るカウンセリングのポイントについて解説した。治療・予防法のない疾患の患者は，主治医からも見放されて疾患について相談する場も見出せないでいるケースも少なくない。根本的な治療・予防法がないといっても，医師および患者が疾患を正確に理解し対応することで避けられる合併症も多く，患者の長期的な予後の改善に大きな影響を及ぼす。また，疾患に対する新規の治療法の開発状況など最新の医療情報を提供することにより，クライエントが将来に対する希望を見出すことができる場合もある。そして何よりも，時間をかけてクライエントの話に耳を傾けることが重要であると自省を込めて考えている。

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内分泌・糖尿病・代謝内科，34(3)：210-220，2012

特集 種々の代謝異常

結合組織脆弱疾患 —Marfan症候群とEhlers-Danlos症候群*

古庄知己**

Key Words：Ehlers-Danlos syndrome, Marfan syndrome, connective tissue, collagen, fibrillin-1

はじめに

Ehlers-Danlos症候群(EDS)は，皮膚・関節の過伸展性，各種組織の脆弱性を特徴とする先天性疾患の総称であり，6つの主病型に分類されている．いずれもコラーゲン分子そのもの，または修飾酵素の遺伝子変異により生じる[1]．近年，主病型に属さない新たな病型が，その生化学的・遺伝学的基盤とともに発見されている(表1)[2]．

Marfan症候群(MFS)は，骨格・眼・心血管症状など多系統の合併症に特徴づけられる常染色体優性遺伝疾患であり，*FBN1*遺伝子の変異により発症する[3]．Loeys-Dietz症候群をはじめとした類縁疾患が見出されている(表2)[4]．

表1 Ehlers-Danlos症候群の分類

	頻度/患者数	遺伝形式	原因遺伝子
主病型			
古典型(Classical type)	1/20,000	AD	*COL5A1, COL5A2*
関節型(Hypermobility type)	1/5,000～20,000	AD	大多数は不明，少数例で*TNXB*
血管型(Vascular type)	1/50,000～250,000	AD	*COL3A1*
後側彎型(Kyphoscoliosis type)	1/100,000	AR	*PLOD*
多発関節弛緩型(Arthrochalasia type)	約30人	AD	*COL1A1*, COL1A2**
皮膚脆弱型(Dermatosparaxis type)	8人	AR	*ADAMTS-2*
その他の病型			
Brittle cornea syndrome	11人	AR	*ZNF469*
EDS-like syndrome due to tenascin-XB deficiency	10人	AR	*TNXB*
Progeroid form	3人	AR	*B4GALT7*
Cardiac valvular form	4人	AR	*COL1A2*
EDS-like spondylocheirodysplasia	8人	AR	*SLC39A13*
Kosho type(D4ST-1-deficient EDS)	22人	AR	*CHST14*

AD：常染色体優性遺伝，AR：常染色体劣性遺伝，*COL5A1*：V型プロコラーゲンα1鎖遺伝子，*COL5A2*：V型プロコラーゲンα2鎖遺伝子，*TNXB*：テナシンX遺伝子，*PLOD*：リジルヒドロキシラーゼ遺伝子，*：スプライス異常によるエクソン6のスキップ，*ADAMTS-2*：プロコラーゲンIN-プロテイナーゼ遺伝子，*ZNF469*：コラーゲン生合成・組織化にかかわる転写因子の遺伝子，*B4GALT7*：β4ガラクトース転移酵素-7(GalT-I)遺伝子，*SLC39A13*：亜鉛トランスポーター機能を持つ蛋白の遺伝子，*CHST14*：デルマタン4-*O*-硫酸基転移酵素(D4ST-1)遺伝子

* Weak connect tissue diseases—Marfan syndrome and Ehlers-Danlos syndrome.

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本稿では，EDSおよびMFSの症状，病態，臨床的マネジメントを概説する．EDSについては，主要病型である古典型，関節型，血管型，および最近われわれが疾患概念を確立した古庄型(暫定名称)について述べる．

症　状

1．古典型EDS

皮膚は滑らかでベルベット様，過伸展性(図1-A)，脆弱性(膝，肘，前脛部，前頭部，下顎などの真皮が容易に裂ける)を有する．創傷治癒が遅れ，瘢痕が薄く伸展する(萎縮性瘢痕)(図1-B)．肩，膝蓋骨，指，股，橈骨，鎖骨などが容易に脱臼するが，自然整復または自力で整復できることが多い．妊婦は，前期破水・早産(罹患胎児の場合)，会陰裂傷，分娩後の子宮・膀胱脱を生じうる[5]．

2．関節型EDS

皮膚の過伸展性は正常もしくは軽度である．関節過伸展性は顕著であり(図1-C)，脱臼・亜脱臼の頻度も高い(四肢，脊椎，肋骨・椎骨，肋骨・胸骨，鎖骨など)．自然に，もしくはごく小さい外傷によって生じ，自然整復または自身・家族・友人により整復できることが多いが，疼痛は数時間～数日持続する．若年より変形性関節症を生じることが多い．関節痛を含めた慢性疼痛が深刻であり，身体的・精神的な障害となりうる．しばしば胃炎，胃食道逆流，過敏性腸炎といった消化器合併症を呈する[6]．

3．血管型EDS

血管破裂・解離，腸破裂，臓器破裂は70％の成人例における初発症状となる．動脈破裂は，動脈瘤，動静脈ろう，解離が先行することもあるが，自然に生じることもある．皮膚は薄く，皮下静脈が透見される(図1-D)．新生児期，内反足，先天性股関節脱臼を呈することがある．小児期，そけいヘルニア，気胸，反復性関節脱臼・亜脱臼の頻度が高い．妊婦は，分娩前後の動脈・子宮破裂により，死亡する危険性がある(～12％)[7]．

4．古庄型EDS

皮膚過伸展・脆弱性，全身関節弛緩・慢性脱臼・変形，巨大皮下血腫などの進行性結合組織脆弱性および顔貌の特徴，先天性多発関節拘縮などの発生異常に基づく特徴的な症状を呈する(図1-E～M)(表3)[2][8][9]．

5．MFS

体幹に対して長い四肢，長い手指(図2-A, B)，

表2　Marfan症候群およびその類縁疾患

	原因遺伝子	Marfan症候群と鑑別すべき臨床所見
Marfan症候群(MFS)	*FBN1*	
Loeys-Dietz症候群(LDS)	*TGFBR1, TGFBR2*	二分口蓋垂/口蓋裂，動脈蛇行，眼間開離，広汎性大動脈/動脈瘤，頭蓋骨早期癒合症，内反足，頸椎不安定性，薄くビロード様の皮膚，易出血性
Shprintzen-Goldberg症候群(SGS)	*FBN1*, ほか	頭蓋骨早期癒合症，精神遅滞
Congenital contractural arachnodactyly(CCA)	*FBN2*	先天性関節拘縮，耳介変形
Weill-Marchesani症候群(WMS)	*FBN1*, *ADAMTS10*	小球状水晶体，短指症，固い関節
Ectopia lentis症候群(ELS)	*FBN1, LTBP2, ADAMTSL4*	大動脈根部拡張を伴わない
Familial thoracic aortic aneurysm (家族性胸部大動脈瘤)症候群(FTAA)	*TGFBR1, TGFBR2, ACTA2*	Marfan症候群の骨格系特徴を伴わない，網状皮斑(livedo reticularis)，虹彩嚢胞(iris flocculi)
二尖大動脈弁(BAV)を伴うFTAA		
動脈管開存(PDA)を伴うFTAA	*MYH11*	
Arterial tortuosity(動脈蛇行)症候群(ATS)	*SLC2A10*	全般的な動脈蛇行，動脈狭窄，特徴的顔貌

FBN1：fibrillin-1遺伝子，*TGFBR1*：transforming growth factor beta receptor 1 遺伝子，*TGFBR2*：transforming growth factor beta receptor 2 遺伝子，*FBN2*：fibrillin-2遺伝子，*ADAMTS10*：A disintegrin-like and metalloproteinase with thrombospondin type-1 motif 10遺伝子，*ACTA2*：actin α2遺伝子，*SLC2A10*：Solute carrier family 2 member 10遺伝子

