms Brain MRI	Every 6 months MRI, if necessary	
Soft tissue sarcoma,	High	Soft tissue visual inspection and	Annual	

osteosarcoma		palpation Interviews for Bone pain		
Malignant melanoma	High	Skin visual inspection	Annual	Avoid excessive exposure to ultraviolet light. Use of sunscreen is recommended
Leukemia, myelodysplastic syndromes	High	Blood cell counts	every 3 months	
Pancreatic cancer	Less	Abdominal ultrasound	If diabetes develops or there's sudden glycemic control deterioration	

Gastric and colorectal cancer	Less	Fecal occult blood tests.	Annual	Upper gastrointestinal endoscopy is preferred over gastric fluoroscopy

ウェルナー症候群全国疫学調査事務局からのお知らせ

ウェルナー症候群はまれな遺伝的早老症で，思春期以降に白髪，若年性の両側白内障，皮膚の萎縮や胼胝，内臓脂肪蓄積，糖尿病，心筋梗塞，悪性腫瘍などの加齢関連疾患を早発し，50代で死にいたる疾患です．世界における報告の三分の二が日本人であり本邦にはおよそ700～2,000人の患者がいるとされておりますが，未だ根治治療はなく，皮膚潰瘍や悪性腫瘍などによりQOLが著しく低下します．一方で，近年は患者の生命予後が改善しており，特に早期からの介入により，血管イベントによる死亡率が減少していることが分かってきました．すなわち，ウェルナー症候群においては早期診断・早期治療の重要性が以前にも増して高くなっております．

ウェルナー症候群患者において最も早く出現し，感度・特異度の高い臨床症状の1つとして若年性(20～30代)の両側白内障があり，本症候群の患者は眼症状を主訴に病院を初診される場合が多いと考えられます(別紙「こんな患者はいませんか？」を参照)．特に若年で両眼の核白内障がみられたときは本疾患を強く疑います．また，日眼会誌第126巻1号にも掲載いたしましたが，ウェルナー症候群患者は同年齢と比べて乳頭周囲網膜神経線維層と網膜神経細胞複合体厚が有意に菲薄化しており，若年で緑内障を発症しやすい可能性が示唆されております．

したがって，ウェルナー症候群の早期発見・早期診断に眼科医が関与する部分が非常に大きいと思われます．日々の診療において疑わしい患者をご覧になりましたら，診断に寄与できる近隣の大学病院等に速やかに紹介していただけるようお願い申し上げます．

本研究班では，厚生労働省科学研究費補助金(難治性疾患研究事業)「早老症のエビデンス集積を通じて診療の質と患者QOLを向上する全国研究」の一環としてウェルナー症候群の実態を把握するための全国疫学調査を実施してきました．10年以上の一連の研究事業の中で，平成21～25年度の難治性疾患克服研究事業においてウェルナー症候群の診断基準改定と世界初のウェルナー症候群診療ガイドラインが作成され，翌平成26年度には重症度分類が作成され，平成26年5月にウェルナー症候群が指定難病に指定されました．平成29年度には診療ガイドライン，重症度分類が改訂され，令和2年度には診療ガイドラインが英文誌に公表されました．現在，ウェルナー症候群のレジストリ研究が進行中で，2023年3月の時点で4年間にわたるウェルナー症候群のレジストリーの登録状況は全国13施設，登録症例数54例となっております．このようなレジストリ研究から，前述の心血管予後の改善といった，ウェルナー症候群の臨床像を明らかにする知見が得られてきています．

ウェルナー症候群に関するご質問は，werner.chiba@gmail.com でお受けいたします．

ウェルナー症候群に関する情報や班研究の経過に関しては下記のホームページに掲載していく予定です．
https://www.m.chiba-u.jp/dept/clin-cellbiol/werner/#item11

厚生労働科学研究費補助金　難治性疾患研究事業
早老症のエビデンス集積を通じて診療の質と患者QOLを向上する全国研究　研究班
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ウェルナー症候群全国疫学調査事務局：
〒260-8670　千葉市中央区亥鼻1―8―1
千葉大学大学院医学研究院　内分泌代謝・血液・老年内科学　講師
分担研究者　前澤善朗
TEL：043-222-7171(ext5257)　FAX：043-222-7171(ext5257)
E-mail：werner.chiba@gmail.com

こんな患者さんいませんか？

ウェルナー症候群（早老症候群）

✓ 年齢の割に外見が老けて見える（白髪、禿頭）

✓ 20～30 代の両眼の（核）白内障（ほぼ 100%）

✓ 足底部に魚の目やたこができやすく、傷が治りにくい

✓ 声帯の萎縮によるかん高いしわがれ声

✓ 高インスリン血症を伴った糖尿病

※このような症状をすべて満たす必要はなく、２～３個の症状がある場合には
ウェルナー症候群を疑います。

※すでに白内障手術が施行されている場合が多く、両眼 IOL 眼の場合は網膜神
経線維層の菲薄化及び脈絡膜の菲薄化が参考所見になります。

ウェルナー症候群の主な特徴

・RecQ 型 DNA ヘリカーゼの変異（常染色体劣性遺伝）

・20 代より種々の老化徴候が出現

・20 歳～　白髪・脱毛

・30 歳～　両側白内障・糖尿病

・40 歳～　心筋梗塞・悪性腫瘍

・平均死亡年齢　59 歳

・悪性腫瘍の合併が多く、非上皮性腫瘍の頻度が高い

※早期発見・早期診断によって早期治療介入することで血管イベントによる死
亡は改善傾向

参考資料

ウェルナー症候群の診断基準（2012）

https://www.m.chiba-u.jp/dept/clin-cellbiol/files/5215/0752/8288/guideline.pdf

Ⅰ 主要徴候（10歳以後、40歳まで出現）

1． 早老性毛髪変化（白髪、禿頭など）

2． 白内障（両眼）

3． 皮膚の萎縮・硬化（鶏眼や胼胝等）、難治性潰瘍形成

4． 軟部組織の石灰化 （アキレス腱等）

5． 鳥様顔貌

6． 音声の異常（かん高いしわがれ声）

Ⅱ その他の徴候と所見

1． 糖、脂質代謝異常

2． 骨の変形などの異常（骨粗髭症等）

3． 非上皮性腫瘍または甲状腺癌

4． 血族結婚

5． 早期に現れる動脈硬化（狭心症、心筋梗塞等）

6． 原発性性腺機能低下

7． 低身長及び低体重

Ⅲ 遺伝子変異

診断方法
確定：主要徴候の**すべ**て。もしくは3つ以上の主要徴候に加え、遺伝子変異を認めるもの。
疑い：主要徴候の1, 2に加えて主要徴候やその他の徴候から2つ以上。
付記 通常ウェルナー症候群では知能低下を認めないことが多い。認知機能に関しては年齢相応であることが多い。

若年ウェルナー症候群患者の症

症例	陽性率（%）	1	2	3	4	5	6
性別		女	女	女	男	男	男
診断時年齢		23	24	18	26	22	22
遺伝子変異		c.1111G>T homo	c.356-1G>A homo	c.3020delG c.1270-2A>T	c.3460_3461ins TTGTG homo	c.3139-1G>C c.1960C>T	c.561A homo
初発時年齢		10代	10代	18	記載なし	記載なし	15
初発時の症状		思春期遅発症	月経不順	糖尿病	記載なし	記載なし	低身長糖尿病
主要徴候							
1. 毛髪の変化	75.0	+	−	NR	+	記載なし	+
2. 白内障	88.8	+	+	+	+	記載なし	−
3. 皮膚の変化	55.6	−	−	+	+	+	−
4. 軟部組織の石灰化	50.0	−	NR	−	+	記載なし	記載な
5. 鳥様顔貌	50.0	NR	NR	+	+	−	−
6. 音声の異常	37.5	−	−	−	−	+	記載な
その他の徴候と所見							
1. 糖、脂質代謝異常	75.0	−	+	+	記載なし	記載なし	+
2. 骨の変化（骨粗鬆症）	42.8	−	記載なし	−	記載なし	+	+
3. 非上皮性腫瘍、甲状腺癌	25.0	−	−	記載なし	記載なし	記載なし	+
4. 血族結婚	77. 8	+	+	−	+	記載なし	+
5. 早期に現れる動脈硬化	20.0	−	記載なし	−	記載なし	記載なし	記載な
6. 原発性性腺機能低下症	83.3	+	+	記載なし	記載なし	+	記載な
7. 低身長および低体重	77.8	+	−	−	+	記載なし	+
その他		甲状腺機能亢進症	脂肪肝炎	脂肪肝			脂肪細芽腫
（参考文献）		Am J Med Genet. 2022;188A:1630−1634	Diabetes Care 2024;47(00):1−5	J Diabetes Investig 2022; 13: 592−598	J Diabetes Investig 2022; 13: 592−598	J Diabetes Investig 2022; 13: 592−598	Mol Genet Genomic M 2024;12:e22

若年ウェルナー症候群患者の

- 29歳女性で WRN遺伝子のナンセンス変異（31
- 変異WRN蛋白はC末端の核移行シグナルを欠
  考えられた。
- 既報で20歳代に診断された場合の症候の陽性
  毛髪変化75%、糖、脂質代謝異常75%、低身長

若年者におけるウェルナー症候群の診断

**20歳代の患者については、若年性両側白内
変化、糖・脂質代謝異常、低身長と低体重の
合併時に遺伝子診断を行**

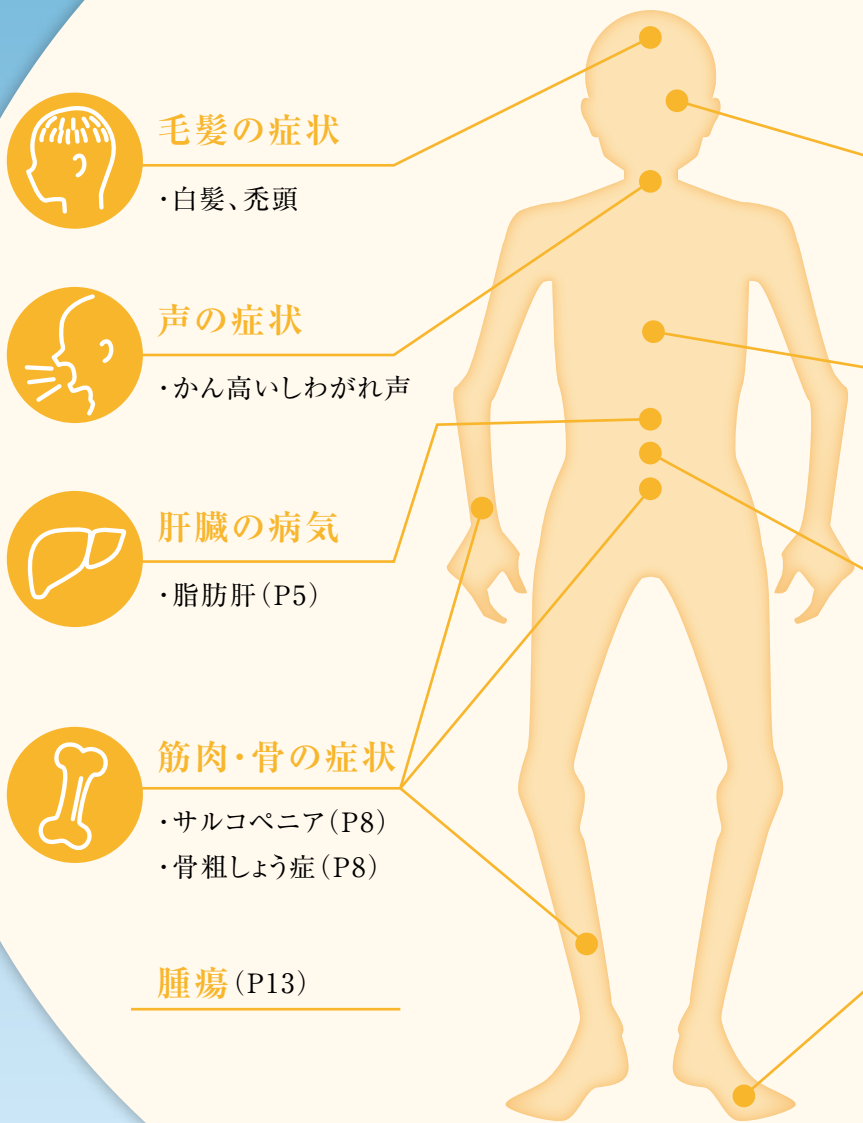
ウェルナー症候群ハンドブック

ウェルナー症候群の皆さんと家族、医療者のためのガイド

第1版

目次

ウェルナー症候群の臨床症状



毛髪の症状
・白髪、禿頭

声の症状
・かん高いしわがれ声

肝臓の病気
・脂肪肝(P5)

筋肉・骨の症状
・サルコペニア(P8)
・骨粗しょう症(P8)

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目の病気
・白内障(P7)

心臓の病気
・動脈硬化
狭心症、心筋梗塞

代謝の異常
・内臓脂肪蓄積
・糖尿病(P3)
・脂質異常症(P4)

足の症状
・皮膚潰瘍(P6、P10)
・末梢動脈疾患

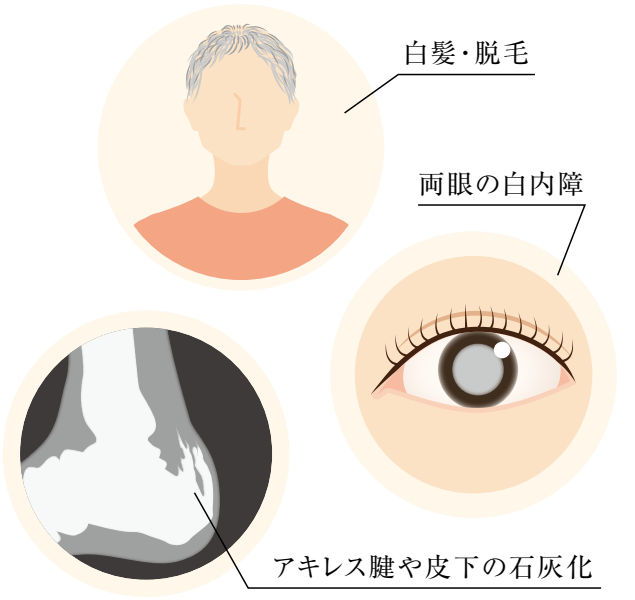
1 ウェルナー症候群とは?

