別添１

研究報告書表紙

厚生労働科学研究費補助金

（難治性疾患政策研究事業）

原発性高脂血症に関する調査研究

令和２年度　総括研究報告書

研究代表者　斯波　真理子

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研究報告書目次

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原発性高脂血症に関する調査研究

研究代表者　斯波真理子　国立循環器病研究センター研究所　非常勤研究員

研究要旨

今期班では前期班（班長：石橋俊）の研究成果を継承しながら、指定難病７疾患（家族性高コレステロール血症（FH）ホモ接合体、レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症、シトステロール血症、タンジール病、原発性高カイロミクロン血症、脳腱黄色腫症、無βリポ蛋白血症）についてそれぞれ疾患担当責任者を決め、全疾患のレジストリ構築、疾患概念のまとめ（システマティックレビューの作成)、診療上の課題の明確化と解決方法の考案（小児慢性特定疾病と成人指定難病の該当疾患の違い等に起因する小児から成人期への移行期医療に関する課題など）をオールジャパン・学会横断的体制で行い、研究班独自のホームページの開設や患者会等との連携、学会シンポジウムや市民公開講座発表等による情報発信・疾患啓発を実施する。これにより難病患者診断率および受給者数の向上と患者 QOL 及び予後の改善が期待できる。

疫学研究（PROLIPID 研究）については７つの担当疾患すべてのレジストリ項目の決定、倫理委員会での承認を経て、登録システムの構築が完了した。また登録患者数が前年度の 587 名から 965 例へと大幅に増加した。FH を除く新診断基準については疾患担当責任者が中心となり、改善案作成後に日本動脈硬化学会理事会で承認を得、難病検討委員会へ新診断基準（案）を提出した。また無βリポタンパク血症の類縁疾患である家族性低βリポタンパク血症１ホモ接合体の診断基準を作成し、動脈硬化学会理事会で承認を得、難病検討委員会に提出した。7 疾患すべての英文総説が疾患担当責任者らにより執筆され、日本動脈硬化学会の英文雑誌 Journal of Atherosclerosis and Thrombosis（JAT）誌にすべてアクセプトされた。FH の新診断基準および診療ガイドライン作成を担当する日本動脈硬化学会の作成班に協力した。また東京大学および香川県の検討結果から、若年および小児の高 LDL-C 血症患者（児）では FH が高頻度で存在することが分かり、健診スクリーニングの有用性が示唆された。移行期医療については移行期に行き場がなくなる（小児慢性特定疾病だが成人指定難病ではない）疾患としてアポリポタンパク A-I 欠損症があることが判明したため、診断基準を作成し、動脈硬化学会理事会で承認を得、難病検討委員会に提出した。

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A. 研究目的

1. 診療体制の構築に資する研究

まず、指定難病である 7 つの原発性脂質異常症について概要を記す。

家族性高コレステロール血症（Familial Hypercholesterolemia: FH）（ホモ接合体）は LDL 受容体およびその関連遺伝子の変異を 2 つ以上有する遺伝病であり、常染色体優性遺伝形式をとる。ヘテロ接合体が 200 人から 500 人に 1 人存在することから、ホモ接合体患者は 16 万人から 100 万人に 1 人の頻度で認められ、わが国における患者数は、数百人と推定される。FH ホモ接合体は、生下時より著明な高 LDL コレステロール（LDL-C）血症を示し、幼児期より動脈硬化症による冠動脈疾患や大動脈弁狭窄症、大動脈弁上狭窄症などを引き起こし、未治療では 30 歳まで生きられないことが多い。多くの脂質異常症治療薬が LDL 受容体の活性化をその主要機序としているために LDL 受容体活性が著しく低い FH ホモ接合体の治療は困難であり、定期的な LDL アフェレシスや LDL 受容体経路を介さない脂質低下治療薬であるミクロソームトリグリセリド転送タンパク（Microsome Triglyceride Transfer Protein: MTP）阻害薬の投与が必要であるが、治療費が極めて高額である。ヘテロ接合体はホモ接合体ほどではないものの生下時からの高 LDL-C 血症による早発性冠動脈疾患のハイリスク群である。

レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症は、LCAT 遺伝子変異による遺伝病で常染色体劣性遺伝形式をとる。低 HDL-コレステロール血症のほか、幼少時から進行する腎障害、角膜混濁により長期にわたり日常生活に高度の支障をきたす。現在のところ有効な治療法は確立されていない。

シトステロール血症は ATP 結合カセットトランスポーター（ATP-binding cassette transporter：ABC）G5 または G8 の遺伝子変異による遺伝病である。植物ステロールが蓄積することにより高率に早発性心血管疾患を発症する。幼少期に黄色腫を認めることから FH ホモ接合体との鑑別が重要である。

タンジール病は ABCA1 の遺伝子変異による遺伝病で常染色体劣性遺伝形式をとる。極端な低 HDL-コレステロール血症とそれに伴う末梢組織への脂質沈着、末梢神経障害などをきたし、早発性冠動

脈疾患の発症が生命予後を規定する。

原発性高カイロミクロン血症は脂質異常症 WHO 分類でのⅠ型およびⅤ型を指し、カイロミクロン代謝に関与する種々の蛋白の欠損・機能異常を背景として発症する。例としてリポ蛋白リパーゼ（Lipoprotein Lipase: LPL）欠損症やアポリポ蛋白 C-Ⅱ欠損症などの遺伝子変異による遺伝病で常染色体劣性遺伝形式をとる。高カイロミクロン血症は急性膵炎のリスクが高く、その発症や重症度が生命予後を規定する。膵炎の予防のために脂肪制限が生涯必要で、現在のところ治療法は確立されていない。しかし高カイロミクロン血症患者のなかでも膵炎を起こさない患者もいれば、重症膵炎を繰り返す患者もおり、予測することが現時点では困難である。高カイロミクロン血症は他疾患や薬剤により生じることもある点、一般検査では中性脂肪高値の中に含まれることから診断が困難な点、患者数が稀少である点などから、高カイロミクロン血症と予後の関連は明らかになっていない。

脳腱黄色腫症は CYP27A1 の遺伝子変異による遺伝病で常染色体劣性遺伝形式をとる。血清コレスタノールが脳を含む末梢組織に過剰に蓄積することによって、巨大な黄色腫の出現や認知症、錘体路症状、精神症状などの神経症状、早発性冠動脈疾患をきたす。

無βリポタンパク血症は MTP の遺伝子変異による遺伝病で常染色体劣性遺伝形式をとる。MTP は肝臓においてリポ蛋白の合成・分泌を担い、腸管では脂質の吸収を担うため、極端な低 LDL-コレステロール血症に加え、脂溶性ビタミン（A, D, E, K）吸収障害の結果、低身長、頻回の下痢、進行性神経障害、夜盲症などをきたし日常生活への支障をきたす。

これら 7 疾患については、著明な脂質異常症（極端な高 LDL コレステロール（LDL-C）血症、極端な高トリグリセライド（TG）血症、極端な低 HDL-C 血症、極端な低脂血症）や黄色腫の出現を契機に発見されることが多いが、専門家が少なく、また脂質代謝学そのものが複雑なために非専門家にとって正確な診断は困難である。そのため速やかな治療の開始もできず、合併症の発症や生命予後の悪化につながっている。

したがって難治性脂質異常症に対する診療体制の構築は重要課題であると考える。そこで非専門医が上記のような極端な脂質異常症や黄色腫を呈する患者に遭遇した場合に専門医に紹介できるシステムづくりや、紹介までの間に可能な検査、疾患の概要が手軽に理解できる日本語総説や患者への説明資料の作成、海外で脂質異常症難病の診療や研究を行っている医師・研究者に向けて英文総説の公開が必要と考えた。

2. 疫学研究（指定難病 7 疾患の予後実態調査（PROLIPID 研究））

本研究事業の中の調査研究の一環として、我が国の原発性高脂血症のうち、前期班（班長：石橋俊）では FH（ホモ・ヘテロ接合体含む）、家族性Ⅲ型高脂血症、高カイロミクロン血症患者の病態および治療実態の調査を行い、登録がスタートしていたが、今期の斯波班では上記に加えて指定難病である LCAT 欠損症、シトステロール血症、タンジール病、脳腱黄色腫症、無βリポ蛋白血症についても病態および治療実態の調査を行うこととした。診療の実際や予後の現状、危険因子などについて把握するとともに、その後前向きに各種イベントの発生および死亡を追跡することにより、難病患者における自然経過・イベント発生率・死亡率を明らかにし、予後改善への貢献、診療ガイドラインの改訂を目的とする。

3. 難病の普及啓発に関する研究（国際協調も含む）

各疾患の一般医家への啓蒙が不十分なために、適切な診断と治療が実施されておらず、難病患者の不安を払しょくできていない現状がある。そこで難病患者および難病患者を診療する医療従事者へ疾患についての啓発を実施し、難病患者の生命予後及び QOL の改善につなげる必要がある。

4. 診断基準・診療ガイドラインの作成に資する研究

平成 27 年 1 月に施行された「難病の患者に対する医療等に関する法律」に基づき新たに指定難病を拡大する方向となったため、前期研究班（班長：石橋俊）ではすでに指定難病であった FH ホモ接合体を除く 6 疾患について診断基準・重症度分類の策定を行ったが、複数の疾患で現行の診断基準に合致しないが遺伝子変異からその疾患と診断される症例などが報告され、次期の診断基準や臨床調査個人票の全面改定時期に備えて改善案を策定し、学会承認まで得ておく必要がある。

特に頻度が比較的高いFHの診断基準については明らかにFHのフェノタイプを呈しながら、遺伝子診断では*LDLR*変異も*PCSK9-GOF*変異を認めない患者が30%以上存在する（Ohta N, Hori M, Ogura M, Harada-Shiba M, J Clin Lipidol 2016)。逆に遺伝子診断でFHと診断できたが、LDL-C値やアキレス腱の厚さが診断基準を満たさない患者も日常診療で経験する。そこで遺伝子診断されたが現行の診断基準では基準を満たさない患者の頻度や特徴を明らかにし、次の診断基準作成時に議論すべき課題に関する情報を提供することを目的として研究を実施する。具体的には以下の3つの研究を実施する。

(1) 遺伝子検査により FH と診断された患者における原稿診断基準の蓋然性の検討（国立循環器病研究センター)

(2) Young FHコホート研究（東京大学)

(3) 小児生活習慣病予防健診を活用した家族性高コレステロール血症の早期診断と継続的支援のための保健と医療の連携モデル構築（香川大学)

5. 小児成人期移行医療（トランジション）の推進に資する研究

原発性脂質異常症のうち成人指定難病と小児慢性特定疾病の該当疾患と分類法が大きく異なっている。両制度は基礎となる法律が異なるため、両者の違い自体は大きな問題ではないが、移行期にスムースに小児科から内科へ連携できるか、また小児科が成人になっても診療すべき疾患か、小児期から内科が診療すべき疾患なのか等は切実な未解決課題である。また小児期から診断・治療を実施することにより、生命予後やQOLが改善する可能性があるのであれば、小児科医への疾患啓発や連携も極めて重要である。

B. 研究方法

1. 診療体制の構築に資する研究

7つの指定難病それぞれに対する疾患担当責任者を決定した。またその疾患担当責任者が中心となって日本語版および英語版の総説を執筆し、他の班員が査読を実施した。また日本語総説などを全国の非専門医にも読んでいただくために、昨年度作成した本研究班独自のホームページに掲載した。一般医家がアクセスしやすいように難病情報センターとリンクさせるようにする。

2. 疫学研究（指定難病 7 疾患の予後実態調査（PROLIPID研究))

最終年度である本年度は、担当7疾患すべてのレジストリ項目を決定し、国立循環器病研究センターの倫理委員会から承認を受けた後に後述のシステムに統合、登録サイトをオープンし、新規患者登録の推進を図った。

本研究への参加に同意した全国の国公立病院、大学病院関連施設および日本動脈硬化学会の会員が所属する医療機関において、研究期間中に来院した原発性高脂血症患者を登録する前向きコホート研究である。本研究の参加に同意した各研究協力施設は、各施設の倫理委員会承認後、患者登録を開始する。協力施設が独自の倫理委員会を有しない場合は、所属長の許可を得たうえで自治医科大学の倫理審査委員会にて審査する。各研究協力施設の担当者は、本研究への参加について研究対象者から文書による同意を取得できた患者を登録する。一部の症例が多い施設に関しては過去に遡り、症例を登録する。

登録は、Electronic Data Captureシステム（以下、EDC）の一つであるResearch Electronic Data Capture (REDCap)を用いる。(REDCap：米国でNIHの援助によりヴァンダービルト大学が開発し、アカデミアを中心に世界で広く使われているデータ管理システム。)REDCap上には個人情報は含まれず、互いの研究者間に個人情報が漏れることはない。各研究協力施設の医師は、本研究に該当する患者が来院した際に、患者を登録し、ベースライン調査項目（後述）を入力する。EDC上には氏名、住所など個人を特定する情報は含めず、研究IDのみを用いる。患者の氏名、住所および家族などの連絡先といった個人情報は各研究協力施設の個人情報担当者が保有し、住民票による追跡を必要とする場合にのみ研究全体の個人情報担当者からの照会を行う。過去の患者を本研究に登録する際は、担当医師がREDCap登録するか、あるいはREDCapに登録する項目をCD-R、またはUSBにて収集し、データマネジメント担当者がREDCapに情報入れる。

登録終了後、1年毎にアウトカム調査を行う。各協力施設の担当者は、イベント発症および死亡の有無を報告する。アウトカム調査時に通院していない患者は、本人または登録時に本人以外の連絡先として申請されている家族に郵送、または電話にて問い合わせる。本研究参加施設以外の医療機関に転院していた場合は、各協力施設担当者が、

該当する医療機関にイベント発症時の状況を問い合わせる。

各協力施設で追跡不可能な場合は、各協力施設から全体の個人情報担当者に報告する。研究者は定期的に（4年に1度）患者や登録時に本人以外の連絡先として申請されている家族に直接連絡を取るか、医療機関や公的機関（保健所、都道府県・市町村等）に問い合わせて、診療・介護・転出入・死亡等に関する情報について一定の請求手続き（閲覧、転記、写しの交付等：例. 住民票請求、死亡小票請求）を経てアウトカムを把握する。追跡手続きについては研究参加時に説明の上で同意を取得する。

2-3) 測定項目

1)ベースライン調査…患者イニシャル、生年月日（重複登録の確認目的)、性別、満年齢、身長、体重、ウエスト周囲長、血圧、特徴的身体所見の有無（アキレス腱肥厚、その他の腱黄色腫、結節性黄色腫、扁平黄色腫、手掌線状黄色腫、発疹性黄色腫、角膜輪、角膜混濁、肝腫大、脾腫、末梢神経障害、浮腫、オレンジ色の特徴的な扁桃腫大、その他）の有無、登録時血液検査データ（検査日、採血条件、総コレステロール、HDL コレステロール、トリグリセリド、LDL コレステロール(総コレステロールがない場合のみ)、遊離コレステロール、FC/CE 比、血糖値、インスリン、HOMA-IR、insulinogenic index、BUN、クレアチニン、GOT(AST)、(以降はデータがあれば入力)GPT(ALT)、γ-GTP、アルブミン、HbA1c、ヘモグロビン、アミラーゼ、膵型アミラーゼ、リパーゼ、尿酸、apoB、apoC-II、apoC-III、apoE、apoA-I、apoA-II、Lp(a)、レムナントリポ蛋白コレステロール(RLP-C)、リポ蛋白リパーゼ(LPL)(ヘパリン前後)、血中脂肪酸分画（EPA、AA、EPA/AA 比)、リポ蛋白分画 HPLC 法(HDL、LDL、IDL、VLDL、Other、その他)、白血球、赤血球、Ht、Plt、総ビリルビン、有棘赤血球の存在、赤血球形態異常、直接ビリルビン、TSH、free T3、freeT4、シトステロール、コレスタノール、ラソステロール、カンペステロール、ビタミン A, D, E, K)、生理学的検査（PWV、ABI 検査値、12 誘導心電図異常の有無、頸動脈エコーでの狭窄の有無、心エコーでの弁膜症有無)、血族結婚の有無、2 親等以内の家族歴（若年性冠動脈疾患・家族性高コレステロール血症・高中性脂肪血症)、合併症の有無(耐糖能障害、糖尿病（病型)、慢性腎臓病(CKD)、末梢動脈疾患(PAD)、冠動脈疾患（発症年齢、治療内容)、高血圧症、脳梗塞・TIA・脳出血、大動脈弁狭窄症、大動脈弁上狭窄、胸・腹部大動脈瘤、甲状腺機能低下症、急性膵炎、肝腫大、脾腫、血液疾患、自己免疫疾患、白内障、慢性の下痢、骨粗鬆症、新生児~乳児期の遷延性黄疸・胆汁うっ滞、神経症状、関節炎、出血傾向、脂肪便、網膜色素変性、視野狭窄、夜盲、視力低下、運動失調、痙性麻痺)、現在の投薬状況(降圧薬、経口糖尿病薬、糖尿病注射薬、抗血小板薬・抗凝固薬)、服用中の脂質異常症治療薬の種類と用量および開始時期、LDL アフェレシスの有無と開始時期および施行頻度、生活習慣（喫煙・飲酒・運動習慣)、栄養士による栄養指導の有無、診断的検査（*LDLR* 遺伝子変異、*PCSK9* 遺伝子変異、*ARH* 遺伝子変異、その他の遺伝子変異、アポ E 遺伝型、アポ E 表現型、シトステロール血症遺伝子変異（*ABCG5*、*ABCG8*)、脳腱黄色腫症遺伝子変異（*CYP27A1*)、LCAT 欠損症遺伝子変異(*LCAT*)、タンジール病遺伝子変異(ABCA1)、無βリポ蛋白血症遺伝子変異（*MTTP*)、低ベータリポ蛋白血症遺伝子変異（*APOB*))、リポ蛋白電気泳動パターン、アポ E 表現型)、アキレス腱軟線撮影でのアキレス腱厚

2)アウトカム調査…冠動脈疾患の有無(急性心筋梗塞、狭心症)とその発症年月日・入院年月日とその関連項目（発症時の症状、心電図変化の有無、心筋逸脱酵素上昇の有無、経皮的冠動脈インターベンションの有無、経皮的冠動脈血栓溶解療法の有無、冠動脈バイパス術の有無、冠動脈 CT/MRI 検査の有無。）脳血管疾患の有無(脳梗塞・脳出血)とその発症年月日・入院年月日とその関連項目（発症時の神経症状、画像検査の有無とその所見)、心房細動の有無、塞栓源の有無、大動脈弁狭窄症および閉鎖不全症・大動脈弁上狭窄の有無、僧房弁狭窄・三尖弁狭窄および閉鎖不全症の有無、大動脈瘤の有無、末梢血管疾患の有無、急性膵炎の有無

主要評価項目は心血管および脳血管イベント、大動脈瘤、末梢動脈疾患、急性膵炎で、副次的評価項目は全死亡としている。

（倫理面への配慮）

本研究は前向き観察研究であり、研究の遂行に伴う研究対象者本人への身体的不利益・危険性は生じない。予後追跡調査のために説明同意文書での本人の同意に基づき個人情報を収集する。その保管は各研究協力施設であり、他の研究者によるアクセスは不可能である。また収集する

個人情報も氏名・住所・電話番号・関係者連絡先と、一般診療の範疇内であり、研究参加者への不利益は発生しないと考える。また本研究はヒトゲノム・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で定めた倫理規定等を遵守するとともに、国立循環器病研究センター倫理員会で承認されている。

3. 難病の普及啓発に関する研究

FH ホモ接合体については「難治性家族性高コレステロール血症患者会」と「高コレステロール血症患者の集い」を共催する。患者会代表による自身の病気や治療に対する思いの講演や食事療法や新しい治療法に関する講演、患者と医療従事者のグループセッションを実施し、患者のニーズを探るために「集い」に関するアンケート調査を実施する。

本研究班の班員および研究協力者は脂質代謝領域や神経領域のエキスパートであり、かつ各関連学会において要職に就いているものが多い。したがって学会等でシンポジウムを企画し、または招待講演等により、非専門医に対して該当疾患に関する疾患啓発を実施することが十分可能である。そこで、そのような機会を生かし、発表や日本語および英語論文・総説の執筆を積極的に行う。

特に今年度はアジアをはじめ海外への脂質難病の疾患啓発を図るため、各疾患担当者が中心となり、英語総説を執筆する。来年度にかけて、班員による査読を実施し、日本動脈硬化学会の英文誌である Journal of Atherosclerosis and Thrombosis 誌に invited review article として令和 2 年度中に 7 疾患すべて publish されることを目指す。

4. 診断基準・診療ガイドラインの作成に資する研究

各疾患について、最新の文献や診療情報から疾患担当責任者を中心に新しい診断基準案やガイドライン案を作成し、班会議で議論を行い、日本動脈硬化学会承認に向けて準備を進める。脳腱黄色腫症は新しい診断基準及びガイドラインを昨年度すでに策定し、日本神経学会で承認を得た。

FH に関する 3 つの研究の方法は以下のとおりである。なお各研究はヒトゲノム・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で定めた倫理規定等を遵守するとともに、それぞれの所属機関における倫理員会で承認されている。

(1) 国立循環器病研究センターおよび金沢大学で遺伝子検査により FH と診断された患者における現行診断基準の蓋然性の検討

対象は臨床的に FH を疑われ、当センターで遺伝子解析をした患者である。FH の診断基準は、2017 年の日本動脈硬化学会の基準 (①未治療時の LDL-C 値：180 mg/dL 以上、②アキレス腱厚：Xp 測定で 9 mm 以上、③FH または早発性冠動脈疾患の家族歴) を用いた。

(2) Young FH コホート研究 (東京大学)

東京大学では以前より新入生健診でLDL-C測定を行なっており (新入生対象、毎年約3,000人) 、平成25年度から、若年成人高LDL-C血症のうち同意を得られたものを対象に、FH遺伝子変異を解析し、LDL-C健診測定のFH診断における有用性を継続的に検討している。また若年成人 (20歳前後) の遺伝子診断されたFHの特徴と現行の診断基準の蓋然性についての検討を行う。

(3) 小児生活習慣病予防健診を活用した家族性高コレステロール血症の早期診断と継続的支援のための保健と医療の連携モデル構築 (香川大学)

平成 29 年度から香川県小児生活習慣病予防健診 (10 歳児童が対象、毎年 8,000 名が受診) を実施、LDL≧140 mg/dL を示した児童に対して、医療機関への受診を勧奨している。平成 30 年度からは金沢大学 (川尻剛照 (分担者)) との共同研究で、小児予防健診で LDL≧140 mg/dL 以上 10 歳小児 (24 名) に遺伝子検査を実施した (LDL 受容体、PCSK9、アポ B 遺伝子など 21 遺伝子を含む遺伝性脂質異常症網羅的遺伝子解析パネル)。

5. 小児成人期移行医療 (トランジション) の推進に資する研究

昨年度は成人指定難病と小児慢性特定疾病において疾患が一致していないことが班内で共有された。今年度は上記が原因で、例えば小児慢性特定疾病であるが成人指定難病でないために移行期に行き場がなくなってしまうなど、小児成人期移行時期に患者が不利益を被る可能性について整理し、その対策を練ることとした。

C&D. 研究結果と考察

下記の研究結果については年に 2 回実施される全体班会議で討議・承認されたものである。班会

議の会議次第は資料１のとおりである。
また、班独自のホームページ（nanbyo-lipid.com）はすでに作成が完了し、令和元年 7 月からアクセスできる。

1．診療体制の構築に資する研究

昨年度、疾患担当責任者を下記のように決定した。

(1) FH ホモ接合体：野原淳
(2) LCAT 欠損症：武城英明、黒田正幸、村野武義
(3) シトステロール血症：川尻剛照、多田隼人
(4) タンジール病：小関正博
(5) 原発性高カイロミクロン血症：後藤田貴也、岡崎啓明
(6) 脳腱黄色腫症：関島良樹、小山信吾
(7) 無βリポ蛋白血症：岡崎啓明、高橋学

一般医家への疾患啓発の一環として昨年度までに各疾患について日本語総説を疾患担当者が中心となり執筆し、すでに班独自のホームページにアップロードされており、PDF ファイルで読むことができるようになっている。

今年度はアジアをはじめとする海外に脂質異常症難病について疾患啓発を行う目的で、各疾患について英文総説を疾患担当者が中心となり執筆した。疾患担当者以外の班員はそれぞれ割り当てられた 2 疾患の英語総説の査読を担当した。その結果、すべての疾患について、日本動脈硬化学会の英文誌 *Journal of Atherosclerosis and Thrombosis（JAT 誌）* に invited review articles として投稿、アクセプトされ、全て早期公開されている。各疾患の英語総説は資料 2 のとおりである。

システマティックレビュー執筆およびレジストリ登録項目決定に責任を持つ各疾患担当者の任命は、本研究班本部（難病診療連携拠点）と各疾患担当者（医療支援ネットワーク）が協調し、できる限り早期に正しい診断ができる難病の医療提供体制を整える。また班独自の HP による積極的な情報発信は上記診療体制に全国の非専門医が容易にアプローチできる機会を与える。このことは難病患者診断率および受給者証取得者数の向上に寄与し、難病法の施策に直接的に反映する。システマティックレビューの英文化と JAT 誌への掲載は海外の難病を治療している医師への貴重な情報を提供し、国際貢献および論文引用等、間接的な波及効果が期待できる。特に JAT 誌（IF：3.876）は、国内のみならず、アジアからの引用件数が急増し、Impact Factor も上昇中である。

2．疫学研究（指定難病 7 疾患の予後実態調査（PROLIPID 研究））

現在までに担当７疾患すべての PROLIPID システムへのレジストリ項目の追加、EDC システムの構築、PROLIPID 研究の変更点に関する倫理委員会への変更申請がレジストリシステム担当の宮本班員および竹上班員（国立循環器病研究センター）により提出され、承認された。また症例登録の推進を図った。

令和 3 年３月末時点の登録患者数（FH（ヘテロ接合体も含む）は 965 例（資料３）と昨年度よりも 378 例増加した。今後は全疾患の登録が可能になるため各施設での倫理委員会における迅速審査申請の依頼がなされた。また今までのプロトコールでは登録時の服薬状況のみが入力されていたが、新薬の登場や治療概念の変化に伴い、難病の治療も変化していくことが予想されるため、5 年目と 10 年目に服薬状況を改めて確認し、入力することが班会議で決定された。

すでに班独自のホームページに PROLIPID の入り口もオープンとなったため、より多くの医療機関からのアクセスや患者登録が期待できる。このことにより、診療の実際や予後の現状、危険因子などについてより大きな N 数で把握するとともに、その後前向きに各種イベントの発生および死亡を追跡することにより、難病患者におけるイベント発生率・死亡率を明らかにし、予後改善への貢献、診療ガイドラインの改訂に寄与することができる。また患者数が非常に少ない脂質異常症難病のデータベースの構築により、実際の診断状況や患者の自覚症状・多覚的所見が明らかになり、今後の診断基準や治療指針作成に資することが可能になる。次年度以降の課題として、「PROLIPID 研究」と「指定難病患者データベースおよび小児慢性特定疾病児童等データベースの第三者利用に基づいた研究」のすみわけに関する議論が不十分であるため、班会議等で議論を深めていく必要がある。

3．難病の普及啓発に関する研究

平成 30 年度は多くの班員が指定難病に関する教育講演やシンポジウム講演、日本動脈硬化学会主

催の FH 疾患啓発研修会等で非専門医をはじめとする医療従事者に向けてメッセージを発信した（**G. 研究発表参照**）。特に本研究班との共催シンポジウムが日本動脈硬化学会および日本臨床化学会で企画・開催された。

FH ホモ接合体については「難治性家族性高コレステロール血症患者会」と「高コレステロール血症患者の集い」を共催してきたが、今年度は新型コロナウイルス感染症の影響で開催を断念した。来年度は WEB 形式を含む患者に安全な方法で実施予定である。

4. 診断基準・診療ガイドラインの作成に資する研究

次の全体改訂に向けて新診断基準案を本研究班で作成し、関連学会で承認を得ておく必要があるため、すでに新しい診断基準案を作成し、令和 2 年 2 月 1 日に日本動脈硬化学会の理事会で承認を得ていた。なお指定難病のうち脳腱黄色腫症については、疾患担当責任者である関島班員および小山班員らが平成 30 年 5 月に新しい診断基準および診療ガイドラインを作成し、すでに日本神経学会で承認され、公開されている（http://www.ctx-guideline.jp/guideline/）。今年度の途中に全体改訂の情報および新診断基準の募集があったため、学会承認された新診断基準案を難病対策課（難病検討委員会）に提出した。提出した診断基準案は**資料３**のとおりである。

また FH ホモ接合体を含む FH についての新診断基準案は「日本動脈硬化学会　動脈硬化性疾患予防ガイドライン（2022 年版）」に反映すべく、斯波班長を委員長として本研究班のメンバー数名も委員となり、動脈硬化学会ガイドライン委員会（委員長：斯波班長）が診断基準の改訂作業と診療ガイドラインの作成を進めているところである。今年度は遺伝子検査により確定診断された FH 患者（国立循環器病研究センター、金沢大学、各 500 名）についての臨床情報を収集・解析が完了し（JAT in press）、次期ガイドラインにおける診断基準の策定に役立てることが決定している。

東京大学（大学入学時健診）および香川大学（10 歳時健診）の検討結果から、若年高 LDL-C 血症では FH が高頻度で見つかること、その親へのリバースカスケイドスクリーニングが可能であることなどの健診スクリーニングの有用性が証明され、これらの成果が学会等で報告された。またその成果内容が次期診断基準への資料となることが決まった。

無βリポ蛋白血症については、岡崎班員から類縁疾患として家族性低βリポタンパク血症（FHBL）1(ホモ接合体)を指定難病に追加することが提案され、診断基準も示された。令和 2 年 1 月 5 日の班会議で承認、2 月 1 日に学会承認を得た。これにより「家族性低βリポタンパク血症（FHBL）1(ホモ接合体)」の新規難病指定を目指す。診断基準は**資料３**のとおりである。

またタンジール病の鑑別疾患であり、小児で登録の可能性があるアポリポタンパク A-I 欠損症(両疾患とも小児慢性特定疾病では、LCAT 欠損症とともに高比重リポタンパク欠乏症に属している）については移行期に行き場がなくなることが判明し、小関班員・山下班員が診断基準を作成し、令和 2 年 1 月 5 日の班会議で承認、2 月 1 日に学会承認のを得た。これにより「アポリポタンパク A-I 欠損症」の新規難病指定を目指す。診断基準は**資料３**のとおりである。

5. 小児成人期移行医療（トランジション）の推進に資する研究

成人指定難病と小児慢性特定疾病の疾患の不一致（**資料４**）について、昨年度から班会議で議論が開始された。表１（成人）と表２（小児）で下記のように対象疾患名や疾患の括りが異なることが班員全体で共有された。①FH は成人はホモ接合体のみ、小児はヘテロも含む、②LCAT 欠損症とタンジール病は小児の「133　HDL 欠乏症」というくくりに含まれると考えられる、同じく難病であるアポ A-I 欠損症も含まれると考えるが、成人指定難病ではない、③シトステロール血症と CTX は、小児では「134　その他の脂質代謝異常症」に含まれると考えられる、④小児では家族性複合型高脂血症、アポリポタンパク E 異常症が含まれている。これらについて、移行期に患者のデメリットにならないような体制の整備が必要であることが共有されたが、現状で上記疾患については、移行期に患者のデメリットはほぼ無いことが確認された（FH ヘテロ接合体は 200-300 人に 1 人と非常に頻度が高いため、成人の FH ヘテロ接合体を指定難病とするのは持続可能な難病支援体制としては非現実的であることも共有された）。アポリポタンパク E 異常症については、移行期に行き場はなくなるものの内服薬である程度管理は可能であり、また類

縁疾患であるリポ蛋白糸球体症（アポリポタンパク E 異常症を伴う）についても腎疾患として難病指定が可能であることから今回は新規難病指定の申請を提出しないこととなった。

上述の通り、「アポリポタンパク A-I 欠損症」についてはいまだ有効な治療方法もなく、HDL 欠乏症として小児慢性特定疾病に登録されてきた患者が移行期に行き場をなくすことが明らかとなったため、診断基準を策定した。その結果、脂質難病の患児が移行期に行き場がなくなる事態はなくなる予定である。

F. 健康危険情報

特になし

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【LCAT 欠損症】

１） 小倉正恒（座長：松永彰,木原進士）：HDL 異常低値・異常高値の話題と原発性脂質異常症の診療・研究の方向性について，シンポジウム 6（日本動脈硬化学会との共催）原発性脂質異常症のスクリーニング，第 60 回日本臨床化学会・年次学術集会,2020 年 10 月 30 日～11 月 1 日（Web 開催）

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4） 小関正博：著名な低 HDL コレステロール血症をきたす原発性脂質異常症の臨床的特徴と鑑別，第 117 回日本内科学会総会・講演会　ポスター発表，2020 年 8 月 9 日（Web 開催）

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【シトステロール血症】

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2） Tada H：本当は楽しい循環器遺伝学「ゲノム」アレルギーを無くそう！，第 84 回日本循環器学会学術集会，2020 年 7 月 27 日～8 月 2 日(Web 開催)

3） 池脇克則、佐々木誠、川尻剛照、多田隼人（座長：斯波真理子，石橋俊）：シトステロール血症の治療標的，シンポジウム 20 原発性脂質異常症の分子メカニズムと治療との関連，第 52 回日本動脈硬化学会総会・学術集会，2020 年 7 月 17 日～31 日(Web 開催)

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【タンジール病】

１） 小倉正恒（座長:松永彰,木原進士）： HDL 異常低値・異常高値の話題と原発性脂質異常症の診療・研究の方向性について，シンポジウム 6（日本動脈硬化学会との共催）原発性脂質異常症のスクリーニング，第 60 回日本臨床化学会・年次学術集会,2020 年 10 月 30 日～11 月 1 日（Web 開催）

２） 小倉正恒（座長：斯波真理子，石橋俊）：タンジール病の治療は可能か?,シンポジウム 20 原発性脂質異常症の分子メカニズムと治療との関連，第 52 回日本動脈硬化学会，2020 年 7 月 17 日～31 日(Web 開催)（総会プログラム・抄録集 143）

３） 武城英明（座長：小倉正恒，千葉仁志）： 低 HDL-C 血症の検査の進め方―LCAT 欠損症とタンジール病―，JSCC 国際学術シンポジウム「HDL 研究のトピックス」，第 60 回日本臨床化学会・年次学術集会,2020 年 10 月 30 日～11 月 1 日（Web 開催）

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【原発性高カイロミクロン血症】

１） Yamashita.S：Role of Pemafibrate in Cardiovascular Risk Reduction,〈Symposium: Lipid II〉Lipid Lowering Treatment, The 17th Asia-Oceania Congress of Endocrinology and the 8th Seoul International Congress of Endocrinology and Metabolism, 2020 年 10 月 28 日～10 月 31 日

２） Hiroaki Okazaki: “Critical Role of SREBP-1c Large-VLDL Pathway in Environment-induced Hypertriglyceridemia of apoA-V Deficiency” Presentations by the 2020 ATVB Journal Early Career Investigator Award Recipients (Daniel Steinberg Early Career Investigator Award in Atherosclerosis/Lipoproteins), Vascular Discovery: From Genes to Medicine Scientific Sessions 2020 (2020 年 5 月 Chicago, USA (virtual))

３） 山下静也：冠動脈疾患リスクとしての高 TG 血症とその治療～SPPARMα への期待～，ランチョンセミナー35 New Horizons of Residual Cardiovascular Risk，第 84 回日本循環器学会学術集会，2020 年 7 月 27 日～8 月 2 日(Web 開催)

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別紙４

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Shizuya Yamashita, Daisaku Masuda, Yuji Matsuzawa	Review: Pemafibrate, a new welective PPARα modulator: Drug concept and its clinical applications for dyslipidemia and metabolic diseases	Curr Atheroscler Rep	22(1)	doi: 10.1007/s11883-020-0823-5	2020

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A Report from the Asian Pacific Society of Atherosclerosis and Vascular Disease Asia Pacific Peripheral Artery Disease Consensus Statement Project Committee:Maria Teresa B. Abola, Jonathan Golledge, Tetsuro Miyata, Seung-Woon Rha, Bryan Yan, Timothy, Marie Simonette Ganzon, Salim Harris, Pankaj Kumar, Rama Krishna Pinjala, Peter Robless, Hiroyoshi Yokoi, Raden Suhartono, Jiang Zhisheng, Elaine Alajar, April Bermudez delos Santos, Elmer Jasper Llanes, Marjorie Obrado, Noemi Pestaño, Felix Eduardo Punzalan C, Bernadette Tumanan. Steering Committee: Edward Janus, Rody G. Sy, Fatima R. Collado, Florimond A. Garcia, Shizuya Yamashita	Asia Pacific Consensus Statement on the management of peripheral artery disease	J Atheroscler Thromb			

Shizuya Yamashita, Daisaku Masuda, Yuji Matsuzawa	Editorial: New horizons for an old, mysterious drug probucol	J Atheroscler Thromb			
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Daisaku Masuda, Shizuya Yamashita	Postprandial glucose and triglyceride increases along with the endothelial malfunction were attenuated by the administration of SGLT2 inhibitor, empagliflozin	J Atheroscler Thromb		doi: 10.5551/jat.ED124. [Epub ahead of print]	2020
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Shizuya Yamashita	New life for old heart drug	TRI (Translational Research Center for Medical Innovation) Advances: Research Highlight			2020
Shizuya Yamashita, Yuji Matsuzawa	Adiposity measures and mortality in an Asian population	Nature Reviews Endocrinology			