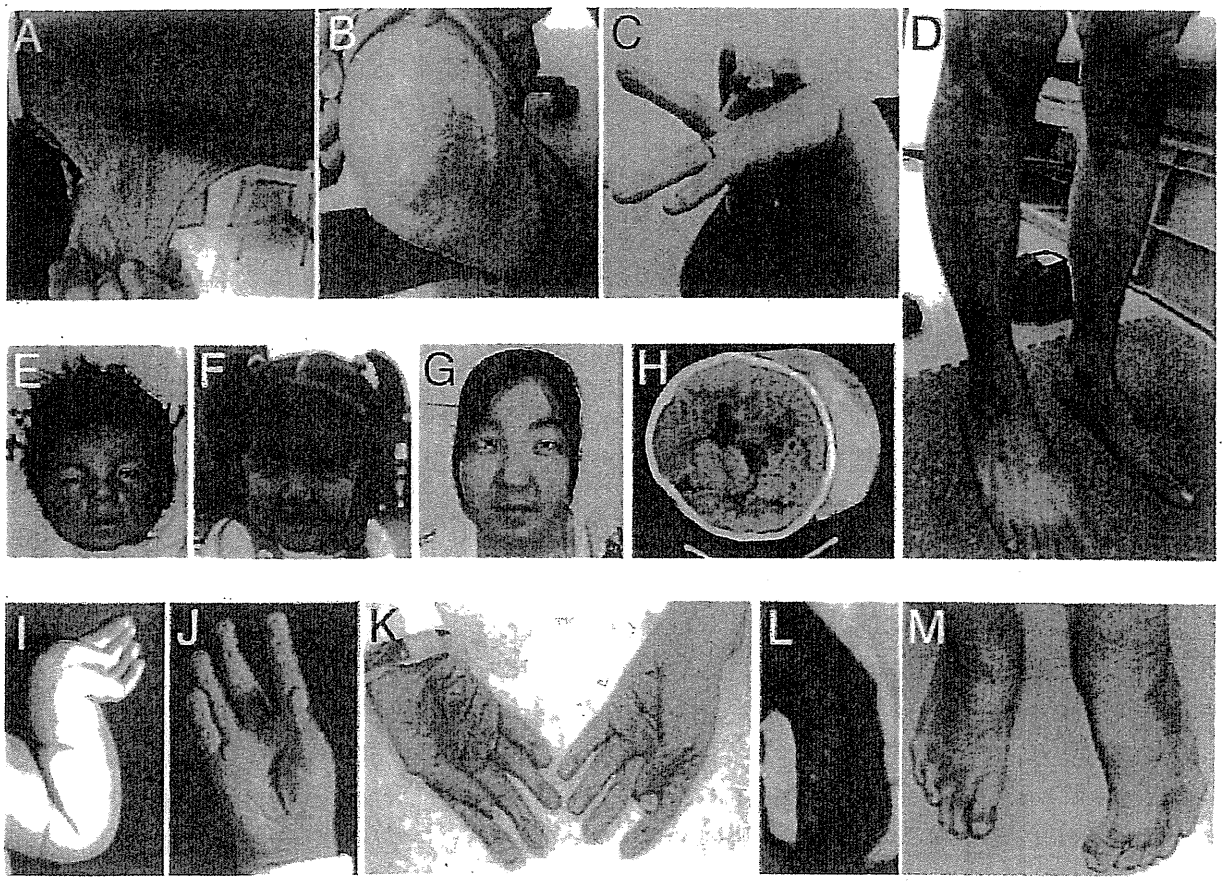

図1　Ehlers-Danlos症候群の各病型の臨床写真
A, B：古典型EDS, 同一男性患者(30歳代)．A：皮膚過伸展性．B：萎縮性瘢痕．C：関節型EDS, 女性患者(27歳)における関節過伸展性．D：血管型EDS, 女性患者(47歳)における皮下静脈透見．E～H, L, M：古庄型EDS, 同一女性患者．E：日齢23, 眼間開離，小眼瞼，眼瞼裂斜下，短い鼻，長い人中，小さい口，小下顎を認める．F：3歳，特徴は目立たなくなっている．G：16歳，面長になっている．I～K：古庄型EDS, 別な女性患者．I：3か月時，内転母指を含む手指および手首の拘縮．J：5歳，拘縮は軽快し，指は円筒型となる．K：28歳，皮膚の皺が多くなり，早老症様の外観となる．

漏斗胸(図2-C)・鳩胸，軽度～重度側彎，扁平足(図2-D)などの骨格症状を呈する．最も頻度が高い眼症状は近視であり，本症の顕著な特徴である水晶体偏位は60％にみられる．ほかに，網膜剥離，緑内障，早期発症白内障のリスクがある．生命予後に影響する最も重要な症状は心血管症状であり，大動脈解離に繋がるValsalva洞部の上行大動脈拡張，僧帽弁逸脱などを呈する[3]．

病　態

1．古典型EDS

V型コラーゲンは，通常α1鎖2本とα2鎖1本からなる3本鎖構造を持ち，さまざまな組織に分布している量的には少ない線維コラーゲンである．I型コラーゲンとともに線維を構成し，その線維の径を調節している．最も頻度の高い病態は(約1/3)，*COL5A1*遺伝子のナンセンス変異またはフレームシフト変異によるハプロ不全である．これにより，正常なV型コラーゲンの量は半減すると推測されている．そのほか，*COL5A1*または*COL5A2*遺伝子のスプライス部位の変異によるexon skippingおよび3本鎖領域のグリシン残基のアミノ酸置換に基づくdominant negative効果によっても発症する[5]．

2．血管型EDS

III型コラーゲンはα1鎖のみの3本鎖構造を持ち，皮膚，血管，管腔臓器の主要構成成分である．多くは3本鎖領域のグリシン残基のアミノ酸置換に基づいて，約1/3の例ではスプライス部位の変異によるexon skippingに基づいてdominant negative効果をきたし発症する[7]．

表3 古庄型EDSの臨床症状

頭蓋顔面
- 泉門開大(乳幼児期)
- 眼間開離
- 小眼瞼，眼瞼裂斜下
- 青色強膜
- 鼻柱低形成を伴った短い鼻
- 耳介異形成(大きい，後傾，低位)
- 口蓋異常(高口蓋，口蓋裂)
- 長い人中，薄い上口唇
- 小さい口/下顎低形成・後退(乳児期)
- 下顎突出し面長となる(学童期以降)
- 非対称な顔(学童期以降)

骨格
- Marfan症候群様体型
- 先天性多発関節拘縮(指，手首，股関節，足)
- 反復性/慢性関節脱臼
- 胸郭変形(平坦，漏斗胸)
- 脊椎変形(側彎，後側彎)
- 独特な形態の手指(先細り，細い，円筒状)
- 進行性の足変形(外反，扁平，凹)

皮膚
- 過伸展性/弛緩
- 易出血性
- 脆弱性/萎縮性瘢痕
- 細かい/早老症様の手掌の皺
- 圧迫に対する過敏性
- 反復性皮下感染症/膿瘍

心臓血管
- 先天性心疾患(ASD)
- 弁の異常(MVP, MR, AR, ARD)
- 巨大皮下血腫

胃腸
- 便秘
- 憩室穿孔

呼吸器
- (血)気胸

泌尿生殖器
- 腎/膀胱結石
- 水腎症
- 膀胱拡張/弛緩
- そけいヘルニア
- 停留精巣
- 乳房発育不全

眼
- 斜視
- 屈折異常(近視，乱視)
- 緑内障/眼内圧亢進
- 小角膜/小眼球
- 網膜剥離

耳
- 聴力低下

中枢神経
- 脳室拡大/非対称

発達
- 筋緊張低下/粗大運動発達遅滞

ASD：心房中隔欠損，MVP：僧帽弁逸脱，MR：僧帽弁閉鎖不全，AR：大動脈弁閉鎖不全，ARD：上行大動脈拡張

3. 古庄型EDS

原因遺伝子*CHST14*は，デルマタン4-*O*-硫酸基転移酵素-1(D4ST-1)をコードする．本症における進行性結合組織脆弱性は「D4ST-1欠損→デコリンに付加するグリコサミノグリカン(GAG)鎖の組成変化(デルマタン硫酸の消失)→デコリンが媒介するコラーゲン細線維のassembly不全」に基づく(図3)[2)10)]．