ウェルナー症候群とは、思春期を過ぎる頃より急速に老化が進んでいくようにみえることから、「早く老いる」病気=早老症のひとつとされています。実年齢より「老けて見える」ようになります。

症状として、20歳代以降に白髪・脱毛や、両眼の白内障、かん高くかすれた声があらわれます。また腕や脚の筋肉がやせたり、皮膚が硬くなってタコができたり、また足や肘などにキズができて治りにくくなることがあります(難治性皮膚潰瘍)。身長は低いことが多く、レントゲンでアキレス腱や皮下の石灰化(カルシウム成分の蓄積)が見つかることがあります。

また糖尿病や脂質異常症(コレステロールや中性脂肪の異常)も多く、動脈硬化や癌になりやすいので、注意深い経過観察が必要です。潰瘍から感染を繰り返すと骨の中の骨髄まで細菌が入ってしまうことがあるので、皮膚のケアがとても重要です。

主な症状



日本のウェルナー症候群の患者数は約2,000人と推定されており、世界中で報告されている患者さんの約6割が日本人であり、我が国に多いと考えられています。以前は、血縁が濃くなる近親婚の多い地域で報告されてきましたが、最近では近親婚によらない患者さんも増加しています。日頃の食べ物や運動などの生活習慣は、発病とは関係ないと考えられています。

ウェルナー症候群はWRNと呼ばれる遺伝子の異常が原因と考えられており、2つのWRN遺伝子の両方に異常がある時だけ発病します。患者さんの両親はそれぞれひとつだけ原因遺伝子を持ち、ご自身は発病していないことがほとんどです。患者さんの兄弟姉妹では確率的に約4人に1人が発病しますが、患者さんのお子さんや、さらにそのお子さんが同じように発病する確率は計算上200 ～ 400人に1人以下であり、可能性は非常に少ないです。

ウェルナー症候群にはまだ根本的に治す方法がありませんが、一方、癌や白内障、糖尿病や脂質異常症などは、手術や薬などが有効であり、早期発見と治療が重要で、これによって予後を改善することができることがわかっています。

かつては、癌や、心筋梗塞などの動脈硬化の病気によって、多くの患者さんが40歳代半ばで亡くなると言われていました。しかし、最近の研究では平均寿命が10年以上延び、今では60歳以上の患者さんも多くなってきています(最高年齢77歳)。

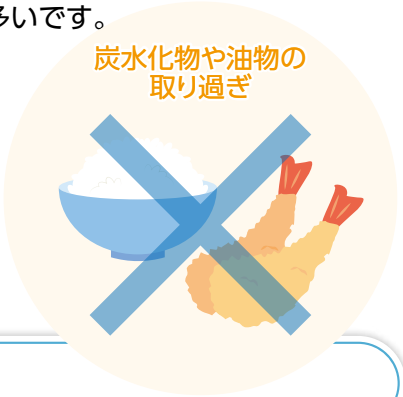
② 生活で気をつけること

内臓脂肪型肥満、糖尿病、脂質異常症の予防・治療

お腹に脂肪がたまりやすく（内臓性肥満）、これにより主に糖尿病や脂質異常症になりやすいため、炭水化物や油物を取り過ぎないようにしましょう。また可能な範囲で運動も行いましょう。糖尿病の治療は、一般の2型糖尿病に準じての治療が推奨されますが、インスリンという血糖値を低下させるホルモンの効きが悪くなることが主な原因なので、インスリンの効きを良くする薬を用いることが多いです。

脂質異常症の治療も、一般的な脂質異常症の治療に準じ、スタチンと呼ばれるLDL-コレステロール低下薬を使われることが多いです。

高血圧症の治療も、塩分を摂りすぎないようにし、必要に応じて、一般的な降圧薬を用います。これらの危険因子を良好にコントロールすることで、動脈硬化の進展を抑え、心筋梗塞の予防につながります。

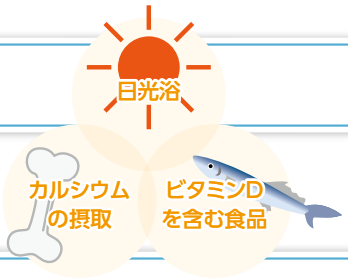


サルコペニア（筋肉が痩せ細ること）の予防

大豆製品、魚や肉などのタンパク質の摂取を心がけましょう。ロイシンと呼ばれるアミノ酸サプリが一般のサルコペニア予防に効果的とされており、ウェルナー症候群患者さんでも有効である可能性があります。

骨粗しょう症の予防

ビタミンDを含む食品、カルシウムの摂取、日光浴を行いましょう。



皮膚のキズ（難治性潰瘍）の予防・治療

足のキズは治りにくく、日常生活に大きな支障をきたすので、足にあった靴を履き、靴ずれを起こさないことが重要です。薄く固くなった皮膚は骨に圧迫されてキズができ、深い潰瘍を生じやすいため、当たって痛い箇所やキズになりかけたところは特殊な靴（装具）を作って保護する方法もあります。日頃からアキレス腱やかかと、足、肘など潰瘍になりやすい部位を保護し観察しましょう。できてしまった場合には、洗浄や消毒・保護・保湿などの対症療法が中心になりますが、自分のからだの他の場所から皮膚を移植する手術が有効な場合もあります。

癌の早期発見

通常よりも癌を発症することが多いため、早期発見・早期治療が大切です。このため、癌検診などを定期的に受けることをお勧めします。

3 糖尿病

糖尿病とは?

糖尿病とは、インスリンというホルモンが少なくなったり、うまく働かなくなったりして血糖値（血液中のブドウ糖濃度）が高くなる病気です。

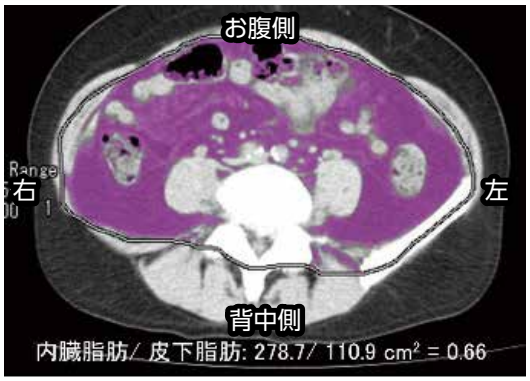
「最近、口が乾く」、「以前よりもおしっこの回数や量が増えた」、「疲れやすい」などの症状が出ることもありますが、症状があまりないこともあります。

糖尿病が怖いのは、病気を放っておくことにより、さまざまな病気があらわれることです。「目が見えなくなる」、「おしっこがうまく作れなくなって体の中に老廃物がたまる（尿毒症）」、「足が腐ってしまう」などの病気に加え、心臓病や脳卒中、さらには癌や認知症を増やしてしまいます。

主な症状

糖尿病とウェルナー症候群

わが国で行われた調査によると、男性、女性に関わらずウェルナー症候群患者の約6割の方に糖尿病を合併することがわかっています。お腹の回りに脂肪がたまる、いわゆるメタボ型の体形になり、インスリンがうまく働かなくなることが原因の一つと考えられています。



内臓脂肪CT（紫色の部分が内臓脂肪）

糖尿病の治療

間食やジュースは控えめにしてください。腹7～8分目を心がけると良いでしょう。可能な範囲での運動（ペットボトルを使った体操など）は有効と考えられます。メトホルミンやピオグリタゾンというお薬に効果があることが知られており、最近ではインクレチン関連薬という薬の効果も示されています。

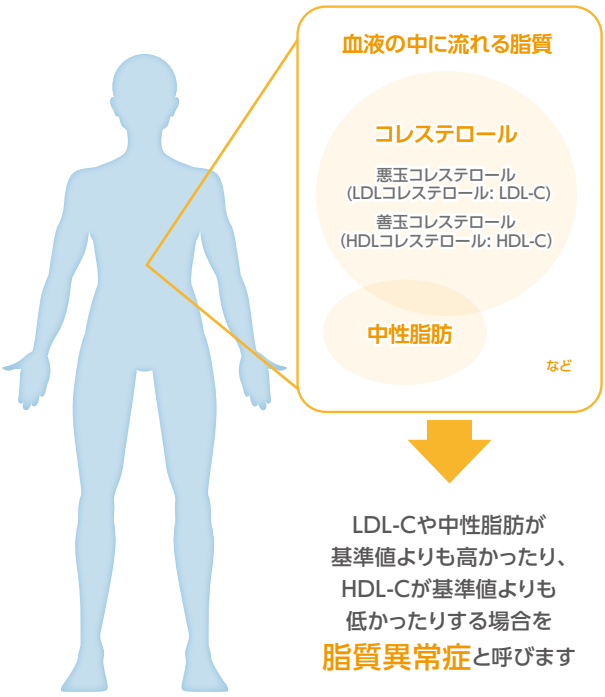
メトホルミン
ピオグリタゾン
インクレチン

4 脂質異常症

脂質異常症と動脈硬化

わたしたちの血液の中にはコレステロールや中性脂肪といったあぶら(脂質)が流れています。

さらにコレステロールは悪玉コレステロール(LDLコレステロール: LDL-C)と善玉コレステロール(HDLコレステロール: HDL-C)に分けられますが、LDL-Cや中性脂肪が基準値よりも高かったり、HDL-Cが基準値よりも低かったりする場合を脂質異常症と呼び、この状態は動脈硬化を起こしやすく、狭心症や心筋梗塞といった心臓の病気や脳卒中の危険因子になります。

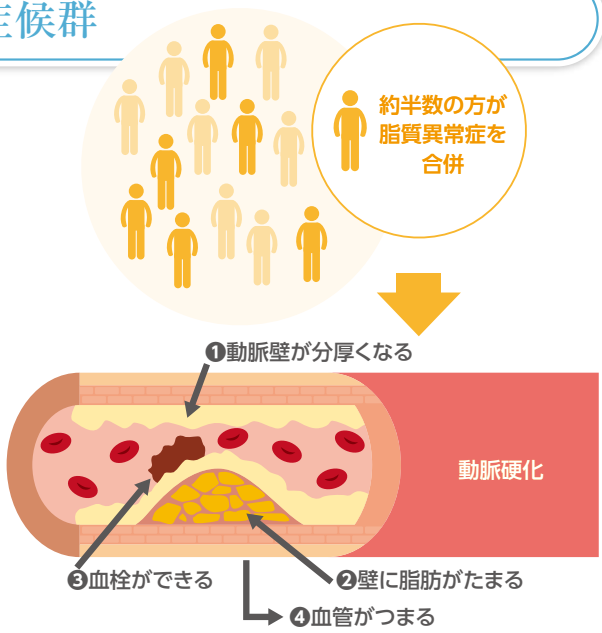


脂質異常症、動脈硬化とウェルナー症候群

日本で行われた調査によると、ウェルナー症候群患者の約半数の方に脂質異常症を合併することがわかっています (高LDL-C血症は約7割、高中性脂肪血症は約8割、低HDL-C血症は約3割)。

糖尿病と同じようにメタボ型の体形になり、インスリンがうまく働かなくなることが脂質異常症をきたす原因の一つと考えられています。

動脈硬化に関してはウェルナー症候群の方は一般の方に比べて狭心症や心筋梗塞が多い一方、脳卒中の発症はむしろ少ないとの報告があります。



脂質異常症の治療

動脈硬化症の予防には、生活習慣の改善、動物性の脂質を控えめにすることや、スタチン薬など、標準的な治療が用いられています。

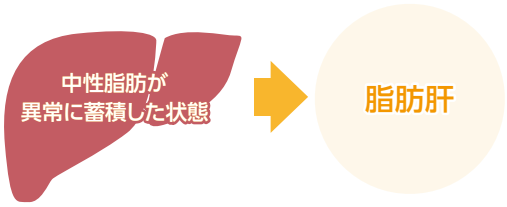
5 脂肪肝

脂肪肝について

肝臓の中に脂質の一種である中性脂肪が異常に蓄積した状態を脂肪肝といいます。

飲酒によるアルコール性脂肪肝がよく知られていますが、最近ではお酒をあまり飲んでもいないのに肝臓に脂肪がたまる非アルコール性脂肪肝が注目されています。

どちらも肝硬変や肝癌といった病気へ進行してしまうことがあります。



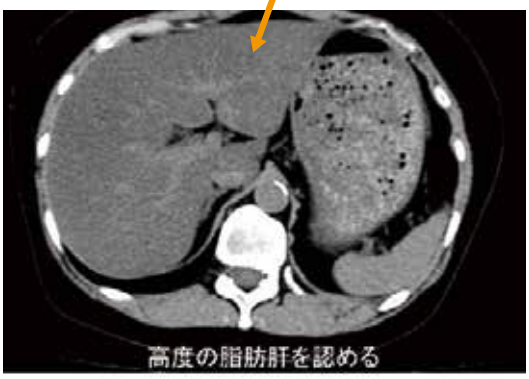
脂肪肝とウェルナー症候群

ウェルナー症候群患者の約3割の方に脂肪肝を合併することがわかっています。

一般的には非アルコール性脂肪肝の場合は太った方に多いのに対して、ウェルナー症候群の方は標準体重を大きく下回っても脂肪肝を合併することが特徴とされます。

脂肪肝を合併したウェルナー症候群の方に肝硬変や肝癌が多いという報告はまだありません。

暗く写っている所が脂肪の蓄積を示す
(普通は白っぽい明るい色)



腹部CT

脂質異常症の治療

脂肪肝に対する特効薬はまだありません。

アスタキサンチンというサプリメントがウェルナー症候群の方の脂肪肝を改善したという1例報告があります。

6 感染症

皮膚潰瘍の感染症について

ウェルナー症候群では皮膚の異常を起こしやすいことから、足底にうおの目（鶏眼）ができやすく、そこから皮膚の表面が炎症を起こして崩れてしまい、内部までキズがおよんでしまう潰瘍ができることがしばしばあります。このような状態は糖尿病でも起こりやすいことが知られています。ウェルナー症候群では糖尿病も合併しやすいことから、足底潰瘍をより起こしやすい状況にあると言えでしょう。また足底のみならず膝や肘にも潰瘍ができやすいことが知られています。

ここで一番大切なのはフットケアです。まずはうおの目を作らないこと、できた場合にはすぐに診察を受けてください。もし皮膚がえぐれて「潰瘍ができたかな」と思ったらすぐに主治医の診察を受けてください。その状態であれば、まだ感染を起こしていません。