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Kimura M, Horie T, Baba O, Ide Y, Tsuji S, Ruiz Rodriguez R, Watanabe T, Yamasaki T, Otani C, Xu S, Miyasaka Y, Nakashima Y, Kimura T, Ono K	Homeobox A4 suppresses vascular remodeling by repressing YAP/TEAD transcriptional activity	EMBO Rep	21(4)	e48389. doi: 10.15252/embr.201948389.	2020
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Tada H, Takamura M, Kawashiri MA	Familial Hypercholesterolemia: A Narrative Review on Diagnosis and Management Strategies for Childrен and Adolescents	Vasc Health Risk Manag	17	59-67	2021
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Minami-Takano A, Iwata H, Miyosawa K, Shiozawa T, Hayashi H, Funamizu T, Ishii K, Nozaki Y, Tabuchi H, Sekita G, Shimada K, Sumiyoshi M, Nakazato Y, Daida H, Minamino T	The association between impairment of HDL cholesterol efflux capacity and atrial remodeling in atrial fibrillation	Sci Rep	11	3547	2021
Goto M, Hagiwara A, Fujita S, Hori M, Kamagata K, Aoki S, Abe O, Sakamoto H, Sakano Y, Kyogoku S, Daida H	Influence of Mild White Matter Lesions on Voxel-based Morphometry	Magnetic resonance in medical sciences : MRMS : an official journal of Japan Society of Magnetic Resonance in Medicine	20	40-6	2021

Fukase T, Dohi T, Kato Y, Chikata Y, Takahashi N, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Daida H, Minamino T	Long-term clinical outcomes and cause of death after endovascular treatment for femoropopliteal artery lesions	J Cardiol	77	417-23	2021
Aoshima C, Fujimoto S, Kawaguchi YO, Dohi T, Kamo Y, Takamura K, Hiki M, Kato Y, Okai I, Okazaki S, Kumamaru KK, Aoki S, Daida H	Plaque characteristics on coronary CT angiography associated with the positive findings of fractional flow reserve and instantaneous wave-free ratio	Heart Vessels	36	461-71	2021
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Shizuya Yamashita, Daisaku Masuda, Yuji Matsuzawa	New horizons for an old, mysterious drug probucol	J Atheroscler Thromb	28(2)	100-102	2021

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Shizuya Yamashita, Daisaku Masuda, Mariko Harada-Shiba, Hidenori Arai, Hideaki Bujo, Shun Ishibashi, Hiroyuki Daida, Nobuhiko Koga, Shinichi Oikawa on Behalf of the FAME Study Group	Effectiveness and safety of lipid-lowering drug treatments in Japanese patients with familial hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study	J Atheroscler Thromb	in press	in press	
Koutaro Yokote, Shizuya Yamashita, Hidenori Arai, Eiichi Araki, Mitsunori Matsushita, Toshiaki Nojima, Hideki Suganami, Shun Ishibashi	Effects of pemafibrate on glucose metabolism markers and liver function tests in patients with hypertriglyceridemia: A pooled analysis of six phase 2 and phase 3 randomized double-blind placebo-controlled clinical trials	Cardiovasc Diabeto	in press	in press	

Daisaku Masuda, Shizuya Yamashita	Editorial: Serum HDL-cholesterol level does not influence cardiovascular event rate under sufficient lowering of LDL-cholesterol by pitavatatin in patients with stable coronary artery disease	J Atheroscler Thromb		doi: 10.5551/jat.ED165. Online ahead of print	2021
Masatsune Ogura, Mariko Harada-Shiba, Daisaku Masuda, Hidenori Arai, Hideaki Bujo, Shun Ishibashi, Hiroyuki Daida, Nobuhiko Koga, Shinichi Oikawa, Shizuya Yamashita, on Behalf of the FAME Study Group	Factors Associated with Carotid Atherosclerosis and Achilles Tendon Thickness in Japanese Patients with Familial Hypercholesterolemia: A Subanalysis of the Familial Hypercholesterolemia Expert Forum (FAME) Study	J Atheroscler Thromb	in press	in press	
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Nakamura M, Ako J, Arai H, Hirayama A, Nohara A, Murakami Y, Ozaki A and Harada-Shiba M	Lipid Management and 2-Year Clinical Outcomes in Japanese Patients with Acute Coronary Syndrome: EXPLORE-J	J Atheroscler Thromb			2021

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Okazaki H, Gotoda T, Ogura M, Ishibashi S, Inagaki K, Daida H, Hayashi T, Hori M, Masuda D, Matsuki K, Yokoyama S, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan.	Current Diagnosis and Management of Primary Chylomicronemia.	J Atheroscler Thromb	In press	In press	2021
Koyama S, Sekijima Y, Ogura M, Hori M, Matsuki K, Miida T, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan.	Cerebrotendinous Xanthomatosis: Molecular Pathogenesis, Clinical Spectrum, Diagnosis, and Disease-Modifying Treatments	J Atheroscler Thromb	In press	In press	2021

Manabu Takahashi, Hiroaki Okazaki, Ken Ohashi, Masatsune Ogura, Shun Ishibashi, Sachiko Okazaki, Satoshi Hirayama, Mika Hori, Kota Matsuki, Shinji Yokoyama, Mariko Harada-Shiba, on behalf of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan	Current Diagnosis and Management of Abetalipoproteinemia	J Atheroscler Thromb	In press	In press	2021

資料 1-1 班会議次第

日時：令和 2 年 1 月 5 日（日）9 時から 15 時
場所：日内会館（本郷 3 丁目）4 階会議室
参加人数：41 名（谷口倫子先生含む）

斯波班長挨拶
（＋遺伝学用語改訂について）
議題１．年度タイムスケジュールの確認
議題２．次回班会議の方式・日程・場所
議題３．成果申告書と計画書の提出報告
議題４．厚生労働科学研究費補助金経費使用について
議題５．患者会との連携についての報告
議題６．班独自の HP の現状報告
議題７．英文総説の公表スケジュールについて
議題８．患者向け資料作成と HP へのアップロード
議題９． AMED-臨床ゲノム情報統合データベース整備事業（溝上班）の報告
議題 10. 関連学会シンポジウム等での疾患啓発計画
議題 11. PROLIPID の拡充と現状・将来展望
議題 12. 指定難病患者データベース及び小児慢性特定疾病児童等データベースの
第三者利用
議題 13. 成人指定難病と小児慢性特定疾病の疾患の不一致
アポ A-I 欠損症・アポ E 欠損症（異常症）の診断基準作成と学会承認
議題 14. 診断基準改定案の学会承認・臨床調査個人票の班会議承認
議題 15. 診断・治療に必須だが未保険収載または効能追加要望項目の現状、進捗状況
議題 16. FH 健診スクリーニングの進捗状況
議題 17. FH、LCAT 欠損症に関する国際協調
議題 18. FH の新しい治療選択に関わる諸問題
議題 19. その他
厚生労働省健康局難病対策課　谷口倫子先生による総括・ご助言

資料 1－2　班会議（令和 2 年 9 月 6 日（日））会議次第

日時：令和 2 年 9 月 6 日（日）13 時から 15 時 30 分
場所：ZOOM を用いた WEB 会議
参加人数：42 名（武田真治先生含む）

斯波班長挨拶
議題 1．全担当疾患のレジストリシステム構築（PROLIPID の拡充）
議題 2. 指定難病患者及び小児慢性特定疾病児童等データベースの第三者利用
議題 3. 班独自のホームページの作成・公開
議題 4. 全担当疾患の総説の執筆と公開
議題 5. 患者向けの療養上の注意点等のまとめと班 HP での公開
議題 6. 関連学会シンポジウム等での疾患啓発の実施
議題 7. 現行診断基準の妥当性評価と次期改訂への準備
議題 8. 診断・治療に必須だが未保険収載または効能追加が望ましい項目の明確化
議題 9. 小児成人移行期医療の課題の明確化と対策
議題 10. FH ホモ接合体の臨床個人調査票に関する論点
議題 11. FH の新しい治療をめぐる諸問題
議題 12. FH の新しい診断基準・診療ガイドライン作成
議題 13. FH のスクリーニングのあり方に関する研究
国立保健医療科学院・研究事業推進官　武村真治先生による総括

資料 1－3　班会議（令和 3 年 1 月 11 日（月祝））会議次第予定

日時：令和 3 年 1 月 11 日（日）13 時から 15 時 30 分
場所：ZOOM を用いた WEB 会議
参加人数：42 名（武田真治先生含む）

斯波班長挨拶
議題 1．全担当疾患のレジストリシステム構築（PROLIPID の拡充）
議題 2. 指定難病患者及び小児慢性特定疾病児童等データベースの第三者利用
議題 3. 班独自のホームページの作成・公開
議題 4. 全担当疾患の総説の執筆と公開
議題 5. 患者向けの療養上の注意点等のまとめと班 HP での公開
議題 6. 関連学会シンポジウム等での疾患啓発の実施
議題 7. 現行診断基準の妥当性評価と次期改訂への準備
議題 8. 診断・治療に必須だが未保険収載または効能追加が望ましい項目の明確化
議題 9. 小児成人移行期医療の課題の明確化と対策
議題 10. FH ホモ接合体の臨床個人調査票に関する論点
議題 11. FH の新しい治療をめぐる諸問題
議題 12. FH の新しい診断基準・診療ガイドライン作成
議題 13. FH のスクリーニングのあり方に関する研究
議題 14. FH ホモ接合体の全例登録の可否について
議題 15. 難病患者に対する就労支援に関する周知

資料2

The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Review

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Homozygous Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is an inherited disorder with retarded clearance of plasma LDL caused by mutations of the genes involved in the LDL receptor-mediated pathway and most of them exhibit autosomal dominant inheritance. Homozygotes of FH (HoFH) may have plasma LDL-C levels, which are at least twice as high as those of heterozygous FH (HeFH) and therefore four times higher than normal levels. Prevalence of HoFH had been estimated as 1 in 1,000,000 before but more recent genetic analysis surveys predict 1 in 170,000 to 300,000. Since LDL receptor activity is severely impaired, HoFH patients do not or very poorly respond to medications to enhance activity, such as statins, and have a poorer prognosis compared to HeFH. HoFH should therefore be clinically distinguished from HeFH. Thorough family studies and genetic analysis are recommended for their accurate diagnosis.

Fatal cardiovascular complications could develop even in the first decade of life for HoFH, so aggressive lipid-lowering therapy should be initiated as early as possible. Direct removal of plasma LDL by lipoprotein apheresis has been the principal measure for these patients. However, this treatment alone may not achieve stable LDL-C target levels and combination with drugs should be considered. The lipid-lowering effects of statins and PCSK9 inhibitors substantially vary depending on the remaining LDL receptor activity of individual patients. On the other hand, the action an MTP inhibitor is independent of LDL receptor activity, and it is effective in most HoFH cases.

This review summarizes the key clinical issues of HoFH as well as insurance coverage available under the Japanese public healthcare system.

Key words: **Homozygous familial hypercholesterolemia, Family study, Genetic diagnosis, Lipoprotein apheresis, MTP inhibitor, PCSK9 inhibitor, Cutaneous and Tendon Xanthoma, Aortic Supra-valvular stenosis**

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism caused by mutations of the genes involved in the LDL receptor-mediated pathway for cellular uptake of LDL. Most FH patients show an autosomal dominant trait. Hyper-LDL-cholesterolemia remains throughout their lives and causes premature coronary heart disease unless properly treated[1-3].

Early diagnosis and initiation of lipid-lowering therapy is essential for preventing development of cardiovascular complications, even in Japan where cardiovascular disease is not the leading cause of death and its prevalence among FH patients seems to be somewhat lower than in Western countries. Heterozygous FH (HeFH) patients who carry the mutated gene in a single allele have plasma LDL cholesterol (LDL-C) levels double normal or higher and may experience the first cardiovascular event as

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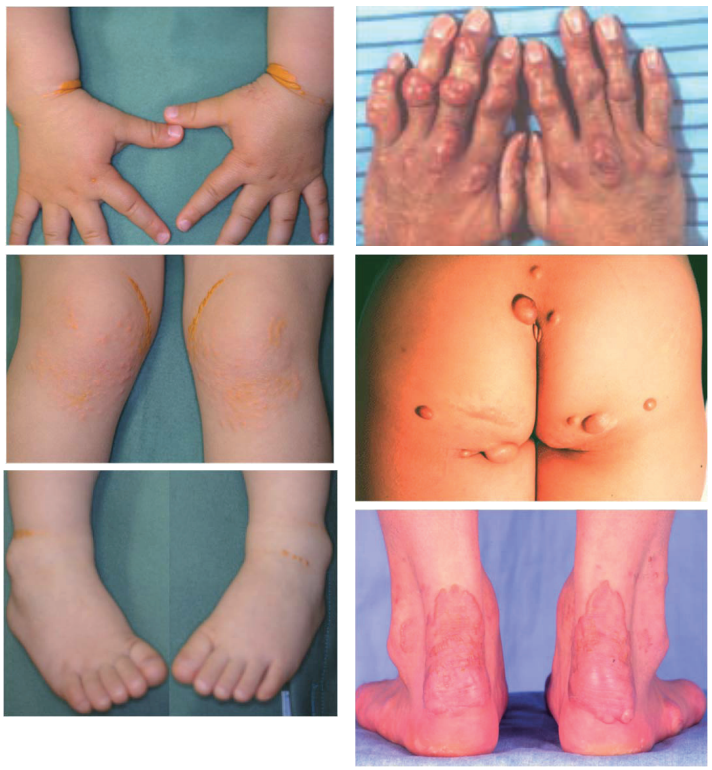

A 3-year-old patient: wrists, knees, ankles

Adult cases: fingers, buttocks, Achilles tendon

Fig. 1. Cutaneous and Tendon Xanthomas in HoFH

Presence of cutaneous xanthomas from childhood is strongly suggestive of HoFH, and tendon xanthomas are generally prominent in adults with HoFH.

early as their thirties. With mutations in both alleles, homozygous FH (HoFH) exhibits LDL-C levels twice those of HeFH, or even higher, and patients develop cardiovascular complications even in the first decade of their lives. Most HoFH is refractory to statins and other standard lipid-lowering drugs as most of them depend on remaining LDL receptor activity. Thus, HoFH has a poor prognosis compared to HeFH and therefore, earlier diagnosis and more aggressive treatments are required to prevent premature death.

1. Clinical Manifestations of HoFH

Familial hypercholesterolemia (FH) is a disease with a triad of clinical characteristics: elevated LDL-C, cutaneous and/or tendon xanthomas, and premature atherosclerotic cardiovascular disease (ASCVD). A genetic defect in LDL receptor function is the cause of FH, and activity of the LDL receptor is completely or almost completely absent in HoFH patients. HoFH includes homozygotes or compound/double heterozygotes of autosomal-dominant disease-causing mutations in the related genes, and their parents are HeFH, but there are rare exceptions that exhibit autosomal recessive inheritance[4, 5].

1) Elevated LDL-C Levels

HoFH patients have very high LDL-C levels from birth, which puts them at very high-risk of coronary heart disease. Plasma LDL-C levels are more than 500 mg/dL in many cases of genetically confirmed HoFH, but there is considerable variation in lipid levels among patients. Those with LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state should consult with specialists as they are probably cases of HoFH.

2) Cutaneous and Tendinous Xanthomas (Fig. 1)

Characteristic cutaneous xanthomas that have developed since infancy are physical findings suggestive of HoFH. They are commonly found on the extensor surfaces of the elbows/knees and wrist/gluteal regions and parents often take a child to a

doctor for the first visit because of them[6]. Tendon xanthomas are pathognomonic for both HeFH and HoFH, but not apparent during childhood and gradually appear around puberty. Xanthomas can be repressed or made to regress with continuous aggressive lipid-lowering treatment.

3) ASCVD

The prognosis for untreated HoFH is extremely poor. It is difficult for patients to live beyond 30 years without treatment. The LDL-C accumulation threshold hypothesis, which uses a calculation of [LDL-C x years of life], has been proposed as a rational explanation for the coronary risk of FH, and according to it, the coronary threshold of HoFH would be around 11 years old even for individuals with lower LDL-C levels[7]. Angina or myocardial infarction from infancy, as well as aortic supravalvular and/or valvular stenosis are often noted in HoFH **(Fig. 2)**, and may become the main cause of death in patients. Even with substantially effective treatment, systemic atherosclerosis, with such manifestations as aortic aneurysms, peripheral artery disease, and cerebrovascular disease, develops along with aging. Aggressive LDL-lowering treatments should be started as young as possible to prevent these atherosclerotic complications.

2. Prevalence

In the 1970s, prevalence of HeFH was estimated as 1 in 500 in the general population, and accordingly, that of HoFH as 1 in 1,000,000 [8]. However, more recent molecular genetic studies have revealed that FH is more common than previously expected. HeFH is now estimated as 1 in 200 to 300 and HoFH as 1 in 170,000 to 300,000 in many countries including Japan[9-13].

3. Genetics

LDL receptor-related disease-causing mutations are identified only in 60 to 80% of clinically diagnosed HeFH[14-16]. Most of them are in the LDL receptor gene (*LDLR*), and those in apolipoprotein B-100 (coded as *APOB* gene), the main ligand for the LDL receptor, have also been reported mainly in Caucasian populations[17]. In 2003, gain-of-function mutations in *PCSK9*, the gene coding proprotein convertase subtilistin/kexin-type 9 and enhancer of LDL receptor degradation, were found. This was considered to be the second major FH-related gene, explaining 5% of HeFH in Japan[18].

Families with FH caused by mutations in *LDLR*, *APOB*, and *PCSK9* all show autosomal dominant inheritance. Since *LDLR* accounts for the majority of the FH mutations, most individuals with HoFH are "true homozygotes" or "compound heterozygotes" for two different mutations in *LDLR*. Some patients are "double heterozygotes", having combined mutations in *LDLR* and *PCSK9* [4], for example. The parents of HoFH children who are "true or compound heterozygotes" mostly show the HeFH phenotype. On the other hand, the family traits of HoFH "double heterozygotes" may not apparently exhibit simple Mendelian inheritance since the heterozygotes for PCSK9 show a variety of phenotypes.

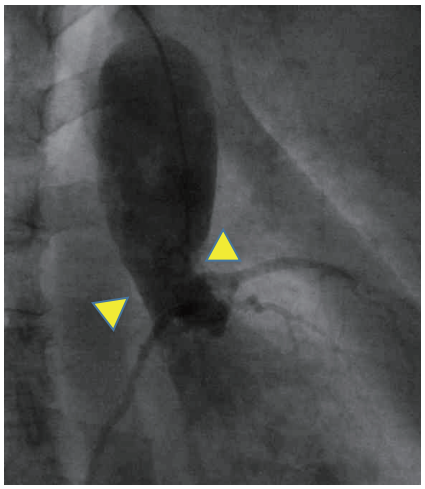

Fig. 2. Aortic Supra-valvular stenosis in HoFH

Supra-valvular stenosis is a pathognomonic finding of HoFH, and one of the causes of premature cardiac death in this disease.

It should be noted that HeFH is underdiagnosed and undertreated in the general population[3]. In the background of one suspected case of HoFH, there are many family members with HeFH , and they must be properly cared for in time to prevent their premature death.

Besides the mutations discussed above, those causing, autosomal recessive hypercholesterolemia (ARH), a rare unique type of FH have been reported in Japan[4, 5]. ARH is caused by mutations in a gene coding low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*). LDLRAP1 is an adaptor protein making a complex with clathrin and LDL receptors for efficient endocytosis of LDL receptors. Heterozygous carriers of this mutation do not exhibit the HeFH phenotype so it apparently shows autosomal recessive inheritance. If the parents in a probable case of HoFH have normolipidemia, ARH may be considered.

Disease-causing mutations cannot be identified in 20% to 40% of clinically diagnosed HeFH[19]. This may be due to still-unknown FH-related genes or limitations of analytic technologies. A clinical

Table 1. Diagnostic criteria for FH in children

1. Elevated serum LDL cholesterol levels: untreated LDL-C level of ≥ 140 mg/dL (If total cholesterol level is ≥ 220 mg/dL, measure LDL-C level)
2. Family history of FH or premature CAD (within second-degree relatives)
• Secondary hyperlipidemia should be ruled out.
• If a patient meets both of the above-mentioned criteria, FH is diagnosed.
• As LDL-C levels fluctuate during growth due to dietary and hormonal influences, careful examination is required.
• Clinical symptoms and findings including angina, xanthomas, and corneal arcus are rare in heterozygous FH children. Therefore, family history of FH is important in making diagnosis
• Premature CAD is defined as occurrence of CAD in men < 55 years old or in women < 65 years old.
• Homozygous FH should be suspected if patient has xanthomas.

Table 2. Diagnostic criteria for heterozygous FH in adults (15 years of age or older)

1. Hyper-LDL-cholesterolemia (an untreated LDL-C level of >=180 mg/dL)
2. Tendon xanthoma (tendon xanthoma on the backs of the hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum
3. Family history of FH or premature CAD (within the patient's second-degree relatives)
• The diagnosis should be made after excluding secondary hyperlipidemia.
• If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In cases of suspected FH, obtaining a diagnosis using genetic testing is desirable.
• Xanthoma palpebrarum is not included in xanthoma tuberosum.
• Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is >=9 mm on X- ray imaging.
• An LDL-C level of >=250 mg/dL strongly suggests FH.
• If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
• Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age, respectively.
• If FH is diagnosed, it is preferable to also examine the patient's family members.

diagnosis of typical HoFH cannot be excluded even if two pathogenic FH gene variants are not identified. A substantial portion of HeFH cases without "known" FH-gene mutations could be "polygenic hypercholesterolemia"[20] or "oligogenic FH"[21-23], though these concepts of FH have not become established. Although genetic analysis provides a definitive diagnosis of HoFH, the possibility of such cases cannot be excluded. Therefore, clinical assessment including thorough physical examination and familial studies is essential. For information, Japanese public healthcare insurance does not cover the expenses for HoFH genetic testing as of February 2021.

4. Pathophysiology

LDL receptor activity is completely or nearly all lost in HoFH. Severely elevated LDL-C levels from birth (more exactly, from fetal period[24]) often cause fatal cardiovascular disease even in infancy. As an example of cholesterol deposition in tissues, pathognomonic skin xanthomas develop from infancy in HoFH and tendon xanthomas become apparent later, and they are more prominent than those in HeFH.

5. Diagnostic Criteria in Japan

1) Clinical Diagnosis

A clinical diagnosis of HoFH can be made on the basis of skin or tendon xanthomas since infancy, and untreated LDL-C levels of twice those of HeFH or higher. Diagnostic criteria for FH in Japanese guidelines apply not only HeFH but also HoFH[1, 4] **(Table 1, Table 2)**. In cases with very high LDL-C and/or prominent xanthomas, HoFH should be suspected[25, 26].

Skin xanthomas since infancy are pathognomonic for HoFH, and sometimes the chief complaint for the first consultation with doctors[4] **(Fig. 1)**. Skin xanthomas in pediatric HoFH are frequently found in flexures of the wrist and ankles, and also in other regions having mechanical stress. Tendon xanthomas are more prominent than in HeFH[27], but become apparent later than skin xanthomas.

Typical HoFH exhibits total cholesterol levels of more than 600 mg/dL in total[1], but there is considerable overlapping of levels between HoFH and severe HeFH[28]. LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state would be sufficient for a diagnosis of probable HoFH and the patient should be referred to

specialists. In pediatric patients, plasma LDL-C levels may fluctuate and should be measured multiple times.

Measurement of LDL receptor activity in the fibroblasts of patients provides useful information in diagnosing HoFH, but is currently not routinely available at the laboratories of commercial or research facilities in Japan. Assaying LDL receptor activity in lymphocytes is feasible[29] but less reliable than fibroblast measurements.

2) Genetic Diagnosis

Genetic testing is recommended for suspected HoFH cases, but is not covered by Japanese public healthcare insurance as of February 2021. Genetic diagnosis indicates the potential efficacy of drug treatment and thereby therapeutic strategies[30, 31]. Conversely, drug ineffectiveness (for example, refractory to PCSK9 inhibitors) may suggest the HoFH genotype so genetic tests should be considered in such cases[32].

The possibility of detecting an FH-causative mutation in HeFH is 60 to 80%. Therefore, diagnosis should be carefully made together with clinical examinations and detailed familial studies even in cases of suspected HoFH where the mutations detected are apparently in 0 alleles or only 1 allele, because a genetic test does not exclude the possibility of HoFH due to unknown gene mutations. Consultation with experienced specialists is required in such cases.

6. Screening/Follow-Up for ASCVD

Most HoFH patients may die of ASCVD before 30 years old if untreated[33, 34]. Once HoFH is suspected, extensive examination for ASCVD should be carried out. In HoFH, the potentially fatal disorders of angina pectoris, myocardial infarction, and aortic supra-valvular and valvular stenosis could occur even in childhood **(Fig. 2)**. Aortic supra-valvular and valvular stenosis in HoFH is sometimes difficult to treat and lethal[35]. If patients are left untreated until around 20 years old, ASCVD risk is extremely high. Heart and aortic disease proceeds and systemic atherosclerosis develops later in life.

Non-invasive tests such as cardiac ultrasonography, carotid ultrasonography, and electrocardiograms should be conducted first, and enhanced CT for the aorta and coronary artery and coronary angiography should be considered when necessary[36]. Exercise stress tests should be carefully performed with consideration for patient safety.

7. Differential Diagnosis

A differential diagnosis should be made using high LDL-C levels and prominent xanthomas. LDL-C may be elevated to HoFH levels by secondary hypercholesterolemia such as hypothyroidism or nephrotic syndrome. Xanthomas may develop due to hypercholesterolemia in primary biliary cholangitis. Sitosterolemia, caused by the ATP-binding cassette transporter ABCG5/ABCG8 gene (*ABCG5/ABCG8*) mutations[37], sometimes exhibits elevation of LDL-C and skin xanthomas comparable to HoFH during the suckling stage[38]. Although LDL-C elevation and skin xanthomas subside after weaning from breastfeeding, elevated levels of plasma plant-sterols (including sitosterol) persist in these patients. There is also cerebrotendinous xanthomatosis (CTX), an autosomal recessive disease caused by sterol 27-hydroxylase gene (*CYP27A*) mutations, which is characterized by prominent xanthomatosis in the tendon and brain and sometimes accompanied by central nervous symptoms (mental retardation, cognitive impairment, or motor ataxia)[39]. CTX is clinically diagnosed by elevated plasma cholestanol levels. A differential diagnosis should be carefully made because these diseases require specific therapeutic approaches.

8. Treatment of HoFH

HoFH patients may suffer fatal ASCVD from infancy so initiation of aggressive LDL-C lowering as early as possible is essential for preventing their premature deaths[1, 4] **(Fig. 3, Fig. 4)**. Specific therapeutic strategies for preventing ASCVD development in individual cases should be planned in addition to LDL lowering.

Patients as well as their families will be burdened by various sources of stress such as anxiety about prognosis, concern about heredity, and costs of treatments. Supportive information should be provided, including that on possible financial aid, the therapeutic options available, and genetic counseling. Financial aid is available under The Program for Designated Intractable Diseases of the Japanese public healthcare system. Pediatric FH patients can receive support separately under The Program of Medical Aid for Chronic Pediatric Diseases of Specified Categories, which covers both HeFH and HoFH. In practice, consultation with specialists should strongly be advised.

1) Adult HoFH (15 years of age or older)

The LDL-C management goal is less than 100 mg/dL in primary prevention, and less than 70 mg/dL in secondary prevention[1] in the Japanese guideline **(Fig. 3)**. Medication should start with statins at appropriate doses[40], followed by increasing them to maximal tolerated doses and combination with other

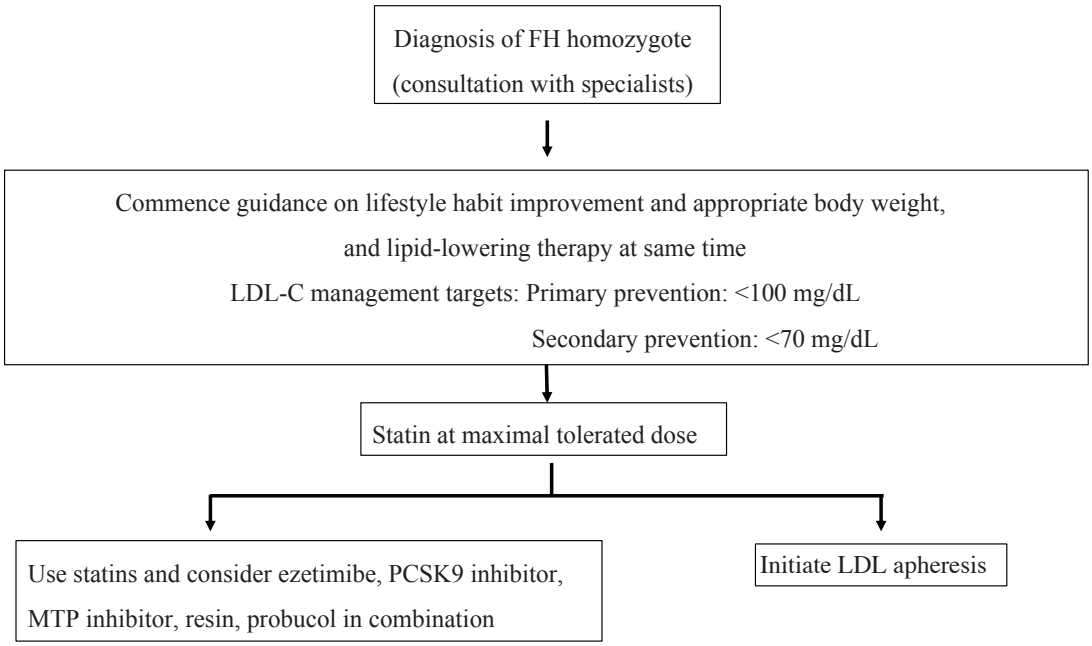

Fig. 3. Algorithm for treatment of adult (15 years of age or older) FH homozygotes

In HoFH, powerful LDL-C lowering therapy is required from a young age to prevent the onset and progression of CAD. Combination of lipid-lowering drugs, including MTP inhibitor, and lipoprotein apheresis is required in many patients with HoFH.
(Adapted from Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 20171) "LDL apheresis" means "lipoprotein apheresis" in this review)

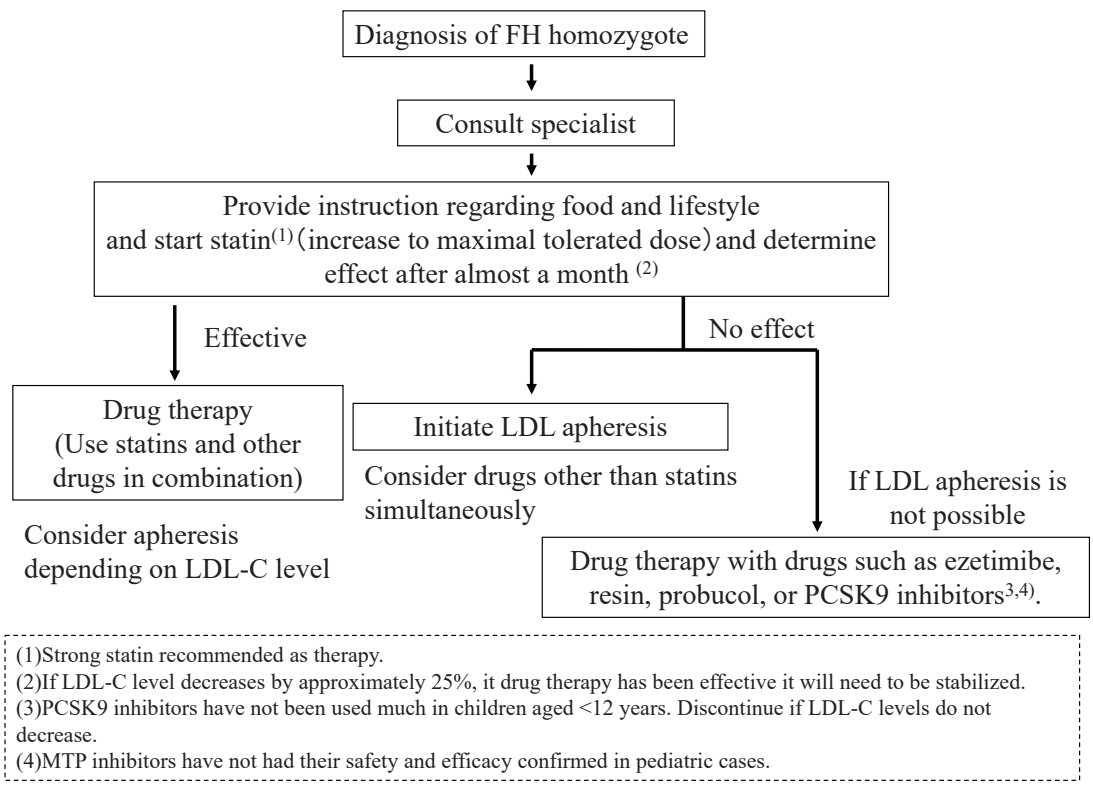

Fig. 4. Algorithm for treatment of pediatric FH homozygotes

Lifestyle interventions and maximally tolerated statin therapy should be started at the initial diagnosis. Since LDL-C targets are rarely achieved, lipoprotein apheresis therapy is recommended, and should be commenced by age 5 ideally.

drugs[41-43]. Achievement of these goals with drug treatment only is, however, not easy in HoFH.

Statins, ezetimibe and PCSK9 inhibitors all act by enhancing LDL receptor activity[44, 45], so their effectiveness depends on residual LDL receptor activity in the individual HoFH patient. Many HoFH patients are refractory to these drugs. However, if any of them are effective in lowering LDL-C, they should be continued together with the additional treatments described below.

MTP inhibitors (lomitapide) are a class of oral drug that is independent of LDL receptor activity. Clinically, they are indicated only for HoFH, and a decrease in LDL-C to approximately half of the pretreatment level can be achieved in many HoFH cases, if tolerated[46-49]. The main adverse effects are gastrointestinal symptoms and liver enzyme elevation accompanied by fat accumulation, similar to the symptoms observed in patients with MTP deficiency[50]. The MTP inhibitor should be started with the lowest dose, taking adequate measures in accordance with nutritional guidance (restricted fat and alcohol intake), and then the dose should be carefully increased gradually.

Lipoprotein apheresis directly removes LDL from plasma through selective absorption or filtration of LDL using an extra-corporal circulation system, and this has been the core therapy for HoFH to date[51-53]. LDL-C levels can be precisely decreased by this procedure, depending upon the treated plasma volume, when properly performed. Lipoprotein apheresis not only removes LDL but also has potential pleiotropic effects in preventing atherosclerosis through removal of cell adhesion molecules[54], coagulation factors[55], and inflammatory cytokines[56]. Lipoprotein apheresis for HoFH once every 1 to 2 weeks is covered by Japanese public healthcare insurance. The use of ACE inhibitors is contra-indicated for patients treated by lipoprotein apheresis with the Liposorber system and selective absorption of LDL by dextran sulfate-cellulose because shock may occur due to an increase in bradykinin activation.

Another option is liver transplantation. While this is highly invasive, it has been shown be a feasible therapeutic option for reversing atherosclerotic changes in HoFH patients that are uncontrollable with conservative therapy[57, 58].

2) Pediatric HoFH

Even in the suckling stage, children with HoFH must be referred to specialists for initiation of lipid-lowering therapy, as this is the key to a better prognosis[4]. The target LDL-C level should be the same as for adult HoFH in secondary prevention (though not clearly stated in the current pediatric guideline[4]). In pediatric HeFH, it is set at less than 140 mg/dL for primary prevention.

Statins and life-style interventions must be started at the time of diagnosis. Statins must be up-titrated and efficacy should be evaluated within a 1-month interval in order to titrate up to the maximal tolerated doses. Combination therapy with ezetimibe, bile sequestering resins, and PCSK9 inhibitors should be considered. These strategies may be effective in cases where there is a response in residual LDL receptor activity. Probucol should also be considered as it could reduce LDL in HoFH due to an unknown mechanism. Administration of an MTP inhibitor could be considered but only with extreme caution because no results of clinical trials in children have been reported. Drug therapy should be conducted until it becomes possible to commence lipoprotein apheresis.

In any case, lipoprotein apheresis must be considered since LDL-C targets are seldom achieved in HoFH only with drug treatment. This extracorporeal circulation therapy is generally commenced at the age of 5 or older, though it has reportedly been started in a patient who was 3.5 years old. In Japan, the main method is selective LDL absorption by dextran sulfate cellulose. However, with the aim of reducing extracorporeal volume, simple plasma exchange can be selected for children with a bodyweight under 30 kg.

3) Treatment during Pregnancy in HoFH

Female HoFH patients could be treated in the same way as for secondary prevention on reaching childbearing age. During pregnancy, LDL and VLDL are generally increased, and continuation of LDL-lowering therapy would be important. Statins and many other drugs are contraindicated during pregnancy and breastfeeding, and only bile sequestering resins can be used, taking proper care, but their LDL-lowering effects are limited[59]. It has been reported that lipoprotein apheresis is effective and feasible during pregnancy, and a case of cardiovascular death caused by suspension of apheresis during pregnancy[60] has been reported. Consultation with experienced specialists is recommended for pregnancy in HoFH.

Future Perspectives

Therapeutic options are still limited for HoFH, and all-out efforts should be made to achieve the best combination of feasible therapies in many cases. However, each therapeutic strategy has its advantages

and disadvantages so new therapies are awaited.

Inclisiran, a new siRNA drug that inhibits translation of PCSK9, is being developed[61]. As the effect of one injection lasts 6 months to 1 year, this drug may be a good option for HoFH patients who respond to PCSK9 inhibitors. Inclisiran was approved in the European Union in December 2020.

Evinacumab, an anti-ANGPTL3 antibody, is a new class of drug that is reportedly effective even in HoFH[62], and clinical trials are ongoing in Japan and other countries[63]. The LDL-C lowering effect of evinacumab is independent of LDL receptor activity.

Mipomersen (Kynamro), an antisense drug for the *APOB* gene, has moderate LDL-lowering effects but has the adverse effects of liver damage and injection site reactions. It was approved by the FDA for HoFH in 2013 [64] but rejected by the European Medicines Agency, and FDA approval was eventually withdrawn in 2019.

Gene therapy for HoFH has been investigated, but is still in the experimental stage. Since HoFH is a relatively rare disease, even if approved, demand for therapies would not be very high anywhere in the world. Lomitapide had been approved only for the treatment of HoFH in just 38 countries as of March 2021, including those in North and South America, the European Economic Area, and only Japan in East Asia. Lipoprotein-apheresis, which requires specific equipment, is available in a limited number of countries. Wider availability of therapeutic measures for HoFH should encourage its more active diagnosis worldwide.

Early diagnosis of FH is essential for preventing premature death in patients, whether they are hetero- or homozygotes[65-67]. Universal screening of plasma lipid levels during childhood has been trialed in some parts of Japan and we expect that such trials on local universal screening will lead to a nationwide system. In addition, reverse cascade screening, in which family members are screened on the basis of child probands, and continued worldwide registry research should improve the effectiveness of finding FH[68-76].