4. MFS

*FBN1*遺伝子は，細胞外マトリックスの主要な構成要素である微小線維の主たる構成蛋白fibrillin-1をコードする．最近，fibrillin-1の持つ調節作用の異常がその病態により深くかかわっていることが明らかにされてきた．マウスモデルの検討から，MFSの肺，心臓血管，骨格，骨格筋病変の多くは，TGF-βの異常活性化に基づくことが示された[3)]．TGF-βは，細胞の増殖・分化，アポトーシス，免疫，組織修復，細胞外マトリックスの形成に重要な役割を持つサイトカインである．不活性なlarge latent complex(TGF-β+latency-associated peptide+latent TGF-β binding protein)として細胞から分泌され，latent TGF-β binding proteinと相同性を有するfibrillin-1と結合し，細胞外マトリックスにおいて不活化状態のまま貯蔵される．このプロセスがTGF-β活性の調節にはきわめて重要である．Fibrillin-1の変異によりこの調節が異常をきたし，TGF-βの異常活性化をひき起こす[3)]．TGF-βの異常活性化は，1型アンギ

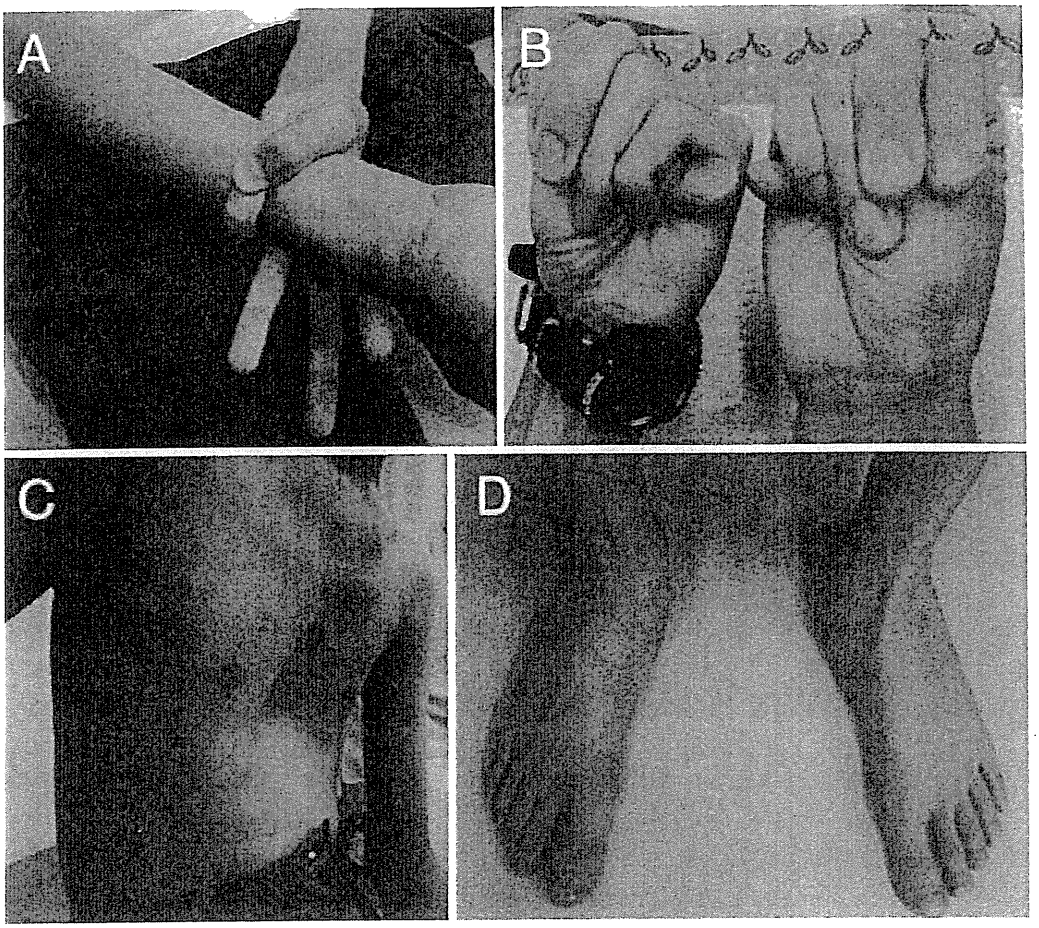

図2　Marfan症候群の臨床写真
A, C, D：同一男児(11歳)．A：Wrist sign．C：漏斗胸．D：扁平足．B：男性患者(22歳)，thumb sign.

オテンシンII受容体(AT_1R)を介した経路により細胞外マトリックスの脆弱性をきたし，動脈病変に至る(図4)[3]．2型アンギオテンシンII受容体(AT_2R)を介した経路も関与している可能性が示唆されていたが，最近の研究では動脈病変を軽減する方向で作用していることが明らかになった(図4)[11]．

臨床的マネジメント

EDS, MFSに共通している診療の要諦は，医療者(関係各科，救急)と患者・家族が疾患についてのあらゆる情報を共有し，起こりうる合併症の早期発見・早期治療を行うことである[12]．

1．古典型EDS

診断は臨床症状に基づいて行われる(表4)[1]．小児では皮膚裂傷を予防するために，前頭部，膝，脛部を保護する．裂傷の縫合は十分注意して行う．筋緊張低下，運動発達遅滞を呈する小児では理学療法を行う．負担のかかる運動は避け，体重をかけない筋力トレーニングにより筋肉の発達・協調性を促す．妊娠中(特に後期～産褥期)は慎重に観察する．ビタミンC投与で内出血が軽減される可能性がある[5]．

2．関節型EDS

診断は臨床症状に基づいて行われる(表4)[1]．適切な理学療法，補装具の使用(頸部，肘，手首，手指，膝，足首などの関節を安定させる装具，車椅子，日常生活補助具の工夫)，鎮痛薬投与(重症例では麻薬の使用を含めた疼痛コントロールを考慮)，胃腸症状があればその対応，疼痛への負担に配慮した心理カウンセリングといった対応を行う．関節の過伸展，負荷の強い運動，上肢に負担のかかる杖・歩行器の使用は控える[6]．