周囲が赤く腫れてきたり、熱感を持つ感じがしたり、痛みがあるようですと、感染を起こしている可能性があります。このような場合には治療が必要になる可能性が高いです。

赤く腫れ上がる部位（発赤）が潰瘍の周り2cm以内の場合には、えぐれている深さにもよりますが抗菌薬の飲み薬で治療できる可能性が高いです。この場合には目安として2週間、長くても4週間の治療が必要となります。しかしながら発赤部位が2cm以上、もしくは深くまで感染している場合には感染している組織を削り取り、点滴で抗菌薬による治療を受ける必要が高くなります。このような場合には入院が必要となることが多いです。このような場合には目安として2〜4週間の治療が必要となります。点滴による治療が終わったあとに飲み薬に切り替えることもあります。

潰瘍が深くまで進むと、皮膚や皮下組織だけではなく関節や骨の感染症を起こすことがあります。こうした状態を関節炎や骨髄炎といいます。このような場合には入院して点滴で抗菌薬による治療を受ける必要があります。抗菌薬だけでは感染がよくならないときには外科的な切除が必要となることが多いです。一般的に関節や骨まで感染がおよんでいると少なくとも4週間以上と治療期間は長くなります。

また感染を繰り返している場合には、抗菌薬が効きにくい細菌（耐性菌）による感染症を起こす場合があります。この場合、飲み薬では治療できないことがありますので軽症でも点滴による治療が必要となります。

その他の感染症で気をつけたいこと

肺炎やインフルエンザなど、ワクチンで予防できる感染症はたくさんあります。主治医と相談して予防接種を受けることをおすすめします。

7 眼の病気

ウェルナー症候群は「早老症」ともいわれますが、文字通り年齢より早く老化がはじまります。目も例外ではなく老化がはじまります。最もよく見られる老化による眼症状は**白内障**です。早ければ20歳以降に発症しますが、平均では30歳で白内障が発症します。

一般の人では50歳頃から10%弱の人に白内障が発症し、70歳で80%以上で白内障が見られます。これに対しウェルナー症候群では100%で白内障が発症します。そのため、白内障を契機にウェルナー症候群の診断に至る場合もあるくらいです。

白内障は水晶体が混濁して視力低下をきたす病気で、症状は視力低下やまぶしさ、かすみなど様々です。初期症状としては単純な視力低下ではなく夜ヘッドライトがまぶしく感じる様になったりします。

また白内障進行に伴い近視化が進むこともあります。診断自体は眼科で一般的に用いられる細隙灯検査で容易にわかりますので開業医でも診断可能ですが、若年発症の白内障の原因は様々であるため、それだけでウェルナー症候群を疑う眼科医は多くはありません。

ただ、年齢に比べて水晶体の中央（核）の混濁・硬化が特徴であるため、若年で両眼の核白内障を認めたときはウェルナー症候群を疑うというのが基本的な考え方になります。

白内障は小切開（2−3mmの切開創）の水晶体再建術で重篤な合併症無く治療可能です。

基本は**超音波乳化吸引術**といって超音波で濁りを破砕して吸引し、残った袋（水晶体嚢）の中に人工レンズを挿入して終わります。ウェルナー症候群の場合、核が硬くなっている症例が多いため、手術の難易度が高くなりやすい傾向はあります。それでも昔の術式と比較すれば切開創は小さくなっているので創閉鎖不全のような重篤な合併症は起きなくなっています。

1つだけ特徴的な術後合併症として**嚢胞様黄斑浮腫**（のうほうようおうはんふしゅ）（網膜の中の黄斑という最も重要な場所にむくみが生じ、ぼやけたり、ゆがんで見えるといった症状が出ます）が見られることがあります。普通の白内障患者の場合、術後点眼の進歩により点眼のみで改善するのですが、ウェルナー症候群の場合、難治性になり恒久的な視力低下をきたす場合がありますので注意が必要です。本来炎症によって発症するものですがウェルナー症候群の場合嚢胞様黄斑浮腫の発症原因が不明のため頻度は不明ですが多くはないようです。総じて白内障手術手技の進歩によりウェルナー症候群の白内障は安全に手術が施行できるようになってきています。

8 サルコペニアと骨粗しょう症

サルコペニアとは

サルコペニアとは加齢により筋肉量が減り、筋力や歩行速度が低下している状態を指します。

サルコペニアは、将来的に介護を必要としたり、日常生活に何らかの支障をきたしたりする原因になります。つまり、サルコペニアは健康で長生きすることを妨げる要因となります。

ウェルナー症候群の患者さんは比較的若い時代（40歳未満）から手足の筋肉量が低下していることが報告されています。その原因はよくわかっていませんが、関節の拘縮（関節の動きが悪くなること）や足底に皮膚潰瘍が生じることが多いため、あまり体を動かすことが出来ないことも原因かもしれません。

主な症状

実際、中には習慣的なレジスタンス運動（筋肉に負荷をかける運動、いわゆる筋トレ）を行っているウェルナー症候群の患者さんでは骨格筋量の低下を認めない患者さんもいることから、適切な運動をすることにより、サルコペニアを予防できる可能性があります。

予　防

サルコペニアの予防には足底やアキレス腱にあまり負担がかからないような、レジスタンス運動と、食事からの十分なたんぱく質(筋肉の元)の摂取を心掛けてください。

たんぱく質は毎食少なくとも25g程度は摂っていただきたいと思います。ただし、慢性腎臓病などをお持ちの患者さんは、かかりつけ医の先生と是非ご相談ください。

骨粗しょう症とは

骨粗しょう症は加齢とともに骨の量（骨量）が減って骨がもろくなり、骨折しやすくなる病気です。

骨折により、日常生活に支障を来したり、寝たきりになったりすることもあり、これも健康寿命の延伸を阻害する危険な病気です。ウェルナー症候群の患者さんは若くして骨粗しょう症になりやすいことが報告されています。

患者さんの年齢にも寄りますが、日本における調査でも41%に、海外の報告では90%以上に骨粗しょう症を認めたとの報告もあります。ウェルナー症候群の患者さんの骨粗しょう症は椎骨（背骨）よりも下肢において重症となるケースが多くみられます。

主な症状

予防・治療

治療としては通常の骨粗しょう症の薬物療法が使用できます。

予防法としては、サルコペニアと同様にできるだけ運動をすることと、日光に適度にあびること（日光により皮膚でビタミンDを産生することが出来ます）も重要です。ビタミンDは食べ物からカルシウムの吸収を促し、骨粗しょう症の予防に重要です。サルコペニアと同様食事からの十分なたんぱく質の摂取も重要です。

サルコペニアも骨粗しょう症の予防も運動が重要ですが、ウェルナー症候群の患者さんの中には上で述べたように足底潰瘍ができやすく、また関節の拘縮がある方もおられるので、過度な運動は避け、できる範囲で負担の無い運動を取り入れることが重要です。

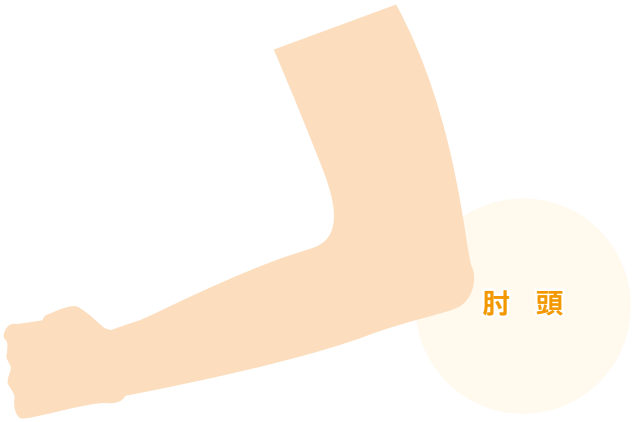
9 足の潰瘍（治りにくいキズ）

ウェルナー症候群では皮膚に治りにくいキズができやすいことが知られています。特にできやすい場所は、**肘、膝から下の足**です。

肘

肘の治りにくいキズは**肘の外側の出っ張ったところ（肘頭：ちゅうとう）**にできます。

皮膚が薄い部分でキズが肘関節の中とつながってしまうことがあるため注意が必要です。

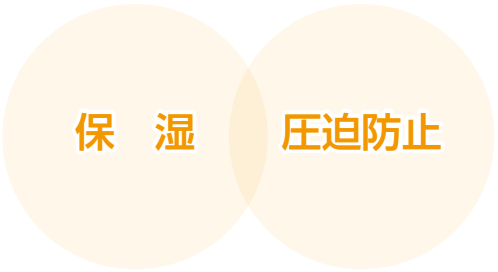


膝

特に治りにくいキズが出来やすい場所は、**アキレス腱のところ、くるぶし、かかと、足の裏、親指の内側、小指の外側**などです。皮膚が薄いため、キズが関節の中や骨の中につながってしまうことがります。

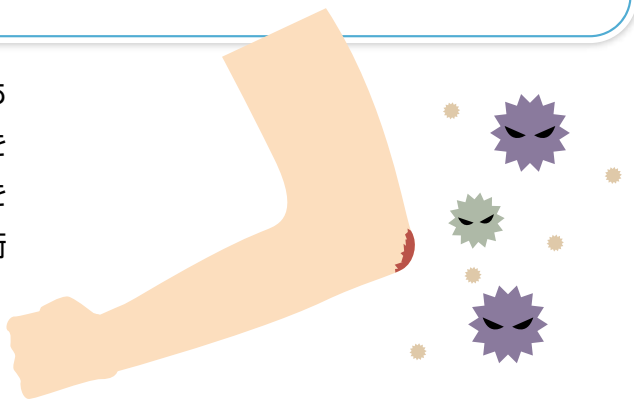
予　防

キズは一旦出来てしまうと治りにくいので予防が大切です。保湿と圧迫防止が大切です。圧迫のサインとしてタコができることがあります。タコを放置するとさらに皮膚が圧迫されてキズができるのでこまめに対処することが大切です。**タコができないようにするために足の形にあった靴を履きましょう。**



治　療

治りにくいキズのところにばい菌が溜まることがあります。ばい菌がそれ以上広がらないようにばい菌を外に出すことが必要です。また、ばい菌がついた組織を除去することも重要です。治りにくいキズに対して手術してふさぐこともあります。

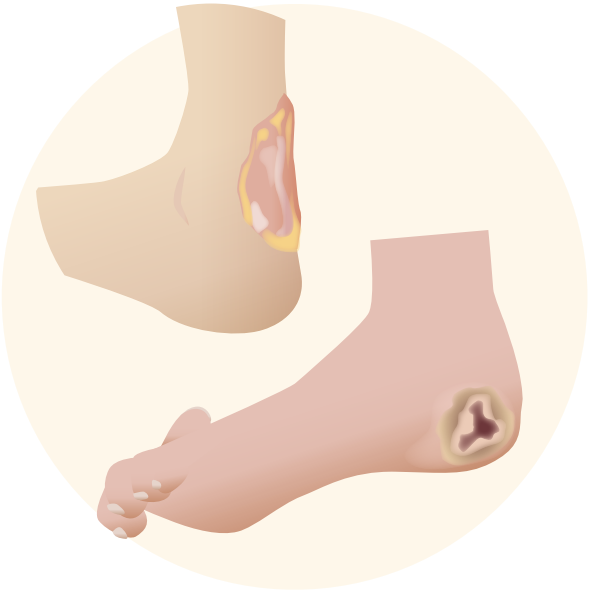


難治性潰瘍の予防・治療

ウェルナー症候群の患者さんは**皮膚にキズ（潰瘍）ができやすく、治りにくいという特徴**があります。特に**足の裏の荷重部位（体重がかかるところ）**にできやすいです。他にも、**アキレス腱部, 足関節, 肘関節**など圧のかかりやすい部位に多くみられます。

キズが治りにくい原因としては、皮膚が薄くなり硬くなっていることと脂肪が少なくなっていることが考えられます。クッションがなくなってしまい骨が直接当たってしまうような感じです。

また、血管が細くなり血流が悪くなってしまうことや、皮膚の中に石灰ができてしまうこと、関節の変形が起こることなども原因として考えられています。

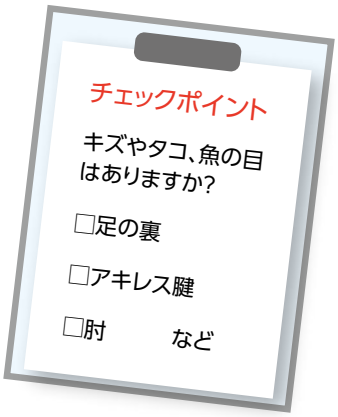


足の裏の体重がかかる部位には、いわゆる「タコ」（胼胝）や「魚の目」（鶏眼）ができやすく歩くときに当たって痛くなってしまいます。なるべく足の大きさにあった靴をはいて「靴擦れ」を防いだり、靴底に軟らかいソール（インソール）を入れたりして、一か所に体重がかからないようにする工夫が必要です。特殊な装具（靴）を作って、骨が出っ張ってキズになりやすい部位を保護する方法もありますので、専門の靴屋や装具販売店にご相談ください。

また、**常に足の裏やアキレス腱、肘などに、キズやタコ、魚の目ができていないかをチェック**してください。

タコや魚の目などの角質が厚くなっているところができはじめたら、早めに、角質を軟らかくする塗り薬や張り薬（尿素の入った角質軟化外用剤など色々あります）を塗る、もしくは貼ってください。角質を軟らかくする外用剤、貼付剤は薬局でも販売していますが、一度、皮膚科などの専門医にご相談ください。

塗り薬や張り薬を使ってもタコや魚の目がとれない場合は、はさみなどで切り取る方法がありますが、ご自身で行うとキズを作ってしまう可能性がありますので、皮膚科などの専門医で削り取ってください。



タコや魚の目を放っておくと、中央にキズができてしまい、なかなか治らなくなってしまいます。キズができてしまった場合には、細菌感染が起こらないように注意が必要です。毎日、石鹸などで良く洗浄して清潔に保ってください。きれいに洗い流したのちにキズを治す塗り薬を塗ってください。塗り薬はキズの具合に合わせた薬を使う必要があります。壊死した部分がある場合は、その部分を溶かすような薬が必要です。

また、赤い肉芽がでてきた場合は、さらに盛り上げてキズを小さくする薬が必要です。もし細菌感染を起こしてしまった場合は、消毒や感染を抑える塗り薬、抗菌剤の飲み薬が必要となります。細菌感染を起こしたり、キズが大きくなってしまうとなかなか治らなくなってしまいますので、キズができてしまったら、なるべく早く皮膚科専門医にご相談ください。