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Review

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Current Status of Familial LCAT Deficiency in Japan

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Lecithin cholesterol acyltransferase (LCAT) is a lipid-modification enzyme that catalyzes the transfer of the acyl chain from the second position of lecithin to the hydroxyl group of cholesterol (FC) on plasma lipoproteins to form cholesteryl acylester and lysolecithin. Familial LCAT deficiency is an intractable autosomal recessive disorder caused by inherited dysfunction of the LCAT enzyme. The disease appears in two different phenotypes depending on the position of the gene mutation: familial LCAT deficiency (FLD, OMIM 245900) that lacks esterification activity on both HDL and ApoB-containing lipoproteins, and fish-eye disease (FED, OMIM 136120) that lacks activity only on HDL. Impaired metabolism of cholesterol and phospholipids due to LCAT dysfunction results in abnormal concentrations, composition and morphology of plasma lipoproteins and further causes ectopic lipid accumulation and/or abnormal lipid composition in certain tissues/cells, and serious dysfunction and complications in certain organs. Marked reduction of plasma HDL-cholesterol (HDL-C) and corneal opacity are common clinical manifestations of FLD and FED. FLD is also accompanied by anemia, proteinuria and progressive renal failure that eventually requires hemodialysis. Replacement therapy with the LCAT enzyme should prevent progression of serious complications, particularly renal dysfunction and corneal opacity. A clinical research project aiming at gene/cell therapy is currently underway.

Key words: **Lecithin cholesterol acyltransferase, Low HDL-cholesterol, Abnormal LDL, Corneal opacity, Proteinuria, Enzyme replacement therapy**

Introduction

The enzyme that esterifies cholesterol in human blood plasma was discovered in 1962 [1]. The reaction was determined to be an acyl transfer reaction from phosphatidylcholine (lecithin) associated with HDL. The enzyme was named LCAT, and the physiological role proposed for it was creating a gradient of cholesterol content between the HDL surface and cell membrane to generate efflux of cell cholesterol[2]. At around the same time, a patient with deficiency of this enzyme was identified in Norway. A 33-year-old woman in a hospital in Oslo was suspected of having chronic nephritis due to proteinuria and exhibited corneal opacity, anemia, and slight hypoalbuminemia, though renal function was normal. Renal biopsy revealed presence of foam cells in the glomerular tufts. Plasma total cholesterol and triglyceride levels were high but most of the cholesterol was found not to be esterified and further biochemical analyses

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demonstrated that the patient was deficient in LCAT activity. Similar signs and symptoms were also noted in her sister, suggesting a hereditary disorder. Therefore, the disorder was named familial LCAT deficiency (FLD, OMIM 245900) by Norum and Gjone[1]. The classical form of this disease exhibits plasma LCAT activity of less than 10% of normal whereas, in partial deficiency the decrease may be 15 to 40%. In FLD, there is lack of esterification activity on both HDL and ApoB-containing lipoproteins. Later, a subtype of this disease was found and named fish-eye disease (FED, OMIM 136120), where esterification is inactive only on HDL[3]. Both FLD and FED are caused by *LCAT* gene mutations. The profile and progression of the accompanying symptoms vary depending on the extent of LCAT activity impairment. In this review, the clinical and biochemical features, genetic backgrounds and current treatment of this hereditary disease are summarized and, referring to cases reported in Japan, clinical practice guidelines for Japan are proposed.

Background Mechanism for Clinical Findings of Familial LCAT Deficiency and Fish-Eye Disease

LCAT is the enzyme that acyl-esterifies cholesterol in plasma, which reduces unesterified cholesterol on the HDL surface to generate efflux of cell cholesterol to HDL. This comprises an important part of cholesterol transport from peripheral organs and cells to the liver for its catabolism. LCAT dysfunction disrupts this process, resulting in marked reduction of HDL-C and deformation of HDL particles due to lack of their major core lipid, cholesteryl acyl-ester. Impaired turnover of cellular cholesterol leads to its accumulation in cells in the cornea, bone marrow, liver, spleen, and glomerular basement membrane of the kidney[4, 5]. It is visible from the abnormal shape of erythrocytes[4, 5]. The clinical prognosis of LCAT deficiency is largely dependent on progression of renal dysfunction[4, 5]. Both FLD and FED are commonly screened for by low plasma HDL-C level and corneal opacity[4, 5].

1) Dyslipidemia

LCAT catalyzes acylesterification of cholesterol on plasma lipoproteins in the steady state, both on α-lipoproteins (HDL) (α-activity) and β-lipoproteins (LDL and VLDL) (β activity). The reaction requires the presence of helical apolipoproteins such as apolipoprotein (apo) A-I and E. It takes place on HDL, where particles are initially assembled as disc-like particles from extracellular helical apolipoproteins such as apoA-I with cellular phospholipid and cholesterol (nascent HDL or preβ-HDL), to generate the core and make particles spherical (mature HDL). This process maintains the efflux of cholesterol from cells to HDL. The reaction also takes place on apoB lipoproteins (β-lipoproteins), which should provide additional efflux of cell cholesterol. Lack of LCAT activity therefore causes a marked decrease in HDL-C and "immature" HDL remains in plasma appearing as rouleaux under electron microscopic observation. Owing to this abnormal HDL, plasma apoA-I and apoA-II, the first and second major apolipoproteins, also decrease. Thus, among FLD plasma lipoproteins, the percentage of esterified cholesterol in total cholesterol (CE/TC) is markedly low. There are also abnormal findings for LDL fractions in ultracentrifugation analysis[6] due to lack of the LCAT reaction, in which three subtypes of particles with different lipid compositions are evident. They are LpX particles, which are called FC-rich, PL-rich and TG-poor particles, and have a larger size (40 nm-60 nm). A large subtype of LDL rich in TG and PL (Lp8)[7] was identified by gel filtration HPLC analysis as a specific subtype for FLD. However, the exact mechanism for generating these abnormal LDL particles is not fully understood. Moreover, specific changes in LDL in FED are not clearly defined.

2) Corneal Opacity

FC and phospholipids accumulate excessively in the cornea due to lack of the LCAT reaction. Corneal turbidity is observed from early childhood in both FLD and FED, with patients presenting severe visual impairment and requiring corneal transplantation. Corneal opacity is frequently observed not only in LCAT deficiency but also in other HDL-deficiencies such as those related to apoA-I and ABCA1 (Tangier disease)[8]. Electron microscopic studies have shown that corneas from FLD patients are similar to those of patients with familial apoA1 deficiency[9-13]. In a patient with Tangier disease, very mild corneal clouding (usually requiring a slit-lamp examination for detection) has been reported, with less abundant extracellular corneal stromal deposits and cholesterol/phospholipid accumulation than in FED[14]. Since FED is usually not accompanied by renal dysfunction, the underlying mechanisms for corneal opacity and renal dysfunction may differ. Since the largest particle size capable of diffusing through the central stromal matrix is about 12 nm[15], it is unlikely that LDL and/or LpX infiltrate into the corneal stroma. On the other hand, small to normal-sized spherical HDL particles are found only in very small amounts in FLD and FED and Tangier disease[16-18]. As cholesterol is

synthesized in the cornea[19] reduced removal is a possible cause of its accumulation.

3) Hemolytic Anemia

Abnormally shaped erythrocytes, called target red blood cells, appear in LCAT deficiency due to the abnormal lipid composition of the cell membranes, which sometimes leads to hemolytic anemia, perhaps due to their fragility[20, 21]. The half-life of red blood cells is approximately half that of healthy people.

4) Splenomegaly

Splenomegaly with sea-blue histiocytosis has been reported[22, 23] in some FLD patients presenting abnormal lipid profiles. The histiocytes contained cytoplasmic vacuoles and membrane-like structures resembling rose petals, indicating that they were composed of phospholipid-containing membranes.

5) Proteinuria and Renal Dysfunction

Proteinuria is detected relatively early in the life of patients and frequently develops into progressive renal failure at 40 to 50 years of age, and eventually requires hemodialysis[24, 25]. It has been reported that proteinuria occurred in FLD patients at 3 years of age[26]. As kidney damage does not generally develop in FED, renal biopsy may be useful for differential diagnosis of the subtypes of LCAT deficiency. Renal lesions begin with deposition of lipid in the glomerular basement membrane, and later in the mesangium and capillary subendothelium. LpX particles, abnormal lipoprotein particles identified in the LDL fractions of FLD, have been considered to be a causative factor of renal damage in many studies[5, 27-29]. Recently, large TG-rich LDL (Lp8)[7] has been reported to be associated with the progression of renal dysfunction. It has also been reported that oxidized lecithin in the LDL of patients causes renal dysfunction[30]. In addition, lipoproteins containing apoE have been shown to be taken up by renal glomerular mesangial cells, causing excessive lipid deposition, possibly leading to renal dysfunction[31]. ApoE is a physiological LCAT activator in β-activity on LDL/VLDL particles[32], and effect of *apoE* genotype on clinical manifestations has been reported[33, 34], although further analyses are required to draw a definitive conclusion. In mice, LpX is taken up by glomerular endothelial cells, podocytes, and mesangial cells, it causes dysfunction in glomerular endothelial cells, and increases secretion of inflammatory cytokines[35]. Recent follow-up studies of families with an FLD mutation for a median of 12 years showed that eGFR deteriorated among homozygous family members at an average annual rate of 3.56 mL/min/1.73 m^2, whereas deterioration in heterozygous members and family controls was 1.33 and 0.68 mL/min/1.73 m^2, respectively[36]. A recent Italian cohort study in which 18 FLD patients (12 males and 6 females) were followed up for 12 ± 8.5 years reported that renal events (dialysis, kidney transplant, or death due to renal complications) occur at a median age of 46 years[37].

6) Atherosclerosis

Based on the inverse association between cardiovascular risk and plasma HDL-C levels found in epidemiological studies and the proposed function of LCAT in cholesterol transport, it is conceivable that the risk of cardiovascular events is increased in genetic low HDL-C patients. However, studies on FLD patients have produced inconsistent findings regarding a correlation between LCAT activity and atherosclerosis[38, 39]. Recently, Italian and Dutch research groups assessed subclinical atherosclerosis using carotid intima-media thickness in 74 patients with heterozygous mutations leading to the FLD and FED phenotypes[40]. Carriers of *LCAT* mutations leading to FLD exhibited less carotid atherosclerosis, whereas carriers of those leading to FED showed marginally more atherosclerosis. Thus, the clinical significance of the function of HDL[41] and other LCAT-associated lipoproteins[7] in the progression of atherosclerosis has not been established from the findings in FLD and FED. Also, no significant information in this regard has been reported in Japanese FLD and FED patients.

Disease Prevalence and Genetics

FLD and FED are autosomal recessive inherited diseases caused by mutations of the *LCAT* gene located in the short arm of chromosome 16. In Japan, the prevalence of these diseases is extremely low so the exact rate of mutation is unknown. **Fig. 1** shows previously identified *LCAT* gene mutations in patients according to The Human Gene Mutation Database[42], showing great diversity in the positions of mutations causing dysfunction of LCAT. An association between position and extent or nature of dysfunction has not been well established. A report by the Ministry of Health, Labor and Welfare Research Group described 13 types of mutations identified in Japan[43] by 2004. Since the report, a further 7 mutations of the *LCAT* gene have been identified as causative mutations of FLD or FED in Japan[34, 44-46]; 5 of them were novel mutations and 2 had already been reported in patients in other countries. Mutations occurring in Japanese are summarized in **Table 1**.

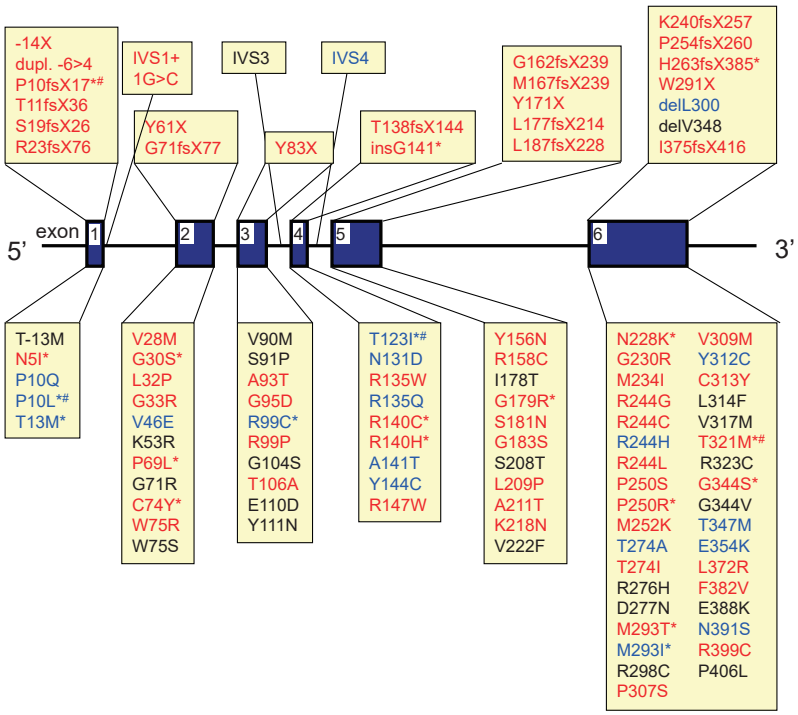

Fig. 1. Previously identified mutations in *LCAT* gene

The *LCAT* gene is composed of six exons. Mutations identified so far are depicted according to The Human Gene Mutation Database (HGMD®) (http://www.hgmd.cf.ac.uk/ac/index.php). Numbers of amino acid residues are expressed based on mature LCAT protein after signal peptide (24 amino acid residues) is cleaved. Mutations in red and bule are causative mutations identified in familial LCAT deficiency (FLD) and fish-eye disease (FED), respectively. The * symbol indicates a mutation reported in Japan, and the # symbol indicates a mutation identified in Japan as well as other countries. Mutations shown in black are variants of uncertain significance found by such as genome-wide nucleotide sequencing of clinical samples.

Table 1. Mutations identified in patients in Japan

Exon	Mutation	Codon	Amino acid substitution	Phenotype
1	c.86A>T	5	Asn>Ile	FLD
1	c.101insC	10	Pro10fsTer17	FLD
1	c.101C>T	10	Pro>Leu	FED
1	c.110C>T	13	Thr>Met	FED
2	c.160G>A	30	Gly>Ser	FLD
2	c.278C>T	69	Pro>Leu	FLD
2	c.293G>A	74	Cys>Tyr	FLD
3	c.367C>T	99	Arg>Cys	FED
4	c.440C>T	123	Thr>Ile	FED
4	c.490C>T	140	Arg>Cys	FLD
4	c.491G>A	140	Arg>His	FLD
4	c.493insGGC	141	ins Gly	FLD
5	c.607G>C	179	Gly>Arg	FLD
6	c.756C>A	228	Asn>Lys	FLD
6	c.821C>G	250	Pro>Arg	FLD
6	c.862del	264	His263fsTer385	FLD
6	c.950T>C	293	Met>Thr	FLD
6	c.951G>A	293	Met>Ile	FED
6	c.1034C>T	321	Thr>Met	FLD
6	c.1102G>A	344	Gly>Ser	FLD

Mutations identified in Japanese patients are summarized. Note that numbering of amino acid residues is based on mature LCAT protein in which 24 signal peptide sequence is removed.

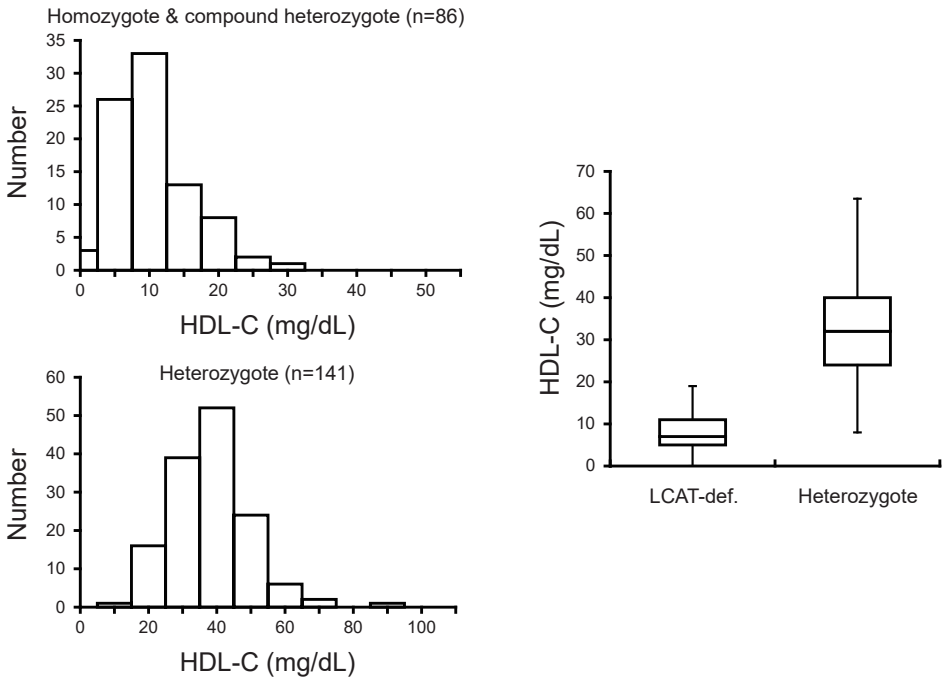

Fig. 2. Distribution of HDL-C in patients

Clinical levels of HDL-C available from published data (until Aug. 2019) for homozygous and compound heterozygous patients (n=86) and heterozygotes (n=141) have been collected and their distribution is shown in the figure. Note that their assay methods are not taken into consideration in the data distribution.

Clinical Examinations and Diagnostic Approach to LCAT Deficiency in Japan

The main clinical findings in FLD and FED are corneal opacity and low HDL-C. They are the key signs for suspecting these diseases. Proteinuria and/or anemia are also observed in many cases of FLD, but not in FED.

1) Lipid Examination

HDL-C values reported in the literature are summarized for homozygous and compound heterozygous FLD patients (n=86) in **Fig. 2** (until Aug. 2019). More than 72% of patients exhibited HDL-C levels less than 10 mg/dL. However, 3.5 % had levels higher than 20 mg/dL though the assay methods were not standardized. When a patient has an HDL-C level less than 25 mg/dL and corneal opacity, LCAT activity analysis should be considered (proposed by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of the Ministry of Health, Labour and Welfare of Japan in 2020). In assays, since α-activity represents LCAT activity using synthetic HDL (specific for HDL) as a substrate[47], measured levels are largely decreased in all plasma samples from patients with FLD or FED and may be below the detection limit in both. Cholesterol esterification rate (CER)[48] represents total esterification activity, including β-activity (specific for β-lipoproteins) and α-activity. As β-activity is also disrupted in FLD but not much in FED, measured levels are usually more decreased in FLD, compared with FED, which is useful for distinguishing FLD and FED. However, these assays are not routinely available in the clinical laboratories of regular hospitals in Japan. Therefore, the CE/TC ratio in plasma is a useful alternative for distinguishing FLD and FED. CE/TC is always reduced in FLD but not in FED and partial LCAT deficiency. ApoA-I and apoA-II are also significantly reduced due to the reduced HDL levels in FLD and FED. In the electrophoretic analysis of lipoproteins (agarose or polyacrylamide), LCAT dysfunction results in the appearance of abnormal lipoproteins, including LpX and IDL. Large and triglyceride-rich LDL (Lp8) is identified through HPLC gel filtration analysis of lipoproteins[7].

2) Ophthalmic Examination

Corneal opacity **(Fig. 3A)** is recognized in most LCAT deficiency patients. Grayish white granular spots are observed in corneal layers excluding the epithelium by the slit-lamp test. To assess the extent of corneal opacity, a contrast sensitivity test[49] is useful.

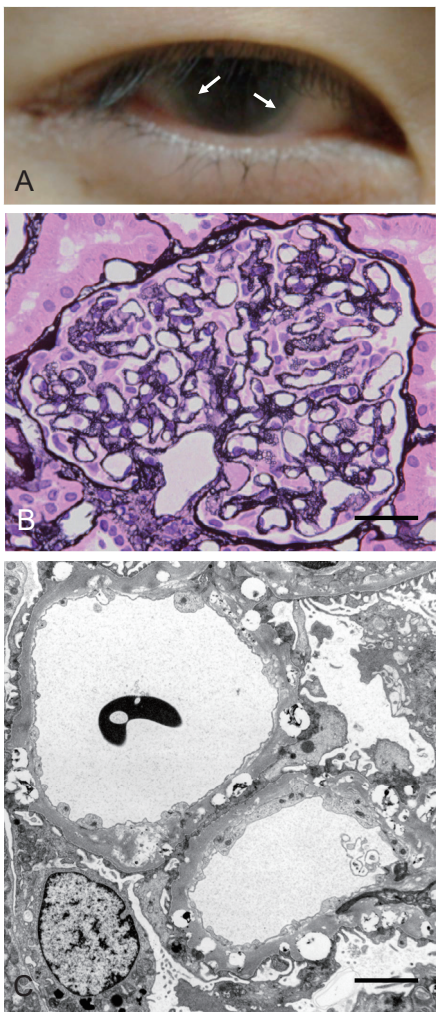

Fig. 3. Case with LCAT deficiency manifesting as corneal opacities and proteinuria (patient from ref. 31)

A) Corneal opacities in right eye (arrows).
B) Light microscopic findings for renal biopsy (Periodic acid methenamine silver stain). Thickened with bubbly, vacuolated, and honeycomb appearance. (Bar = 10 μm)
C) Electron microscopic findings for renal biopsy. Electron micrograph shows glomerular epimembranous, intramembranous, and subendothelial lipid droplets. Electron-lucent deposits with an electron-dense core can be observed in the glomerular basement membrane and mesangial matrix. (Bar = 2 μm)

3) Renal Examination

When proteinuria is present in patients with decreased LCAT activity who present with corneal opacity, renal biopsy may be considered **(Fig. 3B and 3C)**. Deposition of FC and phospholipids in the subendothelium of glomerular basement membrane is often observed. Accumulation of foam cells and thickening of Bowman's sac and glomerular basement membrane are also observed. Electron microscopy reveals an extensive high electron density membrane structure in the capillary lumen, basement membrane, and mesangial region[50].

4) Hematological Examination

Mild hemolytic anemia is present in many cases of FLD. A blood count shows a decreased hemoglobin level. HbA1c and haptoglobin levels are also decreased. Red blood cells with an abnormal appearance (called "target cells", "knizocytes", "stomatocytes", or "spherostomatocytes") are observed in FLD due to cholesterol accumulation in the cell membranes.

5) Gene Analysis

Genetic analysis is useful for the final diagnosis, combined with the results of the above examinations. The recessive inheritance format is determined through identification of mutations in the *LCAT* gene of the FLD or FED patients.

Differential Diagnosis

1) Hereditary Low HDL-Cholesterolemia (Tangier Disease, Familial Hypo-Alpha-Lipoproteinemia and ApoA-I Deficiency)

Patients with apoA-I deficiency and Tangier disease have a marked reduction in plasma HDL-C levels, which are generally lower than those in FLD and FED. Corneal opacity is also observed in these diseases[8]. The apo A-I level is about 30-50 mg/dL in patients with FLD or FED, but levels in Tangier disease are more markedly decreased (less than 10 mg/dL). Thus, the plasma apolipoprotein A-I concentration is useful for the differential diagnosis of these diseases. However, genetic analysis may be needed for final differentiation of diseases with hereditary low HDL-cholesterolemia.

2) Immune-Mediated LCAT Deficiency

There have been reports of patients exhibiting marked reduction in plasma HDL-C and renal dysfunction, similar to those in genetic LCAT deficiency, but are due to the presence of autoantibodies against LCAT protein[51, 52]. Immune-mediated LCAT deficiency is sometimes found through a gradual decrease in HDL-C. Testing for the antibodies and investigation of family history are necessary for differentiating this disorder from genetic LCAT deficiency, especially FLD.

3) Liver Disease (Liver Cirrhosis and Fulminant Hepatitis), Biliary Tract Obstruction, Malnutrition, or Cachexia

LCAT is an enzyme produced in the liver, so its biosynthesis is susceptible to hepatic damage. It is thus necessary to differentiate FLD and FED from

conditions where there is a secondary decrease in the enzyme due to serious liver dysfunction[53].

4) Drug-Induced Low HDL-Cholesterolemia (Probucol and Probucol/Fibrates)

Probucol has been found to reduce plasma HDL by inhibiting ABCA1 activity. In addition, it has been reported that plasma HDL is reduced to an extreme degree when probucol is taken with fibrate, even when fibrate is initiated after discontinuing probucol[54-56]. Patient histories need to be examined for use of these medications.

Since it is a designated intractable disease, diagnostic criteria for familial LCAT deficiency were previously proposed by the research group of the Ministry of Health, Labor and Welfare of Japan. The guidelines have been updated based on additionally accumulated Japanese clinical and laboratory data by a dyslipidemia research group supported by a grant from the Ministry of Health, Labor and Welfare **(Table 2)**.

Table 2. Diagnostic criteria for Japan proposed by research group of Ministry of Health, Labor and Welfare

A. Required item
1. Blood HDL-C level less than 25 mg/dL
2. Decrease in cholesteryl ester/TC ratio (CE/TC) (60% or less)

B. Symptom
1. Proteinuria, renal dysfunction
2. Corneal opacities

C. Laboratory findings
Blood and biochemical examination findings
1. Anemia (hemoglobin level, less than 11 g/dL)
2. Abnormalities in morphology of red blood cells (called "target cells", "knizocytes", "stomatocytes", or "spherostomatocytes")
3. Appearance of abnormal lipoproteins (LpX, IDL, or large TG rich LDL)

Ophthalmic examination findings
Decreased contrast sensitivity

D. Differential diagnosis
Differentiate from following diseases.
1. Other hereditary low HDL-cholesterolemia (Tangier disease, apolipoprotein AI deficiency)
2. Secondary LCAT deficiency (pathophysiology showing decreased protein synthesis such as liver disease (hepatic cirrhosis, fulminant hepatitis), biliary obstruction, malnutrition, cachexia, and autoimmune LCAT deficiency with underlying disease)
3. Secondary low HDL-cholesterolemia (After surgery, hepatopathy (especially cirrhosis, severe hepatitis, including convalescent stage), acute phase of systemic inflammatory disease, debilitating diseases such as cancer. history of oral probucol within the past 6 months, probucol and fibrate combination (including prescription after discontinuation of probucol))

E. Genetic testing
1. Mutation of *LCAT* gene

In a clinical sample in which two essential items are satisfied, the following determinations are made.
Definite: A disease that meets one or more of B and C and excludes any disease to be differentiated from in D, and satisfies E
Probable: Disease that meets one or more of B and C and excludes any disease that should be differentiated from in D

Current Treatment

There is no currently approved effective treatment for FLD and FED. Effective treatments would be replacement with normal or recombinant LCAT enzymes and gene therapy, and they are now under development. To mitigate renal dysfunction, a low-fat diet and renoprotective drugs, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), are prescribed.

1) Diet

There has been a study on the FLD siblings where the younger brother, who was put on a low calorie intake (1900 Cal) with fat restriction (25 g/day), did not develop proteinuria while his elder brother having a total calorie intake of 2500 Cal and fat intake of 65 g/day did[57]. Together with those of other studies[46, 58], these findings indicate that development of renal dysfunction can be delayed by a low-fat diet. A low-fat diet may lead to a decrease in abnormal lipoproteins associated with LCAT deficiency as well as reduced renal damage, although it may not be effective in all cases[59].

2) Blood Transfusion Therapy

Fresh blood (whole blood or plasma) transfusion therapy has been reported to be effective for LCAT replacement[60, 61]. An increase in LCAT activity was observed, but it returned to the pre-transfusion level within one week, indicating that it is difficult to maintain a therapeutic level.

3) Drug Treatment

There is no definitive drug treatment for alleviating decreased or defective LCAT activity in FLD. Drug therapy, combined with diet, has been attempted with the purpose of preventing or mitigating the deterioration in renal function. ACE inhibitors reportedly reduced proteinuria after one

year of treatment[26]. Also, combination therapy of nicotinic acid and fenofibrate lead to a reduction in LpX and an associated reduction in albuminuria in a patient[62]. In addition, high-dose ARB with statin was reported to stabilize the progression of renal dysfunction[63]. Results for corticosteroid treatment (with ACE inhibitor) suggested that reduced inflammatory responses lead to a decrease in proteinuria in a patient[64].

4) Recombinant hLCAT Protein (rhLCAT) Replacement Therapy

A clinical trial on rhLCAT has been conducted in the United States[65]. High-dose rhLCAT (9.0 mg/kg) improved anemia and renal function to some degree with improvement in lipid parameters, including an increase in HDL-C but there was a return to the pre-treatment status by 2 weeks after administration, and the supply of rhLCAT became insufficient during the trial. As with other enzyme replacement therapies, it is necessary to continue administration. Another clinical trial has been conducted to evaluate the safety, pharmacokinetics and pharmacodynamics of rhLCAT in subjects with stable coronary artery disease (NCT02601560)[66]. It was reported that antibodies against rhLCAT appeared in some of the participants on the highest dose of rhLCAT.

5) Gene Therapy

A gene therapy-mediated continuous supply of LCAT would improve patient QOL by reducing the frequency of hospital visits and administration of therapy. No gene therapy has received regulatory approval anywhere. In Japan, the first in-human study on gene therapy/regenerative medicine via auto-transplantation of *LCAT* gene-transduced preadipocytes has been approved by the Ministry of Health, Labor and Welfare, under the Act on Securement of Safety of Regenerative Medicine[67]. The first patient has been followed up for more than three years since transplantation at Chiba University Hospital. It was well-tolerated. The second clinical trial was started in 2020 for the purpose of obtaining regulatory approval in Japan.

6) Organ Transplantation

Kidney transplantation to treat renal dysfunction and corneal transplantation to remedy visual impairment are performed, but the risk of recurrence is inevitably high. In recent years, single-donor sequential kidney and liver transplantation has been performed in one patient[68]. During the 5-year follow-up period, the function of the transplanted organs was maintained, but dyslipidemia recurred within 1 year after liver transplantation.

Future Perspectives

Our current understanding of familial LCAT deficiency and its complications is summarized in this review based on information from the literature, including that from Japan. More than 100 *LCAT* mutations have been identified in the world, but mechanisms of development of subsequent complications remain to be elucidated. A better understanding of the pathophysiology of this disease will be necessary to make further progress in treatment. We hope that this review will be helpful for clinicians in performing diagnosis and medical care for patients suspected of having the disease in Japan.

The diagnosis of the subtypes of this rare genetic disease, FLD and FED, requires the involvement of multiple departments such as lipid metabolism, nephrology, and ophthalmology. Also, the onset of severe renal dysfunction is relatively late (40 to 50 years old). These could be reasons for the delay in diagnosis. Measurement of LCAT activity and genetic testing for FLD and FED are not covered by National Health Insurance in Japan, and this also makes it difficult for physicians to diagnose patients with the disease.

Currently, LCAT enzyme replacement therapy by means of transfusion of a recombinant preparation or gene/cell therapy is under development. We hope that these treatments are put into practice in near future, and improve patients' survival and QOL.

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Conflicts of Interest

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Review

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Diagnosis and Management of Sitosterolemia 2021

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Sitosterolemia is an inherited metabolic disorder characterized by increased levels of plant sterols, such as sitosterol. This disease is caused by loss-of-function genetic mutations in ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* or *ABCG8*, respectively), both of which play important roles in selective excretion of plant sterols from the liver and intestine, leading to failure to prevent absorption of food plant sterols. This disorder has been considered to be extremely rare. However, accumulated clinical data as well as genetics suggest the possibility of a much higher prevalence. Its clinical manifestations resemble those observed in patients with familial hypercholesterolemia (FH), including tendon xanthomas, hyper LDL-cholesterolemia, and premature coronary atherosclerosis. We provide an overview of this recessive genetic disease, diagnostic as well as therapeutic tips, and the latest diagnostic criteria in Japan.

Key words: **Sitosterolemia, ABCG5, ABCG8, Familial hypercholesterolemia**

Introduction

Sitosterolemia (OMIM #210250, and #618666) is an autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, resulting in prominently elevated serum concentrations of plant sterols, such as sitosterol, campesterol, and stigmasterol **(Fig. 1)**[1, 2]. This condition was first described by Bhattacharyya and Connor in 1974 [3]. Patients with sitosterolemia primarily exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling these characteristics in patients with familial hypercholesterolemia (FH)[4-9]. Severity of the phenotypes of sitosterolemia appears to be more variable than for FH possibly due to its greater dependency on dietary sterol intake[10, 11]. In addition, they have a wider variety, which includes hemolysis, splenomegaly, platelet abnormalities, and arthralgia/arthritis[12]. This disease is caused by biallelic (homozygous/compound heterozygous) loss-of-function (LOF) mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively) that play an important role in excreting sterols from the liver and intestine **(Fig. 1)**[13, 14]. Therefore, increased absorption of plant sterols from the intestine and their decreased secretion from the liver are the primary cause of sitosterolemia[15, 16]. Several (adaptive) secondary changes in lipid metabolism have been found to be associated with the accelerated sterol absorption; for

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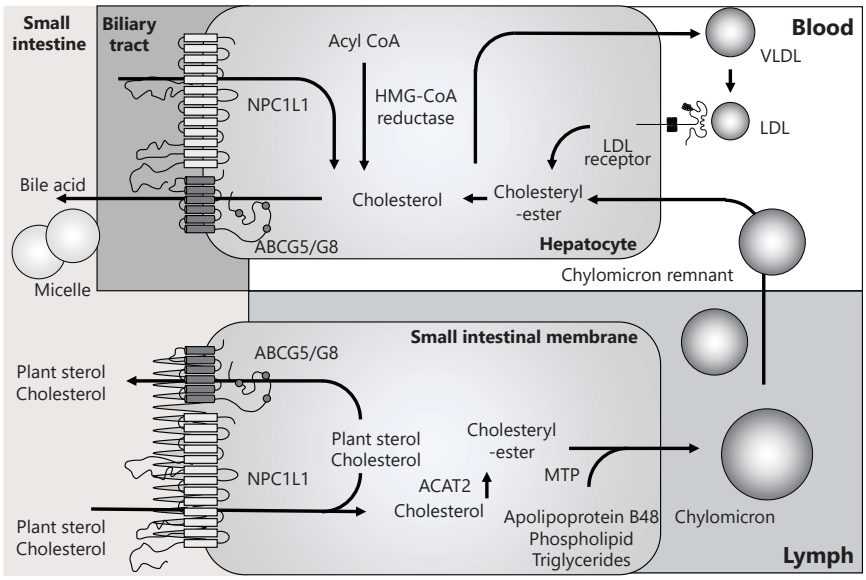

Fig. 1. Schema of sterol metabolism focusing on ABCG5/8 and NPC1L1

In the intestine, plant sterols and cholesterol are absorbed via NPC1L1, while they are excreted via ABCG5/8. The same pattern is observed in hepatocytes.

example, altered solubilization of sterols in intestinal micelles, increased activity of acyl CoA: cholesterol acyltransferase (ACAT), and changes in intracellular transport processes of sterols.

Sitosterolemia used to be considered an extremely rare disorder but recent studies indicate the possibility of a much higher prevalence in the general population[6-10].

Based on the pathophysiology of this disease, ezetimibe, an inhibitor of Niemann-Pick C1 Like 1 (NPC1L1) that mediates absorption of dietary cholesterol in the intestine[17], has been shown to be effective in reducing serum sitosterol as well as cholesterol in sitosterolemic patients, together with dietary management to restrict intake of these sterols[18, 19]. In this review article, we discuss the current understanding of sitosterolemia, its diagnostic criteria, and future perspectives.

Plant Sterols

Plant sterols (sitosterol, campesterol, and stigmasterol) are sterol molecules naturally contained at low levels in plant foods such as fruits, vegetables, nuts and cereals[20]. Sitosterol is usually the most abundant plant sterol in the diet[2] and the average Japanese diet and Western diets contain similar amounts of cholesterol and plant sterols. Although approximately 50% of dietary cholesterol is absorbed, less than 5% of plant sterols is absorbed in normal individuals[21-24], resulting in lower levels of plant sterols than cholesterol in the body. In a recent investigation of plasma concentrations of plant sterols in 667,718 subjects, they seemed to be dependent on age, gender, and apolipoprotein E genotype[25].

Accumulation of plant sterols in patients with sitosterolemia would contribute to atherogenesis. However, dietary intake of plant sterols is generally considered beneficial for normal individuals as they competitively inhibit cholesterol absorption, which is then selectively excreted resulting in lower cholesterol levels[26]. The European Atherosclerosis Society Consensus Panel currently recommends taking plant sterols for patients with a relatively high risk for cardiovascular disease and/or statin intolerance[20]. In addition, the proinflammatory properties of sitosterol appear to be much weaker than those of cholesterol[27].

Epidemiology

Sitosterolemia has long been considered an extremely rare disorder. Indeed, only 45 sitosterolemic subjects were reported in a review article published in 2003 [28]. Its autosomal recessive inheritance may have caused us to think it is a rare disease. However, the Exome Aggregation Consortium (ExAC) Exome Browser, a public genetic database, has suggested that 1 in ~220 general individuals have LOF mutations in the *ABCG5* or *ABCG8* gene[29]. Therefore, a rough estimate of the number of homozygous/compound

heterozygous patients with sitosterolemia is 1 in ~200,000 general individuals. Moreover, a recent study has shown that a certain proportion of patients clinically diagnosed as FH could in fact have sitosterolemia[30]. Accordingly, this disorder appears to be much more prevalent than previously thought.

Genetic Backgrounds and Pathophysiology

In 2001, the cause of this disease was identified as double LOF mutations in the *ABCG5* or *ABCG8* gene[13, 14]. So far, most patients with recognized sitosterolemia have come from consanguineous marriages, which has lead to homozygous mutations in the *ABCG5* or *ABCG8* gene. However, recent advances in genetic analysis have revealed that there are also a number of cases with compound heterozygous mutations in the *ABCG5* and *ABCG8* genes. Relatively common pathogenic mutations are c.1166G>A/p.Arg389His, and c.1256G>A/p.Arg419His in *ABCG5* gene[31-33].