3．血管型EDS

臨床症状から疑い，診断は培養皮膚線維芽細胞を用いたIII型コラーゲン生化学検査または遺伝子

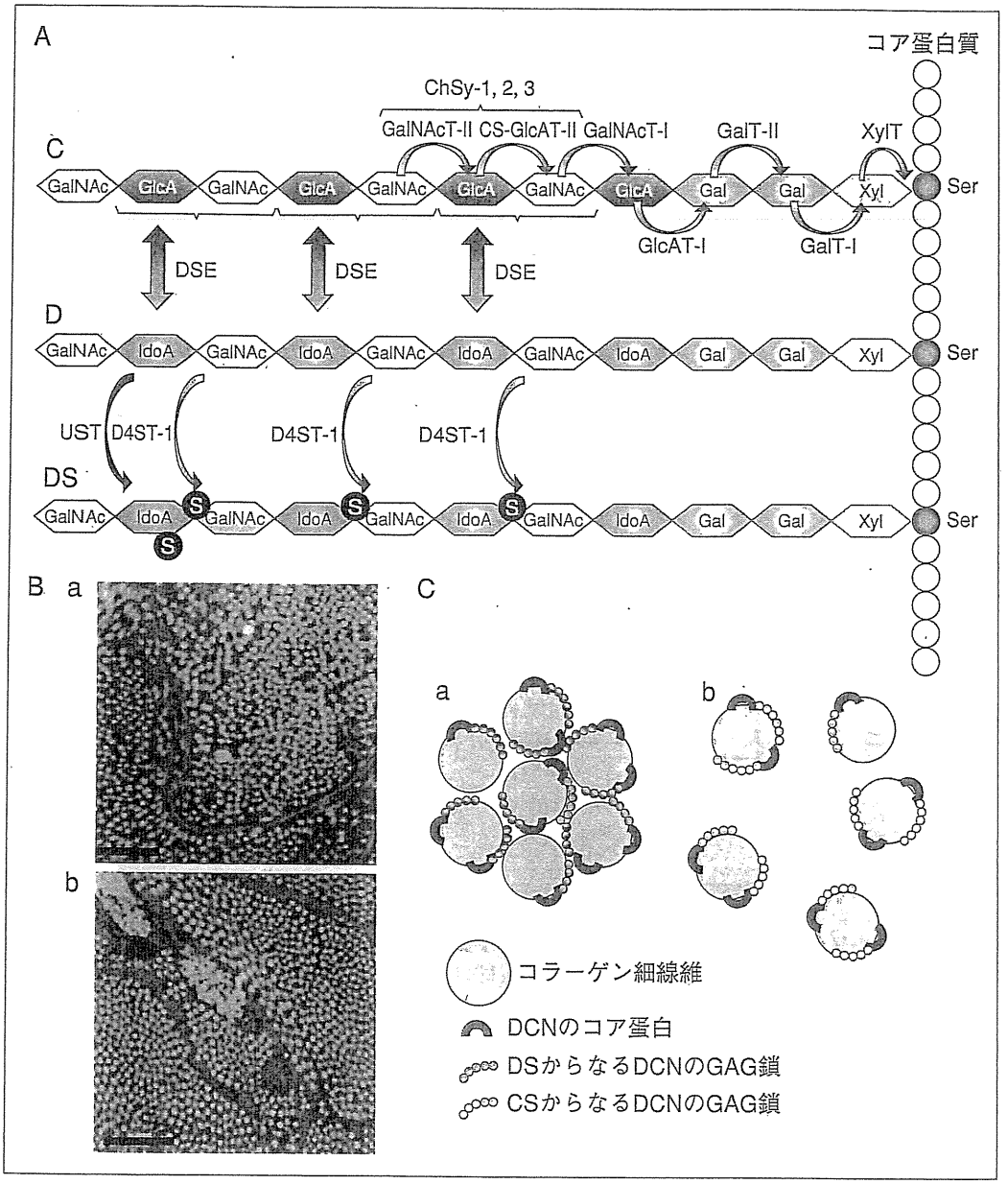

図3　古庄型EDSの病態

A：デルマタン硫酸(DS)の生合成．DSは，コンドロイチン硫酸，ヘパラン硫酸，ヘパリンと同様，プロテオグリカンのコア蛋白質上にある特定のセリン残基(Ser)にキシロース(Xyl)－ガラクトース(Gal)－ガラクトース(Gal)－グルクロン酸(GlcA)の4糖が結合するところから始まる．これらの反応は，それぞれキシロース転移酵素(XylT)，ガラクトース転移酵素-I(GalT-I)，ガラクトース転移酵素-II(GalT-II)，グルクロン酸転移酵素-I(GlcAT-I)によって行われる．N-アセチルガラクトサミン(GalNAc)が，GalNAc転移酵素-I(GalNAcT-I)によってGlcAに転移されると，次いでCS-グルクロン酸転移酵素-II(CS-GlcAT-II)とGalNAc転移酵素-II(GalNAcT-II)により，GlcAとGalNAcが順次転移し，コンドロイチン(C)特有の[GlcA-GalNAc]の2糖繰り返し領域が合成される．コンドロイチン合成酵素(ChSy-1, 2, 3)は，CS-GlcAT-IIとGalNAcT-II両方の活性を持つ．ChSyファミリーによって[GlcA-GalNAc]$_n$の糖鎖骨格が形成された後，または，その反応の途中で，DSエピメラーゼ(DSE)により，GlcA残基のC5位のカルボキシル基が異性化し，イズロン酸(IdoA)となる．これにより，デルマタン(D)の2糖配列[IdoA-GalNAc]$_n$が形成される．その後，主としてデルマタン4-*O*-硫酸基転移酵素-1(D4ST-1)によるGalNAc残基の4位硫酸化(一部はウロノシル2-*O*-硫酸基転移酵素(UST)によるIdoAの2位硫酸化も)による修飾を受けて，成熟したDS鎖が合成される．古庄型ではこの硫酸化不全により，DSとして安定化せずに，すべてDSEを経てCSに変換されてしまう．B：電顕所見(×30,000)．患者(a)では，コントロール(b)に比べ，コラーゲン細線維の径は同等であるが，ばらけて存在している．スケールバーは1 mmを示す．C：正常(a)，古庄型EDS(b)．D4ST-1欠損に基づきデコリン(DCN)に付加するグリコサミノグリカン(GAG)鎖の組成変化〔デルマタン硫酸(DS)が消失しコンドロイチン硫酸(CS)に置換〕が生じ，DCNが媒介するコラーゲン細線維のassembly不全をきたすと考えられる．

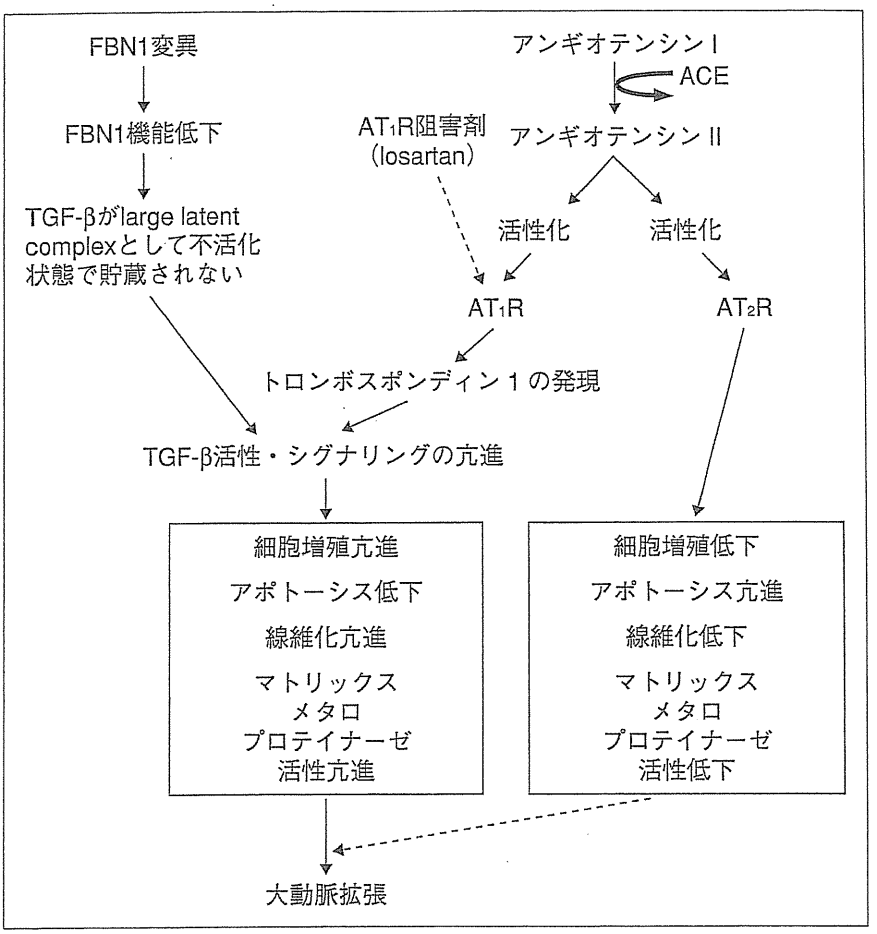

図4　Marfan症候群の病態
ACE：アンギオテンシン変換酵素．AT1R：1型アンギオテンシンII受容体．AT2R：2型アンギオテンシンII受容体．点線矢印は阻害作用を示す．