⑩ 腫瘍

悪性腫瘍とは

悪性腫瘍とは、ある細胞が体の中の秩序を無視して増え、周りの組織に広がったり、転移を起こしたりする腫瘍のことです。悪性腫瘍には上皮性腫瘍（癌）や非上皮性腫瘍（肉腫など）、白血病などの血液の腫瘍があります。癌と非上皮性腫瘍の発症する割合を比べると10:1程度と、一般的には癌が多く非上皮性腫瘍は稀です。

悪性腫瘍とウェルナー症候群

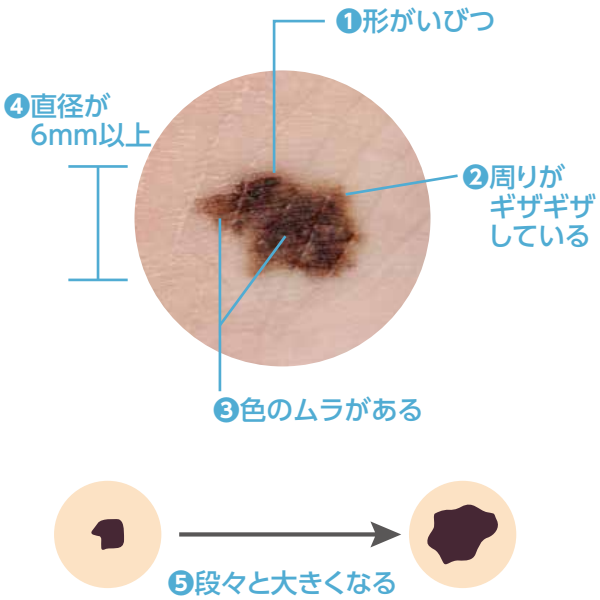
日本で行われた調査によると、ウェルナー症候群の方の約3割に悪性腫瘍が見つかり、比較的若い頃（40歳代）から発症する傾向があります。癌と非上皮性腫瘍の発症する割合は1:2程度と、通常稀な非上皮性腫瘍が多く、その中でも悪性黒色腫や悪性線維性組織球腫、髄膜腫瘍が多いと報告されています。癌では甲状腺癌が多くみられます。また1人に複数の悪性腫瘍が合併する多重癌（重複腫瘍）を発症することも少なくありません。最近、ウェルナー症候群の方の寿命が延長するにしたがって、癌が増えているとの報告もあります。

悪性腫瘍の検査と治療について

このように、ウェルナー症候群の方では悪性腫瘍に気をつける必要があります。できるだけ早く発見して、治療をするためにも定期的な人間ドックや癌検診を受けることが有用です。少なくとも3ヶ月に1回は採血・採尿検査を受け、半年から1年毎に胸部レントゲン写真、甲状腺エコー、腹部エコー、便潜血などの検査を受けることをお勧めします。またご自身で毎日全身を観察することも大切です。特に、皮膚に形がいびつな「ほくろ」ができた場合や皮膚の下にできた「こぶ」が大きくなってくる場合は主治医に相談してください。

悪性腫瘍は一般の方と同様に治療することができます。手足のキズの治りが悪いため、手術を心配される方もいらっしゃいますが、体の中心部（体幹部）の手術（例：肺癌）であればキズの治りも良く、一般の方と同様の手術が行われます。

悪性の「ほくろ」（悪性黒色腫）の特徴



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「早老症の医療水準やQOL向上を目指す集学的研究」

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協力：ウェルナー症候群患者家族の会

2021年3月

Werner Syndrome Handbook

A Guide for People with Werner Syndrome, Their Family and Healthcare Professionals

1st Edition

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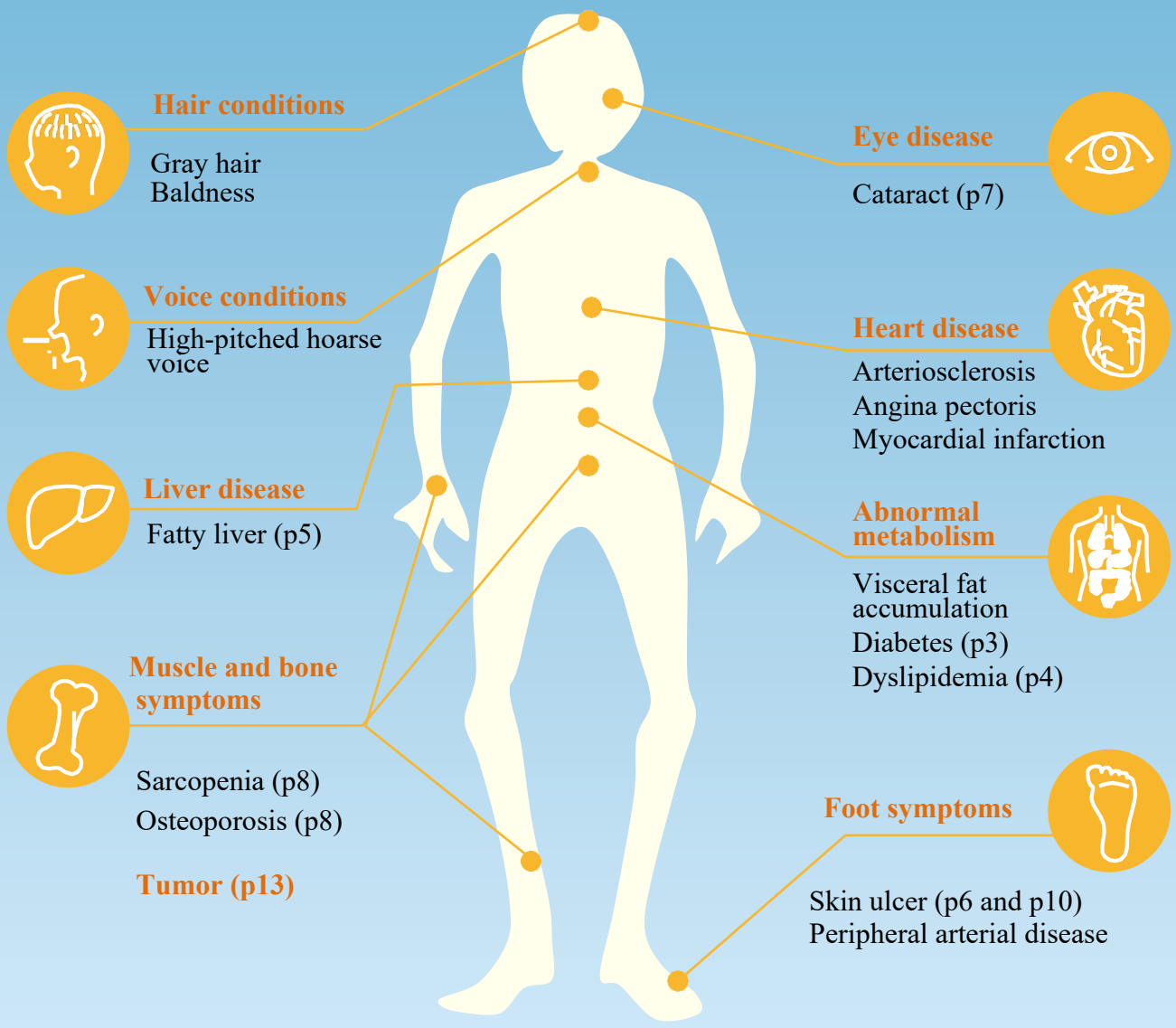
Clinical manifestations of Werner syndrome

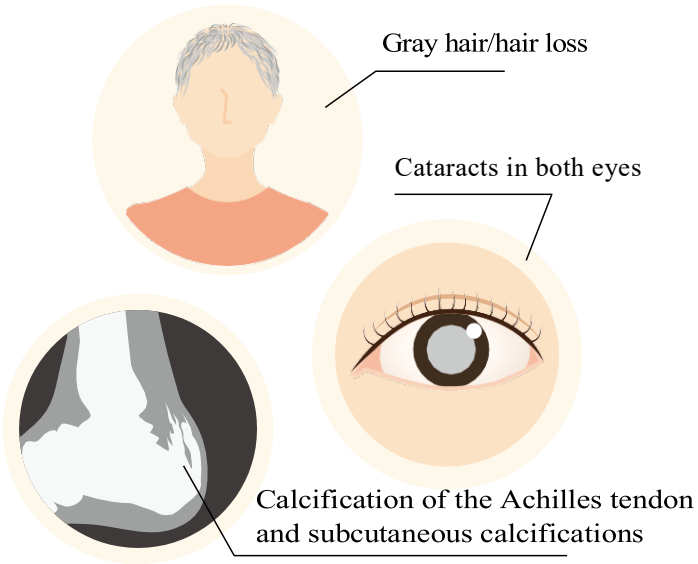


1 What is Werner syndrome?

Werner syndrome is said to be a disease of "premature aging" = a progeroid syndrome because aging seems to progress rapidly after puberty. The patient looks older than their actual age.

People with Werner syndrome starts to develop symptoms such as gray hair/hair loss, cataracts in both eyes, and a high-pitched hoarse voice in their 30s. In addition, muscle atrophy in the arms and legs, formation of calluses due to skin hardening, and hard-to-heal foot/elbow wounds (intractable skin ulcers) may be observed. Patients usually have short stature, and X-rays may reveal subcutaneous calcification (accumulation of calcium components) of the Achilles tendons and subcutaneous tissue.

Main Symptomms



Diabetes and dyslipidemia (abnormal cholesterol and triglyceride levels) are also common among these patients. Therefore, they are at risk of developing arteriosclerosis and cancer; hence, careful follow-up is required. Skin care is necessary as repeated infections from ulcers can cause bacteria to enter the bone marrow.

The number of Werner syndrome patients in Japan is estimated to be 700~2,000. The disease is prevalent in Japan, with 60% of the patients reported worldwide being Japanese. In the past, most of the reported cases were from areas with many consanguineous marriages, which leads to closely related kinship; in recent years, the number of patients whose disease is not related to consanguinity is dramatically increasing. Lifestyle habits such as daily diet and exercise are unrelated to the onset of this disease.

Werner syndrome is caused by an abnormality in the WRN gene. The disease only occurs when both WRN genes are defective. Each of the patient's parents only has one causative gene and does not develop the disease. About 1 in 4 of the patient's siblings will develop the disease; however, the probability that the patient's children or their children will develop the disease like their parent or grandparent is extremely low.

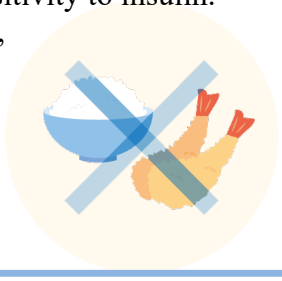
There is no fundamental cure for Werner syndrome. However, early detection and treatment are important for diseases such as cancer, cataracts, diabetes, dyslipidemia, etc., because surgery and medications are effective and they improve the patients' prognosis.

In the past, many patients died from cancer and arteriosclerotic diseases such as myocardial infarction in their mid-40s. However, a recent study shows that the average life expectancy has increased by more than 10 years, and the number of Werner syndrome patients in their 60s is significantly increasing: the oldest patient was aged 77 years.

2 Things to be aware of in life

Prevention and treatment of visceral fat obesity, diabetes, and dyslipidemia

Excessive carbohydrate and fat intake should be avoided as fat tends to accumulate in the abdomen (visceral obesity), thus increasing the susceptibility to diabetes and dyslipidemia. Exercise should be performed regularly. Treatment for general type 2 diabetes is recommended to manage diabetes; medications that improve the sensitivity to insulin, a hormone that lowers the blood sugar levels, are also used in many cases as the primary cause of Werner syndrome is decreased sensitivity to insulin. Dyslipidemia is managed based on the treatment used for general dyslipidemia, and low-density lipoprotein (LDL) cholesterol-lowering drugs called statins are often used. Hypertension is treated by avoiding excessive salt intake and using general antihypertensive drugs as needed. Good control of these risk factors suppresses the progression of arteriosclerosis and prevents myocardial infarction.



Prevention of sarcopenia (muscle wasting)

Protein-rich foods such as soy products, fish, and meat should be consumed. Amino acid supplements for leucine are said to be effective in preventing general sarcopenia and may also be effective for Werner syndrome patient.

Prevention of Osteoporosis

Consumption of foods containing vitamin D, calcium intake are recommended to prevent osteoporosis.

Calcium intake

Foods containing vitamin D

Prevention/treatment of skin wounds (intractable ulcers)

It is important to prevent foot blisters by choosing well-fitting shoes as foot wounds take long to heal and greatly interfere with daily life. Thin and tough skin can break or tear easily due to the pressure applied by the underlying bones. Such wounds are at risk of developing into deep ulcers. Special shoes (orthoses) may be used to protect areas with high pressure or that will likely develop into wounds. Areas prone to ulcers such as the Achilles tendon, heels, feet, and elbows should be protected and assessed on a daily basis. If ulcers form, symptomatic treatment such as cleaning, disinfection, protection, and moisture retention is the primary treatment. However, surgery to graft skin from other areas of the body may be effective in some cases.

Early Detection of Cancer

Early detection and treatment are important because cancer develops more often than usual. Therefore, undergoing regular cancer screening is recommended.

3 Diabetes

What is diabetes?

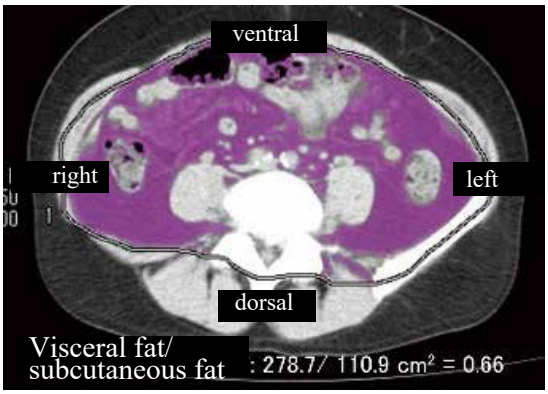
Diabetes is a disease that occurs when the insulin levels are low or the insulin is ineffective, resulting in high blood sugar levels (glucose concentration in the blood).

Symptoms including “recently, my mouth is dry”; “I go to the bathroom more often and pee more”; and “I get tired easily” may appear. Meanwhile, other patients may remain asymptomatic.
What is alarming about diabetes is that other diseases may develop if it is left untreated.
In addition to problems such as “blindness,” “accumulation of waste products in the body due to the inability to urinate properly (uremia),”and “rotting of the foot,” it increases the risk of heart disease, stroke, and even cancer and dementia.