The ABCG5 and ABCG8 proteins form heterodimers and act as a complex, which functions as a transporter of sterols in the bile and intestine. Accordingly, patients with sitosterolemia exhibit either homozygous or compound heterozygous mutations in the *ABCG5* or *ABCG8* gene. Besides the above mutations, Tada *et al.* previously reported a unique case of sitosterolemia caused by double heterozygous mutations in the *ABCG5* and *ABCG8* genes, suggesting that specific combinations of mutations and/or quite deleterious heterozygous mutations may cause sitosterolemia[34].

Recent genome-wide association studies (GWAS) indicated that the *ABCG5* and *ABCG8* genes are significantly associated with LDL cholesterol levels and increased prevalence of coronary artery disease (CAD)[35, 36], suggesting that these genes contribute to high LDL cholesterol and high plant sterol levels in plasma and risk for CAD among the general population as well. In addition, Tada *et al.* have recently shown that deleterious mutations of the *ABCG5* or *ABCG8* gene contribute substantially to mimicking and exacerbation of the FH phenotype[30].

Clinical Manifestations

Individuals suffering from sitosterolemia primarily present with tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling those in FH. Therefore, a certain proportion of patients with sitosterolemia could be misdiagnosed as FH due to tendon xanthomas and elevated LDL cholesterol[30]. However, the severity of LDL cholesterol elevation and xanthomas appears to be more variable in sitosterolemia than in FH. In a case of myocardial infarction in a 25-year-old woman previously described by Kawamura *et al.*[9], Achilles tendon xanthomas, as well as significantly elevated LDL cholesterol levels and sitosterol levels were found, and she was initially misdiagnosed as FH. However, consideration of the recessive pattern of inheritance, great responsiveness to dietary counseling together with statin plus ezetimibe (LDL cholesterol was reduced from 220 mg/dl to 55 mg/dl) lead to the accurate diagnosis of sitosterolemia.

Typical cases in infancy have also been described. LDL cholesterol levels in FH tend to be constantly high, whereas those in sitosterolemia may vary with the latest dietary intake of sterols. The most extreme cases have been infants who are breastfeeding. They have been found to have cutaneous xanthomas associated with significant elevation in LDL cholesterol levels, resembling those in homozygous FH,[6, 37, 38]. It has been noted that weaning alone can reduce their LDL cholesterol levels, causing the cutaneous xanthomas to regress, despite sitosterol levels that remain significantly elevated. These observations suggest that they are quite vulnerable to a sterol-rich diet, and that dietary management is very important in infants with sitosterolemia. However, we have experienced several independent infantile cases of transient hypercholesterolemia associated with breastfeeding without any signs of cutaneous xanthomas, where the patients turned out to be carriers of heterozygous mutations of the *ABCG5* gene (data not shown). Thus, it appears that some infantile cases of "breastfed hypercholesterolemia" can be explained by heterozygous mutations of the *ABCG5* gene.

In addition, a variety of other phenotypes, such as hemolysis, splenomegaly, platelet abnormalities, arthralgia/arthritis have been documented among patients with sitosterolemia, and some of them have been shown to be associated with accumulation of sitosterol in an animal model[39]. The underlying mechanism responsible for the hematologic abnormalities observed in some patients with sitosterolemia appears to be accumulation of circulating sterols in blood cell membranes, leading to abnormal morphology and function[40]. Regarding arthralgia/arthritis, the case of a sitosterolemic patient who also had a history of recurrent arthritis has been described. Whole exome sequencing analysis revealed that this patient had another concomitant genetic disorder that had caused familial Mediterranean fever where arthritis is documented as one of the major manifestations[7].

Since sitosterolemia is a recessive disorder, in

many cases there is a consanguineous marriage in the background. This could lead to the coincidence of other recessive genetic disorders, although there is no clear evidence suggesting an association between their genotypes or inheritance patterns and the severity or variety of sitosterolemia phenotypes. Comprehensive genetic analyses in such patients could shed light on the causal (genetic) backgrounds of their phenotypes.

Sitosterol or Cholesterol?

Sitosterolemia was named for the significant elevation in serum sitosterol level in this disease. As sitosterol and other plant sterols have been shown to accumulate in atherosclerotic lesions of patients with sitosterolemia[4, 41], lowering serum sitosterol has long been considered to be a target for therapy. However, a causative relationship between marked elevation of sitosterol in serum and its tissue deposition and development of atherosclerotic cardiovascular diseases remains to be demonstrated. The results of studies regarding an association between serum sitosterol levels and atherosclerosis have been controversial[42-45].

Currently available data as well as the fact that sitosterolemic patients with premature atherosclerotic cardiovascular diseases tend to exhibit hyper-LDL cholesterolemia suggest that LDL cholesterol, rather than sitosterol is the main causal factor for atherogenicity. Therefore, further studies assessing the role of sitosterol in the development of atherosclerosis are needed

Diagnostic Criteria

Diagnostic criteria for sitosterolemia in Japan are described in **Table 1**. Serum sitosterol levels could be measured using high-sensitive gas chromatography. Their reference ranges in Japanese individuals have been determined as 0.99 - 3.88 μg/mL in males, and 1.03 - 4.45 μg/mL in females[46]. It is vitally important to perform differential diagnosis to distinguish it from FH **(Fig. 2A)**, autosomal recessive hypercholesterolemia (ARH) **(Fig. 2B, 2C)** and cerebrotendinous xanthomatosis (CTX) **(Fig. 2D, 2E)**. It is not easy to make a differential clinical diagnosis of sitosterolemia **(Fig. 2F, 2G)** just based on physical manifestations[47-50].

Diagnostic Tips for Sitosterolemia

As stated above, patients with sitosterolemia typically exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling the manifestations of FH. Therefore, patients with premature coronary atherosclerosis should be examined to see whether they have a special genetic background including that for sitosterolemia. Absence of a family history of hypercholesterolemia as well as premature CAD is likely to indicate sitosterolemia rather than FH. However, it is of note that some patients with sitosterolemia have a family history of hypercholesterolemia and tendon xanthomas despite its recessive pattern of inheritance. The tendon xanthomas of sitosterolemia tend to be more severe than those of heterozygous FH, despite lower levels of LDL cholesterol. Thus, sitosterolemia should be considered in differential diagnosis for heterozygous FH, which is now considered a relatively frequent genetic metabolic disease. In addition, LDL cholesterol levels of sitosterolemic patients tend to vary dramatically depending on their latest dietary intake of plant sterols, and this would be useful information in making a clinical diagnosis of this disease. ARH and CTX are extremely rare autosomal recessive diseases, and almost all patients with these diseases are from consanguineous marriages. It is sometimes quite difficult to differentiate sitosterolemia from ARH based on a single assessment; however, responsiveness to dietary counseling differs between sitosterolemia and ARH. On the other hand, patients with CTX can be differentiated from those with sitosterolemia based on several factors, such as absence of hypercholesterolemia, chronic diarrhea during childhood, juvenile cataracts, and neurological symptoms[49].

Table 1. Diagnostic criteria

A. Clinical manifestations
1. Cutaneous or tendon xanthomas
2. Premature coronary artery disease (male < 45 yr, female < 55 yr)
B. Laboratory testing
1. Serum sitosterol ≥ 1 mg/dL (10 μg/mL)
C. Differential diagnosis
Exclude familial hypercholesterolemia and cerebrotendinous xanthomatosis
D. Genetic analysis
Pathogenic mutations in ABCG5 or ABCG8 gene

Definite: fulfills A-1, B-1, C, and D
Probable: fulfills A-1, B-1, and C
Possible: fulfills A-1, A-2, and B-1

Management of Sitosterolemia

Restriction of plant sterols as well as cholesterol should be the first line strategy. Sitosterolemic patients should avoid plant sterol-rich foods, such as corn oil,

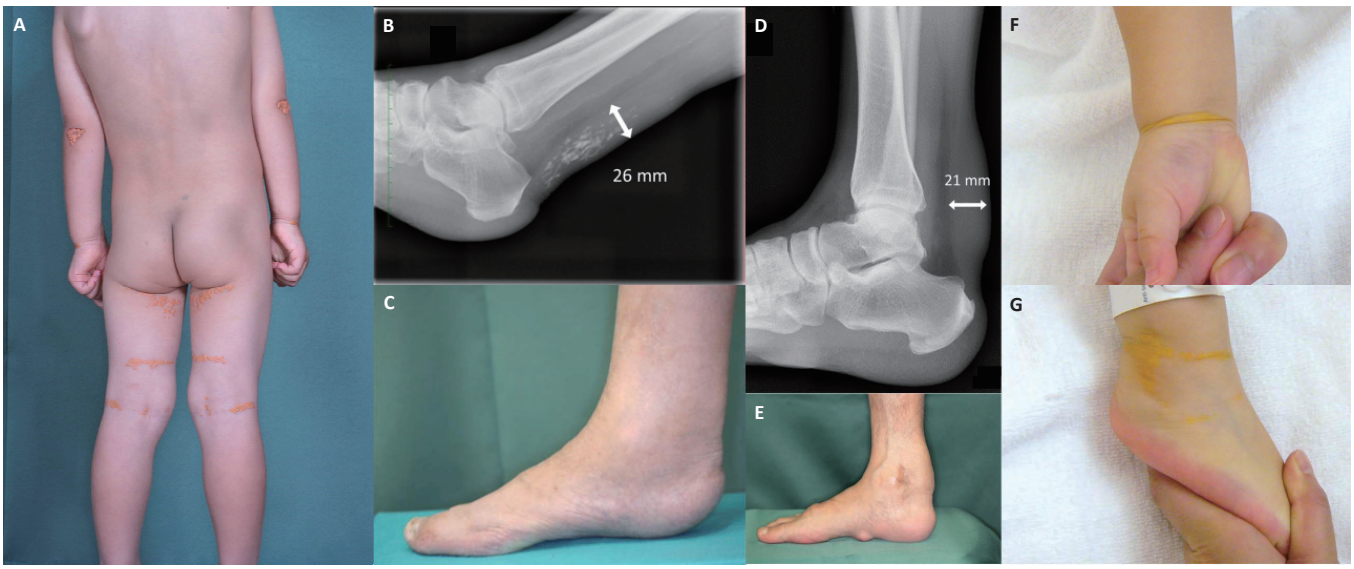

Fig. 2. Xanthomas in patients with dyslipidemias

(A) Systemic xanthomas in a patient with homozygous FH (3-year-old boy)
(B) X-ray of Achilles' tendon in a patient with ARH (67-year-male)
(C) Achilles' tendon xanthomas in a patient with ARH (67-year-male)
(D) X-ray of Achilles' tendon in a patient with CTX (63-year-male)
(E) Achilles' tendon xanthomas in a patient with CTX (63-year-male)
(F) Xanthomas at the ankle in a patient with sitosterolemia (1-year-old girl)
(G) Xanthomas at the wrist in a patient with sitosterolemia (1-year-old girl)

sesame seeds, peanuts, soybeans, rapeseed oil, sesame oil, rice oil, margarine, avocado, chocolate, and shellfish, whereas, other vegetables and fruits, such as potato, carrot, and apple contain less plant sterols[51]. In addition to plant sterols, they also need to avoid cholesterol-rich foods, including animal liver and eggs. Regarding medication, ezetimibe and bile-acid sequestrant resins have been established as standard therapies because the primary cause of this disease is increased absorption of plant sterols from the intestine and their decreased secretion from the liver[15]. Both could reduce sitosterol (~ 20% by ezetimibe, and ~ 30% by resins)[18, 52] and LDL cholesterol in sitosterolemia. Ezetimibe has also been shown to favorably increase platelet count[19].

Patients with sitosterolemia usually do not respond to statins because HMG-CoA reductase activity is already maximally inhibited[52]. However, statins are effective in reducing LDL cholesterol, at least in some sitosterolemic patients[9, 45], although they may increase sitosterol levels in others[53]. Considering the lack of a clear association between sitosterol levels and frequency of atherosclerotic cardiovascular disease[44], as well as the fact that some patients with sitosterolemia are treated with statins due to being misdiagnosed with FH[30], statins could at least be used for patients in a secondary prevention setting. For patients with advanced atherosclerotic lesions and resistance to the standard treatments mentioned above, LDL apheresis could be considered if applicable, although it is not officially covered by the Japanese national health insurance[8].

Liver transplantation was performed in a case of sitosterolemia with liver cirrhosis and reportedly resulted in a dramatic reduction in serum plant sterol levels[54]. Regarding target levels of LDL cholesterol, there is plenty of clinical evidence suggesting that lowering LDL cholesterol is associated with reduced risk for atherosclerotic cardiovascular diseases. In addition, sitosterolemia has been considered as a phenocopy of FH and therefore, the target LDL cholesterol level should be the same as that of FH. However, there has been no definite evidence for an association of sitosterol lowering and prevention of atherosclerotic cardiovascular diseases so far. Accordingly, LDL cholesterol, rather than sitosterol, should be the main biomarker when treating patients with sitosterolemia. Dietary restriction of plant sterols, ezetimibe, and bile-acid sequestrant resins have been shown to reduce both LDL cholesterol and sitosterol levels and thus these strategies should be considered as standard treatment for patients with sitosterolemia. The plant sterol content of foods and food ingredients varies widely from 7 mg/100 g in potatoes and

tomatoes to 686-952 mg/100 g in corn oil[55]. It is therefore rational to recommend patients with sitosterolemia and reduced function of ABCG5 or ABCG8 to avoid vegetables rich in plant sterols.

Conclusions and Perspectives

Sitosterolemia is a monogenic disorder that has been considered rather rare. However, its prevalence may currently be substantially underestimated[56], so we should be more careful to identify this disease among hypercholesterolemic patients with xanthomas. In particular, to raise awareness of sitosterolemia among pediatricians and dermatologists, education for them focusing on its typical manifestations is important. Measurement of serum sitosterol is not covered by Japanese national health insurance but we firmly believe that it is reasonable for it to be covered now that we have reference data for serum sitosterol levels among Japanese healthy individuals as well as patients with sitosterolemia. Ideally, prospective randomized controlled trials investigating if specific lowering of serum sitosterol leads to reduced risk for atherosclerotic cardiovascular diseases should be performed. More large-scale observational studies attempting to demonstrate an independent association between sitosterol levels and atherosclerotic cardiovascular diseases are also needed.

To establish the clinical importance of this disease for public health, more accurate prevalence and clinical manifestation data should be accumulated, supported by the health insurance system and comprehensive genetic analyses. Diagnostic criteria of sitosterolemia proposed by the Japanese Ministry of Health, Labor and Welfare scientific research team for hyperlipidemia would facilitate the accumulation of such data on this unique disorder.

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Conflicts of Interest

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Current Diagnosis and Management of Tangier Disease

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Tangier disease is a genetic disorder characterized by an absence or extremely low level of high-density lipoprotein (HDL)-cholesterol (HDL-C). It is caused by a dysfunctional mutation of the ATP-binding cassette transporter A1 (*ABCA1*) gene, the mandatory gene for generation of HDL particles from cellular cholesterol and phospholipids, and it appears in an autosomal recessive hereditary profile. To date, 35 cases have been reported in Japan and 109 cases outside Japan. With dysfunctional mutations in both alleles (homozygotes or compound heterozygotes), the HDL-C level is mostly less than 5 mg/dL and there is 10 mg/dL or less of apolipoprotein A-I (apoA-I), the major protein component of HDL. In patients with Tangier disease, major physical findings are orange-colored pharyngeal tonsils, hepatosplenomegaly, corneal opacity, lymphadenopathy, and peripheral neuropathy. Although patients tend to have decreased low-density lipoprotein (LDL)-cholesterol (LDL-C) levels, premature coronary artery disease is frequently observed. No specific curative treatment is currently available, so early identification of patients and preventing atherosclerosis development are crucial. Management of risk factors other than low HDL-C is also important, such as LDL-C levels, hypertension and smoking. Additionally, treatment for glucose intolerance might be required because impaired insulin secretion from pancreatic beta cells has occasionally been reported.

Key words: **Tangier disease, HDL, Reverse cholesterol transport, ABCA1, Cholesterol efflux, Orange tonsil, Atherosclerosis**

Introduction

Tangier disease is an autosomal recessive disease characterized by extremely low levels or absence of high-density lipoprotein (HDL)-cholesterol (HDL-C) and apolipoprotein A-I (apoA-I)[1]. The disease was named after Tangier Island in Chesapeake Bay, Virginia, USA, where the first case was discovered in 1960 and reported in 1961[2]. In 1991, generation of HDL particles through the direct action of helical HDL apoproteins on cells was first reported[3], and this was found to be deficient in cells derived from a patient with Tangier disease in 1995[4]. Eventually, ATP binding cassette transporter A1 (*ABCA1*) was identified as the gene responsible for this action and for Tangier disease in 1999[5-7]. Sequential progress in the investigation of HDL biosynthesis showed that HDL particles generated through ABCA1-dependent interaction of apolipoproteins with cells are the main source of plasma HDL. Patients with homozygous or compound heterozygous mutations in the *ABCA1* gene display the phenotype of Tangier disease and heterozygotes have decreases in HDL-cholesterol to various extents.

1. Disease Frequency

The number of cases of Tangier disease reported by 2020 was 35 in Japan and 109 in other countries (possibly including duplicates), indicating that it is a rather rare disease[8, 9]. However, the frequency of dysfunctional mutations in the *ABCA1* gene in the general population is not clear. A recent article using the Exome Aggregation Consortium database reported that 1 in 400 individuals in the general population is a heterozygote for a loss-of-function variant in the *ABCA1* gene on the basis of allele frequencies (frameshift, nonsense and splicing only; not missense), indicating a global prevalence of Tangier disease of at

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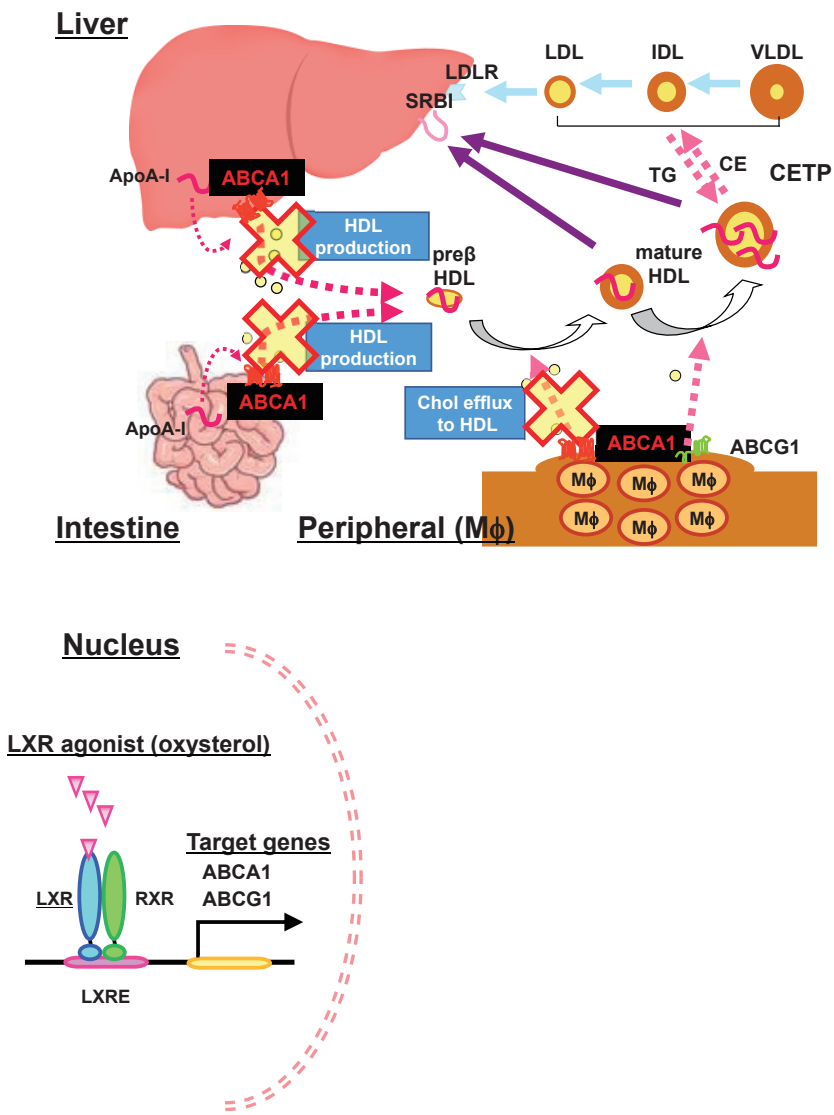

Fig. 1. Roles of ABCA1 in formation of HDL particles, reverse cholesterol transport and pathogenesis of Tangier disease

least 1 in 640,000[10]. It therefore seems that a substantial number of cases might go undiagnosed.

2. Genetic Backgrounds and Pathophysiology

ABCA1 is a member of the ATP-binding cassette transporter membrane protein family. It is an essential factor for generation of nascent HDL particles with extracellular helical apolipoproteins, through transport of cellular phospholipids and cholesterol (Fig. 1). This process is the major source of plasma HDL and one of the major mechanisms of cholesterol export from cells. It may be essential for final processing of cholesterol in mammalian somatic cells that are unable to catabolize cholesterol molecules. Peripheral cells sense intra-cellular cholesterol levels and increase ABCA1 expression for its excretion[11], while it undergoes bidirectional control in hepatocytes to prevent cholesterol recovered from peripheral cells flowing back into blood plasma[12, 13]. With functional deficiency in ABCA1, spherical HDL particles are not produced resulting in extremely low plasma HDL-C levels, which, in Tangier disease patients, are about one third of the normal level. The reason for this is unclear but it has been postulated that a substantial portion of cholesterol molecules in LDL in human plasma are those which have been acyl-esterified in HDL and transferred to VLDL/LDL and that a severe decrease in HDL cholesterol may lead to a decrease in LDL-C level.

In Tangier disease patients, cellular cholesterol export is impaired due to ABCA1 deficiency in peripheral cells, including macrophages and Schwann

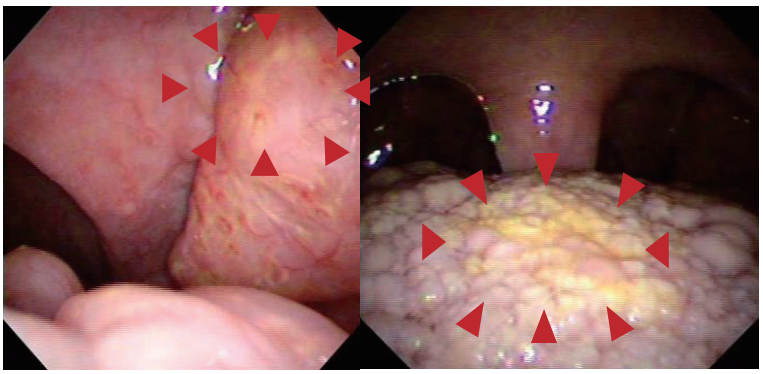

Fig. 2. Orange-colored tonsils observed in male patient with Tangier disease in his 50s
Arrow heads indicate palatine tonsil (left panel) and lingual tonsil (right panel). Reproduced from reference [8].

cells. Cholesterol therefore accumulates in these cells, causing orange-colored pharyngeal tonsillar swelling, corneal opacity, hepatosplenomegaly, lymphadenopathy and peripheral neuropathy. However, impairment of the initial stage of reverse cholesterol transport should be considered to be a risk for developing atherosclerotic diseases even though plasma LDL-C concentrations could be reduced.

ABCA1 appears to destabilize the raft structure, a cholesterol-rich domain of the plasma membrane[14, 15], its deficiency leads to an increase in "lipid" rafts and it has been suggested that this increases secretion of inflammatory cytokines[16]. It has also been reported that the insulinogenic index decreases due to cholesterol accumulation in pancreatic β-cells, which often accompanies glucose intolerance[17, 18]. These metabolic disorders are collectively involved in the development of premature coronary artery disease[8].

In early studies of Tangier disease, Schaefer et al. revealed the kinetics of plasma lipoprotein metabolism using externally labeled injected HDL and found that that apoA-I was catabolized at a much greater fractional rate in patients[19]. Their data, however, should be reinterpreted in terms of external HDL catabolism on the basis of ABCA1 deficiency. A recent study using human pluripotent stem cell-derived hepatocytes has demonstrated that ABCA1 deficiency increases angiopoietin-like protein 3 secretion, which is consistent with increased triglyceride in the plasma of Tangier patients[20].

3. Clinical Manifestations

3.1. Abnormal Plasma Lipoproteins

Plasma HDL-C is mostly low, at 5 mg/dL or less (mean of identified cases 3 ± 3 mg/dL), and the apoA-I concentration is 10 mg/dL or less[21]. Plasma LDL-C is also reduced, to around 37% of the average normal level. The appearance of remnant lipoprotein particles (intermediate products between VLDL and LDL) rich in triglycerides has been reported and this was found to result in abnormal small, dense LDL particles[21]. In subjects with heterozygous mutations of the *ABCA1* gene, plasma HDL-C and apoA-I levels are often reduced to about 50% of that in normal subjects, though the extent of HDL-C decline is not consistent.

3.2. Physical Findings

Impairment of HDL biogenesis results in reduced cholesterol export, which leads to lipid accumulation in cells. A typical finding of this disorder is orange-colored tonsils **(Fig. 2)**[8]. The tonsils of patients are lobulated and swollen and present a bright orange or yellow-grey surface. A history of recurrent tonsillitis or tonsillectomy is often noted. In addition, splenomegaly and associated thrombocytopenia and/or reticulocyte hyperplasia may be present **(Fig. 3)**. Hepatomegaly is also observed in about one-third of cases, but liver dysfunction is not usually present[22]. There is also cholesterol accumulation in other organs, such as lymph nodes, thymus, intestinal mucosa, and skin. Its accumulation in the cornea causes corneal opacity.

3.3. Peripheral Neuropathy

Various peripheral neuropathies, ranging from mild to severe, have been reported. Sensory, motor or mixed disorders appear transiently or persistently. Reduced deep perception and tendon reflexes are rare. Peripheral neuropathy appears as a recurrent asymmetric disorder of peripheral nerves including cranial nerves, as neuropathy with symmetry in the lower limbs, or syringomyelia-like peripheral neuropathy[23, 24].

3.4. Cardiovascular Diseases

It has been reported that 12 out of 35 patients

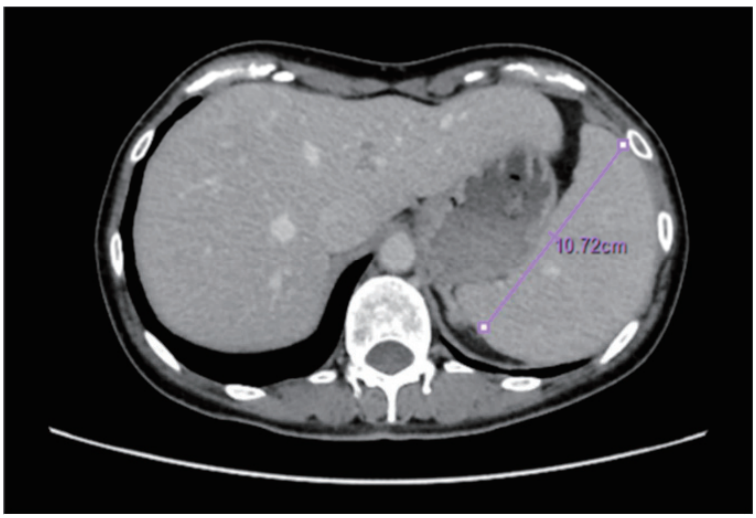

Fig. 3. Abdominal CT scan of splenomegaly in female patient with Tangier disease in her 40s
The photo was kindly provided by one of the co-authors, Prof. Yasushi Ishigaki (Iwate Medical University).

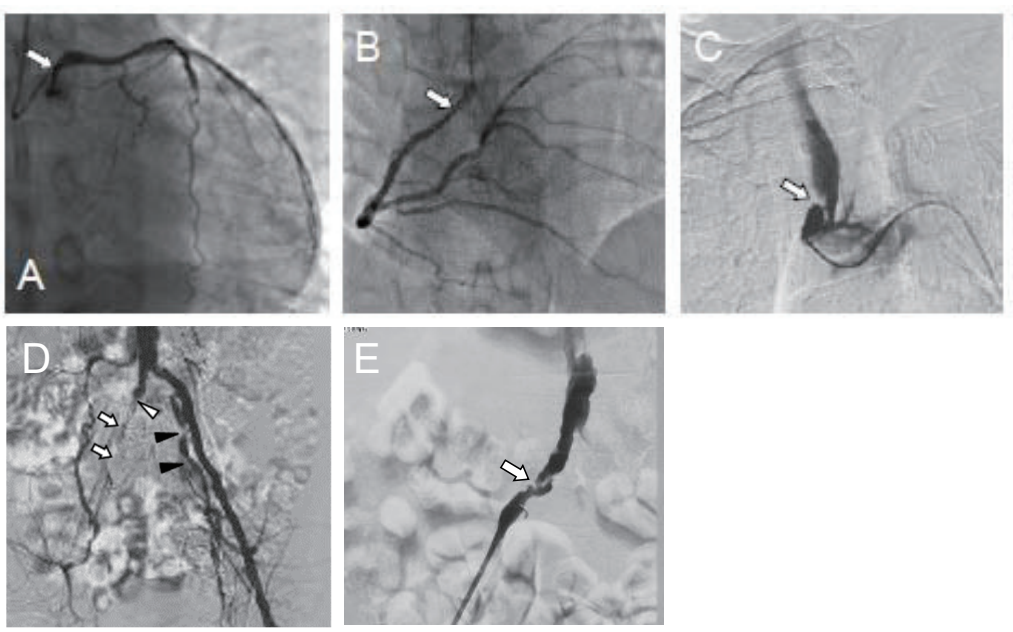

Fig. 4. Advanced systemic atherosclerotic lesions in male patient with Tangier disease in his 50s
Arrows indicate stenosis or occlusion of the artery.
A: left coronary artery, B: right coronary artery, C: brachiocephalic artery, D: left iliac artery, E: right external iliac artery [8].

(34.3%) in Japan and 34 out of 109 patients (31.2%) in other countries had some type of cardiovascular disease, suggesting accelerated atherogenicity in Tangier disease **(Fig. 4)**[8]. A previous case study using intravascular ultrasound (IVUS) revealed diffuse calcified coronary artery lesions[25], which might have been affected by HDL deficiency and glucose intolerance[17].

4. Diagnostic Criteria and Differential Diagnosis

Diagnostic criteria for Tangier disease are given in **Table 1** and the flow chart for differential diagnosis of hypo-HDL-cholesterolemia is shown in **Fig. 5**, based on discussions by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of Japan's Ministry of Health, Labour and Welfare.

Inherited diseases that lead to hypo-HDL-

Table 1. Diagnostic criteria

A. Required laboratory test results
1. Plasma (serum) HDL-cholesterol less than 25 mg/dL
2. Plasma (serum) apoA-I concentration less than 20 mg/dL
B. Clinical symptoms
1. Orange-colored tonsillar swelling
2. Hepatomegaly and/or splenomegaly
3. Corneal opacity
4. Peripheral neuropathy
5. Cardiovascular disease
C. Differential diagnosis
The following diseases should be excluded;
LCAT deficiency, apoA-I deficiency and secondary hypo-HDL-cholesterolemia*
D. Genetic testing**
Identification of pathogenic mutations in the *ABCA1* gene
< Diagnostic category >
Definite: Patients should satisfy both of required laboratory test results (A) AND at least one clinical symptom of (B) AND should be excluded for the diseases of differential diagnosis (C) AND should be positive for genetic testing (D).
Probable: Patients should satisfy both of required laboratory test results (A) AND at least two clinical symptoms of (B) AND should be excluded for the diseases of differential diagnosis (C).
Tangier disease can be diagnosed if patients are categorized "Definite" or "Probable".

*Secondary hypo-HDL-cholesterolemia: After surgery, liver disorders (especially liver cirrhosis and severe hepatitis, including convalescent stage), acute phase of systemic inflammatory disease, debilitating diseases such as cancer, history of oral probucol within the past 6 months, and combined probucol and fibrate (including fibrate administration after discontinuation of probucol).
**When differential diagnosis is difficult, genetic testing for *ABCA1* mutations should be performed. The diagnosis can be definite if pathogenic mutations in the *ABCA1* gene are identified.

cholesterolemia (Familial hypoalphalipoproteinemia) include classical lecithin: cholesterol acyltransferase (LCAT) deficiency, fish-eye disease, and familial apoA-I deficiency. Corneal opacity is commonly observed in these diseases, but tonsillar swelling and peripheral neuropathy are specific to Tangier disease, and xanthomas are found only in familial apoA-I deficiency[24, 26].

Care should be taken to exclude secondary hypo-HDL-cholesterolemia, such as in severe liver diseases, especially liver cirrhosis, and drug-induced hypo-HDL-cholesterolemia, most frequently due to combination of probucol and fibrates. It should be noted that probucol may continue to influence lipid profiles for several months after discontinuation, so HDL-C may be significantly reduced by switching from probucol to fibrates or permafibrate, a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα), in some cases.

5. Current Management of Tangier Disease

Based on the patients identified in Japan to date, there seem to be no distinct differences in clinical or genetic profiles with patients in other countries[8, 9]. No curative treatment, such as gene therapy for the *ABCA1* gene, has yet been established. Since extremely enhanced risk of atherosclerotic diseases is the major clinical problem, patients should be carefully monitored for presence of atherosclerotic lesions through regular testing including exercise electrocardiography, echocardiography and computed tomography coronary angiography[8]. The management of atherosclerotic risk factors, such as hypertension, smoking and diabetes mellitus, is crucial,[27]. Plasma LDL-C levels are generally low in patients with Tangier disease but if this is not the case, they should be reduced through administration of statins or other means. Impairment of the insulinogenic index should be estimated using a 75 g oral glucose tolerance test[17].

Conclusions and Future Perspectives

Gene therapy for *ABCA1* gene may have the greatest potential for Tangier disease. There is the possibility that restoration of ABCA1 expression in the liver would raise serum HDL-C levels but this might not be enough to recover cellular cholesterol efflux and suppress extra lipid accumulation in cells in atherogenic lesions such as macrophages, smooth muscle cells and endothelial cells. It may not be easy to develop a fundamental therapy for Tangier disease.

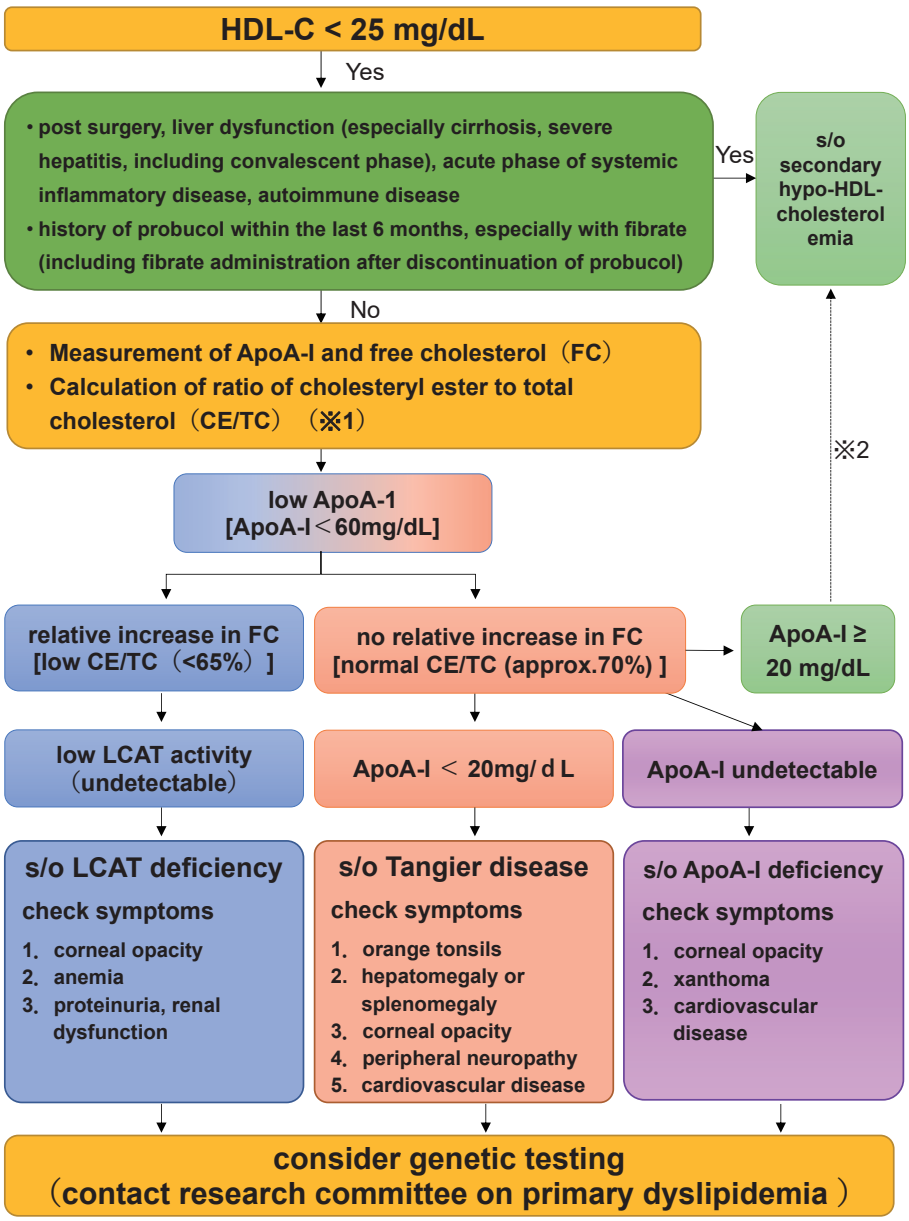

Fig. 5. Differential diagnosis flow chart for hypo-HDL-cholesterolemia

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Conflicts of Interest

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Review

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Current Diagnosis and Management of Primary Chylomicronemia

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Primary chylomicronemia (PCM) is a rare and intractable disease characterized by marked accumulation of chylomicrons in plasma. The levels of plasma triglycerides (TGs) typically range from 1,000 - 15,000 mg/dL or higher.

PCM is caused by defects in the lipoprotein lipase (LPL) pathway due to genetic mutations, autoantibodies, or unidentified causes. The monogenic type is typically inherited as an autosomal recessive trait with loss-of-function mutations in LPL pathway genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, and *APOA5*). Secondary/environmental factors (diabetes, alcohol intake, pregnancy, etc.) often exacerbate hypertriglyceridemia (HTG).