検査により行われる(表4)[1]．疑われたとき，診断がついたとき，および診断後定期的に，造影CTまたはMRIによる頭頸部，胸部，腹部，下肢の動脈病変スクリーニングを行う．瘤，解離などの病変が見出された場合，血圧コントロールを厳密に行う．最近，心臓選択的なβ遮断作用および血管拡張をもたらすβ刺激作用を有するceliprololの有効性に関するランダム化比較試験の結果が報告された．投与群(100mg/日から最大400mg/日まで増量)25例と非投与群28例に無作為に分けられ，投与群の5例，非投与群14例が動脈病変を発症，エンドポイントに達したことから，動脈合併症の予防効果を有すると結論づけられた[13]．急性の動脈病変(瘤，解離)が生じた場合，可能な限り保存的に対処する(安静，降圧剤投与)．保存的治療によっても病状が進行する場合は塞栓やステントといった血管内治療を考慮する．血管内治療にも反応せず，状況が切迫する場合には，血管および組織脆弱性を考慮し慎重に手術を行う．腸破裂の予防としては，穏やかな緩下剤により排便をコントロールし，破裂した場合は組織脆弱性および周術期の動脈破裂に留意しながら迅速に手術する．妊娠はハイリスクであり，カップルに対し十分な情報提供を行った上で，心臓血管外科のバックアップができる施設において，陣痛開始前のコントロールされた分娩(おそらくは帝王切開の方が安全)を行う[7][12]．

4．古庄型EDS

新生児期，多発関節拘縮(特に内転母指と内反足)と顔貌上の特徴から疑い，*CHST14*遺伝子解析で診断する．乳幼児期，内反足に対する整形外科的治療(装具，手術)，運動発達遅滞に対する理学療法を行う．その後，整形外科，眼科，泌尿器科，循環器科検診を行う．皮膚裂傷，関節脱臼，巨大皮下血腫を生じやすいので，転倒などの外傷には細心の注意を払う．思春期以降，

表4 Ehlers-Danlos症候群各病型の診断基準

病型	大基準	小基準
古典型	皮膚過伸展性 広い萎縮性瘢痕 関節過動性	スムーズでベルベット様の皮膚 軟属腫様偽腫瘍(肘・膝など圧力のかかる部位に生じる瘢痕に付随する肉質の隆起病変) 皮下球状物(四肢骨の皮下に生じる可動性の小さく固い結節) 関節過動性による合併症(捻挫，脱臼，亜脱臼，扁平足) 筋緊張低下・運動発達遅滞 内出血しやすい 組織過伸展・脆弱性による合併症(裂孔ヘルニア，脱肛，頸椎不安定性) 外科的合併症(術後ヘルニア) 家族歴
関節型	全身性関節過動性 皮膚症状(やわらかいが，過伸展性はないか，あってもごく軽度) 皮膚，軟部組織の脆弱性その他の異常(皮膚過伸展性が強い，薄い，萎縮性瘢痕がある．皮膚，腱，靱帯，血管，内臓が容易に裂ける)はない	家族歴 反復性関節脱臼，亜脱臼 慢性関節，四肢，背部痛 内出血しやすい 機能性腸疾患(機能性胃炎，過敏性腸炎) 神経因性低血圧，起立性頻脈 高く狭い口蓋 歯芽の密生
血管型	動脈破裂 腸管破裂 妊娠中の子宮破裂 家族歴	薄く，透けた皮膚(胸部，腹部) 内出血しやすい 特徴的顔貌(薄い口唇・人中，細い鼻，大きい眼) 末端早老症 小関節過動性 腱・筋肉破裂 若年発症静脈瘤 内頸動脈・海綿静脈洞ろう (血)気胸 慢性関節脱臼・亜脱臼 先天性股関節脱臼 先天性内反足 歯肉後退
後側彎型	脆弱で過伸展性のある皮膚，薄い瘢痕，内出血しやすい 全身性関節弛緩 出生時の重度の筋緊張低下 進行性側彎(出生時または1歳までに出現) 強膜の脆弱性，眼球破裂	広い瘢痕性萎縮 マルファン症候群様の体型 中程度のサイズの動脈破裂 運動発達マイルストーンの軽度～中等度遅滞
多発関節弛緩型	反復性亜脱臼を伴う重度全身性関節過動性 先天性両側股関節脱臼	皮膚過伸展性 組織脆弱性(瘢痕性萎縮を含む) 内出血しやすい 筋緊張低下 後側彎 X線上軽度の骨密度低下
皮膚脆弱型	重度の皮膚脆弱性 垂れ下がりゆるんだ皮膚	柔らかくたるんだ皮膚の触感 内出血しやすい 前期破水 大きいヘルニア(臍，そけい)

(血)気胸や憩室穿孔を発症すればその治療を行う[2)9)]．

5．MFS

従来，Ghentの診断基準[14)](表5)に基づいて臨床診断が行われてきた．しかし，項目の妥当性，

表5　Marfan症候群の診断におけるGhentの基準

系統	大基準	小基準	関与
家族歴	1度近親がMarfan症候群の診断基準を満たす患者 既知の*FBN1*変異を有する 家族内の診断が明らかなMarfan症候群患者が*FBN1*近傍のハプロタイプを共有	なし	
骨格	以下の4項目を満たす 鳩胸 手術を要する漏斗胸 上節-下節比の減少またはarm span/身長＞1.05 wrist sign(図2-A)，thumb sign(図2-B) 側彎(＞20°)または脊椎すべり症 肘関節伸展制限(＜170°) 扁平足(内踝の内側変位による) 寛骨臼突出	中等度の漏斗胸 関節可動性亢進 高口蓋(歯芽の密生を伴う) 顔貌上の特徴 (長頭症，頬部低形成，眼球陥没，下顎後退，眼裂斜下)	大基準2項目 大基準1項目および小基準2項目
眼	水晶体変位	平坦な角膜(角膜鏡で測定) 眼軸長増加(＞23.5mm，超音波検査で測定) 虹彩または毛様体筋低形成(縮瞳制限をきたす)	小基準2項目
心血管	上行大動脈拡張(少なくともValsalva洞部，大動脈弁逆流はあってもなくてもよい) 上行大動脈解離	僧帽弁逸脱(僧帽弁逆流はあってもなくてもよい) 肺動脈拡張(＜40歳，肺動脈弁狭窄や末梢性肺動脈狭窄などの原因がない) 僧帽弁輪石灰化(＜40歳) 下行または腹部大動脈拡張または解離(＜50歳)	小基準1項目
肺	なし	自然気胸 肺尖部のbleb	小基準1項目
皮膚	なし	体重増加，妊娠，反復性外力と関係のない皮膚線条 反復性または切開痕ヘルニア	小基準1項目
硬膜	腰仙部硬膜拡張(CTまたはMRIで観察)	なし	

発端者の診断：2系統臓器が大基準を満たし，ほかに1系統臓器の関与．既知の遺伝子変異が検出された場合，1系統臓器が大基準を満たし，ほかに1系統臓器の関与．
発端者の血縁者の診断：家族の中に1系統臓器の大基準を満たす者がいて，本人の1系統臓器の大基準，ほかに1系統臓器の関与あり．

臨床症状の幅や鑑別すべき類縁疾患の存在，さらに診断に伴う弊害(保険加入，将来の人生設計における制限)などの問題が指摘され，最近改訂版が示された(表6)[4]．最も重要な大動脈病変の対応については，β遮断薬投与はMFSと診断されたすべての患者に行われるべき標準的治療である[3]．Atenololがよく使われ，心拍数を最大に近い運動後に100/分(5歳以上)未満になるよう微調整する[3]．病態の解明に基づく新たな治療戦略として，マウスモデルの検討によりAT1R阻害作用を持つ降圧剤losartanが，出生前からの投与で大動脈拡張を予防し，ヒトの思春期に相当する2か月からの投与で大動脈病変を改善させた[15]．中等度から重度の大動脈拡張を有する小児18例に対して，β遮断薬に加えてAT1R阻害薬(多くはlosartan 1.4mg/kg/日)が投与され，大動脈根部径の拡張率が有意に減少した[16]．現在，losartanの有効性に関する多施設共同ランダム化コントロール試験(米国ではlosartan対atenololの比較[17]，欧州ではβ遮断薬が投与されている患者におけるlosartan対placeboの比較[18])が行われている．Valsalva洞部の径が5 cmに達したら，急性大動脈解離を予防するため手術(拡張部を弁つきgraftで置換するBentall術)を行う．早期発症大動脈解離の家族歴，拡張の進行度，大動脈弁閉鎖不全の重症度，心室機能，女性患者の場合には妊娠の希望，また自己弁温存術を希望する場合はより早い段階での手術を考慮する[3]．

表 6　Marfan症候群(MFS)および類縁疾患に関する改訂Ghentの診断基準

家族歴がない場合

(1)上行大動脈拡張(Valsalva洞部での径のZ score≧2または大動脈根部解離)および水晶体偏位があればMFSと診断*.