Main symptoms

Diabetes and Werner syndrome

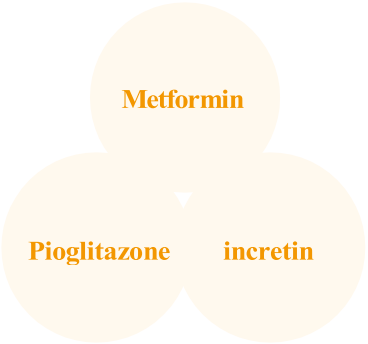
According to a previous survey conducted in Japan, 60% of patients with Werner syndrome, regardless of gender, develop diabetes as a complication. One of the causes is fat accumulation around the abdomen, which contributes to the patient’s metabolic syndrome appearance. As a result, sensitivity to insulin decreases.



Computed tomography scan: the purple-colored area indicates visceral fat.

Treatment for diabetes

The intake of snacks and juice drinks should be limited. Eating until 70%–80% full is highly encouraged. Performing various exercises as tolerated (exercises using plastic bottles, etc.) are effective. Metformin and pioglitazone are known to be effective. Recently, incretin-related drugs have also been shown to be effective.

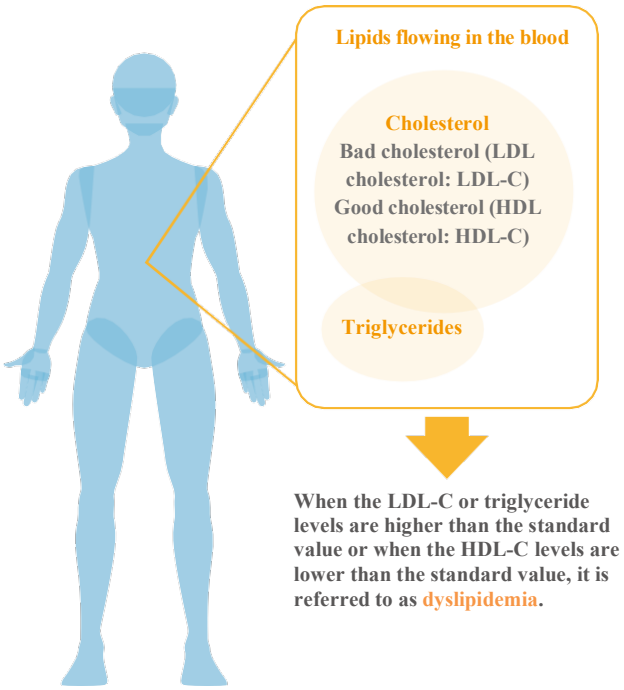


4 Dyslipidemia

Dyslipidemia and arteriosclerosis

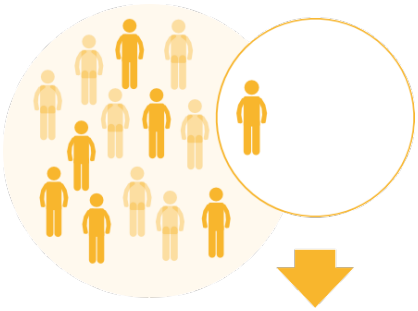
Fats (lipids) such as cholesterol and triglycerides circulate freely in the blood.

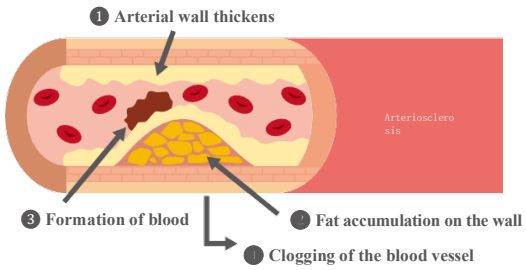
Cholesterol is further divided into bad cholesterol (LDL-C) and good cholesterol (high-density lipoprotein cholesterol [HDL-C]). When the LDL-C or triglyceride levels are higher than the standard value or when the HDL-C levels are lower than the standard value, it is referred to as dyslipidemia. Dyslipidemia increases the likelihood of developing arteriosclerosis and is a risk factor for heart diseases, such as angina pectoris and myocardial infarction, and stroke.



Dyslipidemia, arteriosclerosis, and Werner syndrome

According to a previous survey conducted in Japan, half of Werner syndrome patients develop dyslipidemia (70% with high LDL-C levels, 80% with hypertriglyceridemia, and 30% with low HDL-C levels).
Similar to diabetes, patients develop a metabolic syndrome appearance, leading to insensitivity to insulin, which is believed to be one of the causes of dyslipidemia. Although angina pectoris and myocardial infarction commonly develop in people with Werner syndrome compared with that in the general population, the incidence of stroke is relatively low.





Treatment for dyslipidemia

Lifestyle modification, limited animal fat intake, and standard treatment such as the administration of statin drugs are used to prevent arteriosclerosis.

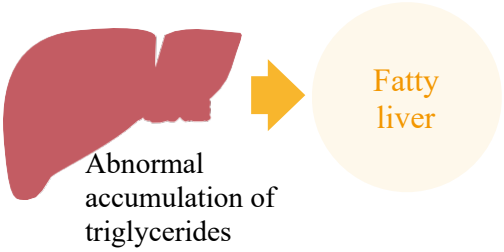
5 Fatty liver

About fatty liver

Fatty liver is defined as an abnormal accumulation of triglycerides, a type of lipid, in the liver.

Alcoholic fatty liver due to alcohol consumption is well known; recently, non-alcoholic fatty liver, in which fat accumulates in the liver even with low alcohol consumption, is drawing attention.

Both may progress to diseases such as cirrhosis and liver cancer.

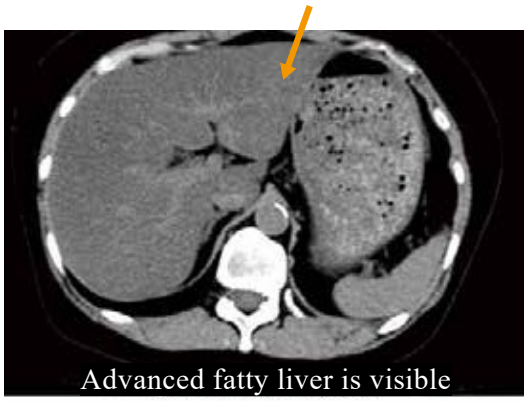


Fatty liver and Werner syndrome

Approximately 30% of patients with Werner syndrome develop fatty liver.

In general, non-alcoholic fatty liver is more common in obese people, whereas Werner syndrome patients develop fatty liver even if their body weight is significantly below normal.

No study has reported that cirrhosis or liver cancer is common in Werner syndrome patients with fatty liver.



Abdominal computed tomography scan

Treatment for dyslipidemia

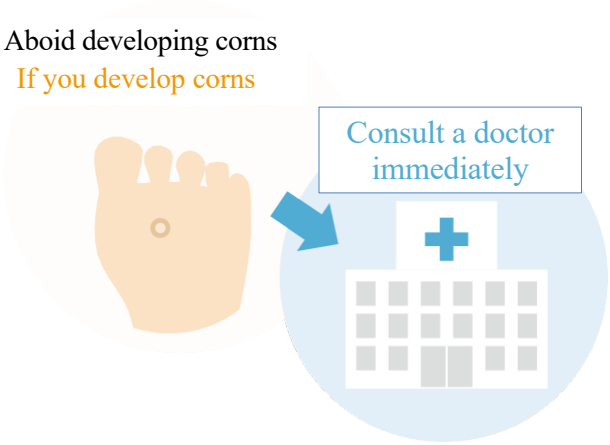
Fatty liver has no specific cure.
A previous study reported that the fatty liver in a Werner syndrome patient improved with the use of astaxanthin.

6 Infection

Infection of skin ulcers

Werner syndrome patients are prone to skin disorders and tend to develop corns (clavuses) on the soles of the feet. The skin surface where the corn is located becomes inflamed and collapses, often resulting in deep ulcers. This also occurs frequently in patients with diabetes. Since Werner syndrome is often complicated by diabetes, patients with this syndrome are prone to developing plantar ulcers. The ulcers develop not only on the soles of the feet but also on the knees and elbows.

Foot care is of utmost importance.
Patients should avoid developing corns. Otherwise, immediate medical advice should be sought. The attending physician should be consulted immediately if the skin becomes gouged and if an ulcer is suspected. At this point, the ulcer is not yet infected.



The ulcer may be infected if the surrounding area becomes red and swollen, feels hot, or is painful. In such cases, treatment is required.

The ulcer can be treated with oral antimicrobial drugs if the red and swollen area (redness) surrounding the ulcer measures 2 cm in diameter, although the depth of the ulcer should also be taken into consideration. In such case, the treatment will generally take two to four weeks. However, the possibility of undergoing intravenous antimicrobial treatment is relatively high if the inflamed area is not within 2 cm from the ulcer or the ulcer is deep. Hospitalization is often required in such cases, and treatment will generally take two to four weeks. The doctor may decide to switch to oral medication administration upon completion of intravenous treatment.

Not only the skin and subcutaneous tissue but also the joints and bones may also become infected as the ulcer extends more deeply. Such cases are called arthritis or osteomyelitis. If this occurs, hospitalization and treatment with intravenous antimicrobials are required. Surgical excision is often necessary if antimicrobials alone do not alleviate the infection. In general, the treatment period will take at least 4 weeks if the joints and bones are infected.

If repeated infection occurs, an infection caused by bacteria that are resistant to antimicrobials (resistant bacteria) is suspected. Intravenous treatment is necessary in such cases even if the infection is mild as it may not be possible to it treat with oral medications.

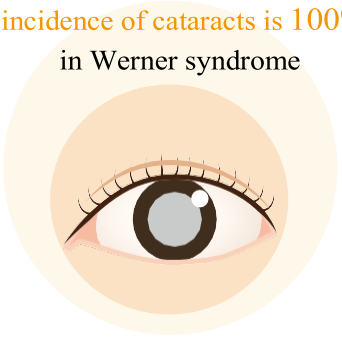
Other infections to look out for

Various infectious diseases can be prevented with vaccines such as pneumonia and influenza. Immediate consultation with a doctor and vaccination are recommended.

7 Diseases of the eye

Patients with Werner syndrome, also known as "progeria," experience premature aging. The eyes are no exception and tend to develop age-related conditions. The most common eye condition associated with aging is **cataract**. Werner syndrome patients develop cataracts as early as 20 years old. On average, they develop cataracts at the age of 30 years.

The incidence of cataracts is 100% in Werner syndrome



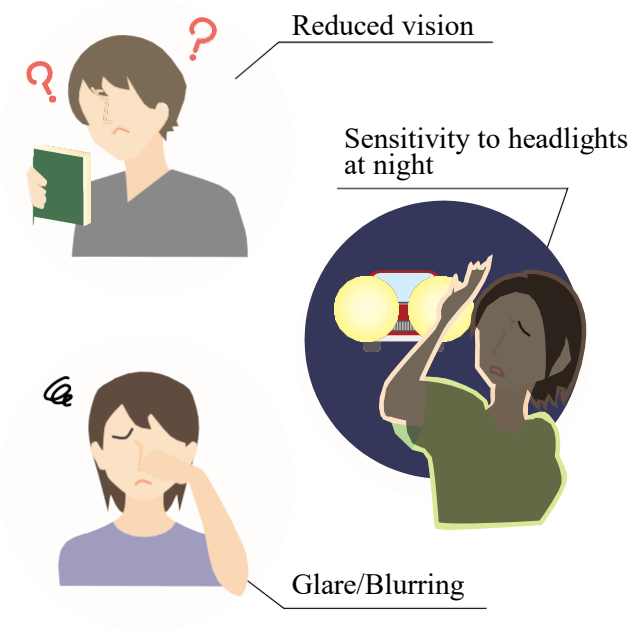
Approximately 10% of the general population develops cataracts at the age of 50 years, and more than 80% by the age of 70 years. By contrast, 100% of Werner syndrome patients develop cataracts. Hence, some patients are diagnosed with Werner syndrome after developing cataracts.

A cataract is a disease in which the lens becomes cloudy and vision is reduced. Its symptoms include reduced vision, glare, and blurred vision. Initial symptoms may not only include decreased vision but also sensitivity to headlights at night.

Myopia may also worsen as the cataracts progress. The diagnosis can be easily made by a slit lamp examination, which is commonly used in ophthalmology clinics, and a general practitioner can make the diagnosis. However, as early-onset cataracts have various causes, Werner syndrome will not be suspected based solely on these findings.

However, as a general rule, Werner syndrome is suspected if bilateral nuclear cataracts are observed at a young age as cataracts in Werner syndrome patients are characterized by opacity and hardening of the center (nucleus) at a younger-than-average age.

Main symptoms



Cataracts can be treated with small-incision (2–3 mm incision) lens reconstruction without serious complications.

Phacoemulsification and aspiration are generally used to ultrasonically break up and suck out the turbidity. An artificial lens is placed into the remaining pouch (lens capsule). In the case of Werner syndrome, the hardened nucleus, which is observed in many patients, tends to pose challenges during surgery. That said, serious complications such as incomplete wound closure do not occur as the incision wound is smaller compared with that in previous surgical procedures.

One characteristic postoperative complication that may occur is **cystoid macular edema** (swelling in the macula, the most important part of the retina, which causes symptoms such as blurred and distorted vision). It improves with eyedrops alone in patients with cataract alone, thanks to advances in postoperative eyedrops. However, care must be taken with Werner syndrome, as cystoid macular edema may become intractable and lead to permanent vision loss. It is generally caused by inflammation, but the factor that triggers the onset of cystoid macular edema in Werner syndrome patients remains unknown. Therefore, the exact incidence is unknown, but it does not seem to be common. Overall, cataract surgery can be safely performed on Werner syndrome patients, thanks to advances in cataract surgery techniques.

8 Sarcopenia and osteoporosis

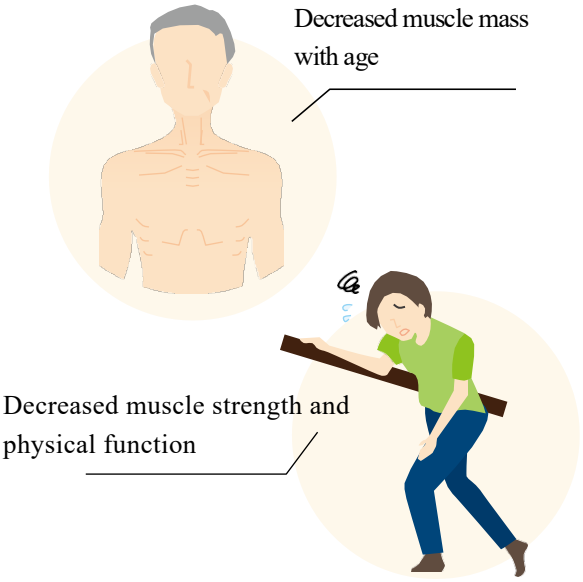
What is sarcopenia

Sarcopenia is a condition characterized by reduction of muscle mass with age, and decrease in muscle strength and walking speed.