The signs, symptoms, and complications of chylomicronemia include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and acute pancreatitis with onset as early as in infancy. Acute pancreatitis can be fatal and recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive.

The main goal of treatment is to prevent acute pancreatitis by reducing plasma TG levels to at least less than 500-1,000 mg/dL. However, current TG-lowering medications are generally ineffective for PCM. The only other treatment options are modulation of secondary/environmental factors. Most patients need strict dietary fat restriction, which is often difficult to maintain and likely affects their quality of life.

Timely diagnosis is critical for the best prognosis with currently available management, but PCM is often misdiagnosed and undertreated. The aim of this review is firstly to summarize the pathogenesis, signs, symptoms, diagnosis, and management of PCM, and secondly to propose simple diagnostic criteria that can be readily translated into general clinical practice to improve the diagnostic rate of PCM. In fact, these criteria are currently used to define eligibility to receive social support from the Japanese government for PCM as a rare and intractable disease.

Nevertheless, further research to unravel the molecular pathogenesis and develop effective therapeutic modalities is warranted. Nationwide registry research on PCM is currently ongoing in Japan with the aim of better understanding the disease burden as well as the unmet needs of this life-threatening disease with poor therapeutic options.

Key words: **Chylomicronemia, Triglyceride, Pancreatitis, Diagnostic criteria, Treatment guide**

1. Definition of Chylomicronemia

Chylomicrons (CMs) are intestine-derived lipoproteins that transport dietary fat to peripheral tissues[1]. CMs are usually quickly cleared from plasma after an overnight fast. The hallmark of chylomicronemia is persistent elevation of CMs in the fasting state (>12h). Plasma triglyceride (TG) levels

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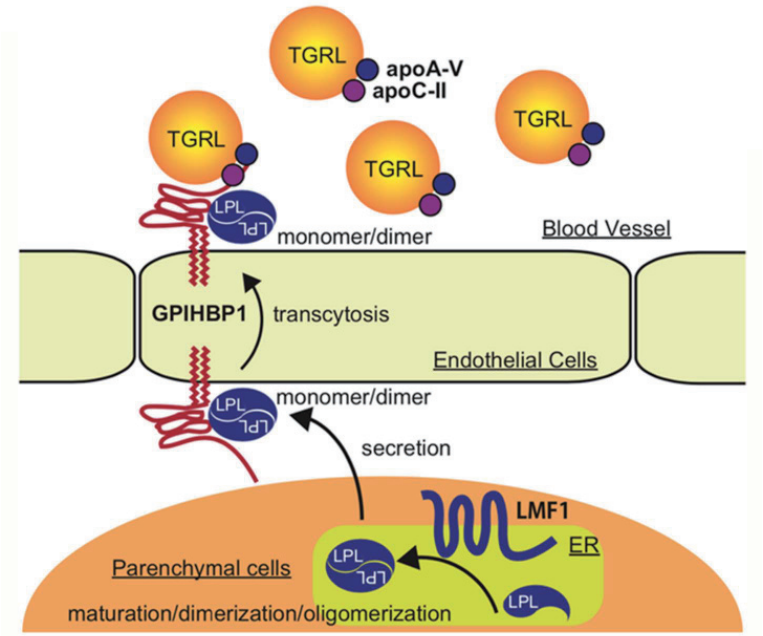

Fig. 1. Molecular basis of primary chylomicronemia

Lipoprotein lipase (LPL) hydrolyzes triglycerides (TGs) in TG-rich lipoproteins (TGRLs), such as very low-density lipoproteins (VLDLs) and chylomicrons (CMs) to liberate free fatty acids (FFAs), which are utilized by peripheral tissues (e.g., muscle, heart, and adipose tissues). Activity of LPL is regulated by a quaternary structure (monomer/dimer/oligomer) as well as by multiple LPL-pathway proteins[210-212]. LMF1 is required for the synthesis of LPL in parenchymal cells of these peripheral tissues. GPIHBP1 is a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues, transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. For the hydrolytic activity of LPL, two apolipoproteins, apoC-II and apoA-V, are required. ApoC-II is necessary for the enzymatic activity of LPL. ApoA-V primarily enhances the interaction between TGRL and LPL by forming TGRL-apoA-V-GPIHBP1-LPL complex via its dual binding affinity to TGRL and GPIHBP1. Defects in LPL pathway proteins (LPL, LMF1, GPIHBP1, apoC-II, apoA-V) due to genetic mutations or autoantibodies cause primary chylomicronemia (PCM). LPL activity can be measured after releasing LPL from the luminal surface into the circulation by i.v. injection with heparin.
Abbreviations: apoA-V, apolipoprotein A-V; apoC-II, apolipoprotein C-II; GPIHBP-1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1.

in chylomicronemia typically range from 1,000 to 15,000 mg/dL or higher[2]. As CMs start to accumulate in plasma when TG levels increase to more than 500 - 1,000 mg/dL[1], it is practical to screen and suspect chylomicronemia if plasma TGs >1,000 mg/dL[2, 3].

2. Metabolism of Chylomicrons

CMs are produced by the intestine after a meal and secreted into the circulation[1]. Their synthesis requires apoB-48 protein, which is transcribed from the edited mRNA of *APOB*, and microsomal triglyceride transfer protein (MTTP), which incorporates dietary TGs into CMs. More than 90% of lipids in CMs are TGs (derived from dietary fatty acids and TGs), which are hydrolyzed by lipoprotein lipase (LPL) on the endothelial cell surface of peripheral tissues (muscle, heart, adipose tissue, etc.) to liberate free fatty acids (FFAs). FFAs are used as an energy source in peripheral tissues, or stored as TGs in adipose tissues, or re-esterified and secreted as very low-density lipoprotein (VLDL)-TG by the liver. CMs are converted to CM remnants after TG hydrolysis by LPL and then cleared from plasma through endocytosis mainly by the liver.

3. Molecular Basis of Chylomicronemia

Plasma levels of CMs are affected by primary factors as well as secondary factors[2, 4, 5]. Primary factors consist of defects in the proteins that metabolize CMs, such as LPL and its related proteins (apolipoprotein(apo)C-II, apoA-V, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1), lipase maturation factor 1 (LMF1)) **(Fig. 1)**. Secondary factors include conditions that impair CM metabolism, such as poor control of diabetes, excessive alcohol intake, and pregnancy. In primary chylomicronemia (PCM), chylomicronemia usually persists even after

management of secondary factors. PCM is caused by defects in LPL pathway genes (*LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *LMF1*) due to genetic mutations or presence of autoantibodies against LPL pathway proteins (GPIHBP1, LPL, and apoC-II)[6-9].

4. Complications of Chylomicronemia

Chylomicronemia is a risk factor for acute pancreatitis[10]. Although the underlying mechanisms are not fully understood, the widely accepted hypothesis is that an excess of FFAs derived from lipolysis of chylomicron-TG by pancreatic lipase damages pancreatic acinar cells or endothelial cells of pancreatic capillaries, leading to activation of inflammatory processes[11]. In addition, high levels of plasma CM may increase the viscosity of pancreatic microcirculation and impair pancreatic blood flow, further exacerbating inflammation. Genetic predisposition may also contribute to the pathogenesis[12].

Based on this hypothesis, it is generally believed that chylomicronemia per se induces pancreatitis and, therefore, reducing plasma CM levels should lower the risk of pancreatitis[10]. The widely accepted treatment goal is to reduce plasma TG levels to at least less than 1,000 mg/dL[2, 4, 5, 12-14].

5. Primary Factors of Chylomicronemia

Five genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, *APOA5*) have been identified as the causative genes of monogenic chylomicronemia **(Fig. 1)**[4, 5]. All of them are required for the normal function of LPL. Homozygous, compound heterozygous, or double heterozygous loss-of-function mutations of these LPL pathway genes usually cause monogenic chylomicronemia with an autosomal recessive mode of inheritance[15]. Heterozygous mutations or pathological variants in HTG-susceptible genes, including those for hepatic lipase (HL) and apolipoprotein E, may also predispose to chylomicronemia[3, 5, 16-18].

Loss-of-function mutations in LPL-pathway genes have been identified in only less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. In some cases, autoantibodies against LPL pathway proteins can cause PCM. Additional genetic factors or unknown causes may also underlie PCM.

•***LPL*** (LPL deficiency, OMIM: 238600): *LPL* is the most common causative gene of monogenic chylomicronemia. More than 220 pathogenic variants in *LPL* have been described (missense, nonsense, splicing variants, insertion/deletion of nucleotide(s), deletion/duplication/insertion/rearrangement of exon(s))[2, 4, 15, 20-22]. A list of mutations in *LPL* has been comprehensively summarized in exon-intron diagrams by Rabacchi C *et al.* and Rodrigues R *et al.*[20, 22]. LPL activity is usually tested in post-heparin plasma taken 10-15 min after iv. heparin injection (10-60 IU/kg body weight)[4, 23].

•***LMF1*** (LMF1 deficiency, OMIM: 246650): *LMF1* encodes LMF1, a transmembrane chaperone protein of parenchymal cells (muscle, adipose tissues, etc.). LMF1 is localized to the endoplasmic reticulum and is required for proper synthesis and secretion of LPL and HL. In addition to nonsense mutations that were originally reported, several other mutations, including missense loss-of-function mutations, have been identified in *LMF1*[24-29].

•***GPIHBP1*** (GPIHBP1 deficiency, OMIM: 615947): *GPIHBP1* encodes GPIHBP1, a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis[30, 31]. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues (skeletal muscles, heart, adipose tissues, etc.), transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. So far, at least 23 pathogenic mutations in *GPIHBP1* have been reported in severe HTG patients, including those causing total GPIHBP1 deficiency[21, 32-36]. Mutations in *GPIHBP1* are comprehensively summarized in the exon-intron diagram by Rabacchi *et al.*[35]. GPIHBP1 deficiency may be differentiated from LPL deficiency in that LPL activity or protein in post-heparin plasma is not totally lacking in GPIHBP1 deficiency[37].

•***APOC2*** (apoC-II deficiency, OMIM: 207750): *APOC2* encodes apoC-II, a co-factor required for LPL activity. *APOC2* is the second most common causative gene of monogenic chylomicronemia. At least 24 mutations have been reported worldwide[2, 4, 5, 38-41], and are comprehensively summarized in the exon-intron diagram by Wolska *et al.*[41]. In some cases, plasma levels of apoC-II have been severely decreased but are detected with apparently normal electrophoretic patterns (so-called hypoapoC-II)[42-45]. In apoC-II deficiency, symptoms often develop at an older age (13-60 years) than in LPL deficiency[1, 4]. As apoC-II deficient patients tend to be subjected to strict fat restriction at an older age, they may have poorer dietary adherence and more frequent episodes of acute pancreatitis in adulthood than LPL deficient patients, often accompanied by high VLDL levels[2].

•***APOA5*** (apoA-V deficiency, OMIM: 144650): *APOA5* encodes apoA-V, a co-factor of LPL that enhances interaction between LPL and TG-rich lipoproteins (TGRLs)[46, 47]. ApoA-V has dual binding

affinity for both TGRL and GPIHBP1, thereby forming the TGRL-apoA-V-GPIHBP1-LPL complex to facilitate lipolysis[31, 48, 49]. So far, at least 21 mutations in *APOA5* have been reported, which are comprehensively summarized in exon-intron diagrams by Albers *et al.*[50-53]. In most cases, severe HTG develops later in life due to the combinatorial effects of primary (genetic) and secondary factors (aging, diabetes, pregnancy, HIV therapy, etc.)[53]. The underlying molecular mechanisms of apoA-V deficient HTG in terms of gene-environmental interactions has only begun to be elucidated[54, 55].

•**Autoantibodies against LPL pathway proteins**: Autoimmune chylomicronemia due to autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II) has been reported[6-9]. Autoimmune chylomicronemia may be complicated by other autoimmune diseases and be ameliorated by steroid or immune-suppressive therapy.

6. Secondary Factors of Chylomicronemia

The following factors have been reported to induce chylomicronemia[3-5, 13, 35, 56-61]. Among them, excess alcohol consumption and diabetes mellitus are the two most common factors associated with severe HTG[18, 62, 63].

Pregnancy is another important factor that can induce chylomicronemia. Hormonal changes during pregnancy result in hyperlipidemia even in healthy subjects, as a physiological response to ensure nutrient supply to the fetus[64-66]. Plasma TG levels progressively increase in healthy subjects by 2- to 4-fold[67], and markedly increase in subjects with PCM[68-74]. Pregnancy increases TGRL (VLDL) production and decreases TGRL clearance[75-78].

•**Lifestyle-related factors**: Dietary factors such as excessive alcohol intake, high-fat diet, high-carbohydrate diet rich in fructose and other simple sugars. Less exercise and excessive intake of total calories, particularly in subjects who are overweight, have metabolic syndrome, or diabetes mellitus.

•**Pathophysiological conditions**: Pregnancy, obesity, metabolic syndrome, anorexia nervosa, glucose intolerance, diabetes mellitus with insulin resistance or insulin deficiency, endocrine diseases such as hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, glycogen storage diseases, amyloidosis, renal disease (nephrotic syndrome, proteinuria, uremia, glomerulonephritis, etc.), liver disease, autoimmune disorders, lipodystrophies, Weber-Christian disease, multiple myeloma, paraproteinemia, and lymphoproliferative disorders, etc.

•**Medications**: Glucocorticoids, oral estrogens (contraceptives, postmenopausal replacement therapies), clomiphene, tamoxifen, exogenous testosterone; retinoids such as isotretinoin, bexarotene; immunosuppressants and anticancer drugs such as sirolimus, cyclosporine A, tacrolimus, capecitabine, cyclophosphamide, asparaginase; antihypertensives such as thiazides, loop diuretics, non-selective β -blockers; bile acid-sequestrants; antiviral drugs such as entecavir, ritonavir and other antiretroviral protease inhibitors; second-generation antipsychotics (atypical antipsychotics), such as dozapine, clozapine, olanzapine, risperidone, quetiapine; antidepressants such as mirtazapine, venlafaxine; selective serotonin reuptake inhibitors (sertraline, etc.); anticonvulsants, such as valproate; anesthetic drugs, such as propofol.

7. Classification of Chylomicronemia

Chylomicronemia was formerly classified as type 1 and 5 hyperlipoproteinemia (HLP) in the Fredrickson classification (WHO classification)[5, 79], where increased plasma lipoproteins are CM for type 1 and CM+VLDL for type 5 HLP. However, differentiation of type 1 and type 5 HLP is often difficult because of considerable overlaps in phenotypes and genetic backgrounds[3, 5, 17].

Differentiation of monogenic from polygenic chylomicronemia is also difficult[80]. Even when monogenic chylomicronemia is suspected, causative mutations have been identified in less than 30-40%[19, 20].

For practical reasons, we prefer to use the term PCM, which is defined as a condition with persistent elevation of TG >1,000 mg/dL even after management of secondary factors. The term familial chylomicronemia syndrome (FCS) is not used here, as monogenic chylomicronemia is typically autosomal recessive, and most cases are sporadic, without a family history. The term "familial" may confuse both patients and doctors, and may lead to underdiagnosis[3, 81].

8. Prevalence of Chylomicronemia

The prevalence of severe HTG (TG >10 mmol/L (885 mg/dL)) is estimated at ~1 in 600 in North America[5]. In a population of 440,240 subjects in the US, severe HTG (886-2,000 mg/dL) and very severe HTG (>2,000 mg/dL) were observed in 0.15% and 0.014%, respectively[36].

The monogenic type of chylomicronemia is very rare and its frequency is estimated at 1 to 2 per million in the general population[1, 4, 5]. The most common causative gene is *LPL*, followed by other LPL pathway

genes (*APOC2*, *GPIHBP1*, *APOA5*, and *LMF1*)[5, 15, 53].

Severe HTG is more often due to polygenic causes[3, 82]. Dron *et al.* reported that the etiology of severe HTG (TG >10 mmol/L (885 mg/dL)) is monogenic in 1.1%, polygenic in 46%, and genetically unidentified in the rest of cases[83]. Another study identified monogenic causes in 0.96% of patients with very severe HTG (TG >20 mmol/L (1770 mg/dL)) recorded at least once during regular medical care[22].

9. Prevalence of HTG-Induced Acute Pancreatitis

Regardless of the underlying etiology of HTG, the risk of acute pancreatitis increases as TG levels increase, particularly when they exceed 1,000 - 2,000 mg/dL[84].

HTG is the third leading cause (5-38%) of acute pancreatitis after alcohol and gallstones[1, 12, 85-87]. HTG is the leading cause (25~50%) of acute pancreatitis during pregnancy[12, 74, 88], which is most often seen in the third trimester (19%, 26%, 53% in the 1st, 2nd, and 3rd trimester, and 2% in postpartum period)[89]. The frequency of HTG-induced acute pancreatitis in pregnancy is estimated as 1 in 1000-12,000 pregnancies[14, 73, 74].

Risk of acute pancreatitis increases by ~4% for every 100 mg/dL increase in plasma TG[56, 84, 87, 90, 91]. According to the 2010 Endocrine Society guidelines, HTG can be classified into mild HTG (150-199 mg/dL), moderate HTG (200-999 mg/dL), severe HTG (sHTG, 1000-1999 mg/dL), or very severe HTG (vsHTG, >2000 mg/dL). The prevalence of pancreatitis in sHTG and vsHTG is about 10% and 20%, respectively[5, 13, 14, 87, 92].

Clinically, it remains difficult to predict if a HTG patient will develop acute pancreatitis or not. Some patients do not develop acute pancreatitis even at TG levels higher than 30,000 mg/dL[1, 2]. Conversely, patients can develop acute pancreatitis at TG levels of 5-10 mmol/L (442-885 mg/dL)[93]. The underlying etiology of monogenic chylomicronemia seems to confer a potent risk of acute pancreatitis[53, 94-96]. Compared to normolipidemic individuals, the risk of acute pancreatitis increased by 16-fold, 56-fold, and 361-fold in HTG (5-9 mmol/L (442-796 mg/dL)) without LPL deficiency, HTG (>9 mmol/L (796 mg/dL)) without LPL deficiency, and HTG (>9 mmol/L (796 mg/dL)) with LPL deficiency (genetically-confirmed), respectively[94]. Greater cumulative exposure of HTG to the pancreas due to genetic causes may impose higher pancreatitis risk[53, 94-97](See **sections 12 and 16(B)** for other suggested risk factors of acute pancreatitis among HTG subjects).

10. Signs, Symptoms, and Complications of Chylomicronemia

Depending on the severity of the mutation, signs, symptoms, and complications of chylomicronemia may manifest as early as in infancy, in childhood, or later in life[4, 95].

•**Abdominal pain, fat intolerance, failure to thrive**: Abdominal pain affects ~60% of monogenic chylomicronemia patients and can be mild to incapacitating[4, 95, 96]. Recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive. Body weight may be lower because of restricted food intake.

•**Pancreatitis**: Acute pancreatitis can be severe, recurrent, and life-threatening[1, 4, 95]. Acute pancreatitis may lead to chronic pancreatitis and diabetes. Irrespective of its etiology, severe HTG should be carefully monitored for the possible complications of pancreatitis. Compared to polygenic chylomicronemia, monogenic chylomicronemia is associated with a higher risk of acute pancreatitis and tends to manifest severe phenotypes[86, 94, 95]. According to a survey of lipidologists, ~67% of monogenic patients were hospitalized for acute pancreatitis vs. ~14% of polygenic patients[95, 96]. It should be noted that high levels of plasma TG may interfere with assays of plasma pancreatic enzymes (lipase, amylase), resulting in falsely low levels[2, 98-100]. HTG-induced acute pancreatitis should not be misdiagnosed due to apparently low serum levels of pancreatic enzymes.

•**Lipemic plasma**: Lipemic plasma (milky-looking plasma) is characterized by a creamy CM layer floating above the bottom layer, after leaving serum standing overnight in a refrigerator (the "refrigerator" test)[1]. In type 5 HLP, the bottom layer contains VLDLs and has a lactescent appearance. In type 1 HLP, the bottom layer is clear without apparent VLDL accumulation. Type 1 HLP is more frequently observed than type 5 in monogenic chylomicronemia[19]. (See reference by Yuan G *et al.* for a photograph of lipemic plasma[56].)

•**Eruptive xanthomas**: Eruptive xanthomas affect 10-50% of the monogenic type[95, 96]. They appear when plasma TG levels increase to more than 2,000 mg/dL as yellow papules on the skin of the trunk, buttocks, and extremities (extensor surfaces of the arms and knees) as a result of TG uptake by macrophages (see references by Nayak KR *et al.* and Yuan G *et al.* for photographs)[2, 4, 56, 101]. Along with reduction in plasma TG levels, they gradually

Table 1. Diagnostic criteria for primary chylomicronemia

A. Entry Criterion:
A1 and A2 with exclusion of differential diagnosis in E
A1) Plasma TG level ≧1,000 mg/dL (after fasting for 12 hours or longer)
A2) Presence of chylomicrons in serum (from appearance of supernatant cream layer after allowing serum to stand for 24 hours or longer at 4℃, ultracentrifugation, or electrophoresis (agarose gel, polyacrylamide gel, or HPLC))
B. Clinical manifestations (major (B1-B4) and minor (B5, B6))
B1) Recurrent episodes of abdominal pain and/or acute pancreatitis
B2) Eruptive xanthomas
B3) Lipemia retinalis
B4) Hepatomegaly and/or splenomegaly
B5) Dyspnea
B6) Neurological symptoms (cognitive impairment, memory impairment, depression, etc.)
C. Laboratory findings
C1) LPL activity and/or protein in post heparin plasma, adipose tissue, or macrophages is absent or markedly decreased (＜10% of normal subjects)
C2) Plasma apoC-II is absent or markedly decreased (＜10% of normal subjects)
C3) Plasma apoA-V is absent or markedly decreased (＜10% of normal subjects)
C4) Autoantibodies against LPL, heparin, apoC-II, or GPIHBP1.
D. Genetic test
Identification of causative mutation(s) in *LPL*, *APOC2*, *GPIHBP1*, *LMF1*, or *APOA5*
E. Differential diagnosis
Type 3 hyperlipidemia, familial combined hyperlipidemia (FCHL), and secondary hyperlipidemia due to following: excess alcohol intake, nephrotic syndrome, anorexia nervosa, pregnancy, diabetes mellitus, lipodystrophies, Weber-Christian disease, hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, multiple myeloma, systemic lupus erythematosis, malignant lymphoma, sarcoidosis, etc.; medications such as estrogens, steroids, diuretics, β-blockers, antipsychotics including selective serotonin reuptake inhibitors (SSRIs), retinoids such as isotretinoin, antiretroviral protease inhibitors, immunosuppressants, etc.
<Diagnosis>
Definite: Entry criterion (A) associated with at least one item from C or D
Probable: Entry criterion (A) associated with at least one item from B1-B4
Possible: Entry criterion (A) with or without item(s) from B5-B6

disappear over several weeks to a few months[2].

•**Lipemia retinalis**: Lipemia retinalis affects ~40% of the monogenic type[95, 96] and is characterized by retinal blood vessels with a milky appearance (a pale pink color) on fundoscopy (see references by Kumar J *et al.* and Yuan G *et al.* for photographs)[56, 102]. Vision is not impaired. It is usually visible when plasma TG levels increase to more than 4,000 mg/dL[2].

•**Hepatomegaly and splenomegaly**: Hepatomegaly and splenomegaly affect 10-50% of the monogenic type[95, 96] as a result of TG uptake by macrophages and other cell types in these tissues[1, 4]. Both conditions are reversible and rapidly improve within a week, along with reduction in plasma TG levels[2].

•**Other symptoms (fatigue, dyspnea, and neurological symptoms)**: Other clinical symptoms include fatigue, dyspnea, and neurological symptoms[1] such as memory impairment (transient memory loss), cognitive impairment, mild dementia, cloudy thought, brain fog, neurosis, irritability, anxiety, and depression[4, 95, 103-107]. Neurological symptoms affect ~8% of the monogenic type[95]. Although little is known about the underlying mechanisms of these symptoms, large surveillance studies among chylomicronemia patients have shown that they dominantly and adversely affect patients' quality of life and increase the burden of the disease[104-107].

11. Diagnosis of Chylomicronemia

Undertreatment and underdiagnosis of chylomicronemia are one of the major risks for acute pancreatitis[84, 87]. In order to achieve early diagnosis and treatment for chylomicronemia, simple diagnostic criteria that can be readily translated into general practice are required.

Based on TG levels that lead to suspicion of chylomicronemia (TG ＞1,000 mg/dL), clinical manifestations and the available data on diagnostic tests, here we propose diagnostic criteria for PCM

(Table 1).

It should be noted that PCM is genetically confirmed in less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. Therefore, we have set three categories (definite, probable, and possible) so that PCM patients will not be missed even without a genetic diagnosis.

To achieve timely diagnosis and improve the diagnostic rate of PCM, screening of plasma TG levels in the following settings will be helpful. Clinicians across multiple disciplines, such as primary care physicians, gastroenterologists, gynecologists, and other doctors who have occasionally encountered severe HTG patients, should consult lipidologists concerning further diagnostic tests for chylomicronemia.

•**Health checkup or opportunistic blood test**: All patients who have TG levels of more than 1,000 mg/dL in universal lipid screening[108] or a routine clinic visit should be suspected of chylomicronemia[96, 109].

•**Acute abdomen (including pancreatitis)**: Those who have acute abdomen or are suspected of pancreatitis should have their plasma TG levels measured[96]. Plasma TG should be measured as early as possible after the onset of abdominal pain, as TG levels rapidly decrease within 24-48 hours of onset[110].

•**Pregnancy**: Many cases of monogenic chylomicronemia have been discovered in the third trimester of pregnancy[111-118]. HTG-induced acute pancreatitis in pregnancy can be lethal to both mother and fetus[119]. Gestational HTG may also increase the risk of hyperviscosity syndrome[120], pre-eclampsia[121], fetal macrosomia, and fetal pancreatitis-related complications (in-utero fetal death, preterm labor, and prematurity)[66]. Pregnant women who are suspected of pancreatitis should be tested for plasma TG. Pregnant women at high-risk for HTG-induced acute pancreatitis may benefit from plasma TG screening and monitoring on a weekly basis[122]. Such patients include: those with HTG or pancreatitis prior to or during pregnancy; high predisposition for HTG-induced acute pancreatitis due to diabetes mellitus, obesity, hypertension, hypothyroidism, renal disease, liver disease, family history of HTG, alcohol consumption, and medications that cause HTG; HTG with abdominal pain or other symptoms typical to chylomicronemia[84, 87, 122](See **sections 12 and 16(B)** for suggested risk factors of acute pancreatitis among HTG patients).

•**Family members of chylomicronemia patients**: Evaluation of plasma TG levels in family members is beneficial for early diagnosis and management of possible complications[96].

12. Features for Suspecting Monogenic Chylomicronemia

Clinical features that lead to suspicion of monogenic chylomicronemia have been suggested by previous studies and in expert opinions, but further validation in various cohorts is required[2-5, 15, 18, 53, 80, 96, 109, 123, 124]. These features may be useful not only for indicating the likelihood of monogenic chylomicronemia but also for predicting a higher risk of pancreatitis[53, 86, 94-96]:

- Intractable, severe HTG (TG >10 mmol/L or 1,000 mg/dL)
- Fasting severe HTG on multiple occasions
- Very severe HTG
- No history of normal to mild plasma TG levels (<200 mg/dL)
- Severe HTG with no secondary factors (except for pregnancy and oral estrogens)
- Severe HTG with pregnancy
- No response (TG decrease <20%) to hypolipidemic agents
- Severe HTG with type 1 rather than type 5 HLP
- History of recurrent abdominal pain or acute pancreatitis
- Younger age at onset
- Lower body mass index (BMI)
- Eruptive xanthomas
- Lipemia retinalis
- Hepatosplenomegaly
- Consanguinity

On the other hand, the polygenic type of chylomicronemia is more frequently associated with secondary/environmental factors, such as high-alcohol intake, diabetes mellitus, hypertension, and obesity[2, 18, 96].

13. Treatment of Chylomicronemia

The treatment goal of chylomicronemia is to lower plasma TG levels enough to reduce the risk of pancreatitis. Data from large healthcare databases suggest that sustained HTG (>500 mg/dL) increases the risk of pancreatitis (hazard ratio 1.79 [CI 95%: 1.10-1.28])[125] and lowering TG from >500 mg/dL to less than 200 mg/dL can reduce the incidence of acute pancreatitis from 1.1 to 0.4 per 100 person-year (adjusted OR 0.45 [CI 95%: 0.34-0.60])[126]. Due to the rareness of the disease, there have been no randomized control trials (RCTs) to determine treatment TG targets for prevention of pancreatitis. Mainly based on clinical experience, the opinion of

experts is to recommend maintaining plasma TG levels below 500-1,000 mg/dL to prevent pancreatitis[2, 4, 5, 12-14].

A) Control of Secondary Factors

Comorbid conditions that aggravate chylomicronemia should be thoroughly evaluated in order to rule them out. If any are present, they should be managed adequately. Bodyweight reduction, reduced calorie intake, and increased energy expenditure through regular physical exercise may help reduce plasma TG levels, particularly in overweight subjects. Regular physical exercise may also help in the non-obese[93, 127]. Bodyweight should be carefully controlled as rebound weight gain might elicit pancreatitis[13].

B) Dietary Therapy

Strict dietary control is currently the primary treatment modality for chylomicronemia, although it is often insufficient and difficult to maintain in the long term[128, 129]. Children and adolescents should be carefully monitored to ensure proper growth and development. Adjustment of social life might be a challenge throughout life[104-107].

•**Fat restriction**: The mainstay of dietary treatment is a low-fat diet. Restriction of total dietary fat to <15-20 g per day (<10-15 % of total energy intake) is usually required to reduce plasma CMs and prevent pancreatitis[128, 129]. Under fat restriction, adequate intake of essential fatty acids (EFA; 2-4% of daily calories) and fat-soluble vitamins (A, D, E, and K) should be ensured to avoid deficiency. Signs and symptoms typical of EFA deficiency include: inadequate growth in pediatric patients, dry or dull hair, dry or scaly skin, skin lesions, particularly raised bumps on the skin, soft and brittle nails, and impaired wound healing[129]. Food sources of EFAs include soybeans, tofu, flaxseeds, walnuts, and chia seeds for alpha-linolenic acid (ALA) and whole grains for linoleic acid (LA).

•**Medium-chain triglycerides (MCTs)**: In a very-low-fat diet, MCTs containing fatty acids of ≦ 10 carbon atoms in length may be used to provide sufficient calories in meals or infant formula[4, 36, 128, 129]. MCTs are absorbed directly into the circulation via the CM-independent pathway. MCTs may help reduce plasma TG levels[130]. In order to avoid possible adverse effects (diarrhea, abdominal pain, etc.), MCTs should be introduced slowly. The safety of long-term MCTs is not established and patients should be carefully monitored for possible complications such as hepatotoxicity. MCTs should not be confused with coconut oil, which contains lauric acid (C12) and other long-chain fatty acids[129].

•**Carbohydrate restriction**: Restriction of carbohydrates, particularly fructose and other simple and refined carbohydrates, is advisable for patients with increased VLDL levels such as those with diabetes mellitus, metabolic syndrome, and obesity. As both CMs and VLDLs are substrates for LPL, reduced production of VLDLs due to carbohydrate restriction enhances the catabolism of CMs by LPL[131]. In cases where carbohydrate intake needs to be adequate, such as in pregnancy-associated HTG, carbohydrate iv may be a better therapeutic choice, as oral carbohydrate intake may produce a greater rise in plasma TG than carbohydrate iv[122, 132].

•**Alcohol restriction**: Alcohol intake should be restricted[4, 128, 129].

C) Lipid-Lowering Medications

Current lipid-lowering medications (fibrates, n-3 polyunsaturated fatty acids (PUFAs), niacin, etc.) generally have little to no TG-lowering effects in patients with PCM, as they lower plasma TGs mainly by enhancing the LPL pathway and reducing VLDL levels. Treatment with n-3 PUFA or fish oil may be useful for lowering TG and preventing pancreatitis as suggested in patients with *APOA5* mutations[21]. However, the effect of n-3 PUFAs needs to be monitored carefully, as their effectiveness has only been suggested by small studies without controls[3, 5]. Fish oil supplements may increase the production of chylomicrons and are contraindicated according to an expert opinion[4]. In patients with autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II), immune-suppressive agents may ameliorate HTG as well as the comorbid autoimmune diseases[7].

14. Treatment of HTG-Induced Acute Pancreatitis

The clinical course of HTG-induced acute pancreatitis may be more severe than acute pancreatitis due to other causes in terms of complications and mortality rates[12, 14, 133, 134], but more controlled studies are required to produce firm evidence. Meta analysis of acute pancreatitis is difficult due to the heterogeneity of scoring systems for its severity[86].

A) Standard Care for Acute Pancreatitis

Treatment of HTG-induced acute pancreatitis is based on standard care, including cessation of oral food intake, admission to hospital, intravenous hydration, hypocaloric parenteral nutrition avoiding excess calories and glucose infusions, pain management, prophylactic antibiotics, and protease inhibitors[12, 130, 135]. Any precipitating factors should be treated appropriately (e.g., insulin treatment for

diabetes). Patients should be carefully monitored for development of pancreatic complications (necrosis, abscesses, etc.).

B) Specific Therapy for HTG-Induced Acute Pancreatitis

When patients can tolerate, oral TG-lowering medications (fibrates, n-3 PUFAs, niacin, etc.) may be administered[12, 130, 135]. MCTs may help reduce plasma TG levels as well as the risk of pancreatitis[130]. With a few exceptions, current TG-lowering medications are not based on the etiology of chylomicronemia. In apoC-II deficiency, infusion of normal human plasma containing apoC-II can greatly reduce plasma TG levels, and plasmapheresis has been suggested as a treatment of choice for pancreatitis due to apoC-II deficiency[4, 58].

C) Management of Chronic Pancreatitis

As acute pancreatitis can lead to chronic complications, patients with a history of it are better monitored for complications such as chronic pancreatitis, pancreatic pseudocysts, pancreatic insufficiency, steatorrhea, and insulin-dependent diabetes mellitus[4, 86]. Although chronic complications are not invariably associated with HTG-induced acute pancreatitis[136], they are not uncommon despite modern medical care[95].

D) Other Therapeutic Options for HTG-Induced Acute Pancreatitis

•**Insulin (should be individualized)**: Insulin therapy is advised in patients with diabetes mellitus. Insulin stimulates LPL activity, thereby reducing plasma TG levels. Administration of insulin or insulin plus glucose may be considered in non-diabetic patients in the case of severe HTG-induced acute pancreatitis[14, 137-139]. Detailed protocols for insulin/glucose administration have been summarized elsewhere[137, 139].

•**Heparin (not usually recommended)**: Heparin infusion has been used as a therapeutic option but is not usually recommended as a monotherapy in treatment guides by experts[12, 14]. Heparin transiently increases plasma LPL levels by releasing LPL from the endothelial cell surface, which temporarily reduces plasma TG levels. However, heparin can also deplete LPL, causing a rebound increase in plasma TGs[140]. Heparin may increase the risk of pancreatic hemorrhage when pancreatic necrosis is present[66].

•**Heparin plus insulin (should be individualized)**: Combination of heparin and insulin may be a therapeutic option for severe HTG-induced acute pancreatitis[14]. Although heparin infusion alone is usually not advised, a recent study has suggested that combination of heparin and insulin may be effective[14]. Evaluation in RCTs is awaited.

•**Apheresis for HTG-induced acute pancreatitis (should be individualized)**: In the acute setting, apheresis (lipoprotein apheresis (LA), plasmapheresis, or plasma exchange (PEX), etc.)[141, 142] can rapidly reduce plasma TG levels (40-80%) by directly removing TGRLs, as reported in case reports, case series, and multi-center studies[12, 14, 36, 57]. However, it is not proven whether rapid TG reduction by apheresis leads to better clinical outcomes than other therapeutic modalities in terms of pancreatic complications and mortality[59]. Plasmapheresis is costly, has only a transient TG- lowering effect (usually for a day), and may have adverse reactions (e.g., allergic reactions, anaphylactic shock, infusion-related infections, thromboses, etc.)[14]. A recent systematic review and case-control studies indicated that while plasmapheresis decreased plasma TG, it did not conclusively affect the morbidity or mortality of acute pancreatitis[14, 86]. A recent RCT, the first one in HTG-induced acute pancreatitis, has demonstrated that although plasma apheresis lowers plasma TG more efficiently than insulin plus heparin, it is costly and does not lead to better clinical outcomes[143]. In the guideline of the American Society for Apheresis (ASFA), plasmapheresis is a category III indication with Grade 2C recommendation ("optimum role of apheresis therapy is not established. Decision making should be individualized"; "Weak recommendation, low-quality or very low-quality evidence due to observational studies or case series")[144], and generally not recommended by experts in treatment guides for chylomicronemia[4, 5]. Plasmapheresis may be a therapeutic option for: 1) severe HTG-induced acute pancreatitis with persistent TG elevation past the first 48-72h with no other therapeutic choice[57, 59, 86, 120]; 2) HTG-induced acute pancreatitis in pregnancy or postpartum with no other therapeutic choice[14, 36, 74, 120, 145-149]; or 3) severe HTG-induced acute pancreatitis with high levels of serum lipase, hypocalcemia, lactic acidosis, worsening inflammation or organ dysfunction[149, 150]. However, such advice is experience-based, not evidence-based.

•**Prophylactic apheresis to prevent HTG-induced acute pancreatitis (should be individualized)**: Prophylactic apheresis may be a therapeutic choice for preventing severe recurrent HTG-induced acute pancreatitis but evidence for it is limited to several case reports of HTG-induced acute pancreatitis[12, 14, 57, 151-154] and gestational HTG-induced acute pancreatitis[155, 156].

15. Treatment of HTG and HTG-induced Acute Pancreatitis in Pregnancy

There are currently no formal guidelines for gestational HTG and HTG-induced acute pancreatitis due to the rarity of these conditions and insufficient evidence. The treatment approach for gestational HTG and HTG-induced acute pancreatitis is well summarized by Wong *et al.* [66].