(2)上行大動脈拡張(Valsalva洞部での径のZ score≧2または大動脈根部解離)および*FBN1*変異♭があればMFSと診断.

(3)上行大動脈拡張(Valsalva洞部での径のZ score≧2または大動脈根部解離)および多系統症状#(7点以上)があればMFSと診断*.

(4)水晶体偏位，*FBN1*変異♭，および，上行大動脈拡張#があればMFSと診断.

・水晶体偏位があり(多系統症状はあってもなくても)，*FBN1*変異♭はあっても上行大動脈拡張(Valsalva洞部での径のZ score≧2または大動脈根部解離)の有無が不明，または，*FBN1*変異♭がない場合，水晶体偏位症候群(Ectopia lentis syndrome；ELS)と診断.

・上行大動脈径の軽度拡張(Valsalva洞部での径のZ score＜2または大動脈根部解離)があり，多系統症状#(少なくとも1つの骨格症状を含み合計5点以上)があるが，水晶体偏位がない場合，近視・僧帽弁逸脱・ボーダーライン大動脈根部拡張・皮膚線条・骨格症状を含む表現型〔myopia, mitral valve prolapse, borderline (Valsalva洞部での径のZ score＜2) aortic root dilatation, striae, skeletal findings phenotype；MASS〕と診断.

・僧帽弁逸脱，上行大動脈径の軽度拡張(Z score＜2または大動脈根部解離)，多系統症状#(5点未満)があるが，水晶体偏位がない場合，僧帽弁逸脱症候群(mitral valve prolapse syndrome；MVPS)と診断.

家族歴がある場合

(5)水晶体偏位および上記で診断されたMFSの家族歴があればMFSと診断.

(6)多系統症状#(7点以上)および上記で診断されたMFSの家族歴があればMFSと診断*.

(7)上行大動脈拡張(20歳以上でValsalva洞部での径のZ score≧2, 20歳未満でValsalva洞部での径のZ score≧3)および上記で診断されたMFSの家族歴があればMFSと診断*.

* Shprintzen-Goldberg症候群，Loeys-Dietz症候群，血管型EDSの臨床的特徴がない，または，必要に応じて*TGFBR1*および*TGFBR2*遺伝子検査やIII型コラーゲン生化学検査または*COL3A1*遺伝子検査を行った後に診断.

多系統症状のスコアリング

・Wrist signおよびthumb sign→3点(どちらか→1点)
・鳩胸→2点(漏斗胸または胸郭左右差→1点)
・足変形→2点(単純な扁平足→1点)
・気胸→2点
・硬膜拡張→2点
・寛骨臼突出→2点
・上節/下節比の減少およびarm span/身長比の増加および重度側彎がないこと→1点
・側彎または胸腰椎後彎→1点
・肘関節進展制限→1点
・顔貌上の特徴(長頭，眼球陥凹，眼瞼裂斜下，頬部低形成，下顎後退のうち3項目以上)→1点
・皮膚線条→1点
・近視(3ジオプトリを超える)→1点
・僧帽弁逸脱(あらゆるタイプ)→1点

すべてを満たすと20点，7点以上で多系統症状の関与ありと判断.

♭ *FBN1*変異の判断基準

・Marfan症候群家系において過去に認められている変異
・de novo(新規の)変異(社会的父親が遺伝学的父親であると確認されていること，両親に症状がないこと，変異が下記のカテゴリーに属すること)
・ナンセンス変異
・欠失または挿入変異(フレームシフトがあっても，なくても)
・スプライス変異(標準的なGT-AGルールを障害するもの，または，mRNA/cDNAレベルでスプライス異常が示されたもの)
・ミスセンス変異(システイン残基を置換するもの，または，新たにシステイン残基が生じるもの)
・ミスセンス変異〔進化的に保存されているEGFのコンセンサス配列“(D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F)”を障害するもの．mおよびnはさまざまな数のアミノ酸残基を示す．Dはアスパラギン酸を，Nはアスパラギンを，Eはグルタミン酸を，Qはグルタミンを，Yはチロシンを，Fはフェニルアラニンを示す〕.
・その他のミスセンス変異
・6回以上の減数分裂において*FBN1*遺伝子と連鎖

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SURGERY TODAY

Case Report

Sigmoid Colon Perforation Induced by the Vascular Type of Ehlers–Danlos Syndrome: Report of a Case

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Abstract
The vascular type of Ehlers–Danlos syndrome (vEDS) is a rare inherited disease of the connective tissues, and is caused by abnormal type III collagen resulting from heterogeneous mutations of the type III collagen *COL3A1* gene. We herein report the case of a vEDS patient who developed a sigmoid colon perforation and was given a definitive diagnosis by a genetic and biomolecular assay. The patient demonstrated clinical manifestations caused by tissue weakness such as frequent pneumothorax events and a detached retina. During the operation, we noticed easy bruising and thin skin with visible veins on the patient's abdominal wall. Finally, a diagnosis was confirmed by the reduction of type III collagen synthesis and by the identification of a mutation in the gene for type III collagen. We conclude that it is difficult to diagnose a vEDS patient without clinical experiences and specialized genetic methods. Furthermore, all organs must be treated gently during therapy, because the tissues of vEDS patients are extremely fragile.

Key words Ehlers–Danlos syndrome · Vascular type · Perforation · Type III collagen · *COL3A1*

Introduction

The vascular type of Ehlers–Danlos syndrome (vEDS, Ehlers–Danlos syndrome type IV) is a rare, autosomal dominant disease of the connective tissues caused by abnormal type III collagen resulting from heterogeneous mutations of the type III collagen *COL3A1* gene.[1–4] vEDS is characterized by four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features, and the rupturing of arteries and organs.[1–4] In addition, classic EDS patients exhibit hypermobility of the large joints and hyperextensibility of the skin.[1,2] Typically, Ehlers–Danlos syndrome (EDS) is divided into six types, and vEDS patients follow a particularly poor clinical course caused by complications from tissue weakness.[1,2] Twenty-five percent of vEDS patients develop one or more complications associated with tissue weakness by 20 years of age, and 80% develop some complications by 40 years. Pepin et al. reported that the calculated median survival time of vEDS patients was 48 years of age.[1] We herein present a case report of a vEDS patient who was clinically and genetically diagnosed following a sigmoid colon perforation, and review the pertinent literature.