Sarcopenia may require long-term care in the future and cause some difficulties in daily life. In other words, sarcopenia prevents an individual from living a long and healthy life.

The muscle mass of the hands and feet start to decrease at a relatively young age (below the age of 40 years) in Werner syndrome patients. Although the cause is unclear, it may be attributed to the patient's limited mobility due to the presence of contractures (impaired joint movement) and skin ulcers on the soles of the feet, which are common among Werner syndrome patients.

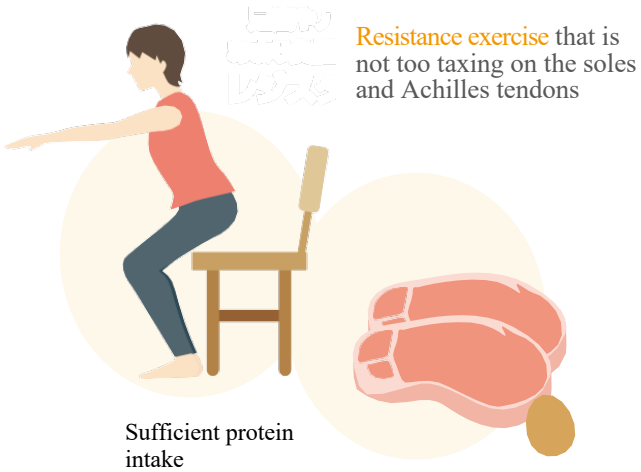
Main symptoms



In fact, some Werner syndrome patients who engage in habitual resistance exercise (exercise that puts a load on the muscles, so-called muscle training) do not experience a reduction in the skeletal muscle mass. As such, sarcopenia may be preventable by performing appropriate exercise.

Prevention

Engaging in resistance exercise that does not put too much strain on the soles of your feet and the Achilles tendons is recommended, and sufficient protein (ingredients for muscle) intake is highly encouraged.
Each meal should contain at least 25g of protein. However, if chronic kidney disease and other diseases develop, a family doctor should be consulted.



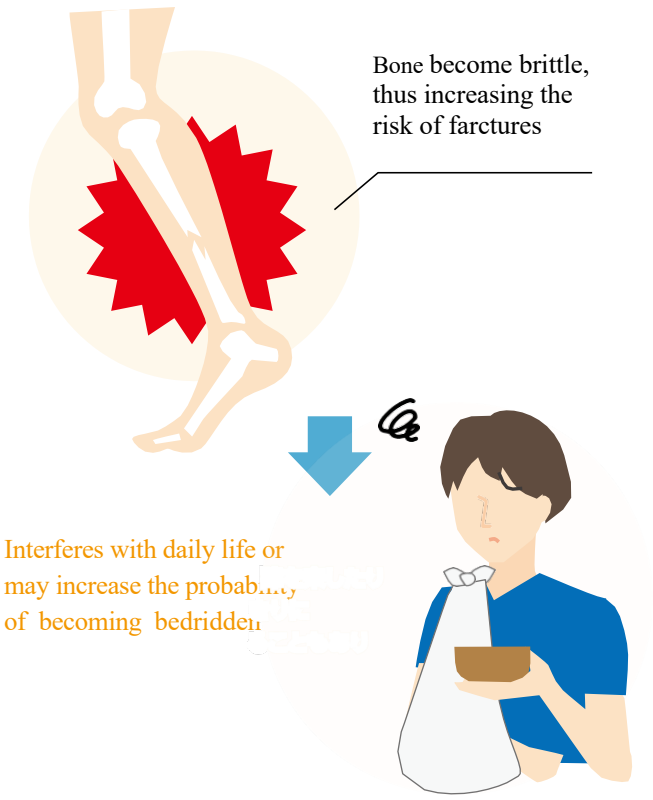
What in osteoporosis

Osteoporosis is a disease in which the bone mass decreases with age, making the bones brittle and prone to fractures.

Osteoporosis is also a dangerous condition that may affect an individual's life expectancy as fractures can interfere with daily life and increase the probability of becoming bedridden. Patients with Werner syndrome are prone to osteoporosis at a young age.

Although it depends on the patient's age, a previous Japanese survey reported osteoporosis in 41% of Werner syndrome patients, while an overseas study reported osteoporosis in >90% of patients. In patients with Werner syndrome, osteoporosis is more severe in the lower limbs than that in the vertebrae (spine).

Main symptoms



Prevention and treatment

Conventional osteoporosis medications can be used for treatment.

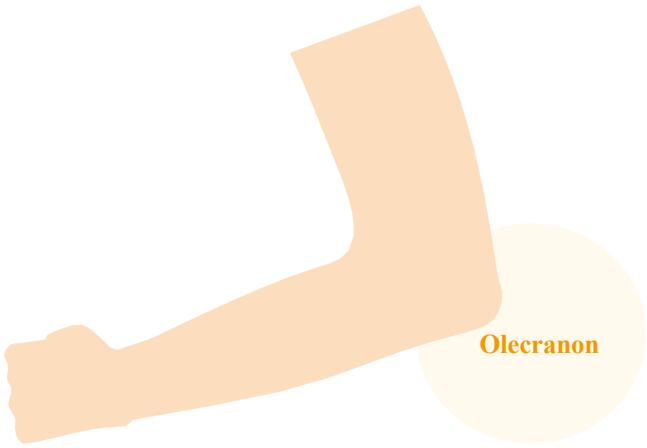
Similar to sarcopenia, performing exercises is one of the preventive measures. Vitamin D intake promotes the absorption of calcium from food and is important for the prevention of osteoporosis. As with sarcopenia, adequate dietary protein intake is also important.

Exercise is important for the prevention of both sarcopenia and osteoporosis. It is important to avoid excessive exercise and incorporate exercise that is not too taxing since some Werner syndrome patients are prone to developing ulcers on the soles of their feet and some have joint contracture.

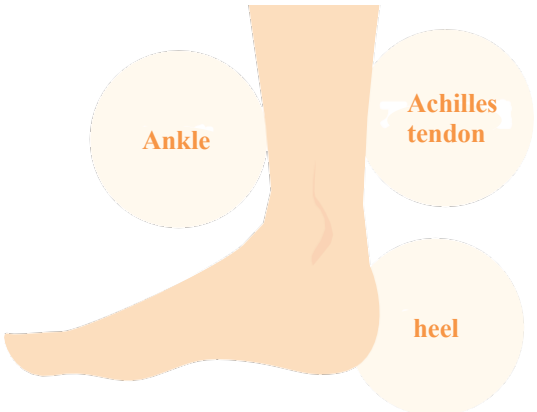
9 Foot ulcers (hard-to-heal wounds)

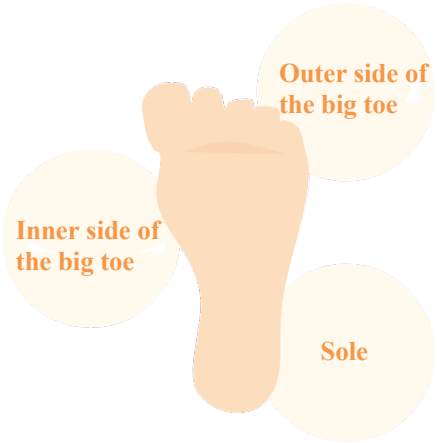
Werner syndrome causes hard-to-heal wounds on the skin. The most common areas are the elbows and below the knees.

Hard-to-heal wounds on the elbow form on **the lateral protruding portion of the elbow (olecranon)**.
If the wound may be extended to the elbow with thin skin, you need to consult the dermatologist



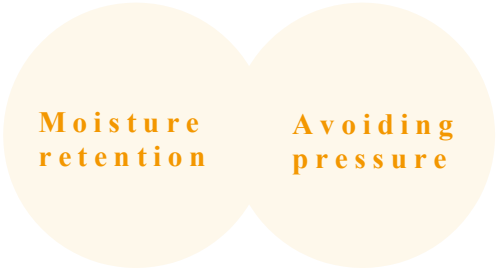
The areas where hard-to-heal wounds are likely to form include the Achilles tendon, ankles, heels, soles, inner side of the big toe, and outer side of the small toe.
The wound may extend deeply into the joint or bone because the skin is thin.





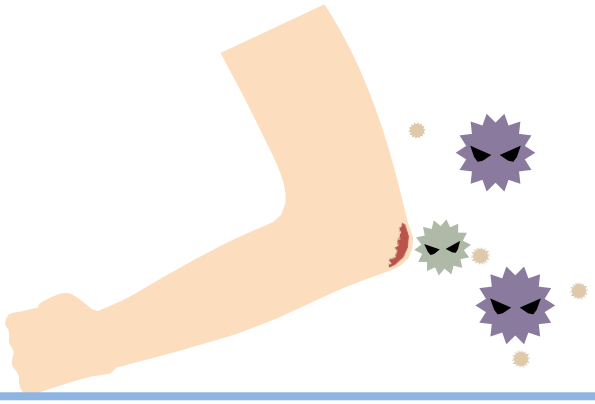
Prevention

Prevention is important because once a wound forms, it is difficult to heal. Moisture retention and avoiding pressure are important. A callus may form as a sign of pressure. The callus should be treated as the skin will be pressed further and a wound will possibly form if it is left unattended. **Well-fitting shoes should be worn to prevent the formation of calluses.**



Treatment

Bacteria may accumulate inside the hard-to-heal wounds. They should be removed to reduce the risk of spread. The tissues infected with bacteria should also be removed. Surgery may be performed to close the wounds that do not heal easily.

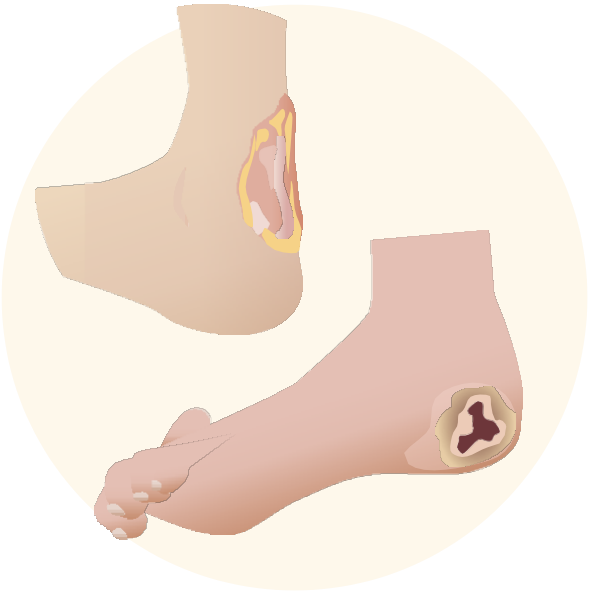


Prevention and treatment of intractable ulcers

One of the characteristics of Werner syndrome is that **wounds easily form on the skin (ulcers) and are hard to heal**. Wounds frequently develop in the **weight-bearing part of the sole of the foot**. In addition, they are common in areas where pressure is likely to be applied such as the **Achilles tendon, ankle joint, and elbow joint.**

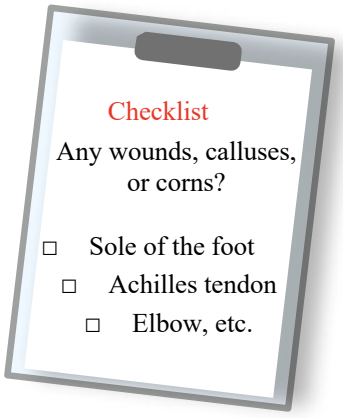
The wounds are difficult to heal in these areas because the skin has thickened/toughened and the amount of fat is relatively low. It is as if the cushion has been removed, and the bone comes in direct contact.

Moreover, poor blood flow due to narrowing of the blood vessels, calcium oxide formation in the skin, and deformation of the joints are also thought to cause ulcer formation.



The callus should be treated as the skin will be pressed further and a wound will possibly form if it is left unattended. **Well-fitting shoes should be worn to prevent the formation of calluses.** Prevention is important because once a wound forms, it is difficult to heal. Moisture retention and avoiding pressure are important. A callus may form as a sign of pressure.

The soles of the feet, Achilles tendons, and elbows should be assessed for presence of scratches, calluses, and corns. An ointment or plaster (various dead-skin-softening topical agents containing urea) that softens dead skin should be applied as soon as possible if thickened dead skin such as calluses or corns begin to form. Dead-skin-softening topical agents and plasters are sold at pharmacies, but a specialist such as a dermatologist should be consulted first. Scissors are used in some cases to remove calluses and corns that do not come off with ointment or plasters alone. However, a specialist such as a dermatologist should be consulted as doing so on your own may lead to wound formation.



If a callus or corn is left unattended, a wound will form in the center and will take a long time to heal. Care must be taken to prevent bacterial infection if a wound forms. It should be kept clean by washing it with soap every day. Ointment should be applied for wound healing after rinsing thoroughly. If necrotic areas are noted, a drug that dissolves them should be used. If red granulation occurs, an appropriate medication should be applied to further raise the granulation tissue and eventually reduce the wound size. If bacterial infection occurs, disinfectants, ointments that suppress infection, and oral antibiotics are needed. If bacterial infection is noted or if the scratch increases in size, it will be difficult to heal; hence, a dermatologist should be consulted as soon as possible.

A dermatologist should be consulted as soon as possible.

10 Tumor

What is a malignant tumor?

A malignant tumor is a tumor in which certain cells disregard the order established in the body and proliferate, spread to the surrounding tissues, or cause metastasis. Malignant tumors include epithelial tumors (cancer), non-epithelial tumors (such as sarcoma), and blood tumors such as leukemia. In general, cancer is common, while non-epithelial tumors are rare. When the incidence of cancer and that of non-epithelial tumors are compared, the ratio is about 10 to 1.

Malignant tumors and Werner syndrome.