•**Dietary therapy (restriction of dietary fat, MCTs, n-3 PUFA)**: There have been reports of successful management of HTG and prevention of HTG-induced acute pancreatitis during pregnancy through early intervention with a low-fat or very-low fat diet, MCTs, and n-3 fatty acids[4, 66, 113, 122, 149, 157-162]. For pregnant women at high-risk of pregnancy-associated pancreatitis, extreme fat restriction to <2 g/day may be required during the 2nd and 3rd trimesters for successful delivery[1, 4, 122, 159]. Topical application of sunflower oil or corn oil in pregnancy with an extra-low-fat diet may help prevent EFA deficiency[122, 129, 159]. In pregnancy-induced HTG, carbohydrate may need to be restricted, but an adequate amount should be taken. Carbohydrate iv may be a better therapeutic choice during carbohydrate restriction, as carbohydrate per os may produce a greater rise in plasma TG than carbohydrate iv[122, 132]. The risk of MCTs to the fetus is thought to be low[66]. The safety of maternal n-3 fatty acid supplementation (DHA 2.2 g and EPA 1.1 g/day) for the mother and the fetus has been confirmed through a RCT[66].

•**TG-lowering medications (some are contraindicated in Japan)**: There have been several reports on the use of niacin, or fibrates (gemfibrozil and fenofibrate) for pregnancy-associated HTG [66,120,122,159,163-166]. However, the safety of niacin or fibrate use during pregnancy has not been established, and the use of fibrates during pregnancy is contraindicated in Japan.

•**Admission to hospital**: For gestational HTG, admission to hospital may be advised in the following cases: suspected pancreatitis, persistent abdominal pain, steep increase in plasma TG in the 3rd trimester, or TG >40 mmol/L (3540 mg/dL)[66, 122, 159]. Gestational acute pancreatitis is managed through standard care, which has been extensively reviewed by Papadakis EP *et al.*[73].

•**Other therapeutic options**: When uncontrollable, further management may include: insulin, insulin pus glucose, insulin plus heparin, or plasmapheresis[36, 66, 119, 120, 137-139, 149, 156, 161]. In a treatment guide for gestational HTG, the use of insulin is recommended only for hyperglycemic pregnant women, and the use of heparin is not recommended due to the paucity of clinical evidence [66].

16. Unanswered Questions

A) Molecular Basis and New Therapeutic Modalities

Unraveling the molecular basis of chylomicronemia may lead to the development of new therapeutic modalities[167].

Emerging therapeutic targets for chylomicronemia include: a microsomal triglyceride transfer protein (MTTP) inhibitor (lomitapide)[168-170]; an *APOB* antisense oligonucleotide (ASO) inhibitor (mipomersen)[171-173]; *APOC3* ASO inhibitors, e.g., volanesorsen[174], which has been approved by the EMA for genetically confirmed chylomicronemia at high-risk for pancreatitis[93]; diacylglycerol O-acyltransferase 1 (DGAT1) inhibitors (AZD7687, LCQ908 (Pradigastat))[175-177]; angiopoietin-like protein 3 (ANGPTL3) inhibitors, e.g., *ANGPTL3* ASOs (IONIS-ANGPTL3-LRx)[178] and ANGPTL3 antibody (evinacumab)[179-182].

For these new therapies, potential adverse effects need to be carefully evaluated, including fatty liver associated diseases for lomitapide and mipomersen[168-170, 172] as a consequence of their inhibition of VLDL secretion; thrombocytopenia for volanesorsen[174]; gastrointestinal adverse effects (diarrhea, nausea, etc.) for DGAT inhibitors[175-177], consistent with the fact that homozygous loss-of-function mutations of DGAT1 cause a congenital diarrheal disorder (OMIM: 615863)[183].

Other agents under development include CAT-2003, a niacin-eicosapentaenoic acid conjugate that blocks sterol regulatory element-binding protein (SREBP). Inhibition of SREBP-1c has ameliorated environment-induced severe HTG in mouse models of hyperlipidemia, including apoA-V deficient mice, by blocking secretion of large-sized VLDL particles[54, 55].

Orlistat, an inhibitor of intestinal lipase, may help reduce TG levels in PCM[21, 184, 185] but may have adverse effects such as oily stools and fat-soluble vitamin insufficiency[128].

Treatment that targets a specific genetic cause of PCM is not available. A gene therapy for LPL (alipogene tiparvovec) was approved by the EMA in 2012, but is costly and has been withdrawn from the market[94, 186].

B) Risk and Management of CM-Related Complications

Not all patients with severe HTG manifest pancreatitis. Suggested risk factors of acute pancreatitis among HTG patients include underlying genetic

etiology of monogenic type, underdiagnosis and undertreatment, younger age, higher baseline TG levels, prior history of acute pancreatitis, male, alcohol use, obesity, diabetes, hypertension, renal disease, liver disease, and hypothyroidism[84, 87, 94, 95]. Further elucidation and validation of the risk factors and genetic predisposition for HTG-induced acute pancreatitis is awaited[187-191]. Understanding the molecular basis of HTG-induced acute pancreatitis is necessary for developing diagnostic markers as well as effective therapeutic modalities.

There has been controversy as to the atherogenicity of HTG, including chylomicronemia[136, 192, 193]. Although it remains uncertain whether HTG is a causal factor or a mere marker of atherosclerosis[3, 91, 194-196], recent mendelian randomization studies have indicated an association between risk of cardiovascular diseases and variants in HTG-related genes, including causative genes of chylomicronemia (*APOA5*, *LPL*, etc.)[197-199]. Chylomicronemia, particularly when it is polygenic, may be associated with higher risk of cardiovascular diseases[53, 96, 200], which warrants further studies.

C) Genotype-Phenotype Relationship of PCM

The genetic etiology of chylomicronemia may influence the risk of complications such as pancreatitis and atherosclerotic diseases[86, 94-96]. The benefit, risk, and cost-effectiveness of genetic testing for chylomicronemia should be carefully evaluated[15, 109, 201-203]. Some expert reviews, which include the Consensus Panel report of the European Atherosclerosis Society, do not recommend routine genetic testing for severe HTG[3, 204].

D) Underdiagnosis and Undertreatment

Underdiagnosis of chylomicronemia is one of the major risks for pancreatitis[84, 87]. A web-based patient survey reported that patients with chylomicronemia typically visit 5 physicians (range, 1-30) on average before receiving a final diagnosis of chylomicronemia[106, 107]. Owing to the variety of symptoms and complications, patients with chylomicronemia may visit not only lipidologists and endocrinologists but also other diverse specialists, such as primary care physicians, pediatricians, obstetricians, emergency physicians, gastroenterologists, pancreatologists, and psychologists. Simple diagnostic criteria as well as cooperation among different medical specialists will be necessary to achieve timely diagnosis and treatment.

E) Unmet Needs and Burden of Disease

Due to the rarity of the disease, the clinical experience of each doctor is limited. Large registry studies[205, 206] as well as patient-oriented observational studies[104-107] from the patient's perspective are useful for understanding the unmet needs and burden of the disease from the physical, psychological, social, and financial viewpoints[104-107].

A recent web-based patient survey revealed physical, emotional, and cognitive symptoms that are relevant to patient's quality of life but have not been recognized by physicians[207, 208], including abdominal pain (41%), fatigue (23%), feeling sad/down/blue/depressed (18%), difficulty in concentrating (16%), impaired judgment (11%), brain fog (8%), forgetfulness (8%), and recent memory loss (5%)[106, 107]. This survey also revealed actual handicaps felt at school, in society, and work, and family-related issues[106, 107].

Self-monitoring of plasma TG may be an unmet need that could help patients with the long-term management of the disease. It may enable patients to individualize their low-fat diets, hopefully leading to fewer episodes of acute pancreatitis[209].

F) Support for Patients

The mainstay of the current treatment for chylomicronemia is dietary interventions. Supporting information and materials for patients on diets will help develop recipes and menu plans that would be more enjoyable and sustainable. Information and support for patients can be found at FCS Foundation (www.livingwithfcs.org; www.facebook.com/livingwithfcs), FCS Focus (fcsfocus.com), LPLD Alliance (UK) (www.lpldalliance.org), the National Organization for Rare Disorders (NORD) (https://rarediseases.org), and the Japan Intractable Diseases Information Center (https://www.nanbyou.or.jp/entry/4883). Supportive care from other healthcare professionals, such as medical social workers and mental health professionals, will be necessary to reduce the burden of the disease as well as to improve the quality of life of patients with chylomicronemia[105-107].

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Cerebrotendinous Xanthomatosis: Molecular Pathogenesis, Clinical Spectrum, Diagnosis, and Disease-Modifying Treatments

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Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disorder caused by mutations in the *CYP27A1* gene, which encodes the mitochondrial enzyme sterol 27-hydroxylase. Decreased sterol 27-hydroxylase activity results in impaired bile acid synthesis, leading to reduced production of bile acids, especially chenodeoxycholic acid (CDCA), as well as elevated serum cholestanol and urine bile alcohols. The accumulation of cholestanol and cholesterol mainly in the brain, lenses, and tendons results in the characteristic clinical manifestations of CTX. Clinical presentation is characterized by systemic symptoms including neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and a broad range of neuropsychiatric manifestations. The combinations of symptoms vary from patient to patient and the presenting symptoms, especially in the early disease phase, may be nonspecific, which leads to a substantial diagnostic delay or underdiagnosis. Replacement of CDCA has been approved as a first-line treatment for CTX, and can lead to biochemical and clinical improvements. However, the effect of CDCA treatment is limited once significant neuropsychiatric manifestations are established. The age at diagnosis and initiation of CDCA treatment correlate with the prognosis of patients with CTX. Therefore, early diagnosis and subsequent treatment initiation are essential.

Key words: **Cerebrotendinous xanthomatosis, CTX, CYP27A1, Cholestanol, Chenodeoxycholic acid**

Introduction

Cerebrotendinous xanthomatosis (CTX: OMIM#213700), first described by van Bogaert *et al.* in 1937, is a rare autosomal-recessive lipid storage disease caused by deficiency of the mitochondrial cytochrome P 450 enzyme, sterol 27-hydroxylase (CYP27A1, EC 1.14.15.15) due to mutations in the *CYP27A1* gene[1]. Clinical presentation is characterized by neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and progressive neuropsychiatric disturbances including mental retardation or dementia, psychiatric symptoms, pyramidal and cerebellar signs, progressive myelopathy, peripheral neuropathy, extrapyramidal manifestations, and seizures[2-9]. CTX is associated with considerable variability in clinical manifestations among patients and even within the same family[2]. The broad and diverse clinical symptoms cause a substantial diagnostic delay[2-4, 9]. Replacement treatment with chenodeoxycholic acid (CDCA) in the early stage of the disease has been reported to improve or even prevent clinical symptoms of CTX[10, 11]; however, after significant neurological pathology is established, the effect of the treatment is limited and deterioration of clinical manifestations may continue[3, 8, 12, 13]. Therefore, it is crucial to treat CTX patients at the initial stage of the disease. In this article, we provide the current understanding of the underlying pathomechanisms, clinical manifestations, diagnosis, and treatment of CTX.

Pathophysiology

CTX is caused by mutations in the *CYP27A1* gene encoding sterol 27-hydroxylase, a key enzyme in the bile acid synthesis pathway. A schematic

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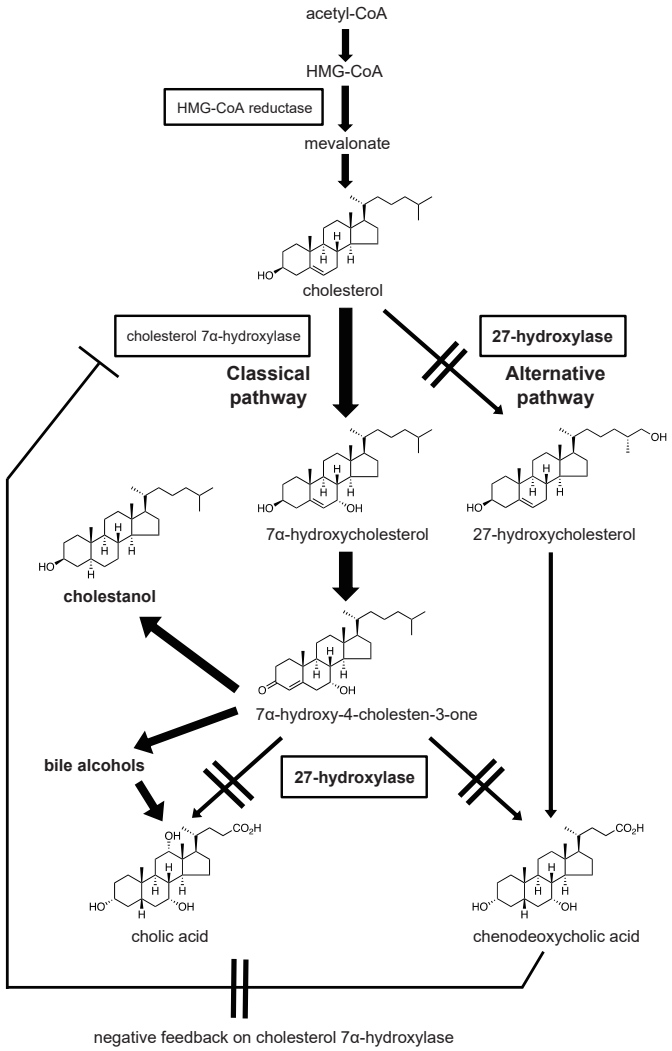

Fig. 1. Impaired bile acid synthesis in cerebrotendinous xanthomatosis (CTX)

In CTX, mutations in the *CYP27A1* gene lead to sterol 27-hydroxylase deficiency, resulting in reduced production of chenodeoxycholic acid and upregulation of the rate-limiting enzyme in the bile acid synthesis pathway, cholesterol 7α-hydroxylase. Increased levels of serum cholestanol and urinary bile alcohols are biological markers in CTX. HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA.

representation of the bile acid synthesis pathway is shown in **Fig. 1**. The classical pathway is initiated by 7α-hydroxylation of cholesterol, catalyzed by the rate-limiting enzyme cholesterol 7α-hydroxylase. The alternative pathway is initiated by 27-hydroxylation of cholesterol, which is catalyzed by sterol 27-hydroxylase. Decreased activity of sterol 27-hydroxylase leads to impaired bile acid synthesis in both the classical and alternative pathways[14], resulting in reduced production of bile acids, especially CDCA, and to a lesser extent cholic acid[15]. The absence of a negative feedback effect of CDCA on cholesterol 7α-hydroxylase accelerates these metabolic abnormalities, leading to increased levels of the bile acid intermediate 7α-hydroxy-4-cholesten-3-one as a precursor for cholestanol and bile alcohols[16]. Elevated serum cholestanol and urine bile alcohols are the biochemical diagnostic hallmarks in CTX. Consequently, increased cholesterol metabolites, such as cholestanol, accumulate mainly in the brain, lenses, and tendons, leading to the characteristic clinical manifestations of CTX. Elevated levels of cholestanol have been found in the serum and tissues, including those of the central nervous system, tendon xanthomas, and atheromatous lesions, in CTX patients. Although the cholestanol-to-cholesterol ratios of various tissues were higher than that of serum, cholesterol was more abundant than cholestanol in both serum and tissues[17]. Cholestanol is widely used as a diagnostic marker but the usefulness of 7α-hydroxy-4-cholesten-3-one

quantification in both the diagnosis and monitoring of CTX has also been reported[18]. It has also been shown that quantification of a panel of plasma ketosterol bile acid precursors (7α-hydroxy-4-cholesten-3-one, 7α,12α-dihydroxy-4-cholesten-3-one, and 7α,12α-dihydroxy-5β-cholestan-3-one) provides a more sensitive biochemical approach when compared with measurement of cholestanol[19].

In 1968, Menkes *et al.* discovered accumulation of cholestanol and cholesterol in the cerebrum and cerebellum of patients with CTX[20]. Although the mechanism by which cholestanol accumulates in the brain remains unclear, one possible explanation is that the bile acid precursor 7α-hydroxy-4-cholesten-3-one, which passes through the blood-brain barrier (BBB) more efficiently than cholestanol, can be converted to cholestanol by neurons, astrocytes, microglia, and human monocyte-derived macrophages[21, 22]. Another possible explanation is impairment of the BBB. Increased levels of cholestanol and apolipoprotein B were observed in the cerebrospinal fluid of patients with CTX, indicating disrupted function of the BBB[23]. It has also been proposed that large plasma bile alcohol glucuronides play a role in the abnormal BBB permeability in CTX, leading to increased transport of cholestanol and cholesterol in the brain[24].

Although the major pathway for production of cholestanol in CTX has been clarified, little is known about its metabolism. Under normal conditions, the 7α-hydroxy-4-cholesten-3-one-dependent pathway accounts for only about 30% of cholestanol biosynthesis in the brain, and cerebral cholestanol is mainly formed from cholesterol[25]. Using *Cyp27a1* and *Cyp46a1* knockout mice, Mast *et al.* demonstrated that CYP46A1 plays an important role in cholestanol removal from the brain and that CYP27A1 deficiency results in a preferential increase in cholestanol in the cerebellum[25].

CTX patients develop premature atherosclerosis and xanthomas despite normal serum cholesterol concentrations. However, abundant deposits of cholesterol are detected in addition to cholestanol in the respective lesions in CTX[17]. Although the mechanism leading to premature arteriosclerosis and tendon xanthomas in CTX remains unclear, reduced capacity for reverse cholesterol transport has been proposed as a possible cause[26-31]. Sterol 27-hydroxylase, which is expressed in macrophages, endothelial cells, and tenocytes as well as in the liver, seems to contribute to the transport of peripheral cholesterol to the liver by transforming intracellular cholesterol into 27-hydroxycholesterol, which has a higher capacity for passing through lipophilic membranes compared with cholesterol[26-28]. In addition, 27-hydroxycholesterol is an endogenous ligand for liver X receptor (LXR). LXR activation induces upregulation of ATP-binding cassette transporter A1 (ABCA1) expression, leading to increased cholesterol efflux[29-31]. Fu *et al.* demonstrated that upregulation of ABCA1 in response to cholesterol loading was impaired in primary fibroblasts derived from a CTX patient[29]. In addition, since 27-hydroxycholesterol was found to be the major oxysterol in human atherosclerotic lesions[28], extrahepatic sterol 27-hydroxylase is thought to be an anti-atherosclerotic enzyme. Absence of the two above defense mechanisms may contribute to premature atherosclerosis and xanthoma formation in CTX.

Epidemiology

CTX patients have been reported worldwide but prevalence of the disease is considered to be underestimated[32]. Based on the carrier frequency of the pathogenic *CYP27A1* c.1183C>T (p.R395C) mutation in 115 control subjects, the prevalence of CTX in the USA among Caucasians of European ancestry was estimated to be 3-5:100,000 individuals[32]. Pilo-de-la-Fuente *et al.* estimated a minimum prevalence of 1/1,8000,000 individuals in Spain[3]. Estimates of the incidence of CTX vary among locations. A recent genetic epidemiological study based on the Exome Aggregation Consortium (ExAC) cohort, a large cohort of over 60,000 unrelated subjects, evaluated the allele frequency of 57 known and 29 predicted CTX-causing variants and estimated the incidence of CTX to be 1:134,970-1:461,358 in Europeans, 1:263,222-1:468,624 in Africans, 1:71,677-1:148,914 in Americans, 1:64,247-1:64,712 in East Asians, and 1:36,072-1:75,601 in South Asians[33]. Prevalence among Jews of Moroccan origin and the Druze sect in Israel has been reported to be particularly high[34, 35].

Molecular Genetics

In 1991, human sterol 27-hydroxylase cDNA was isolated from a liver cDNA library. The *CYP27A1* gene consists of nine exons and eight introns and spans 18.6 kb of DNA on chromosome 2q33-qter[36, 37]. Sterol 27-hydroxylase consists of a 33-residue mitochondrial signal sequence followed by a mature protein of 498 amino acids containing putative binding sites for heme and adrenodoxin[1]. Cali *et al.* first identified two *CYP27A1* missense mutations, p.R395C and p.R479C, in patients with CTX and demonstrated that a loss-of-function mechanism is responsible for CTX[1].

CYP27A1 is the only gene known to be

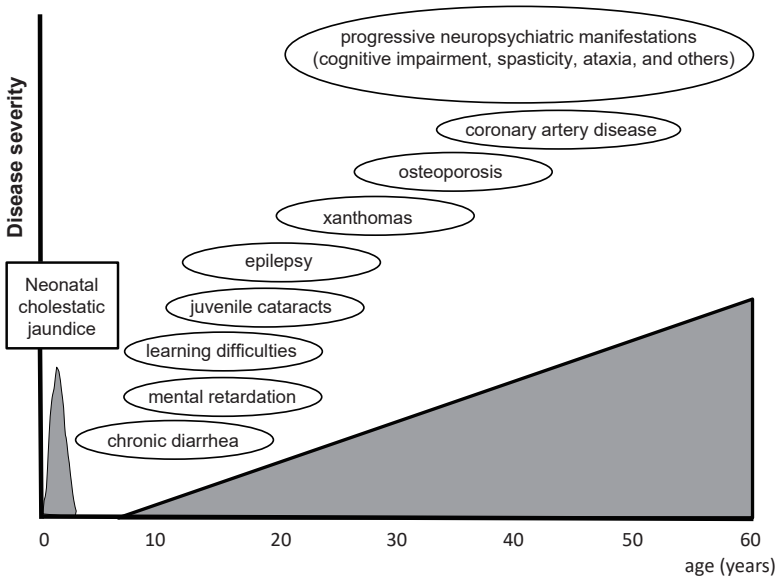

Fig. 2. Representative clinical course of classical form CTX
Figure shows typical ages of onset of CTX-related symptoms.

associated with CTX. Therefore, the diagnostic gold standard is genetic analysis of the *CYP27A1* gene[4, 38]. The diagnosis is confirmed by the presence of biallelic pathogenic *CYP27A1* mutations[4, 38]. To date, over 99 pathogenic mutations, including missense mutations, nonsense mutations, splice-site mutations, and insertion/deletion mutations, have been reported worldwide[6]. A relatively high frequency of *CYP27A1* mutations in particular ethnic groups has been reported: c.1016C>T (p.T339M), c.1183C>T (p.R395C), and c.1263+1G>A in the Netherlands[13], c.646G>C (p.A216P), c.1183C>T (p.R395C), c.1184+1G>A, c.1263+1G>A, and a 1.9 kb deletion including exons 7-9 in Italy[38], c.1183C >T (p.R395C) in northwestern Spain and c.1213C>T (p.R405W) in southern Spain[3], c.1214G>A (p.R405Q), c.1421G>A (p.R474Q), c.435G>T (p.G145=), and c.1420C>T (p.R474W) in Japan[9], which seems to be reasonable considering the allele frequency reported in the ExAC[33]. The allele frequencies of these variants in six global populations according to the ExAC database (version 0.3) are shown in **Supplementary Table 1**. Although no genotype-phenotype correlation has been reported[2, 3, 13], our nationwide survey revealed possible associations between c.1421G>A (p.R474Q) and classical form CTX, c.1241G>A (p.R405Q) and spinal form CTX, and c.435G>T (p.G145=) and non-neurological form CTX despite considerable phenotypic variation among patients with the same genotype[9].

Clinical Features

Clinical Phenotypes

Clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms vary from patient to patient. Systemic symptoms include neonatal jaundice or cholestasis, chronic diarrhea, juvenile cataracts, xanthomas, osteoporosis, and coronary heart disease. The neurological and psychiatric manifestations of CTX vary widely. Intellectual disability as well as pyramidal and cerebellar signs are the most frequent and are cardinal clinical features[2-4, 7, 9]. In addition, CTX patients can present with extrapyramidal manifestations, peripheral neuropathy, epilepsy, and psychiatric disturbances. Autonomic involvement has also been reported[39].

A representative clinical course of classical form CTX, the most common form of this condition, is shown in **Fig. 2**. Patients with classical form CTX develop neuropsychiatric symptoms attributed to the cerebrum, cerebellum, and/or brainstem, in combination with various systemic manifestations. The concept of spinal form CTX, also called spinal xanthomatosis, was proposed by Virrips *et al.* in 1999[40]. Patients exhibit clinical symptoms and signs related to involvement of the corticospinal tracts and dorsal columns of the spinal cord, without intellectual impairment, cerebellar signs, or peripheral neuropathy, at the time of presentation of the spinal cord syndrome[40]. Although most patients with spinal form

CTX also exhibit various systemic and neurological symptoms, spinal form CTX without other neurological manifestations has been reported[41-46]. Spinal form CTX has a relatively mild clinical course compared with classical form CTX[40].

We have proposed non-neurological form CTX[9] as another clinical phenotype. Although patients with the non-neurological form may develop neurological symptoms later in life, two genetically confirmed CTX patients in their fifties showed no evidence of neurological manifestations ≥ 20 years after disease onset. Therefore, we regarded the non-neurological form as a distinct clinical phenotype of CTX[9].

All CTX patients exhibit increased serum cholestanol levels at the time of diagnosis[2-4, 9]. While a significant relationship between serum cholestanol and clinical phenotype or disability was not detected[3], Sekijima *et al.* showed that classical form patients had significantly higher levels of cholestanol than spinal form patients[9].

Systemic Manifestations/Neonatal Jaundice or Cholestasis

Prolonged neonatal jaundice or cholestasis could be the earliest clinical presentation of CTX[47]. Laboratory findings have revealed conjugated hyperbilirubinemia with raised transaminases and alkaline phosphatase, whereas levels of γ-glutamyl transferase were normal or minimally elevated[47-50], which is the characteristic feature of inborn errors of bile acid synthesis[51]. In one study, hepatomegaly or hepatosplenomegaly was evident[50]. Liver biopsy specimens have revealed nonspecific chronic active hepatitis with giant cell transformation, piecemeal or focal bridging necrosis, and fibrosis, in addition to intralobular cholestasis[47-50]. Cirrhosis was detected in an explanted liver[50]. In addition, retrospective cohort studies have demonstrated that about 8–16% of patients had a past medical history of neonatal cholestatic jaundice[4, 13, 47]. Furthermore, family histories have revealed fetal deaths or jaundice-related infantile deaths among siblings of affected individuals[47].

Von Bahr *et al.* described a patient with genetically confirmed CTX who had fatal cholestatic liver damage[48]. Recently, Gong *et al.* reported on eight patients who presented with neonatal cholestasis. Among their cohort, this was fatal in four and one underwent liver transplantation. Although neonatal cholestasis associated with CTX has been generally assessed as transient and self-limiting with patient survival, a substantial proportion of patients could experience a more severe clinical course than previously recognized[50]. The mechanism by which mutations in the *CYP27A1* gene lead to cholestasis may involve nuclear receptors such as farnesoid X receptor (FXR). CDCA is a potent stimulator of FXR[52]. Marked reduction of CDCA in CTX leads to decreased activation of FXR, which results in reduced expression of the bile salt export pump, causing a decrease in canalicular bile salt transportation[48, 52].

Systemic Manifestations/Chronic Diarrhea

Chronic unexplained diarrhea begins in infancy and continues into adulthood[2]. It may be the earliest symptom of CTX and could start within the first year of life[53]. Gastrointestinal tract investigations in patients with diarrhea did not produce any abnormal findings[54]. Also, rectal biopsy did not demonstrate any accumulation of cholestenol or cholesterol and fatty acids could not be detected in the feces[54]. Usually, diarrhea ceases immediately after starting treatment with CDCA[11]. Although the pathogenesis of diarrhea is still unclear, presence of bile alcohol in the lumen of the gut and/or intraluminal deficiency of CDCA are the most likely causes[54].

Systemic Manifestations/Ocular Manifestations

Juvenile cataracts are one of the earliest clinical signs and often precede tendon xanthomas and neurological symptoms, and are usually noted in the second decade of life. Lens nuclei from CTX patients had a greater cholestanol content compared with the senile lens nuclei used as a control[55]. Although stabilization of cataracts with CDCA treatment has been reported[11], complete resolution is unlikely[56] and operations should be considered. Early onset of cataracts is uncommon and therefore, juvenile cataracts are arguably an important cue for early diagnosis of CTX. A screening for CTX among 170 patients with idiopathic bilateral cataracts diagnosed between the ages of 2 and 21 years identified 3 cases[57].

In addition to cataracts, ophthalmological manifestations include optic neuropathy with optic disc paleness, premature retinal vessel sclerosis, and cholesterol-like deposits[58]. Optic neuropathy with features suggestive of optic neuritis has also been reported[59].

Systemic Manifestations/Xanthomas

Xanthomas usually appear during the second or third decade of life. They typically occur on the Achilles tendon, but may be found on the elbow, neck, knee, and the bottom of the foot **(Fig. 3)**. The patellar and finger extensor tendons are also common sites for development of tendon xanthomas[60-64]. Xanthomas in the lung[65] and choroid plexus have also

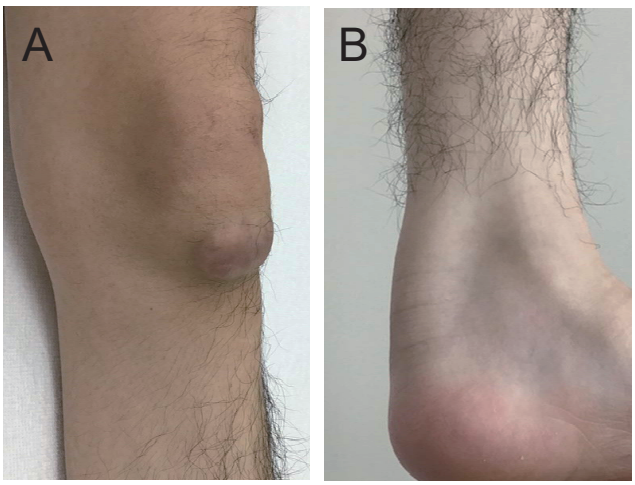

Fig. 3. Xanthomas in a patient with CTX

Figure shows xanthoma on the knee (A) and one on the Achilles tendon (B).

been reported[60, 66, 67]. It is noteworthy that presence of xanthomas is a characteristic feature of the disease, but it is not mandatory for CTX diagnosis[68]. Biopsy specimens of xanthomas show lipid crystal clefts with infiltration of foamy macrophages[64, 69]. In gallium-67 scintigraphy, there can be abnormal uptake in Achilles tendons[70], even if Achilles tendon xanthomas were not evident in a physical examination or on MRI[44]. In addition, positron emission tomography (PET) using ^{18}F-2-deoxy-2-fluoro-glucose (FDG) showed abnormally high radioactivity in the Achilles tendons and adjacent regions[5]. Although CDCA treatment does not significantly reduce tendon xanthomas[10], a decrease in size has been reported in some subjects[71, 72].

Systemic Manifestations/Skeletal System Involvement

Osteoporosis and increased bone fractures are CTX-associated systemic manifestations. However, the underlying pathogenesis of osteoporosis in this condition is still unknown. Decreased levels of serum 25-hydroxyvitamin D were detected in CTX patients[73-75]. In contrast, however, Federico *et al.* reported that levels of 25-hydroxyvitamin D were substantially within the normal range[76], indicating that a deficiency in vitamin D metabolites may not be the only factor responsible for the development of osteoporosis in CTX[74]. An alternative hypothesis for explaining the cause of osteoporosis is impairment of intestinal calcium absorption due to changes in the quantity and composition of bile acids[76]. In general, osteoporosis has been considered to occur in the later stages of the disease[4, 9]. However, teenage CTX patients could have early osteoporosis and a history of bone fracture[77]. CDCA treatment has been shown to improve bone mineral density (BMD)[74, 76].

Skeletal deformities including kyphosis, pectus excavates, pes equinovarus, and pes cavus were found in CTX patients[77] and Ginanneschi *et al.* reported that pes cavus occurrence was not significantly different in groups with and without peripheral nerve abnormalities[78].

Systemic Manifestations/Cardiovascular System Involvement

Premature atherosclerosis and cardiovascular disease have been reported as systemic manifestations in CTX patients even in their thirties[79-82]. Myocardial infarction is a cause of premature death in this condition[82]. Kuriyama *et al.* reviewed 144 cases of CTX and reported that 15 patients (10.4%) had cardiovascular disease, consisting of coronary artery disease in ten patients, ischemic changes on electrocardiogram in four, and mitral valve insufficiency in one patient[79]. Coronary artery disease was evident in 8 of 40 CTX patients (20%) in a nationwide survey on CTX in Japan[9]. In this survey, the mean age at onset of coronary artery disease was 52.5. ± 5.8 years (mean ± standard deviation (SD))[9]. Duell *et al.* reported that 3 of 43 CTX patients (7%) had premature cardiovascular disease, consisting of myocardial infarction in two patients, and angina pectoris in one patient in the USA[8]. Abdominal aortic aneurysm, coronary artery dissection, aneurysmal coronary artery disease, advanced carotid atherosclerotic lesions, and thickening of the interatrial septum compatible with lipomatous hypertrophy have also been reported in CTX [81, 83-86].

Systemic Manifestations/Pulmonary Involvement

Elevated levels of cholestanol in bronchoalveolar lavage fluid as well as in serum have been reported in CTX patients without pulmonary symptoms, or radiological and pulmonary function abnormalities. Transbronchial lung biopsy specimens have revealed foamy macrophages and small granulomas in alveolar septa[87].

Neuropsychiatric Manifestations/Intellectual disability

Among CTX patients, 48–74% present with intellectual disability[2-4, 9], which is one of the most frequent neurological symptoms. It is particularly important to take developmental delays, mental retardation, and learning difficulties beginning in childhood into consideration for early diagnosis of CTX[2-4, 7, 9, 53]. Cognitive decline, presenting in adolescence or early adulthood, is also frequently observed[2, 3, 9]. Although a neuropsychological profile

of patients with CTX remains undetermined, a fronto-temporal dementia phenotype exhibiting behavioral and personality changes[88], extensive cerebral cortex symptoms including left-right disorientation, constructional apraxia, and temporal and spatial disorientation in addition to frontal lobe dysfunction[89], and a corticobasal syndrome phenotype[90] have been reported.

Neuropsychiatric Manifestations/Pyramidal and Cerebellar Signs

Pyramidal and/or cerebellar signs typically emerge in the third or fourth decade and lead to gait disturbance in CTX patients[2, 4, 9]. Pyramidal and cerebellar signs have been detected in 64–92% and 36–83% of patients with CTX, respectively[2-4, 9]. Pyramidal signs such as spasticity, hyperreflexia, and extensor plantar response can be cardinal clinical signs especially in patients with spinal form CTX[40-46]. Owing to dorsal column involvement, simultaneous occurrence of impaired position and vibration sensation in the lower extremities can lead to spastic-ataxic gait in this form[41, 45]. Mignarri *et al.* have reported the usefulness of transcranial magnetic stimulation in detecting corticospinal tract damage[91]. Cerebellar signs include nystagmus, ataxic dysarthria, as well as limb and truncal ataxia[69, 92-94]. Pyramidal signs frequently coexist with cerebellar signs[2, 3].

Neuropsychiatric Manifestations/Extrapyramidal Manifestations

CTX patients can present with a wide range of movement disorders including parkinsonism[90, 95, 96], dystonia[97-99], myoclonus[98, 100, 101], and postural tremor[100, 102]. When movement disorders are diagnosed, patients have a tendency to present with other CTX-associated systemic and neuropsychiatric manifestations[103]. Parkinsonism usually occurs later in life[7, 95, 103] and is the most frequently reported type of movement disorder in CTX, followed by dystonia, myoclonus, and postural tremor[103]. Parkinsonism seems to be a treatment-resistant feature in CTX[13], with CDCA treatment seemingly having no effect. In addition, CTX patients may develop parkinsonism during treatment with CDCA[103]. The effect of L-dopa is controversial[90, 95, 103-105]. In addition to the characteristic brain MRI findings of CTX, signal hyperintensities on T2-weighted images in the substantia nigra, globus pallidus, and striatum [90, 95, 96, 103] have been described and functional dopaminergic imaging has demonstrated a pre-synaptic dopaminergic deficit in CTX patients presenting with parkinsonism[90, 95, 96, 104, 105]. Although movement disorders are considered a late disease manifestation, Zubarioglu *et al.* reported that all six patients who were diagnosed before 18 years of age had intention tremor[77].

Neuropsychiatric Manifestations/Peripheral Nervous System Involvement

Peripheral neuropathy is an established clinical feature of CTX; however, it is still being debated whether the underlying pathogenesis of CTX-related polyneuropathy is demyelinating or axonal in origin. Based on the presence of onion bulbs, which are generally considered a hallmark of chronic demyelination, the pathological process has been interpreted as demyelinating[106, 107]. On the other hand, Verrips *et al.* reported that axonal degeneration was the predominant process on the basis of nerve conduction velocity (NCV) studies and sural nerve biopsy specimens showing features of axonal degeneration[108]. In addition to axonal polyneuropathy and demyelination polyneuropathy, a mixed type of neuropathy has been reported, indicating that CTX could exhibit any type of neuropathy[109]. CTX-related polyneuropathy seems to be predominantly motor neuropathy[78, 109]. Although neurophysiologically confirmed neuropathy frequently occurs in CTX, signs and symptoms related to polyneuropathy are often absent or difficult to appreciate because central nervous system involvement may dominate the clinical picture[4, 78, 109]. The disease severity of polyneuropathy varies greatly among patients, ranging from asymptomatic presentations to severe polyneuropathy[78, 109, 110]. Thickening of the nerve roots and trunks of the lumbosacral plexus or cauda equina has been reported[90, 111].

Neuropsychiatric Manifestations/Muscle Involvement

Controversy exists regarding whether muscle involvement is a characteristic feature in CTX. Federico *et al.* noted mild myopathic changes[112], while Verrips *et al.* reported that muscle biopsies demonstrated neurogenic changes without any definite myopathic characteristics[108]. The results for mitochondrial respiratory chain enzymatic activity are also controversial[108, 113]. Abnormal findings from ultrastructural studies of muscles include changes in the mitochondria and membranous system, and an increased amount of lipid droplets, lipofuscin, and glycogen; however, the significance of these findings remains to be determined[39, 108, 112].

Neuropsychiatric Manifestations/Epilepsy

In CTX, 10–33% of patients have epileptic seizures[2-4, 7, 9]. Epilepsy can develop at any stage in life and is often seen in the early phase of the disease[7].

Epilepsy could be a diagnostic cue in some cases[114-116]. A CTX patient presenting with infantile spasms has also been reported, but this is a rare case[117]. Electroencephalographic abnormalities are frequently observed in cases of CTX even without clinical signs of seizures[11, 118]. In addition to slow background activity composed of theta and delta waves, bursts of high voltage slow activity are frequently demonstrated. Spike and sharp wave complexes can also be detected[10, 11, 118]. CDCA treatment leads to improvement or normalization of electroencephalographic findings[10, 11, 60, 118], and epilepsy in CTX seems to respond well to anti-epileptic agents[12, 114-116, 119]. CDCA treatment could lead to improved seizure control[12, 60, 120], even in patients with drug-resistant epilepsy[121].