Case Report

A 20-year-old male patient was admitted to our hospital with severe abdominal pain. The patient's abdominal wall was very hard, and muscular guarding was palpated. Enhanced computed tomography was performed immediately, and revealed free air and stool containing barium in the abdominal cavity, because the patient's colon had been examined 2 days prior for causal ascites and abdominal pain by a barium enema (Fig. 1A,B). As soon as we diagnosed the patient with generalized peritonitis due to colon perforation, an emergency operation was performed. During the operation, the patient's abdominal skin was observed to be markedly thin, with visible veins. After we decided that the sigmoid colon perforation was the cause of the generalized peritonitis, the lesion was removed and Hartmann's procedure was performed. In addition, it was revealed that the patient suffered from frequent spontaneous pneumothorax events in the past, and that his creatine kinase levels

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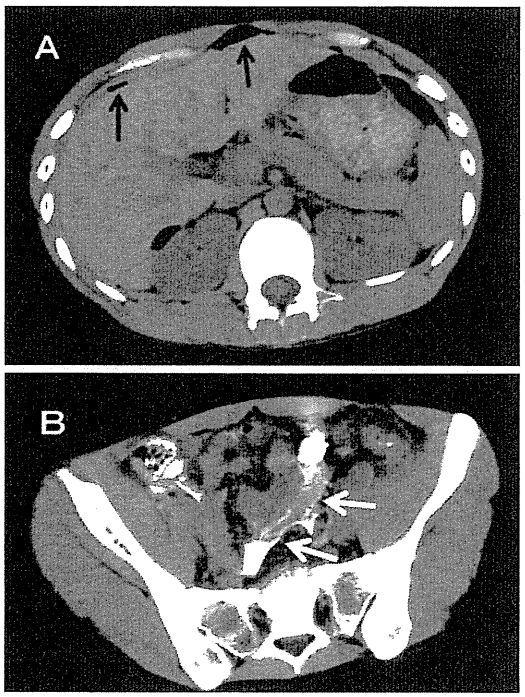

Fig. 1A,B. Enhanced computed tomography at the sigmoid colon perforation. Free air (*black arrows*) and stool containing barium (*white arrows*) were observed in the abdominal cavity

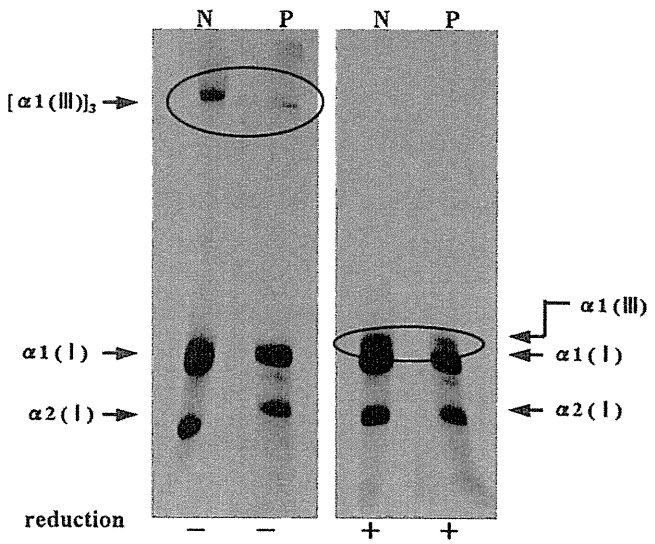

Fig. 2. Production of type I or type III collagen in the patient's cultured fibroblasts. The synthesis of type I collagen in this patient was the same as in controls. However, the synthesis of type III collagen was reduced by approximately 22.7% compared with the normal control values (*inside circle*). *N*, normal control; *P*, patient with vascular type of Ehlers–Danlos syndrome

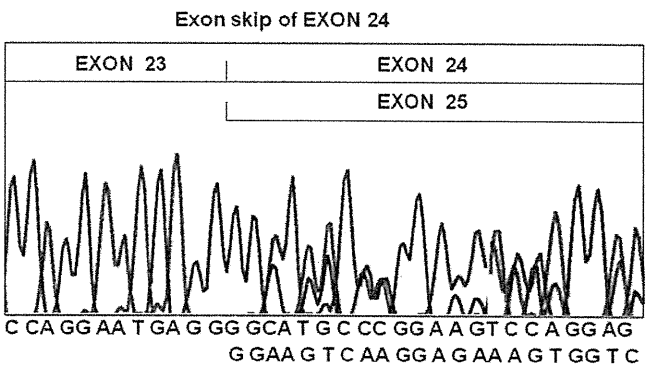

Fig. 3. Genetic analysis of the complementary DNA from the patient's cultured fibroblasts. A skip in exon 24 of *COL3A1*, which encodes collagen type III, was identified by the genetic analyses of the complementary DNA from the cultured fibroblasts

were increased to severalfold higher than in normal subjects. Although a paralytic ileus developed as a complication, the patient was discharged from our hospital 1 month after the operation. However, 3 days after discharge, he was readmitted due to his eighth spontaneous pneumothorax and a detached retina in his left eye. Because many complications caused by tissue weakness had developed over such a short period, very rare vEDS was diagnosed according to the four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features, and rupture of the arteries and organs.

To confirm this diagnosis, the patient's skin and blood samples were sent to Dokkyo Medical University, and were examined by genetic and molecular biological assays. Accordingly, the diagnosis of vEDS was confirmed by the reduction of type III collagen synthesis in cultured skin fibroblasts and by the identification of a mutation in the gene for type III collagen (*COL3A1*). The synthesis of type I collagen in this patient was the same as in controls. However, the synthesis of type III collagen was reduced by approximately 22.7% compared with normal controls (Fig. 2). A skip in exon 24 of *COL3A1*, which codes for collagen type III, was identified by genetic analysis of the complementary DNA from cultured fibroblasts (Fig. 3). Furthermore, the region near the genomic DNA was amplified by polymerase chain reaction (PCR) for the analyses of genomic DNA; the result revealed a G-to-A transition at the donor splice-site +1 of intron 24 (IVS 24 G+1 to A) of the *COL3A1* gene (Fig. 4). Because the mother of the present patient also demonstrated characteristic facial features and easy bruising of the skin, we genetically examined her blood samples to determine the genetic background of this patient. Consequently, we were able to confirm that the mother had the same mutation in *COL3A1* gene.

Less than 6 months after the sigmoid colon perforation, the patient was admitted with a developing

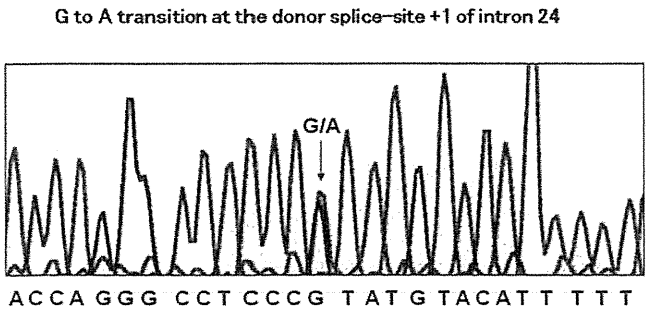

Fig. 4. Sequence analysis of genomic DNA from the patient's blood cells. The region near the genomic DNA was amplified by polymerase chain reaction for the analysis of genomic DNA. The results revealed a G-to-A transition at the donor splice site +1 of intron 24 (IVS 24 G+1 to A) of the *COL3A1* gene

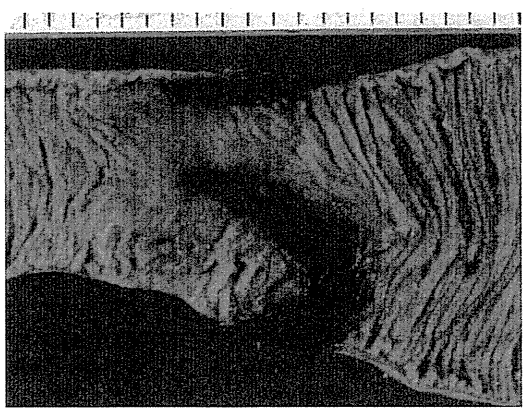

Fig. 5. Resected specimen of the jejunum from the second operation. The seromuscular layer of the patient's jejunum was torn throughout, and the entire layer of the intestine had become partly necrotic

adhesive ileus. Although conservative therapy was appropriated because there was no ischemic change of the intestine at admission, an emergency operation was performed because of the sudden onset of severe abdominal pain, which was not relieved by analgesic drugs. The operative and histopathological findings revealed the seromuscular layer of his jejunum to be torn, thus resulting in partial necrosis of this entire layer of the patient's intestine (Fig. 5). Therefore, we performed a partial resection of the small intestine, and the colostomy was not closed.