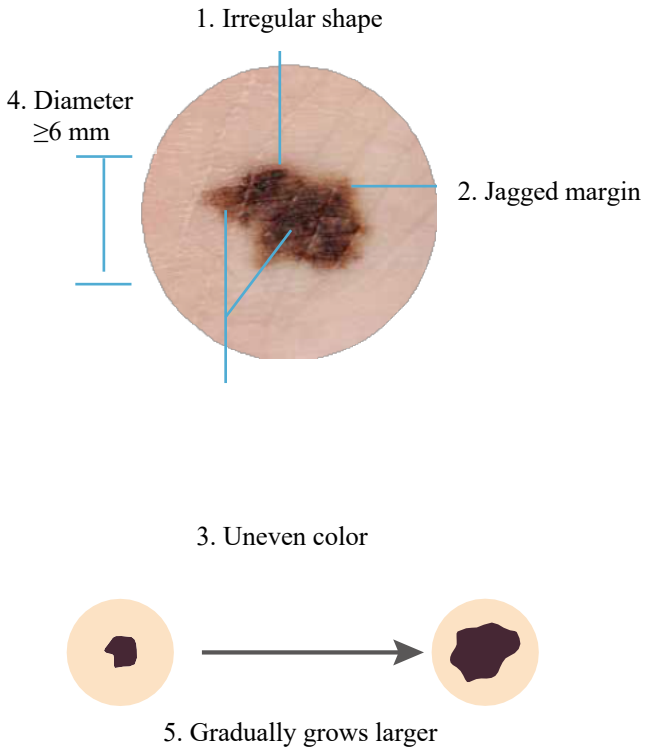
According to a previous survey conducted in Japan, malignant tumors were found in approximately 30% of people with Werner syndrome. They tend to develop at a relatively young age (40 years). Non-epithelial tumors, which rarely develop, are common in Werner syndrome patients with a cancer to non-epithelial tumors ratio of 1 to 2. Among them, malignant melanoma, malignant fibrous histiocytoma, and meningeal tumors are common. With regard to cancer, thyroid cancer is commonly observed. Moreover, it is not uncommon for a Werner syndrome patient to develop multiple cancers (multiple tumors), in which several comorbid malignant tumors develop. Recently, the number of cancer cases has dramatically increased as the life expectancy of people with Werner syndrome increases.

Screening and treatment for malignant tumors

Patients with Werner syndrome should be assessed for presence of malignant tumors. Regular medical checkups and cancer screening lead to early detection and treatment. Patients should undergo blood and urine tests at least once every 3 months, and chest X-rays, thyroid ultrasound, abdominal ultrasound, fecal occult blood tests, etc. every 6 months to 1 year. A whole body assessment should be performed daily. In particular, a doctor should be consulted if an irregularly shaped “mole” develops on the skin or if a “swelling” under the skin increases in size.

The treatment for malignant tumors that develop in Werner syndrome patients is the same as that in the general population. Some patients express concern about undergoing surgery because the wounds that form on their hands and feet do not easily heal. Wounds caused by surgery (e.g., lung cancer) on the central part of the body (trunk) easily heals, and the patients undergo the same procedures that are usually performed.

Characteristics of malignant mole melanoma



Ministry of Health, Labour and Welfare Research Grant
Intractable Disease Policy Research Project
Multidisciplinary research aimed at improving the medical standards and QOL for progeria

Koutaro Yokote, Endocrinology, Hematology, and Gerontology, Graduate School of Medicine and School of Medicine, Chiba University

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Masafumi Kuzuya, Department of Geriatrics, Nagoya University Graduate School of Medicine

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Cooperation：Werner Syndrome Patient/Family Group

March 2021

Werner syndrome

Werner syndrome

日本語

About our efforts to improve the prognosis of Werner syndrome

A prospective, single-center study (EMPOWER study) to evaluate the safety and efficacy of nicotinamide riboside in Werner syndrome

There is no definitive treatment for Werner syndrome. Symptomatic treatment is usually employed and focuses on treating intractable ulcers, sarcopenia, arteriosclerotic diseases, etc. However, the effects are limited, and treatments with better efficacy are needed.

In recent years, geriatric research has discovered sirtuins. Sirtuins, also known as longevity genes or anti-aging genes, are said to extend the lifespan when activated. Nicotinamide adenine dinucleotide (NAD) is important for the activation of sirtuins. Decreased NAD levels have been observed in patients with Werner syndrome (Nat Commun. 2019 Nov 21;10(1):5284), thus suggesting that supplementation with NAD's precursor may be effective for treating Werner syndrome.

Chiba University is conducting an EMPOWER study to investigate the safety and efficacy of nicotinamide riboside, a precursor of NAD, which is said to be effective in suppressing the symptoms of aging such as intractable ulcers, sarcopenia, and arteriosclerotic diseases, in patients with Werner syndrome. Recruitment of patients was performed until the end of September 2021.

For more information on the study, please refer to:
https://jrct.niph.go.jp/en-latest-detail/jRCTs031190141

Werner Syndrome Q&A

1. What is "Werner syndrome"?

Werner syndrome is a rare genetic disease initially reported in 1904 by German physician Otto Werner. This condition is classified a disease of "premature aging" (progeria) because aging seems to progress rapidly after puberty. Gray hair, hair loss, and cataracts in both eyes appear when the patient is in their 20s, while the muscles and skin of the hands and feet become thin and tough, making them look older than their actual age. Diabetes and dyslipidemia (abnormalities in cholesterol and triglyceride levels) are also common, and, in the past, many patients died of malignant tumors or myocardial infarction in their 40s. Life expectancy has been extended, thanks to the advances in treatment; nowadays, some Werner syndrome patients reached the age of 50 years and 60 years. On the contrary, some patients develop deep wounds on the toes or elbow that do not heal (intractable skin ulcers) leading to amputation of the foot due to repeated infection; even today, many patients experience extreme difficulties in their day-to-day life.

2. How many individuals have been diagnosed with Werner syndrome?

According to some studies, there are an estimated up to 2,000 people with Werner syndrome in Japan, with a prevalence of 1 in approximately 50,000 to 60,000 people.

3. What kind of people are most prone to Werner syndrome?

Regionally, the disease is prevalent in Japan, with 60% of the patients reported worldwide being Japanese. In the past, the patients reported were from areas with many consanguineous marriages (cousin marriages and second-cousin marriages); in recent years, the number of patients whose disease onset is not related to consanguinity is relatively increasing. Lifestyle habits such as daily diet and exercise are thought to be unrelated to the onset of this disease.

4. Is the cause of Werner syndrome known?

It is thought to be caused by an abnormality in the WRN gene. WRN (also known as deoxyribonucleic acid (DNA) helicase) plays a role in repairing DNA *1, which is the blueprint of our body, when it is damaged. However, the reason why abnormalities in WRN accelerate aging remains unknown.

5. Is Werner syndrome hereditary?

Humans have a pair (two) of genes inherited from each parent. Werner syndrome only occurs when both WRN genes are defective. In most cases, each of the patient's parents only has one causative gene and does not develop the disease. About 1 in 4 of the patient's siblings will develop the disease, but the probability that the patient's children or their children will develop the disease like their parent or grandparent is less than 1 in 200 to 400. In conclusion, the possibility is extremely low.

6. What are the symptoms of Werner syndrome?

After the age of 20 years, symptoms such as gray hair and hair loss, cataracts (often in both eyes), and a high-pitched hoarse voice occur. In addition, muscle atrophy in the arms and legs occurs, the skin becomes hard and thin, and deep wounds that are difficult to heal develop (intractable skin ulcers). They are often short in stature, and X-rays often reveal calcifications in the Achilles tendons and subcutaneous tissues (accumulation of calcium components). In addition, many people develop diabetes and dyslipidemia, and menopause, when the level of sex hormones declines, is more likely to occur at an early age.

7. What treatments are available for Werner syndrome?

Werner syndrome has no cure, and treatment or preventive measures for signs of "visual aging" including gray hair, hair loss, and skin changes are not available. Foot wounds are difficult to heal and can seriously interfere with day-to-day life. It is therefore important to take preventive measures such as avoiding the formation of blisters on the feet. If it occurs, symptomatic treatments such as cleaning, disinfection, protection, and moisture retention are required. However, surgery to transplant skin from other areas of the body may be effective in some cases. On the contrary, early detection and treatment are important for certain diseases such as malignant tumors, cataracts, diabetes, dyslipidemia, etc.; surgery and medication treatment are effective in patients with Werner syndrome as they are in the general patients.

8. How does Werner syndrome progress?

In the past, many patients with Werner syndrome died in their mid-40s from arteriosclerotic diseases such as malignant tumors (cancer) or myocardial infarction. However, recent studies show that the average life expectancy has increased by more than 10 years, and the number of patients in their 60s is relatively increasing. On the contrary, many patients develop intractable wounds (intractable skin ulcers) on the heel, feet, elbow, etc., and are forced to undergo foot amputation due to continuous pain and repeated infection. This interferes with their day-to-day life and poses a major problem.

9. What precautions need to be taken in daily life for Werner syndrome?

First, it is important to protect and observe areas that are prone to ulcer formation such as the Achilles tendon, heels, feet, and elbows to prevent the formation of deep wounds that are difficult to heal (intractable skin ulcers). Skin that has become thin and tough is easily wounded due to the pressure exerted by the underlying bones. Such wounds are prone to develop into deep ulcers. Special shoes (orthoses) may be used to protect the areas that are tender to pressure or are about to form wounds. Assessment should be performed to detect the presence of malignant tumors during regular hospital visits, and metabolic abnormalities such as diabetes and dyslipidemia should be treated to prevent the rapid progression of arteriosclerosis.

*1 DNA :
A substance found in the cells that make up the human body. It serves as a blueprint to produce proteins necessary for sustaining life.

Download PDF（＊in Japanese)

Download PDF（＊in Japanese)

Wiley Online Library

to improve medical standards and QOL for progeria

2020 research group member list（＊in Japanese)

PDF

Diagnostic Criteria and Severity Classification (Intractable Disease Treatment Center)

http://www.nanbyou.or.jp/entry/5321（＊in Japanese)

A message from a Werner syndrome patient: What I expect from medicine

0:00 / 2:19

The patient provided consent to the publishing of their unaltered images and voice on this website.
Unauthorized use of images and audio is strictly prohibited.

Werner syndrome national survey

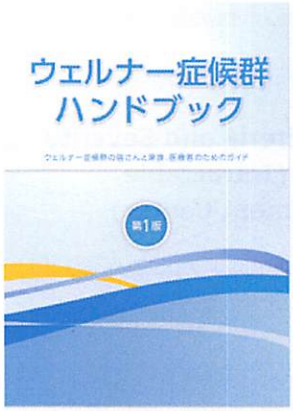
This nationwide epidemiological survey aimed to understand the circumstances surrounding Werner syndrome in Japan based on the Japan Agency for Medical Research and Development (Practical Research Project for Intractable Diseases) "Creation of Evidence through Nationwide Survey of Werner Syndrome with Progeria and Construction of a Case Registration System."

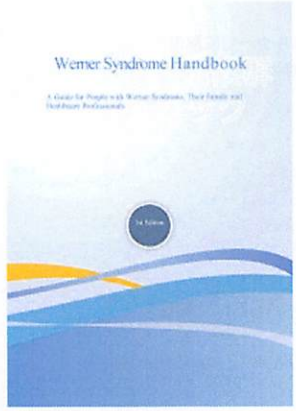
Werner syndrome is a rare genetic progeria and is highly prevalent in Japan, with two-thirds of the patients reported worldwide being Japanese. A nationwide survey was conducted in 2009. As a result, 200 Werner syndrome patients were identified, and the disease was designated as an intractable disease. Based on the results of this survey, the diagnostic criteria for Werner syndrome were revised for the first time in 25 years, and the treatment guidelines, which did not exist up until then, were created. Currently, there are an estimated up to 2,000 people with Werner syndrome in Japan. However, the circumstances surrounding the patients and the disease are not fully understood, and it has no curative treatment. We therefore aim to compile useful evidence collected in Japan to improve the patients' prognosis and quality of life (QOL).

We would like to thank half of the participating facilities who responded to this survey. We would appreciate it if the doctors who are in charge of the facilities where the questionnaire was sent and have not responded yet would take the time to fill out the enclosed survey form with the number of patients admitted in the department in the last 10 years who meet the criteria or suspected patients and to send the forms back it to us by faxing it to 043-226-2095. If none of the patients meet the criteria, it is still necessary to provide the estimated number of patients diagnosed with Werner syndrome nationwide; hence, please mark "none" on the survey form and return it.

*Werner Syndrome Handbook

A guide for patients with Werner syndrome, their family, and medical professionals. 1st edition





Download PDF（*in Japanese）

Download PDF（*in English）

Diagnostic criteria for Werner syndrome (revised in 2012)

I. Cardinal signs and symptoms (onset over 10 until 40 years-of-age)

Progeroid changes of hair Progeroid changes of hair (gray hair, baldness, etc.)
Cataract (bilateral)
Changes of skin, intractable skin ulcers (atrophic skin, tight skin, clavus, callus)
Soft-tissue calcification(Achilles tendon, etc.)
Bird-like
Abnormal voice (high pitched, squeaky, hoarse voice)

II. Other signs and symptoms

Abnormal glucose and/or lipid metabolism
Deformation and abnormality of the bone (osteoporosis, etc.)
Malignant tumors (non-epithelial tumors, thyroid cancer, etc)
Parental consanguinity
Premature atherosclerosis (angina pectoris, myocardial infarction, etc.)
Hypogonadism
Short stature and low bodyweight

III. Genetic testing

Diagnosis

Confirmed: Presence of all cardinal signs, OR, presence of biallelic WRN gene mutations in addition to at least three cardinal signs.
Suspected: Presence of both I-1 (progeroid changes of hair) and I-2 (cataract), AND, at least two more signs or symptoms from I or II.

Takemoto M, Mori S, Kuzuya M, Yoshimoto S, Shimamoto A, Igarashi M, Tanaka Y, Miki T, Yokote K. Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr Gerontol Int. 2013 Apr;13(2):475-81.

Guidelines on the diagnosis and treatment of Werner syndrome

2012 edition

2020 edition

Ministry of Health, Labour and Welfare Intractable Disease Policy Research Project Multidisciplinary research aiming

We also accept inquiries from doctors who have examined new patients and requests for genetic testing.

You can also download the questionnaire and the attached materials here (*in Japanese) PDF.

We may send individual survey forms at a later date if there are patients who meet the criteria or are suspected to meet the criteria. In such cases, we would appreciate your cooperation.

We promote the establishment of a case registration system for Werner syndrome through this survey; we strive to enhance the quality of medical care for this disease to improve the prognosis of patients by revising the treatment guidelines. We appreciate your cooperation.