Neuropsychiatric Manifestations/Behavioral manifestations

Psychiatric and behavioral manifestations include personality changes with irritability and aggressivity, depression, delusional syndrome, catatonia, psychosis, attention-deficit hyperactivity disorder, oppositional-defiant disorder, and autism spectrum disorder[13, 122]. Behavioral disorders and affective/mood disorders associated with learning difficulties or mental retardation appearing during childhood or adolescence should lead to biochemical investigations to exclude CTX.

Radiological, Pathological, and Neurophysiological Examinations

Neuroimaging

The most distinctive neuroradiological findings are signal hyperintensities on T2-weighted and/or FLAIR images in the dentate nuclei and adjacent cerebellar white matter[123, 124]. Abnormal signal changes in the dentate nuclei can be more clearly detected on FLAIR images than on T2-weighted images[123]. It was found that abnormal hyperintensities on T2-weighted and/or FLAIR images could be detected in the globus pallidus, internal capsule, substantia nigra, cerebral peduncles, inferior olive, and periventricular white matter, with a tendency to spare the U-fibers and corpus callosum[125]. Supratentorial and/or infratentorial atrophy are also observed[123, 124, 126] **(Fig. 4)**. Cortical volume, rather than white matter volume, was correlated with clinical status and cortical atrophy could be detected in all neocortical regions, with a preference for the fronto-parietal cotrtex[126]. In addition, cerebellar vacuolation, which is detected as hypointense lesions on both T1-weighted and FLAIR images, has been recently indicated as a marker of a poor prognosis in CTX[127, 128], while absence of dentate nuclei signal alteration is considered an indicator of a better prognosis[128]. Furthermore, calcifications were detected in the dentate nuclei in a subgroup of patients[128] and the hot cross bun sign in the pons, a characteristic finding of multiple system atrophy, has been reported[69].

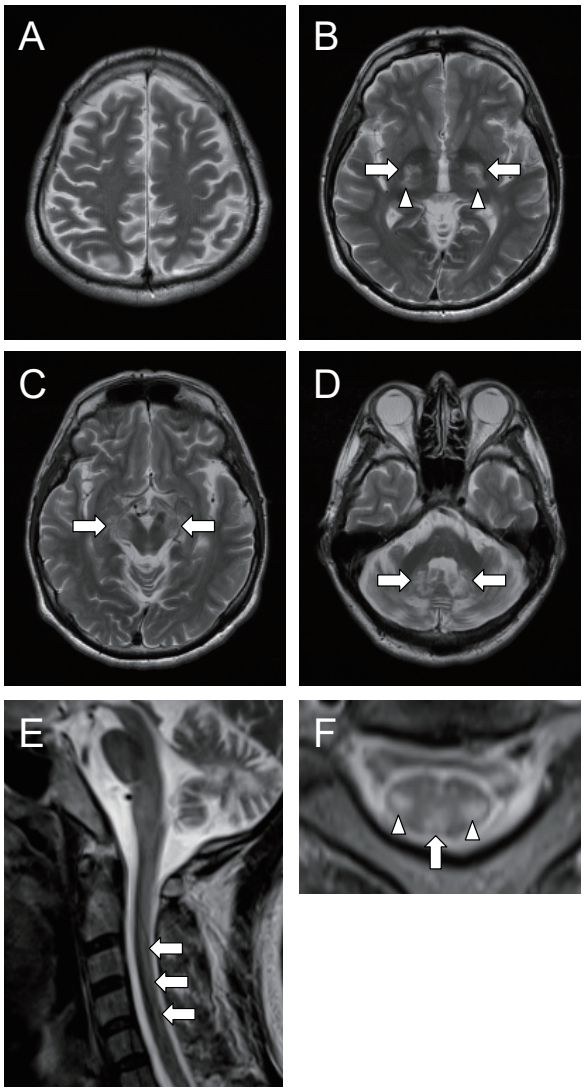

Fig. 4. Brain magnetic resonance imaging (MRI)

Axial T2-weighted images of the brain showing abnormal hyperintensities in the globus pallidus (arrows in B), internal capsules (arrowheads in B), cerebral peduncles (arrows in C), and dentate nuclei (arrows in D). Diffuse cerebral (A) and cerebellar (D) atrophy are evident. Sagittal T2-weighted image of the spinal cord exhibiting longitudinally extensive hyperintense lesions (arrows in E). Axial T2-weighted image at the C3 level showing involvement of lateral corticospinal tracts (arrowheads in F) and gracile tracts (arrow in F).

In patients with spinal cord involvement, a spinal cord MRI demonstrated longitudinally extensive

hyperintense lesions involving lateral corticospinal tracts and gracile tracts on T2-weighted images[40, 44-46]. It is noteworthy that absence of signal changes on spinal cord MRI cannot rule out the possibility of spinal form CTX[42, 43].

On magnetic resonance spectroscopy (MRS), decreases in N-acetylaspartate (NAA) intensities and increases in lactate signals point to axonal damage and brain mitochondrial dysfunction, respectively[123]. In addition to decreased NAA intensities, lipid peaks were evident on MRS using a short TE[129]. Increased levels of myo-inositol indicate gliosis and astrocytic proliferation[129, 130].

Cerebellar glucose hypometabolism in ^{18}F-2-deoxy-2-fluoro-glucose positron emission tomography (FDG-PET) and cerebellar hypoperfusion in single photon emission computed tomography (SPECT) with ^{99m}Tc-ethylcysteinate dimer (ECD) have been reported despite normal cerebellar morphology[88, 131, 132]. In addition to in the cerebellum, SPECT using ^{99m}Tc-ECD and ^{123}I-*N*-isopropyl-*p*-iodoamphetamine (^{123}I-IMP) revealed cerebral hypoperfusion, predominantly in the fronto-parietal lobes[88, 89, 132]. Gray matter atrophy patterns were correlated with hypoperfusion in SPECT using ^{99m}Tc- ECD[133].

Diffusion tensor imaging (DTI) revealed that fractional anisotropy (FA) reduction preceded structural alterations detected by voxel-based morphometry and correlated with cognitive function[133]. Widespread reductions of FA and decreased track-density were demonstrated[120, 134].

Neuropathology

At macroscopic examination, nonspecific brain and cerebellar atrophy and a yellowish soft tissue in the cerebellum, cerebrum, choroid plexus, cerebral peduncles, and globus pallidus were observed[135-138]. In the cerebral peduncles, cystic necrosis of the corticospinal tracts has been reported[139]. Microscopic examinations have revealed lipid crystal clefts, neuronal loss, demyelination, reactive astrocytosis, and foamy macrophages in the affected regions, especially in the dentate nucleus and surrounding area, as well as in the cerebrum, basal ganglia, brainstem, and, spinal cord[65, 124, 135-139]. In patients with spinal cord involvement, extensive symmetric loss of myelin and axons was detected particularly in the lateral corticospinal tracts and gracile tracts of the spinal cord[40].

Neurophysiological Examinations

In addition to NCV studies and electroencephalography, abnormalities have been found in neurophysiological examinations. The P100 peak latency of visual evoked potentials (VEPs) was delayed[109, 140, 141] and the Ⅰ to Ⅲ, Ⅲ to Ⅴ, and Ⅰ to Ⅴ interpeak latencies of brain stem evoked potentials (BAEPs) were prolonged[109, 140, 141]. Central conduction time in somatosensory evoked potentials (SSEPs)[109, 142] and motor evoked potentials (MEPs)[89, 91, 141] were increased, with lower extremity predominance.

Diagnosis

Importance of Early Diagnosis and Treatment

CTX is a treatable metabolic disorder; however, once significant neurological symptoms are established, clinical deterioration can occur despite normalization of cholestanol levels after treatment with CDCA[3]. Even with therapy, only 28% of the patients remained stable, whereas 60% continued to deteriorate and 20% died, in a cohort of 25 patients with CTX in Spain[3]. Duell *et al.* reported that clinical deterioration during follow up was observed in patients who had significant neurological symptoms when they were diagnosed at the age of 25 years or older[8]. Yahalom *et al.* and Stelten *et al.* have shown that the age of diagnosis and initiation of CDCA treatment correlates with the prognosis of patients with CTX[12, 13]. Berginer *et al.* reported two siblings with CTX who began CDCA treatment from 2 and 7 years of age, respectively, and did not develop any neurological manifestations during a 14-year follow-up period[142]. These findings strongly suggest that early diagnosis and treatment are crucial in CTX. However, retrospective cohort studies on CTX have revealed a substantial diagnostic delay of 15–25 years[2-4, 9].

Juvenile cataracts are usually the earliest clinical sign that precedes tendon xanthomas and neurological symptoms. Cruysberg *et al.* emphasized that the combination of juvenile cataracts and chronic diarrhea is noteworthy in the early diagnosis of CTX[143]. It is recommended that all patients with cataracts before the age of 30 years are screened for CTX, especially if they also have CTX-related conditions such as chronic diarrhea, tendon xanthomas, and/or neuropsychiatric symptoms[8]. Verrips *et al.* emphasized that presence of tendon xanthomas is not obligatory for a diagnosis of CTX and recommended that presence of two of the four clinical features of premature cataracts, intractable diarrhea, progressive neurological signs and symptoms, and tendon xanthomas prompt thorough biochemical screening for CTX[68]. It is also important to consider intellectual disability, usually presenting at school age, for early diagnosis of CTX[4]. In addition, because affected relatives may be asymptomatic, biochemical examination of all siblings of a patient with CTX is recommended[2, 4].

Table 1. Diagnostic criteria for cerebrotendinous xanthomatosis (Sekijima *et al.*[9])

A. Symptoms
1. Tendon xanthoma
2. Progressive neurological dysfunction[a] or mental retardation
3. Juvenile cataract
4. Juvenile coronary artery disease
5. Chronic unexplained diarrhea
6. Juvenile osteoporosis
7. Prolonged neonatal cholestasis
B. Biochemical finding
Elevated serum cholestanol level
C. Genetic testing
Pathogenic mutation in *CYP27A1* gene (homozygosity or compound heterozygosity)
D. Differential diagnosis
Increased serum cholestanol level due to following diseases should be excluded
· Familial hypercholesterolemia
· Sitosterolemia
· Obstructive biliary tract disease
· Hypothyroidism
Diagnostic category
Definite: At least one of symptom in A and B+C+D
Probable: At least one of symptom in A and B+D
Possible: At least one of symptom in A and B

[a] Representative progressive neurological dysfunction includes cognitive dysfunction, cerebellar symptoms, pyramidal symptoms, extrapyramidal symptoms, seizure, peripheral neuropathy, and sensory disturbance attributed to spinal cord.

To identify and treat CTX patients at an initial stage of the disease, Mignarri *et al.* created a suspicion index and developed a diagnostic algorithm for early diagnosis of CTX[4]. Their suspicion index comprised weighted scores assigned to indicators such as family history characteristics and common systemic and neurological symptoms. They suggested that their proposed algorithm would be useful for early diagnosis, even in patients before the onset of disabling neurological symptoms including ataxia, spasticity, and psychiatric disturbances[4].

Diagnostic Criteria

In the absence of generally accepted diagnostic criteria for CTX, we recently proposed new diagnostic criteria with emphasis on early diagnosis **(Table 1)**[9]. They include clinical symptoms, biochemical findings, genetic analysis, and differential diagnosis. We established three diagnostic categories in accordance with levels of certainty: definite, probable, and possible CTX. The diagnosis of possible CTX is made when there is at least one CTX-related clinical symptom and elevated levels of serum cholestanol (≥ 4.5 μg/mL, mean ± SD: 2.35 ± 0.73 μg/mL). Excluding other conditions with elevated levels of cholestanol is necessary for diagnosis of probable CTX. A definite diagnosis of CTX is confirmed by the presence of biallelic mutations in the *CYP27A1* gene.

Differential Diagnosis

Differential diagnosis of CTX differs substantially according to presenting symptoms. Inborn errors of bile acid metabolism including CTX lead to neonatal cholestasis or hepatitis[144, 145], which can be the first manifestation in this disease. In patients with juvenile bilateral cataracts and/or progressive mental deterioration, CTX should be considered[2, 57]. When xanthomas are evident, differential diagnosis includes familial hypercholesterolemia (FH) and sitosterolemia. FH is characterized by elevated levels of LDL cholesterol, the presence of tendon xanthomas, and premature coronary artery disease, and mutations in *LDLR*, *APOB*, and *PCSK9* have been reported to cause FH[146]. Sitosterolemia is an autosomal recessive sterol storage disorder characterized by elevated levels of LDL cholesterol and plant sterols such as sitosterol and campesterol, tendinous and tuberous xanthomas, and premature atherosclerosis. It is caused by biallelic mutations in either *ABCG5* or *ABCG8*[147]. The presence of juvenile cataracts, chronic unexplained diarrhea, and progressive neuropsychiatric manifestations can distinguish CTX from these two disorders. Other

conditions with elevated levels of cholestanol include obstructive biliary tract diseases and hypothyroidism. In patients with cerebellar ataxia, CTX patients might be misdiagnosed as spinocerebellar atrophy, multiple system atrophy, or Marinesco-Sjögren syndrome[68]. CTX should be included in the differential diagnosis of spastic paraplegia[42, 44].

Clinical Management

CDCA has been approved as first-line treatment for CTX. In a landmark study published in 1984, Berginer *et al.* demonstrated the long-term efficacy of oral CDCA treatment[10]. In addition to a decrease in serum cholestanol and elimination of abnormal urinary and biliary excretion of bile alcohols, CDCA treatment led to an improvement in electroencephalographic findings and neurological manifestations including intellectual impairment, pyramidal and cerebellar signs, and peripheral neuropathy[10, 11]. CDCA treatment is recommended at a dose of 750 mg/day for adults and 15 mg/kg/day for children in three divided oral doses[10, 11]. It has been shown to result in a gradual decline in serum cholestanol during the first 2 years[148, 149]. Assessment of cholestanol levels may be useful in monitoring patient adherence to treatment. However, it should be noted that a decreased level of cholestanol does not necessarily suggest a good prognosis[3]. In Japan, CDCA has been approved for dissolution of gallstones, but not for the treatment of CTX.

Although CDCA is a relatively safe drug, gastrointestinal manifestations and drug-induced liver damage may occur[44, 60, 150]. Huidekoper *et al.* reported an infantile patient with CTX who developed jaundice with hepatomegaly within 6 weeks after initiating CDCA administration at a dosage of 15mg/kg/day[151]. After treatment with CDCA was stopped, liver size and function rapidly normalized. CDCA supplementation was then restarted and maintained at 5 mg/kg/day with no further evidence of liver dysfunction and adequate metabolic control. Duell *et al.* reported that 9% of patients required dose adjustment for CDCA owing to moderate drug-induced liver damage[8]. These findings suggest that clinical and laboratory monitoring and dosage adjustment for CDCA are essential in the treatment of CTX, especially in infants and young children[8, 151].

CDCA was initially preferred to cholic acid because it was more effective in reducing cholesterol 7α-hydroxylase and had a stronger negative feedback effect on it[127, 152]. Cholic acid has been shown to be effective in the treatment of other genetic defects in bile acid synthesis[153]. Since CDCA is intrinsically hepatotoxic, cholic acid is considered the safer option in CTX, especially in infancy[49]. Mandia *et al.* reported potential efficacy for cholic acid in adult patients with CTX, including individuals whose CDCA treatment was discontinued due to supply difficulties[127]. Treatment with cholic acid not only significantly reduced cholestanol levels in all patients but also led to improvement or stabilization of systemic and/or neurological manifestations[127]. No adverse effects were reported in patients undergoing cholic acid treatment, suggesting that cholic acid may be a suitable alternative treatment, especially in patients with adverse effects related to CDCA, such as drug-induced liver damage[60, 127].

Treatment with ursodeoxycholic acid, which does not inhibit cholesterol 7α-hydroxylase, has been shown to be ineffective[10, 154]. When ursodeoxycholic acid was substituted for CDCA, plasma cholestanol returned to pretreatment levels[10].

The effectiveness of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins) remains controversial. Lewis *et al.* reported that mevinolin normalized serum cholestanol and reduced the size of xanthomas[155], whereas Batta *et al.* found that lovastatin did not affect abnormal bile acid synthesis or reduce plasma cholestanol levels[154]. Although synergistic effects of combination therapy with CDCA and HMG-CoA reductase inhibitors on serum cholestanol or urine bile alcohols have been observed[71, 81, 149], absence of an additive effect has also been reported[148]. After switching from combined therapy of CDCA and HMG-CoA reductase inhibitors to HMG-CoA reductase inhibitor monotherapy, clinical symptoms such as xanthomas and neurological manifestations, and electroencephalographic findings were re-exacerbated with reappearance of abnormal bile alcohol excretion or elevated plasma cholestanol [71, 156]. Therefore, HMG-CoA reductase inhibitors could be beneficial when combined with CDCA, but long-term clinical benefits should be proven.

Low-density lipoprotein (LDL) is a major carrier of serum cholestanol. LDL-apheresis, usually combined with CDCA and HMG-CoA reductase inhibitors, has been performed to reduce serum cholestanol[157-160] Levels of serum cholestanol or 7α -hydroxy-4-cholesten-3-one decreased after each LDL-apheresis, but returned to their initial levels within 1–2 weeks[159, 161], suggesting that LDL-apheresis at a frequency of at least once every 2 weeks is necessary. The effects of LDL-apheresis on clinical manifestations are still controversial despite the decrease in cholestanol. In addition, the invasiveness of this procedure and its necessity for the long-term management of the disease should be taken into

account[161].

Symptomatic treatments for epilepsy[115, 120], psychiatric manifestations[122], and movement disorders such as dystonia[97, 98] and parkinsonism[90, 95] should be considered. Cataract extraction is also usually required[57].

After treatment with CDCA, improvements in neurophysiological examinations including NCV studies[78], VEP[72, 78], SSEP[72], MEP[72, 91], and EEG[10, 11] have been reported. Besides conventional MRI, DTI and tractography, MRS, and SPECT imaging might have potential as neuroimaging modalities for monitoring treatment response[120, 132-134, 162, 163].

Conclusions and Perspectives

CTX is considered a rare inherited metabolic disorder. However, it may be under- or misdiagnosed, although effective treatment is available. There is a crucial "point of no return" in CTX, after which treatment initiation can no longer prevent the progression of the disease[12]. The earlier the diagnosis is made and the sooner treatment is started, the more likely it is that the significant neurological manifestations that diminish the quality of life of patients with CTX can be improved or even prevented. Neonatal jaundice, chronic unexplained diarrhea, developmental delays, mental retardation, and learning difficulties are non-specific symptoms, but they could be diagnostic cues for pediatricians. Ophthalmologists have an opportunity to diagnose CTX, because bilateral cataracts are one of the earliest clinical symptoms and juvenile-onset bilateral cataracts could be useful as a screening marker for CTX[57]. Furthermore, it could be beneficial to screen newborns for CTX in the future[164].

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Conflicts of Interest

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Supplementary Table 1. Allele frequencies of *CYP27A1* variants according to Exome Aggregation Consortium database (version 0.3)

variant	AFR	AMR	EAS	FIN	NFE	SAS
p.G145=	0.00000	0.00000	0.00040	0.00000	0.00000	0.00000
p.A216P	0.00000	0.00000	0.00000	0.00000	0.00004	0.00000
p.T339M	0.00000	0.00000	0.00010	0.00000	0.00002	0.00007
p.R395C	0.00010	0.00020	0.00000	0.00030	0.00020	0.00006
p.R405W	0.00000	0.00009	0.00000	0.00000	0.00000	0.00006
p.R405Q	0.00010	0.00009	0.00050	0.00000	0.00004	0.00000
p.R474W	0.00000	0.00000	0.00000	0.00000	0.00002	0.00000
p.R474Q	0.00000	0.00000	0.00010	0.00000	0.00002	0.00000
c.1184+1G>A	0.00000	0.00000	0.00000	0.00000	0.00006	0.00070
c.1263+1G>A	0.00000	0.00009	0.00010	0.00000	0.00007	0.00000

AFR: African; AMR: Admixed American; EAS: East Asian; FIN: Finnish; NFE: Non-Finnish European; SAS: South Asian.

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Review

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Current Diagnosis and Management of Abetalipoproteinemia

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Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder caused by biallelic pathogenic mutations in the *MTTP* gene. Deficiency of microsomal triglyceride transfer protein (MTTP) abrogates the assembly of apolipoprotein (apo) B-containing lipoprotein in the intestine and liver, resulting in malabsorption of fat and fat-soluble vitamins and severe hypolipidemia. Patients with ABL typically manifest steatorrhea, vomiting, and failure to thrive in infancy. The deficiency of fat-soluble vitamins progressively develops into a variety of symptoms later in life, including hematological (acanthocytosis, anemia, bleeding tendency, etc.), neuromuscular (spinocerebellar ataxia, peripheral neuropathy, myopathy, etc.), and ophthalmological symptoms (e.g., retinitis pigmentosa). If left untreated, the disease can be debilitating and even lethal by the third decade of life due to the development of severe complications, such as blindness, neuromyopathy, and respiratory failure. High dose vitamin supplementation is the mainstay for treatment and may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life. However, it cannot fully prevent or restore impaired function. Novel therapeutic modalities that improve quality of life and prognosis are awaited. The aim of this review is to 1) summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL, and 2) propose diagnostic criteria that define eligibility to receive financial support from the Japanese government for patients with ABL as a rare and intractable disease. In addition, our diagnostic criteria and the entry criterion of low-density lipoprotein cholesterol (LDL-C) <15 mg/dL and apoB <15 mg/dL can be useful in universal or opportunistic screening for the disease. Registry research on ABL is currently ongoing to better understand the disease burden and unmet needs of this life-threatening disease with few therapeutic options.

Key words: **Abetalipoproteinemia, MTTP, Fat-soluble vitamin, Chylomicron, VLDL, Hypolipidemia**

1. Introduction

Abetalipoproteinemia (ABL; OMIM 200100) is a rare inherited disease characterized by the absence of plasma apolipoprotein (apo) B-containing lipoproteins and fat-soluble vitamins in the plasma. In 1950, Bassen and Kornzweig first described the syndrome, which is characterized by acanthocytes ("star-shaped" erythrocytes with irregular cytoplasmic projections, i.e., acantha, "thorn" in Greek), retinitis pigmentosa, and ataxia[1]. In 1960, the absence of beta-lipoprotein in the plasma of the syndrome was reported[2]. Later, in 1992, the activity of microsomal triglyceride transfer protein (MTTP) was found to be absent in the intestinal mucosa of ABL patients[3]. In 1993, mutations in the *MTTP* gene, which encodes the large subunit of MTTP, were identified in ABL patients (Fig. 1)[4, 5]. In this review, we summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL. We also propose diagnostic criteria for ABL, which have been used to determine the eligibility to receive financial aid from the Japanese

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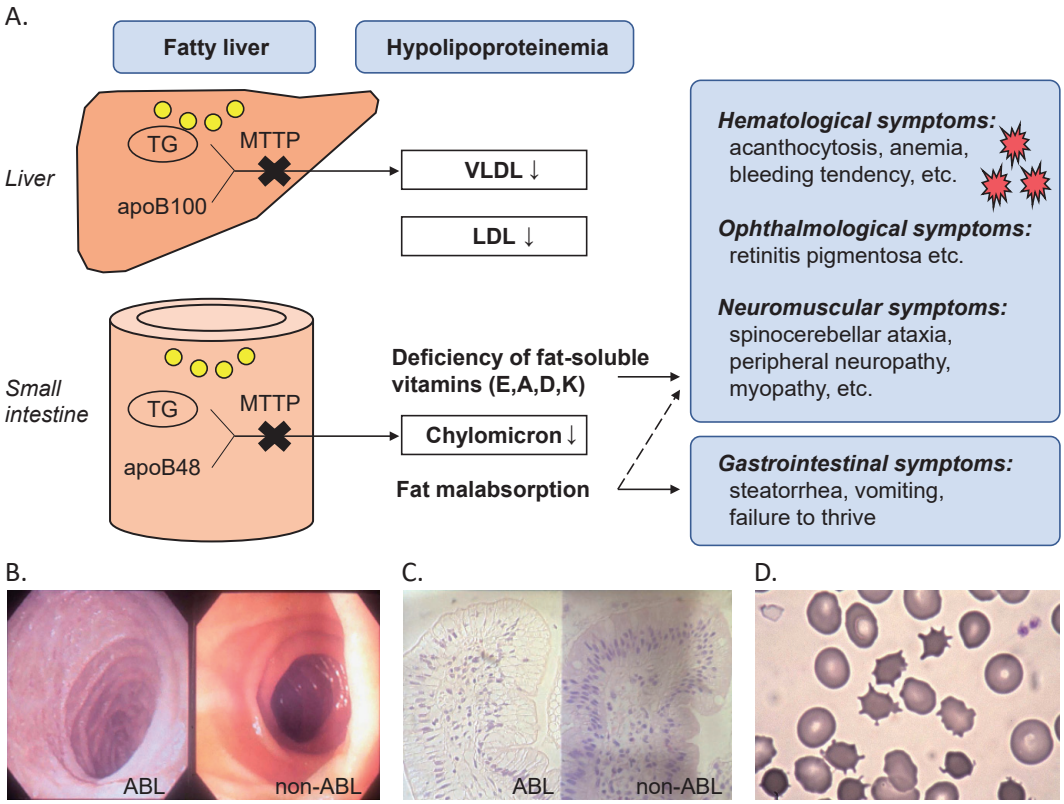

Fig. 1. Overview of abetalipoproteinemia

(A) MTTP is a prerequisite for the assembly and secretion of VLDL and CM by the liver and small intestine, respectively. Homozygous *MTTP* deficiency causes fat malabsorption, steatorrhea, vomiting, failure to thrive, hypolipoproteinemia, fatty liver, as well as symptoms related to deficiencies of fat-soluble vitamins. (B, C) Endoscopic examination and histological analysis of the duodenal mucosa of an ABL patient and a non-ABL control. Accumulation of intracellular lipids in epithelial cells (C) results in a snowy appearance (B), called snow-white duodenum, a gelee blanche, or white hoar frosting. (D) Acanthocytes of an ABL patient (Patient 1 in Ref 29). Figures 1B, 1C, and 1D are reproduced with permission from Ishibashi S and Ohashi K (The Lipid, 2014; 25: 200-203).

government for patients with ABL as a rare and intractable disease. The financial aid is provided by The Program for Designated Intractable Diseases under the Japanese Public Healthcare system. Pediatric ABL patients can be supported separately under The program of Medical Aid for Chronic Pediatric Diseases of Specified Categories.

2. Genetic and Molecular Basis

ABL is an autosomal recessive disorder caused by biallelic mutations in the *MTTP* gene. The estimated frequency of ABL is as rare as less than 1 in 1,000,000 [6]. Approximately 100 cases and at least 74 different *MTTP* mutations have been reported, including five (c.61+1G>C, c.1237-1G>A, c.1389del, p.I564T, p.N780Y) in four Japanese patients (Fig. 2)[7-35]. About one-third of patients were the progeny of consanguineous marriages[7]. The male-to-female sex ratio is reportedly 1:1 [7] or 3:2 [2], although both males and females should theoretically be equally affected. Genetic and clinical features of Japanese ABL patients are listed in Table 1. As the number of patients is limited, it is difficult to clarify the characteristics of Japanese cases of ABL.

MTTP is localized in the lumen of the endoplasmic reticulum of hepatocytes and intestinal epithelial cells. By transferring triglyceride (TG) and cholesterol ester to apoB, MTTP is essential for the formation of very low-density lipoproteins (VLDLs) and chylomicrons (CMs). A lack of MTTP abrogates the secretion of apoB-containing lipoproteins, which results in malabsorption of dietary fat and fat-soluble vitamins as well as accumulation of intracellular lipids in hepatocytes and intestinal epithelial cells. MTTP is a heterodimer of a large 97 kDa subunit containing 894 amino acids (encoded by *MTTP*) and a 55 kDa protein disulfide isomerase (PDI) subunit (encoded by *P4HB*)[36]. The *MTTP* gene consists of 18 coding exons. Crystal structure analysis reveals three structural

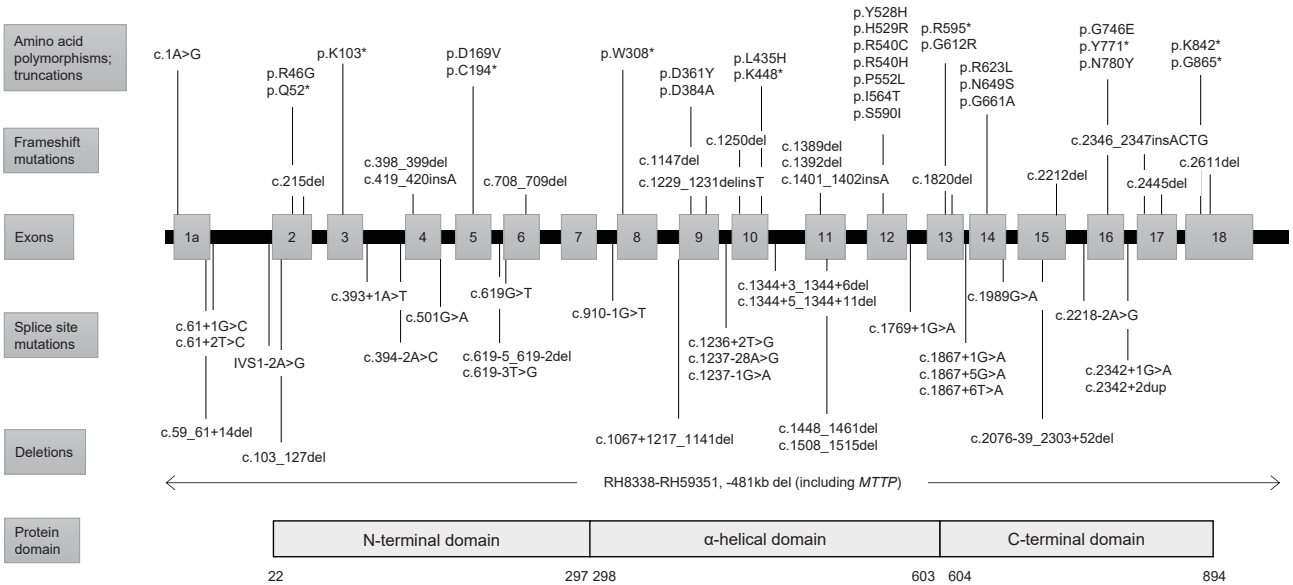

Fig. 2. Mutations in the *MTTP* gene

At least 74 *MTTP* mutations have been reported. The type of mutation may influence the severity of the disease[29]. The exon-intron structure of the *MTTP* gene encoded by exons 1a to 18 has been described[52]. Gray boxes represent exons. Lines represent the position of each mutation and polymorphism. Adapted from Zamel R, *et al.*[41], Narcisi TM *et al.*[27], and Suzuki T *et al.*[52]

domains in the large subunit of MTTP: an N-terminal β-barrel domain (amino acids 22-297), which interacts with the N-terminus of apoB; a central α-helical domain (298-603), which interacts with apoB as well as PDI; and a C-terminal domain (604-894)[7, 37-39]. The interaction between the α-helical domain and PDI is required for lipid-transfer activity, and the C-terminal domain mediates lipid-binding and lipid-transfer activity **(Fig. 2)**[37].

3. Clinical Manifestations

Gastrointestinal Symptoms (Fat Malabsorption and Failure to Thrive):

Symptoms of ABL typically develop in infancy after breastfeeding, including vomiting, steatorrhea due to fat malabsorption, and failure to thrive[2]. Patients often avoid dietary fat to relieve these gastrointestinal symptoms[2]. Endoscopic examination of the intestinal mucosa may reveal a snowy appearance, which is also called snow-white duodenum[40], a gelee blanche, or white hoar frosting **(Fig. 1B and 1C)**[7, 8].

Symptoms Related to Vitamin Deficiencies:

Chronic lipid malabsorption leads to a deficiency of fat-soluble vitamins (vitamins E, A, D, K). These vitamins require apoB-containing lipoproteins for their absorption and transport to peripheral tissues almost totally (for vitamin E and β-carotene) or partially (for vitamins A, D, and K)[7]. The resulting deficiency of these fat-soluble vitamins, particularly vitamin E and β-carotene, causes a variety of symptoms and complications, as described below.

• **Neuromuscular symptoms** develop mainly as a result of vitamin E deficiency, which is often associated with demyelination of spinocerebellar axons[2, 41, 42]. Typical symptoms include spinocerebellar ataxia, peripheral neuropathy, and myopathy[2]. Myopathy may result from both neural degeneration and an intrinsic myositis[7], which may be caused by pigment deposition due to the loss of vitamin E's anti-oxidant activity[2, 7]. The first symptom is often diminution of deep tendon reflexes as early as in the first few years or the first decade of life[7], followed by progressive abnormalities such as loss of vibratory sense, position sense, proprioception, a positive Romberg sign, spinocerebellar ataxia, dysmetria, dysarthria, wide-based spastic gait, hypesthesia, myopathy, muscular weakness, pes cavus, pes equinovarus, kyphoscoliosis, and lordosis. When left untreated, these symptoms gradually worsen and severely affect the quality of life, eventually rendering patients wheelchair-bound or bedridden. Without early treatment with vitamin E, patients may not survive past the third decade[2, 41, 43]. Mental retardation has been reported in some cases, although the evidence for causality is lacking[2, 17, 26]. There might be other

Table 1. Genetic and clinical features of Japanese patients with abetalipoproteinemia

Authors	Age	Gender	Mutation (*MTTP*)	Type	Consanguinity	Biochemical parameters (mg/dL)						
						TC	TG	LDL-C	HDL-C	cLDL-C	apoB	Vitamin E
Yang XP *et al.*[28]	29	M	c.1237-1G>A	Ho	No (Uniparental disomy)	33	0	N.D.	28	5	0	<0.1
Ohashi K *et al.*[29]	32	F	c.1389del	Ho	Yes	42	0.2	N.D.	36	6.0	0.9	<0.1
Ohashi K *et al.*[29]	27	M	c.2338A>T (p.N780Y)	Ho	Yes	34	2.6	N.D.	23	10.5	0.6	<0.1
Sakamoto O *et al.*[30]	15mo	M	c.61+1G>C c.1691T>C (p.I564T)	C. het	N.D.	46-92	10-100	N.D.	N.D.	-	<7.0	0.43

Authors	Clinical features			
	Gastrointestinal	Neuromuscular	Ophthalmological	Hematological
Yang XP *et al.*[28]	Frequent diarrhea, fat malabsorption with malnutrition, and short stature (from childhood); lipid-laden enterocytes by intestinal biopsy (29 years old).	Cerebellar and posterior spinal column dysfunction, decreased deep tendon reflexes, impaired vibratory sense and proprioception, dysmetria, ataxia, spastic gait, and positive Chaddock sign (29 years old).	Suspected loss of night vision (3 years old); descreased vision in dim light, visual field defects, and pigmentary retinal degeneration (29 years old).	Acanthocytosis
Ohashi K *et al.*[29]	Intolerance for fat-rich meals; snow-white duodenum and lipid-laden enterocytes by biopsy (32 years old).	Absent ankle and knee jerks, positive Romberg's sign (32 years old).	Fine mottling in the retina (32 years old).	Acanthocytosis (32 years old).
Ohashi K *et al.*[29]	Mild fatty liver, no history of steatorrhea	Normal	Normal	Acanthocytosis
Sakamoto O *et al.*[30]	Hepatomegaly and fatty liver, no steatorrhea.	Normal	Normal	No acanthocytosis

*Age (years or months (mo)) at molecular diagnosis; M=Males; F=Females; Ho=homozygous; C. het=compound heterozygous; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; cLDL-C, calculated LDL-C; N.D., Not described.

rare mutations due to consanguinity that could cause mental retardation[2, 17].

• **Cardiomyopathy**, supposedly due to vitamin E deficiency, may develop and can be lethal[7, 41, 43].

• **Ophthalmological symptoms** develop most likely as a consequence of deficiency of vitamin A and E. Retinitis pigmentosa is typically present by adolescence. Alterations in visual acuity, loss of night vision and color vision may appear as the first ophthalmological symptoms, followed by a gradual loss of vision, progressive scotoma, typically annular scotomas with macular sparing[2], and narrowing of the visual field, which ultimately lead to complete loss of vision. In some cases, ptosis, ophthalmoplegia, anisocoria, nystagmus, strabismus, and corneal ulcers may develop[2, 7, 41, 42].

• **Hematological abnormalities** include acanthocytosis **(Fig. 1D)**, low erythrocyte sedimentation rate (ESR), anemia, hemolysis, reticulocytosis, hyperbilirubinemia, and elevation of prothrombin time international normalized ratio (PT-INR)[41]. Acanthocytes are often observed, in more than 50% of the erythrocyte population, likely due to abnormal composition and distribution of lipids in the bilayer leaflets of the cell membrane[2, 44]. Low ESR is due to impaired rouleaux formation[7]. Anemia may be observed due to malabsorption of iron, folate, vitamin B12, and other nutrients secondary to fat malabsorption[2, 41]. Loss of vitamin E's anti-oxidant activity may cause autohemolysis, by accelerating hydroperoxidation of fatty acids[2]. Decreases in the levels of vitamin K-dependent coagulation factors (II,

Ⅶ, Ⅸ, Ⅹ) may result in bleeding tendency with elevated PT-INR[2, 41].

• **Abnormal bone metabolism and skeletal deformities** may be observed due to Vitamin D deficiency, as documented in some cases[41, 45, 46].

• **Hypothyroidism** may be observed in ABL patients, although the causality remains uncertain[39].

• **Fatty liver** may develop due to impaired secretion of VLDL. Steatohepatitis and liver cirrhosis may develop, requiring liver transplantation in some cases[9, 47].Causality needs to be carefully assessed as supplementation of medium-chain triglycerides (MCTs) may cause liver cirrhosis[2].