Office of Werner Syndrome National Epidemiological Survey: 1-8-1 Inohana, Chuo-ku, Chiba 260-8670
Endocrinology, Hematology, and Gerontology, Graduate School of Medicine and School of Medicine, Chiba University
Practical Research Project for Intractable Diseases, Japan Agency for Medical Research and Development
"Creation of Evidence Through Nationwide Surveys of Werner Syndrome with Progeria and Construction of a Case Registration System"
Research group
Research group leader: Koutaro Yokote
Research group leader: Koutaro Yokote Person in charge for the National epidemiological survey of Werner syndrome: Masaya Koshizaka
(Endocrinology, Hematology, and Gerontology, Graduate School of Medicine and School of Medicine, Chiba University)
Phone: 043-226-2092, Fax: 043-226-2095

Werner syndrome: Results of the 2017 nationwide primary survey

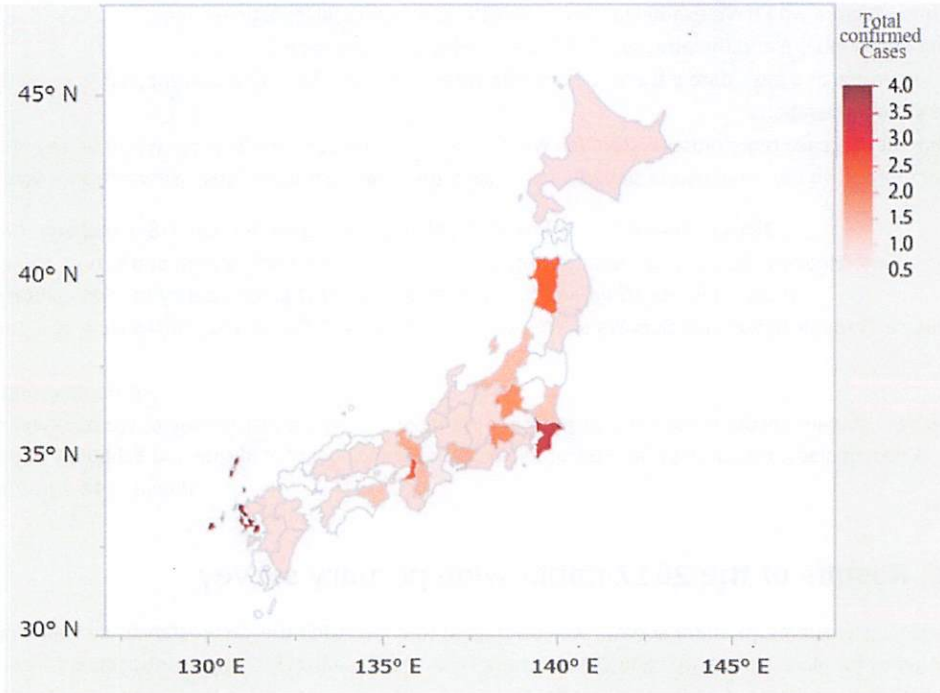
The 2017 nationwide epidemiological survey (primary survey) was conducted to understand the circumstances surrounding Werner syndrome in Japan based on the Japan Agency for Medical Research and Development (Practical Research Project for Intractable Diseases) "Creation of Evidence through Nationwide Survey of Werner Syndrome with Progeria and Construction of a Case Registration System." The compiled results will be made publicly available.

The survey was conducted in the form of a questionnaire survey conducted from February 2017 and included 7,889 clinical departments (internal medicine, ophthalmology, dermatology, orthopedics, plastic surgery, etc.) in hospitals with 200 or more beds nationwide. We received a total of 3,154 responses (response rate: 40%). We would like to take this opportunity to once again thank the doctors in all facilities for their cooperation.

We were able to identify 200 Werner syndrome patients from the previous nationwide survey conducted in 2010. In addition to this, we were able to identify 116 patients with confirmed cases of Werner syndrome (57 men and 59 women) in this survey. Furthermore, 51 patients (29 men and 22 women) were suspected of having Werner syndrome. Patients suspected of having Werner syndrome are currently undergoing genetic testing in our department. Additionally, we identified 153 patients (80 men, 71 women, and 2 of unknown gender) with a confirmed diagnosis who have visited one of the medical institutions in Japan in the last 10 years (patients with confirmed cases with previous hospital visits). A total of 320 patients in Japan comprising those with confirmed cases, those with suspected cases, and those with previous hospital visits have been identified.

	Werner syndrome confirmed male cases	Werner syndrome confirmed female cases	Werner syndrome suspected male cases	Werner syndrome suspected female patients	Werner syndrome confirmed male cases With previous hospital visits	Werner syndrome confirmed female cases With previous hospital visits	Total
小計	57	59	29	22	80	71	
その他					Gender/number unknown 2		
合計	116		51		153		320

No regional difference was observed in terms of the distribution of patients nationwide*. This finding suggests that there is no clear regional difference in the incidence of the disease, and patients well distributed nationwide.



Confirmed cases

Confirmed cases + suspected cases + confirmed cases with previous hospital visits

We plan to conduct a secondary survey in the future in the facilities that reported confirmed cases in the primary survey. In the secondary survey, based on the data obtained, we will investigate the disease, recruit patients for studies including clinical trials**, and provide information to registered patients and attending physicians with the use of the Werner syndrome case registration (registry) system.

The primary survey has been completed, but we are still accepting inquiries from doctors who have examined new patients and requests for genetic testing as needed.

* The number of cases reported in Chiba is relatively high compared with that in other prefectures. This is probably because a large number of patients are referred to Chiba University Hospital.

** Dr. Nakagami of Osaka University is taking the lead in recruiting patients who wish to participate in the clinical trial for "the treatment of intractable ulcers using novel peptides," which will be conducted in September this year. Chiba University is also conducting a study using induced pluripotent stem (iPS) cells.

Office of Werner Syndrome National Epidemiological Survey: 1-8-1 Inohana, Chuo-ku, Chiba 260-8670
Endocrinology, Hematology, and Gerontology, Graduate School of Medicine and School of Medicine, Chiba University
Practical Research Project for Intractable Diseases, Japan Agency for Medical Research and Development
"Creation of Evidence Through Nationwide Surveys of Werner Syndrome with Progeria and Construction of a Case Registration System"
Research group
Research group leader: Kotaro Yokote

Person in charge for the National epidemiological survey of Werner syndrome: Masaya Koshizaka
(Endocrinology, Hematology, and Gerontology, Graduate School of Medicine and School of Medicine, Chiba University)
Phone: 043-226-2092, Fax: 043-226-2095

International Meeting on RECQ Helicases and Related Diseases 2018

Date: February 16th (Friday) – 18th (Sunday), 2018
Venue: Kazusa Academia Park
URL : http://www.jtbw-mice.com/recq2018/

This meeting has been held in the United States to discuss RECQ helicase-related progeria syndromes such as Werner syndrome, Bloom syndrome, and Rothmund-Thomson syndrome. It was initially held in Asia in 2018. In addition to xeroderma pigmentosum, Cockayne syndrome, and Hutchinson-Gilford progeria syndrome, a wide range of aging-related conditions associated with these diseases was discussed including, cellular aging, mitochondrial disorders, and iPS cell biology. The meeting was attended by 135 participants (29 from outside Japan) and was a great success. A total of 27 speakers, including 12 from overseas, provided advanced lectures followed by lively discussions. Twenty-one patients, including 5 from overseas, were present, and their participation led to the active exchange of information between researchers and patients. It was a unique symposium with participants from both Japan and overseas commenting that the interaction with patients delineated the issues and made them feel more motivated.

はじめに

この冊子を手にとっていただき、
ありがとうございます。
ロスムンドトムソン症候群は日本に10人と
言われている稀少難病です。
それゆえ患者さんやその家族は、まわりから
理解を得られず、悲しい思いをするこが
多々あります。
わたしたち家族会は、この病気のことを
もっと知ってもらいたい
という思いからこの冊子を作りました。

家族会のご案内

患者さんご本人またはご家族の方
家族会に参加しませんか？

患者さんが少ない病気だからこそ、病気の正しい
知識の共有が大切です。定期的に情報交換会を
開催しておりますので、ぜひご参加ください。

問い合わせ先
rts-family@outlook.jp

ロスムンド・トムソン症候群家族会
https://rts-family.wixsite.com/my-site/

知ってください
ロスムンド・トムソン
症候群のこと

監修
岐阜県総合医療センター小児療育内科部長
岐阜大学医学部客員臨床系医学教授
金子英雄先生

どんな
病気なの？

遺伝子の異常が原因の
主に骨と皮膚の病気です。

皮膚に紅斑・浮腫・水疱のような症状が
現れます。その一部は色素沈着して
シミのように残ることがあります。

骨は両手の親指がなかったり
あっても機能しなかったりします。
また上腕骨に奇形を伴うことが多いです。
必要に応じて手術・リハビリを行います。

そのほかに小柄な体形・難聴
まばらな頭髪、眉毛
歯の欠損、白内障、口蓋裂
などが認められています。

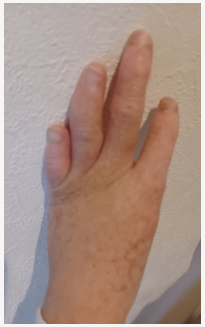
骨肉腫（おおよそ3人に1人）と
皮膚がんのリスクが高く
早期発見のために定期受診をします。

頭蓋骨の早期癒合が特徴の
バレージェロルド症候群も同じ遺伝子
異常の病気といわれています。

生活の中で
わたしたちが
気をつけていること

紫外線の対策をしています

紫外線を沢山あびると皮膚が赤く
なったり、シミができやすいです。
皮膚がんのリスクが高い病気なので、
日焼けどめクリームや帽子などの日よけが
欠かせません。多くの時間を過ごす家や
集団生活の場でも紫外線の対策が
必要です。



親指の欠損

ほほの色素沈着

さいごに

この病気は紫外線を避けて生活
しなければなりません。
集団生活においては、定期的な
日焼けどめクリームの塗布や
紫外線カットフィルムを貼る
などの環境設定をお願いする
ことがあるかもしれません。
すべて対応していただくことは
難しいと思います。
できる範囲でご協力をお願い
いたします。

ロスムンド・トムソン症候群
バレー・ジェロルド症候群
家族会　2023年作成

令和６年３月１８日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　大学院医学研究院・教授

（氏名・フリガナ）　横手幸太郎・ヨコテコウタロウ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■　□	■	千葉大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

令和６年３月１８日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

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２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　大学院医学研究院・講師

（氏名・フリガナ）　前澤善朗・マエザワヨシロウ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■　□	■	千葉大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

令和6年　　3月　14日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）医学部附属病院・助教

（氏名・フリガナ）加藤　尚也　（カトウ　ヒサヤ）

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み　審査した機関		未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	■　□	■	千葉大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年５月２３日

国立保健医療科学院長　殿

機関名　国際医療福祉大学

所属研究機関長　職　名　学長

氏　名　鈴木　康裕

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部・教授（代表）

（氏名・フリガナ）　竹本　稔（タケモト　ミノル）

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和 6 年　2 月　7 日

国立保健医療科学院長　殿

機関名　国立大学法人大阪大学

所属研究機関長　職　名　大学院医学系研究科長

氏　名　熊ノ郷　淳

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）大学院医学系研究科・寄附講座教授

（氏名・フリガナ）中神　啓徳・ナカガミ　ヒロノリ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

令和６年３月１８日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　大学院医学研究院・准教授

（氏名・フリガナ）　窪田吉孝・クボタヨシタカ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和　6年　2月　21日

国立保健医療科学院長　殿

機関名 国立成育医療研究センター

所属研究機関長　職　名 理事長

氏　名 五十嵐　隆

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　遺伝診療センター遺伝診療科・診療部長

（氏名・フリガナ）　小﨑　里華・コサキ　リカ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和　6年　　2月　22日

国立保健医療科学院長　殿

機関名　国立大学法人群馬大学

所属研究機関長　職　名　学長

氏　名　石崎　泰樹

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　大学院医学系研究科・教授

（氏名・フリガナ）　茂木 精一郎・モテギ セイイチロウ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	■　□	■	群馬大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年３月１８日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部附属病院・准教授

（氏名・フリガナ）　谷口　俊文・タニグチ　トシブミ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年４月１２日

国立保健医療科学院長　殿

機関名　国立大学法人大分大学

所属研究機関長　職　名　学長

氏　名　北野　正剛

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部小児科学講座・教授

（氏名・フリガナ）　井原　健二・イハラ　ケンジ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	☑	□	☑	大分大学医学部	□
遺伝子治療等臨床研究に関する指針	□	☑	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	☑	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	☑	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ☑　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ☑　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ☑　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ☑　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ☑（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年５月１６日

国立保健医療科学院長　殿

機関名　岐阜県総合医療センター

所属研究機関長　職　名　理事長

氏　名　桑原　尚志

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　小児療育内科・部長

（氏名・フリガナ）　金子　英雄・カネコ　ヒデオ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■　□	■	岐阜県総合医療センター	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和　6　年　2　月　29　日

国立保健医療科学院長　殿

機関名　国立大学法人東海国立大学機構

所属研究機関長　職　名　名古屋大学医学部附属病院長

氏　名　　小寺　泰弘

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部附属病院・病院講師

（氏名・フリガナ）　渡邊一久・ワタナベカズヒサ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■　□	■	名古屋大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年２月１日

国立保健医療科学院長 殿

機関名　公立大学法人奈良県立医科大学

所属研究機関長　職　名　理事長

氏　名　細井　裕司

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部・准教授

（氏名・フリガナ）　谷口　晃・タニグチ　アキラ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学・医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和６年　４月　８日

国立保健医療科学院長　殿

機関名　佐賀大学

所属研究機関長　職　名　学長

氏　名　兒玉　浩明

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　医学部小児科・教授

（氏名・フリガナ）　松尾宗明・マツオムネアキ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	■　□	■	佐賀大学医学部附属病院臨床研究倫理審査委員会	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

令和６年３月１８日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学長代行

氏　名　中谷 晴昭

次の職員の令和５年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患政策研究事業

２．研究課題名　早老症のエビデンス集積を通じて診療の質と患者 QOL を向上する全国研究

３．研究者名　（所属部署・職名）　大学院医学研究院・特任教授

（氏名・フリガナ）　忍足俊幸・オシタリトシユキ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
人を対象とする生命科学･医学系研究に関する倫理指針（※3）	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」、「臨床研究に関する倫理指針」、「ヒトゲノム・遺伝子解析研究に関する倫理指針」、「人を対象とする医学系研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。