4. Diagnosis

ABL is typically suspected in infants who have steatorrhea, vomiting, and failure to thrive. However, the severity of the disease varies depending on the type of mutation in *MTTP*, and the diagnosis of ABL may be delayed until adulthood[2, 29]. ABL patients may be found opportunistically at health examinations in adulthood because of extremely low plasma cholesterol levels[29]. For early diagnosis and treatment of ABL, simple diagnostic criteria are warranted. Clinicians across multiple disciplines, including pediatricians, primary care physicians, neurologists, ophthalmologists and gastroenterologists, should consult lipidologists regarding further diagnostic tests when they suspect ABL.

Typical Levels of Plasma Lipids and Lipoproteins:

Plasma levels of total cholesterol (TC) in ABL patients are typically less than half normal, ranging from 20 to 50 mg/dL, with most of TC derived from high-density lipoprotein (HDL). Plasma levels of HDL are typically decreased by ~50%. The decrease in HDL may result in part from absence of phospholipid transfer from VLDL to HDL during the lipolysis of VLDL-TG. Catabolism of HDL, particularly apoE-containing HDL, may be increased, contributing to the apparently normal delivery of cholesterol to peripheral tissues in the absence of apoB-containing lipoproteins in ABL patients[7]. Plasma TG levels in ABL are typically less than 10 mg/dL[7] and do not increase after a dietary fat load[2, 7, 48]. Although the levels of TC and TG are variable in ABL patients, plasma levels of low-density lipoprotein (LDL) and apoB are consistently absent or extremely low. We searched PubMed for all previously reported cases and found that ABL patients have LDL-C <15 mg/dL and/or apoB <15 mg/dL (typically apoB <5 mg/dL)[7, 9, 28, 29], except for three cases of the mild-moderate phenotype[34]. Therefore, patients who have such levels of hypolipidemia should be suspected of having ABL.

Diagnostic Criteria:

A definitive diagnosis of ABL requires genetic testing of *MTTP*. Clinical diagnosis of ABL based on diagnostic criteria would help identify suspected cases for early diagnosis and treatment. Based on lipid levels of ABL and the clinical manifestations described above, we propose diagnostic criteria for ABL **(Table 2)**. Our criteria have been used to define the eligibility of ABL patients to receive financial support from the Japanese government as a rare and intractable disease. The entry criterion (LDL-C <15 mg/dL and/or apoB <15 mg/dL) of the criteria will also be useful for identifying suspected cases at health checkups or opportunistic blood testing (i.e., universal or opportunistic screening) for further referral to lipidology specialty clinics.

Differential Diagnosis:

Hypocholesterolemia in combination with fat malabsorption may result from the following diseases.

• **Familial hypobetalipoproteinemia 1(FHBL1; OMIM 615558)** is caused by mutations in *APOB* (mostly nonsense or frameshift) with an autosomal dominant mode of inheritance. The homozygous type of FHBL1 (Ho-FHBL1) presents with similar biochemical and clinical characteristics to ABL. Ho-FHBL1 can be differentiated from ABL only by family history. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL1 patients have <50% of normal plasma levels of LDL-C and apoB. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. The estimated frequency of Ho-FHBL1 is as rare as less than 1 in 1,000,000, and that of heterozygote FHBL1 is 1 in 1,000 to 3,000 [42, 49].

• **Chylomicron retention disease (CMRD; OMIM 246700),** also referred to as Anderson disease, is a rare autosomal recessive disorder caused by biallelic mutations in the *SAR1B* gene encoding Sar1b (secretion-associated and Ras-related GTPase 1B). The deficiency of Sar1b, which is a prerequisite for the secretion of CMs, causes severe hypocholesterolemia as well as steatorrhea, vomiting, and failure to thrive[50]. As VLDL secretion is preserved, CMRD can be differentiated from ABL and FHBL1 by plasma lipid levels: In CMRD, plasma levels of total cholesterol, LDL-C, and HDL-cholesterol (HDL-C) are more than 50% decreased, whereas the plasma TG level is normal.

Table 2. Diagnostic criteria for ABL in Japan

A. Entry criterion
- Plasma LDL-C level ＜15 mg/dL AND/OR plasma apoB level ＜15 mg/dL.

B. Clinical manifestations
1. Gastrointestinal: fat-malabsorption related symptoms (steatorrhea, chronic diarrhea, vomiting, failure to thrive, etc.).
2. Neuromuscular: ataxia, spastic paralysis, hypoesthesia due to peripheral neuropathy, diminution of deep tendon reflexes, etc.
3. Ophthalmological: retinitis pigmentosa, loss of night vision, constriction of visual field, decreased visual acuity, etc.

C. Laboratory findings
1. Acanthocytosis

D. Differential diagnosis
Familial hypobetalipoproteinemia 1 (FHBL1)(OMIM 615558), chylomicron retention disease (Anderson disease) (OMIM 246700), hyperthyroidism.
*ABL and homozygous FHBL (Ho-FHBL) can not be distinguished only from the clinical manifestations and laboratory findings of a proband. Family history is helpful. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL1 patients have ＜50% of normal LDL-C and apoB plasma levels. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. Plasma levels of lipids, apoB, and fat-soluble vitamin of other family members may be helpful.

E. Genetic test
Pathogenic mutations in the *MTTP* gene

<Diagnosis>

Definite ABL:
Entry criterion (A) is associated with at least one item of B or C AND exclusion of differential diagnosis (D) AND genetic diagnosis (E).

Probable ABL:
Entry criterion (A) is associated with at least two items of B or C AND exclusion of differential diagnosis (D).

5. Assessment, Treatment, and Management

The current strategy and recommendations for the treatment and management of ABL, which are adapted and modified from reviews by Hegele *et al.* and others, are summarized below[2, 6, 7, 39, 41, 42].

Assessment:

The recommended assessments for ABL patients include[2, 6, 7, 39, 41, 42]:

- **Evaluation of growth** at every visit.
- **Annual blood analysis** including lipid profiles (TC, TG, LDL-C, HDL-C, apoB, apoA-I), liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total and direct bilirubin, alkaline phosphatase, albumin), fat-soluble vitamins (Vitamin A (retinol), β-carotene, 25-OH vitamin D, vitamin E, vitamin K), other micronutrients (vitamin B12, iron, folate), complete blood count, PT-INR, reticulocyte count, ESR, calcium, phosphate, uric acid, and thyroid stimulating hormone (TSH).
- **Ophthalmological and neurological evaluation** every 6-12 months.
- **Hepatic ultrasonography, bone mineral density measurements, echocardiography** every 3 years.

Treatment and Management:

For the treatment of ABL patients, the standard of care includes[2, 6, 7, 39, 41, 42]:

- **Restriction of fat intake** is necessary to prevent steatorrhea. Total fat intake should be restricted to less than 30% of the total energy intake, or less than 15 to 20 g per day, or even less than 5 g per day in children[2, 6, 7, 39, 42]. Increased fat in the stool may induce oxalate urolithiasis by binding dietary calcium and increasing dietary oxalate absorption. This might be prevented by providing sufficient dietary calcium, fluid intake, and reducing dietary oxalate[2].
- **Adequate calorie intake** is essential to avoid growth retardation. It should be noted that fat malabsorption may lead to malabsorption of carbohydrates proteins, and other nutrients[7]. A fat-restricted diet may mitigate such secondary malabsorption.
- **Medium-chain triglyceride (MCT) administration** can help correct malnutrition, particularly in infants, though not absolutely necessary. MCTs are absorbed and then transported in the circulation not by CMs but by albumin. Since hepatic fibrosis is a potential adverse effect of MCTs, liver enzymes should be monitored in infants who are administered MCTs, and long-term administration is better avoided[2, 7].

• **Oral essential fatty acid supplementation.** The daily requirement for essential fatty acids, e.g., up to 1 teaspoon per day of oil rich in polyunsaturated fatty acids (e.g., soybean or olive oil) is recommended[7, 39, 42].

• **High dose oral vitamin E supplementation** (100-300 IU/kg/day[6, 7, 39, 42]; 1,000-2,000 mg/day (infant), 5,000-10,000 mg/day (older children and adults)[2]; 2,400-12,000 IU/day[41]; 1IU=1mg tocopheryl acetate) delays or prevents progression of neurological complications[2, 6]. Even with such high dose vitamin E supplementation, serum vitamin E levels increase to at most 30% of the lower limit of normal serum levels of vitamin E[7, 41]. However, serum vitamin E levels may not correlate with tissue vitamin E levels[7, 39, 41]. Better methods of monitoring tissue vitamin E concentrations are awaited. Vitamin E may be administered via alternative routes (intravenous, intramuscular, etc.). However, oral supplementation is favored due to: 1) feasibility for life-long supplementation, 2) no apparent inferiority in increasing tissue vitamin E levels compared to other methods, 3) no apparent toxicity (Other routes of supplementation may induce fatty liver and other complications[42]). It should be noted that absorption of large doses of vitamin E may induce or exacerbate vitamin K deficiency[6, 7, 41]

• **High dose oral vitamin A supplementation** (100-400 IU/kg/day[39, 41, 42]) and vitamin E supplementation can prevent or arrest ophthalmological complications[2, 6, 7, 39].

• **Supplementation of vitamin D** (800-1,200 IU/day[39, 42]) should be considered in cases of vitamin D deficiency.

• **Supplementation of vitamin K** (5-35 mg/week[39, 41, 42]) should be considered in cases of vitamin K deficiency with hypothrombinemia and prolonged PT-INR. Supplementation of vitamin K will normalize its blood levels[2, 41].

• **Supplementation of iron, folate, or vitamin B12** may be necessary in the case of anemia[2, 6, 41, 42].

• **Multidisciplinary care for neurological complications** involving neurologists, physiatrists, physical therapists, occupational therapists, and speech therapists[39].

Particular caution should be taken to avoid vitamin A toxicity[2, 39, 41], which can be seen even in those who have a normal plasma vitamin A concentration[39]. To avoid toxicity, it is recommended that the target vitamin A concentration goal should be set at the lower limit of normal levels[41], and the dose of vitamin A supplementation should be titrated by monitoring blood concentrations of vitamin A and β-carotene[39, 41, 42]. Women who are pregnant or planning to conceive should receive 50% of the dose of vitamin A supplementation to avoid vitamin A toxicity with careful monitoring of the blood concentrations of vitamin A and β-carotene[39, 42]. Supplementation of vitamin A should be continued in pregnancy as its deficiency could induce lethal complications in pregnant women[39, 41].

6. Burden of Disease and Unmet Needs

If left untreated, ABL patients start manifesting systemic complications related to fat-soluble vitamin deficiencies as early as in the first decade of life, gradually developing into lethal conditions in the third decade[7, 41]. Early diagnosis and adequate supplementation of vitamin E, A, and other fat-soluble vitamins may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life[7, 39]. Successful pregnancies in ABL patients have been reported [2, 7, 41]. This review and our simple diagnostic criteria aim to contribute to the early diagnosis and treatment of ABL by facilitating cooperation among various medical specialists.

However, the growth potential of patients may not be fully restored by dietary therapy[39, 42]. High dose vitamin therapy is insufficient for most patients, and even ineffective for some, to recover from vitamin deficiencies and their complications[42]. Deficiency of other lipids or nutrients, such as essential fatty acids, could also contribute to the pathogenesis of ABL. Therefore, a good understanding of its pathogenesis and keeping abreast of novel therapeutic developments are necessary. Gene therapies that correct *MTTP* deficiency in the liver and small intestine may be promising therapeutic candidates[51].

More studies are needed to unravel the pathogenesis, genotype-phenotype relationship, burden of disease, and unmet needs. Considering the paucity of patients, a nation-wide registry for a long enough period to evaluate the prognosis would help clarify these issues. To this end, a registry study for rare and intractable lipid disorders including ABL (the PROLIPID study) is ongoing in Japan.

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Conflicts of Interest

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資料 3. PROLIPID 研究の登録患者数およびその内訳（令和 3 年 3 月末時点）

疾患名	N	（疑い症例）
① FH ホモ接合体	17	0
② FH ヘテロ	789	12
③ 家族性 III 型高脂血症	18	
④ 高カイロミクロン血症	47	
⑤ シトステロール血症	2	
⑥ 脳腱黄色腫症	2	
⑦ LCAT 欠損症	1	
⑧ タンジール病	0	
⑨ アポ A1 欠損症	0	
⑩ 無βリポタンパク血症・低βリポタンパク血症	0	
合計	876	12
未回答	89	

資料４．学会承認を得た各疾患の新しい診断基準（案）

259 レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症の新診断基準（案）

Ａ．必須項目

１．血中 HDL コレステロール値　25 mg/dL 未満

２．コレステロールエステル比の低下（60%以下）

Ｂ．症状

１．　　蛋白尿、腎機能障害

２．　　角膜混濁

Ｃ．検査所見

血液・生化学的検査所見

(1) 貧血（ヘモグロビン値＜11 g/dl）

(2) 赤血球形態の異常（いわゆる「標的赤血球」「大小不同症」「奇形赤血球症」「口状赤血球」）

(3) 異常リポ蛋白の出現（Lp-X、大型 TG rich LDL）

眼科検査所見

コントラスト感度の正常範囲からの逸脱

Ｄ．鑑別診断

以下の疾患を鑑別する。

他の遺伝性低 HDL コレステロール血症（タンジール病、アポリポタンパク A-Ⅰ欠損症）

続発性 LCAT 欠損症（肝疾患（肝硬変・劇症肝炎）、胆道閉塞、低栄養、悪液質など蛋白合成低下を呈する病態、基礎疾患を有する自己免疫性 LCAT 欠損症）

二次性低 HDL コレステロール血症[*1]

（＊１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））

Ｅ．遺伝学的検査

１．　　*LCAT*遺伝子の変異

＜診断のカテゴリー＞

必須項目の 2 項目を満たした例において、以下のように判定する。

Definite：**Ｂ・Ｃ**のうち 1 項目以上を満たし，**Ｄ**の鑑別すべき疾患を除外し、**Ｅ**を満たすもの

Probable：**Ｂ・Ｃ**のうち 1 項目以上を満たし**Ｄ**の鑑別すべき疾患を除外したもの

Definite、Probable を対象とする。

260．シトステロール血症の新診断基準（案）

Ａ．症状

１．　皮膚黄色腫または腱黄色腫の存在

２．　早発性冠動脈疾患（男性 45 歳未満、女性 55 歳未満）

Ｂ．検査所見

血清シトステロール濃度１mg/dL（10μg/ml）以上

Ｃ．鑑別診断[*1]

以下の疾患を鑑別する。

家族性高コレステロール血症、脳腱黄色腫症

*1：鑑別診断が困難な場合や上記疾患とシトステロール血症の合併が否定できない場合は，*ABCG5/8*遺伝子検査を実施する．*ABCG5/8*遺伝子の病原性変異が確認された場合は，上記の疾患を合併していてもシトステロール血症の診断が可能である．

Ｄ．遺伝学的検査

*ABCG5/8*遺伝子の変異

＜診断のカテゴリー＞

Definite：Ａ−１及びＢを満たし、Ｃの鑑別すべき疾患を除外し、Ｄを満たすもの

Probable：A-１及びＢを満たし、Ｃの鑑別すべき疾患を除外したもの
Possible：A-１、２及びＢを満たすもの
Definite、Probable を対象とする。

補足事項：
高 LDL コレステロール血症を呈したシトステロール血症では、コレステロール吸収阻害薬（エゼチミブ、コレスチミド）が著効する点が家族性高コレステロール血症と異なる。

261．タンジール病の新診断基準（案）

Ａ．必須項目
１．　血清 HDL コレステロールが 25 mg/dL 未満
２．　血中アポ A-Ⅰ濃度 20 mg/dL 未満

Ｂ．症状
１．オレンジ色の特徴的な扁桃腫大
２．肝腫大または脾腫
３．角膜混濁
４．末梢神経障害
５．心血管病変

Ｃ．　鑑別診断
以下の疾患を鑑別する。
LCAT 欠損症、アポリポ蛋白質 A-I 欠損症、二次性低 HDL コレステロール血症[*1]
（*１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））

Ｄ．遺伝子検査
ABCA1 遺伝子変異の同定

＜診断のカテゴリー＞
Definite: 必須項目の 2 項目を全て満たす例のうち、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外し、D を満たすもの
Probable: 必須項目の 2 項目を全て満たす例のうち、Ｂの２項目以上を満たし、Ｃの鑑別すべき疾患を除外したもの
Definite、Probable を対象とする。

補足事項：鑑別診断が困難な場合は，*ABCA1* 遺伝子検査を実施する．*ABCA1* 遺伝子の病原性変異が確認された場合は診断が可能である．

262．原発性高カイロミクロン血症の新診断基準（案）

Ａ．必須条件：１および２を認め、鑑別診断（下記Ｅ）が除外される。
１．血清トリグリセリド値　1,000 mg/dL以上（空腹時採血(食後 12 時間以上)）
２．カイロミクロンの証明（血清静置試験[*1]、超遠心法、電気泳動法、HPLC法による）
（*1: 血清を４℃で 24～48 時間静置した後に、血清の上清にクリーム層を認める）

Ｂ．症状 主症状：１～４、副症状：５、６

１．繰り返す腹痛かつ/または急性膵炎
２．発疹性黄色腫
３．網膜脂血症の存在
４．肝腫大かつ/または脾腫大
５．**呼吸困難**
６．神経精神症状（認知症、うつ病、記憶障害）

Ｃ．検査所見

１．LPL活性・蛋白の欠損あるいは著明な低下（正常の 10%以下）。
（ヘパリン静脈注射後血漿、脂肪組織生検検体、単球由来マクロファージ。）
２．アポリポ蛋白C-IIの欠損あるいは著明な低下（正常の 10%以下）。
３．アポリポ蛋白A5 の欠損あるいは著明な低下（正常の 10%以下）。
４．LPL、ヘパリン、アポリポ蛋白C-II、GPIHBP1 に対する自己抗体の証明。

Ｄ．遺伝学的検査

１．　リポ蛋白リパーゼ遺伝子の変異
２．　アポリポタンパクC-ＩＩ遺伝子の変異
３．　*GPIHBP1* 遺伝子の変異
４．　*LMF1* 遺伝子の変異
５．　アポリポタンパクA-V遺伝子の変異

Ｅ．鑑別診断

１．III型高脂血症
２．家族性複合型高脂血症（FCHL）
３．二次性高脂血症（アルコール多飲、ネフローゼ症候群、神経性食思不振症、　　妊娠、糖尿病、リポジストロフィー、ウェーバー・クリスチャン（Weber-　Christian）病、甲状腺機能低下症、先端巨大症、クッシング症候群、ネルソン　　症候群、薬剤（エストロゲン、ステロイド、利尿薬、βブロッカー、SSRIなど抗　　精神病薬、痙攣治療薬、HIV治療薬、免疫抑制剤など）、その他高TG血症を来す　　疾患（多発性骨髄腫、全身性エリテマトーデス（SLE）、悪性リンパ腫、サルコ　　イドーシスなど））

＜診断のカテゴリー＞

Definite（確定診断）：必須条件に、**Ｃ**あるいは**Ｄ**のいずれかの異常（疾患関連あり）が確認された場合。
Probable（臨床的診断）：必須条件に、**Ｂ**の主症状のいずれかを認める場合。
Possible（疑い例）：必須条件のみ、あるいは、必須条件に**Ｂ**の副症状を認める場合。
Definite、Probableを対象とする。

264.　無 β リポタンパク血症の新診断基準（案）

Ａ．必須項目

血中 LDL コレステロール 15 mg/dL 未満（Friedewald 式による）または血中アポリポ蛋白 B 15 mg/dL 未満

Ｂ．症状

１．消化器症状（脂肪吸収障害による脂肪便、慢性下痢、嘔吐、成長障害など）
２．神経症状（運動失調,痙性麻痺,末梢神経障害による知覚低下や腱反射消失など）
３．網膜色素変性症（夜盲,視野狭窄,視力低下など）

Ｃ．検査所見

１．有棘赤血球の存在

Ｄ．鑑別診断

以下の疾患を鑑別する。
家族性低 β リポタンパク血症,カイロミクロン停滞病（アンダーソン（Anderson）病）,甲状腺機能亢進症
※家族性低βリポタンパク血症ホモ接合体との確実な鑑別は,本人のデータのみでは困難であり遺伝子変異

の同定を要するが,以下の所見を参考に鑑別可能である.
・ホモ接合体発端者の第1度近親者のコレステロール低値
本症は常染色体潜性遺伝（**劣性遺伝**）でありホモ接合体発端者の第1度近親者のヘテロ接合体に軽度低脂血症を認めないが,家族性低 β リポタンパク血症（FHBL）1は常染色体共顕性遺伝（**共優性遺伝**）であるため,ホモ接合体発端者の第1度近親者のヘテロ接合体に低脂血症を認める.両親・兄弟の血清脂質・血中アポB濃度、脂溶性ビタミン濃度の測定も参考になる.

Ｅ．遺伝学的検査

*MTTP*遺伝子の変異

＜診断のカテゴリー＞

Definite：必須項目を満たす例で，**Ｂ・Ｃ**の計４項目のうちいずれか１項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外し,**Ｅ**を満たすもの.

Probable：必須項目を満たす例で，**Ｂ・Ｃ**の計４項目のうちいずれか２項目以上を満たし,**Ｄ**の鑑別すべき疾患を除外したもの.

Definite、Probableを対象とする。

264類縁　家族性低βリポタンパク血症（FHBL）1(ホモ接合体)の診断基準（案）

Ａ．必須項目

血中LDL-コレステロール15 mg/dL未満（Friedewald式による）または血中アポリポ蛋白B 15 mg/dL未満

Ｂ．症状

１．消化器症状（脂肪吸収障害による脂肪便、慢性下痢、嘔吐、成長障害など）

２．神経症状（運動失調、痙性麻痺、末梢神経障害による知覚低下や腱反射消失など）

３．網膜色素変性症（夜盲、視野狭窄、視力低下など）

Ｃ．検査所見

１．有棘赤血球の存在

Ｄ．鑑別診断

以下の疾患を鑑別する。

無βリポタンパク血症、カイロミクロン停滞病（アンダーソン（Anderson）病)、甲状腺機能亢進症

※無βリポタンパク血症との確実な鑑別は、本人のデータのみでは困難であり遺伝子変異の同定を要するが、以下の所見を参考に鑑別可能である。

・ホモ接合体発端者の第1度近親者のコレステロール低値

家族性低β リポタンパク血症（FHBL）1は常染色体共顕性遺伝（**共優性遺伝**）であるため、ホモ接合体発端者の第1度近親者のヘテロ接合体に低脂血症を認めるが、無βリポタンパク血症は常染色体潜性遺伝（**劣性遺伝**）であり、ホモ接合体発端者の第1度近親者のヘテロ接合体に軽度低脂血症を認めない。両親・兄弟の血清脂質・血中アポB濃度、脂溶性ビタミン濃度の測定も参考になる。

Ｅ．遺伝学的検査

*APOB*遺伝子の変異

＜診断のカテゴリー＞

Definite：必須項目を満たす例で、**Ｂ・Ｃ**の計４項目のうちいずれか１項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外し、**Ｅ**を満たすもの。

Probable：必須項目を満たす例で、**Ｂ・Ｃ**の計４項目のうちいずれか２項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外したもの。

Definite、Probable を対象とする。

新規：アポリポタンパクA-Ⅰ欠損症　-診断基準（案）-

○概要

１．　概要

高比重リポ蛋白（high density lipoprotein: HDL）の主要構成アポ蛋白である、アポリポタンパク A-Ⅰ（アポ A-Ⅰ）の欠損、異常により生ずる病態である。アポ A-Ⅰとともにアポ C-Ⅲ、アポ A-Ⅴを欠損する場合もある。血清 HDL コレステロール、アポ A-Ⅰ濃度が著しい低値を示す。タンジール病で認められるオレンジ色の扁桃肥大や、LCAT 欠損症で認められるコレステロールエステル比の低下や腎障害は、認められない。早期に冠動脈疾患を合併する危険性があり、動脈硬化性疾患の早期診断と危険因子の管理が重要である。アポ A-1 の変異の一部にアミロイドーシスの合併が報告されているが、アミロイドーシスが主要な病態であり HDL 低値を伴わない場合は、全身性アミロイドーシス（指定難病 28）にて取り扱う。

２．　原因

血中の遊離アポ A-Ⅰが ABCA1 に結合することが、HDL 形成の第一段階である。ABCA1 は細胞内からコレステロール搬出する機能を持ち、アポ A-Ⅰと結合することでコレステロールを付加して preβ-HDL となる。本症ではアポ A-1 の欠損または機能喪失により HDL が産生されないため、血清 HDL コレステロール、アポ A-Ⅰ濃度が著しい低値となる。

３．　症状

角膜混濁

　角膜混濁がしばしば認められる

皮膚病変

　黄色腫がしばしば認められる

心血管病変

　冠動脈疾患の合併が多く認められる

血清脂質検査

　著明な低 HDL-C 血症（HDL- C＜25mg/dL）で、血清アポ A-Ⅰは 20 mg/dl 未満

　アポ A-Ⅰ含有血清 HDL の欠損、正常～低下したトリグリセライド，正常レベルの LDL-C を認める

４．　治療法

遺伝子治療などの根本的な治療はなく、合併する動脈硬化性疾患の予防・治療が中心となる。糖尿病（耐糖能異常）を合併することが多くその治療が重要であり、また高血圧、喫煙などの危険因子の管理も重要である。

５．　予後

冠動脈疾患などの動脈硬化性疾患により大きく異なる。狭心症、心筋梗塞などの発症に留意し、定期的な動脈硬化性疾患のチェックが重要である。

○要件の判定に必要な事項

１．　患者数

100 人未満（わが国では 9 例が報告されている）

２．　発病の機構

不明（アポ A－1／C－III／A－Ⅳ遺伝子変異が関与する。）

３．　効果的な治療方法

未確立（併存する動脈硬化性疾患危険因子の治療が重要である。）

４．　長期の療養

必要（遺伝子異常を背景とし、代謝異常が生涯持続するため。）

５．　診断基準

あり（研究班作成の診断基準）

６．　重症度分類

先天性代謝異常症の重症度評価で、中等症以上を対象とする。

○情報提供元

「原発性高脂血症に関する調査研究班」

研究代表者　国立循環器病研究センター研究所　病態代謝部　部長　斯波真理子

研究分担者　国立大学法人大阪大学　循環器内科　小関正博

アポリポタンパク A-Ⅰ欠損症の診断基準（案）

Ａ．必須項目

1. 血清 HDL コレステロールが 25 mg/dL 未満

2. 血中アポ A-Ⅰが 20 mg/dL 未満

Ｂ．症状

1. 角膜混濁
2. 黄色腫
3. 早発性冠動脈疾患（男性 55 歳未満、女性 65 歳未満）

Ｃ．鑑別診断

以下の疾患を除外できる。

タンジール病、LCAT 欠損症、二次性低 HDL コレステロール血症[*1]

（＊１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））

Ｄ．遺伝子検査

APOA1 遺伝子変異の同定

＜診断のカテゴリー＞

Definite：Ａの必須項目を満たす例で、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外し、Ｄを満たすもの。

Probable：Ａの必須項目を満たす例で、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外したもの。

Definite、Probable を対象とする。

資料 5. 成人指定難病と小児慢性特定疾病の該当疾患の違い

表１．「難病の患者に対する医療等に関する法律」にもとづく 2015 年１月 1 日および　7 月 1 日施行の厚生労働省「指定難病」のうち原発性高脂血症該当疾患

告示番号	病名
79	家族性高コレステロール血症（ホモ接合体）
259	レシチンコレステロールアシルトランスフェラーゼ欠損症
260	シトステロール血症
261	タンジール病
262	原発性高カイロミクロン血症
263	脳腱黄色腫症
264	無βリポ蛋白血症

表２．2015 年施行「児童福祉法の一部を改正する法律」による厚生労働省　「小児慢性特定疾病」のうち原発性高脂血症該当疾患（大分類 12 脂質代謝異常）

小分類番号	病名
129	原発性高カイロミクロン血症
130	家族性高コレステロール血症
131	家族性複合型高脂血症
132	無βリポ蛋白血症
133	高比重リポタンパク（HDL）欠乏症
134	129 から 133 まで掲げるもののほか、脂質代謝異常症

令和 3 年 3 月 11 日

国立保健医療科学院長　殿

国立研究開発法人
機関名　国立循環器病研究センター
所属研究機関長　職　名　理事長
氏　名　小川　久雄　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　分子病態部・非常勤研究員

（氏名・フリガナ）　斯波　真理子・シバ　マリコ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	国立循環器病研究センター	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	国立循環器病研究センター	□
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」や「臨床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３年３月15日

国立保健医療科学院長　殿

機関名　自治医科大学

所属研究機関長　職　名　学長

氏　名　永井　良三　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部　・　教授

（氏名・フリガナ）　石橋　俊　・　イシバシ　シュン

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	自治医科大学倫理委員会	□
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）

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６．利益相反の管理

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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３年４月９日

国立保健医療科学院長　殿

機関名　中部大学

所属研究機関長　職　名　学長

氏　名　竹内　芳美　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　応用生物学部生物機能開発研究所・客員教授

（氏名・フリガナ）　横山信治・ヨコヤマシンジ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	中部大学倫理審査委員会	□
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：　　）	□	■	□		□

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その他（特記事項）

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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

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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 3年 3月 16日

国立保健医療科学院長　殿

機関名　国立大学法人筑波大学

所属研究機関長　職　名　国立大学法人筑波大学長

氏　名　永田恭介　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学医療系・教授

（氏名・フリガナ）　島野　仁・シマノヒトシ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	筑波大学附属病院	□
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」や「臨床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 3 年 3 月 24 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

氏　名　徳久　剛史　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・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)
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針 (※3)	□　■	□		□
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」や「臨床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 3 年 3 月 15 日

国立保健医療科学院長　殿

機関名　東　邦　大　学

所属研究機関長　職　名　学　長

氏　名　高　松　　研　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部・教授

（氏名・フリガナ）　武城 英明・ブジョウ ヒデアキ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　☑	□		□
遺伝子治療等臨床研究に関する指針	□　☑	□		□
人を対象とする医学系研究に関する倫理指針（※3）	☑　□	☑	佐倉病院倫理委員会	□
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」や「臨床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。

2021年3月12日

国立保健医療科学院長　殿

機関名　地方独立行政法人
りんくう総合医療センター

所属研究機関長　職　名　理事長

氏　名　山　下　静　也　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　循環器内科・理事長

（氏名・フリガナ）　山下　静也・ヤマシタ　シズヤ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	りんくう総合医療センター	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	りんくう総合医療センター	□
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」や「臨床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３年３月31日

国立保健医療科学院長　殿

機関名　帝京大学
所属研究機関長　職　名　学長
氏　名　冲永佳史　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部　教授

（氏名・フリガナ）　塚本　和久　・　ツカモト　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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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：　）	有
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：　）	有
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：　）	有
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：　）	有

（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　3年　3月　31日

国立保健医療科学院長　殿

機関名　名古屋大学大学院

所属研究機関長　職　名　医学系研究科長

氏　名　門松　建治　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学系研究科・教授

（氏名・フリガナ）　林 登志雄　（ハヤシ トシオ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	名古屋大学	□
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」や「臨床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３年３月31日

国立保健医療科学院長　殿

機関名　防衛医科大学校
所属研究機関長　職　名　学校長
氏　名　四ノ宮　成祥　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　抗加齢血管内科　教授

（氏名・フリガナ）　池脇克則（イケワキカツノリ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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3年3月26日

国立保健医療科学院長　殿

機関名　杏林大学

所属研究機関長　職　名　学長

氏　名　大瀧　純一　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部・教授

（氏名・フリガナ）　後藤田　貴也　（ゴトウダ　タカナリ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
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」にチェックレ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」や「臨床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。

R3 年3月17日

国立保健医療科学院長　殿

機関名　国立大学法人山梨大学

所属研究機関長　職　名　学長

氏　名　島田　眞路　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　山梨大学　大学院総合研究部小児科　医学研究員

（氏名・フリガナ）　土橋一重　（ドバシ　カズシゲ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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　3　年　4　月　1日

国立保健医療科学院長　殿

国立研究開発法人
機関名　国立循環器病研究センター

所属研究機関長　職　名　理事長

氏　名　大津欣也

次の職員の令和２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　難治性疾患等政策研究事業

２．研究課題名　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　オープンイノベーションセンター　・　センター長

（氏名・フリガナ）　宮本　恵宏（ミヤモト　ヨシヒロ）

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)
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	国立循環器病研究センター	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針 (※3)	■	□	■	国立循環器病研究センター	□
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」や「臨床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3年3月9日

国立保健医療科学院長　殿

機関名　国立循環器病研究センター
所属研究機関長　職　名　理事長
氏　名　小川　久雄　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　予防医学・疫学情報部　室長

（氏名・フリガナ）　竹上　未紗　・　タケガミ　ミサ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	国立循環器病研究センター	□
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」や「臨床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　3年　3月29日

国立保健医療科学院長　殿

機関名　国立大学法人信州大学

所属研究機関長　職　名　学長

氏　名　濱　田　州　博　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部　・　教授

（氏名・フリガナ）　関島　良樹・　セキジマ　ヨシキ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	信州大学	□
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」や「臨床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　3　年　3　月　31　日

国立保健医療科学院長　殿

機関名　岩手医科大学

所属研究機関長　職　名　学長

氏　名　祖父江　憲治　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部　教授

（氏名・フリガナ）　石垣　泰（イシガキ　ヤスシ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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３年５月２０日

国立保健医療科学院長　殿

機関名　東京大学
所属研究機関長　職　名　総長
氏　名　藤井　輝夫　印

次の職員の令和 2 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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）医学部附属病院・助教

（氏名・フリガナ）岡崎　啓明・オカザキ　ヒロアキ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	東京大学	□
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」や「臨床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 3年　3月15日

国立保健医療科学院長　殿

機関名　石川県立中央病院

所属研究機関長　職　名　院長

氏　名　岡田　俊英　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　遺伝診療科　診療部長

（氏名・フリガナ）　野原　淳　（ノハラ　アツシ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	石川県立中央病院	□
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」や「臨床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：　当院倫理委員会にて審査　）
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３年　２月　１９日

国立保健医療科学院長　殿

機関名　山形大学

所属研究機関長　職　名　学長

氏　名　玉手　英利　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）医学部付属病院・講師

（氏名・フリガナ）小山　信吾・コヤマ　シンゴ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■　□	■	山形大学	□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	山形大学	□
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」や「臨床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３年３月２６日

国立保健医療科学院長　殿

機関名　日本医科大学

所属研究機関長　職　名　学長

氏　名　弦間　昭彦　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部・講師

（氏名・フリガナ）　稲垣　恭子（イナガキ　キョウコ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	日本医科大学付属病院倫理委員会	□
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」や「臨床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3年3月9日

国立保健医療科学院長　殿

機関名　国立大学法人京都大学

所属研究機関長　職　名　医学研究科長

氏　名　岩井　一宏　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）大学院医学研究科・准教授

（氏名・フリガナ）尾野　亘　（オノ　コウ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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。

2021年 2月 24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　森井　英一　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学系研究科・助教

（氏名・フリガナ）　小関　正博・コセキ　マサヒロ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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３年４月１日

国立保健医療科学院長　殿

機関名　順天堂大学

所属研究機関長　職　名　学長

氏　名　新井　一　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　保健医療学部　特任教授

（氏名・フリガナ）　代田　浩之　（ダイダ　ヒロユキ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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３年３月15日

国立保健医療科学院長　殿

機関名　自治医科大学

所属研究機関長　職　名　学長

氏　名　永井　良三　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部　・　学内講師

（氏名・フリガナ）　高橋　学　・　タカハシ　マナブ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	自治医科大学倫理委員会	□
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」や「臨床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。

R3年 3月22日

国立保健医療科学院長　殿

機関名　国立大学法人熊本大学

所属研究機関長　職　名　学長

氏　名　原田　信志　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　生命科学研究部　・　教授

（氏名・フリガナ）　中村　公俊　・　ナカムラ　キミトシ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	☑	□	☑	熊本大学	□
遺伝子治療等臨床研究に関する指針	□	☑	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	☑	□		□
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」や「臨床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３年４月１日

国立保健医療科学院長　殿

機関名　順天堂大学

所属研究機関長　職　名　学長

氏　名　新井　一　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学研究科　教授

（氏名・フリガナ）　三井田 孝　（ミイダ　タカシ）

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	順天堂大学	□
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」や「臨床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：申告する経済的利益関係がないため）
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3年　4月　1日

国立保健医療科学院長　殿

機関名　　国立大学法人金沢大学

所属研究機関長　職　名　　学長

氏　名　山崎　光悦　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　大学院医薬保健研究総合研究科　・准教授

（氏名・フリガナ）　川尻　剛照　・カワシリ　マサアキ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	金沢大学	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	金沢大学	□
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」や「臨床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 3年　3 月 16日

国立保健医療科学院長　殿

機関名　　国立大学法人香川大学
所属研究機関長　職　名　　学長
氏　名　　筧　善行　　印

次の職員の令和２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　　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　医学部 循環器・腎臓・脳卒中内科学　・　教授

（氏名・フリガナ）　南野　哲男　・　ミナミノ　テツオ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
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」や「臨床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3年 3月 23日

国立保健医療科学院長　殿

機関名　国立大学法人東京大学
所属研究機関長　職　名　総長
氏　名　五神　真　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　保健・健康推進本部　助教

（氏名・フリガナ）　岡崎　佐智子　　オカザキ　サチコ

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	東京大学	□
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」や「臨床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3年　4月　1日

国立保健医療科学院長　殿

機関名　国立大学法人金沢大学

所属研究機関長　職　名　学　長

氏　名　山崎　光悦　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　附属病院・助教

（氏名・フリガナ）　多田　隼人・タダ　ハヤト

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	金沢大学	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	金沢大学	□
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」や「臨床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　3年　3月　12日

国立保健医療科学院長　殿

機関名　国立大学法人岡山大学

所属研究機関長　職　名　学長

氏　名　槇野　博史　　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）大学院医歯薬学総合研究科・教授

（氏名・フリガナ）和田　淳・ワダ　ジュン

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）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	岡山大学	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	岡山大学	□
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」や「臨床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：　　）
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（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 3 年 3 月 11 日

国立保健医療科学院長　殿

国立研究開発法人
機関名　国立循環器病研究センター
所属研究機関長　職　名　理事長
氏　名　小川　久雄　印

次の職員の令和２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　原発性高脂血症に関する調査研究

３．研究者名　（所属部局・職名）　病態代謝部・室長

（氏名・フリガナ）　小倉　正恒・オグラ　マサツネ

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）		
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ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	国立循環器病研究センター	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	国立循環器病研究センター	□
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。

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