Methods of Genetic Examination

Dermal fibroblasts were obtained from the patient's skin and were cultured.[5–7] The protein synthesis of type I and type III collagen were assessed as described previously.[5–8] After RNA was extracted from the cultured fibroblasts, complementary DNA was synthesized by reverse transcription from the RNA as a template. The complementary DNA was amplified by PCR, and analyzed by electrophoresis on polyacrylamide gels to identify the abnormal fragments. Abnormal DNA fragments were directly sequenced by an ABI PRISM 3100 genetic analyzer (ABI Advanced Biotechnologies, Columbia, MD, USA).[2,3,8] Furthermore, genomic DNA was extracted from the blood cells, and all mutations were confirmed in the genomic DNA of *COL3A1* by a sequence analyzer.[2,3,8]

Discussion

Ehlers–Danlos syndrome (EDS) is a rare inherited disease of the connective tissue.[1,2] Most surgeons generally consider EDS to be a dermatologic disease.[1–4] However, patients who are affected by EDS, particularly the vascular EDS type (vEDS), develop complications associated with tissue weakness, and surgical or interventional therapy is often required.[1–4,9–11] Until genetic and biochemical testing was sufficiently developed, a considerable number of patients who died unexpectedly could not be diagnosed as having vEDS. In the present case, the reason for the colonic perforation was unclear after a histopathological examination, and 6 months passed until the diagnosis of vEDS could be made by genetic and biomolecular assays. Even if we suspected the possibility of vEDS based on the patient's clinical symptoms, the genetic and biomolecular assays could not be easily performed in most hospitals. Fortunately, we obtained advice from an authority in genetics and had technical support with the genetic and biomolecular assays. If this patient had not been definitively diagnosed, it is likely that the patient and his family might have lost any hope. Our belief is that a system for diagnosing rare inherited diseases, such as vEDS, should therefore be established as expeditiously as possible in Japan.

In general, most surgeons encounter vEDS patients who are affected by perforative peritonitis and perform surgery by creating an intestinal stoma, because the abdominal cavity is polluted with stool and the patient's tissues are very fragile. Furthermore, the intestinal stoma helps in the management of constipation, which these patients often experience to a severe extent.[1] The existence of an intestinal stoma is also preferable in order to prevent high intestinal pressures. However, patients who receive a colostomy creation are typically frustrated by the limited lifestyle. Therefore, while we understand why a patient may prefer bowel reconstruction, it is difficult to proceed down this path. It is necessary to consider the future of the vEDS patients, as it may be safer not to remove the intestinal stoma to

prevent high intrabowel pressure that causes constipation and adhesive ileus. It is an important to note that complications and tissue weakness increase in vEDS patients after the age of 20 years.[1,2] Several authors have recommended that the perforative lesion and its distal colon should be removed at the same time to prevent reperforation in the sigmoid colon and rectum.[10] Other authors have also recommended a subtotal colectomy as a reasonable treatment because of the high rate of reperforation in vEDS patients.[12] Although these suggestions have validity and are based on a safety-first concept, we were unable to perform a subtotal colectomy for the present vEDS patient at the time of the first operation, when a definitive diagnosis had not yet been determined. Moreover, it is difficult for us to perform both a partial resection of the small intestine and a subtotal colectomy, even at a second operation, because of the risk of short bowel syndrome and anastomotic leakage. It appears that a unique procedure for perforation of the colon in vEDS patients cannot be standardized, because individual patients have widely divergent background factors, such as age, performance status, accuracy of the diagnosis, frequency of perforation, and medical expertise in their country.

We recommend a therapeutic approach for the ileus in vEDS patients based on the clinical course of the present vEDS patient. vEDS patients who are affected by ileus must be surgically treated before too many fissures develop in the intestine, regardless of the presence of ischemic changes. In general, patients who are diagnosed with a paralytic ileus or adhesive ileus after prior operations are conservatively treated by decompression with a nasogastric tube or a Miller–Abbott tube. However, we were unable to treat our vEDS patient conservatively, because the wall of his small intestine was easily torn and became necrotic under high pressure. The timing for a surgical operation must be carefully considered, and a massive bowel resection should always be prevented if at all possible.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Delineation of Dermatan 4-*O*-Sulfotransferase 1 Deficient Ehlers–Danlos Syndrome: Observation of Two Additional Patients and Comprehensive Review of 20 Reported Patients

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Loss-of-function mutations in *CHST14*, dermatan 4-*O*-sulfotransferase 1 (D4ST1) deficiency, have recently been found to cause adducted thumb-clubfoot syndrome (ATCS; OMIM-#601776) and a new type of Ehlers–Danlos syndrome (EDS) coined as EDS Kosho Type (EDSKT) [Miyake et al., 2010], as well as a subset of kyphoscoliosis type EDS without lysyl hydroxylase deficiency (EDS VIB) coined as musculocontractural EDS (MCEDS) [Malfait et al., 2010]. Lack of detailed clinical information from later childhood to adulthood in ATCS and lack of detailed clinical information from birth to early childhood in EDSKT and MCEDS have made it difficult to determine whether these disorders would be distinct clinical entities or a single clinical entity with variable expressions and with different presentations depending on the patients' ages at diagnosis. We present detailed clinical findings and courses of two additional unrelated patients, aged 2 years and 6 years, with EDSKT with a comprehensive review of 20 reported patients with D4ST1 deficiency, which supports the notion that these disorders constitute a clinically recognizable form of EDS. The disorder, preferably termed D4ST1-deficient EDS, is characterized by progressive multisystem fragility-related manifestations (joint dislocations and deformities, skin hyperextensibility, bruisability, and fragility; recurrent large subcutaneous hematomas, and other cardiac valvular, respiratory, gastrointestinal, and ophthalmological complications) resulting from impaired assembly of collagen fibrils, as well as various malformations (distinct craniofacial features, multiple congenital contractures, and congenital defects in cardiovascular, gastrointestinal, renal, ocular, and central nervous systems) resulting from inborn errors of development.

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Am J Med Genet Part A 155:1949–1958.

Key words: dermatan 4-*O*-sulfotransferase 1 deficiency; adducted thumb-clubfoot syndrome; Ehlers–Danlos syndrome Kosho type; musculocontractural Ehlers–Danlos syndrome; congenital contractures; progressive multisystem fragility-related manifestations; malformations

Additional supporting information may be found in the online version of this article.

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INTRODUCTION

Dermatan 4-*O*-sulfotransferase 1 (D4ST1) is a regulatory enzyme in the glycosaminoglycan biosynthesis that transfers active sulfate to position 4 of the *N*-acetyl-D-galactosamine residues of dermatan sulfate [Evers et al., 2001; Mikami et al., 2003]. Dermatan sulfate, as well as chondroitin sulfate and heparan sulfate, constitutes glycosaminoglycan sidechains of proteoglycans; and has been implicated in cardiovascular disease, tumorigenesis, infection, wound repair, and fibrosis via dermatan sulfate-containing proteoglycans such as decorin and biglycan [Trowbridge and Gallo, 2002]. Carbohydrate sulfotransferase 14 (*CHST14*), localized on 15q12, is the gene encoding D4ST1. Recently, loss-of-function mutations in *CHST14* (D4ST1 deficiency) have been found to cause adducted thumb-clubfoot syndrome (ATCS; OMIM#601776) in 11 patients from four families [Dündar et al., 2009] and a variant of Ehlers–Danlos syndrome (EDS) in six patients from six families [Miyake et al., 2010], tentatively coined as EDS Kosho Type (EDSKT) in the London Dysmorphology Database (http://www.lmdatabases.com/index.html) and POSSUM (http://www.possum.net.au/). ATCS was originally recognized as a new type of arthrogryposis, focused on characteristic clinical pictures from birth to early childhood, including adducted thumbs and talipes equinovarus as well as facial dysmorphisms (prominent forehead, large fontanelle, hypertelorism, down-slanting palpebral fissures, low-set ears), and arachnodactyly [Dündar et al., 1997; Sonoda and Kouno, 2000; Dündar et al., 2001; Janecke et al., 2001]. In a recent study by Dündar et al. [2009], ATCS has been categorized again as a connective tissue disorder, based on additional clinical pictures from childhood to adolescence, including skin fragility and bruisability, joint laxity, and osteopenia. EDSKT comprises a pattern of distinct craniofacial features, multiple congenital contractures, progressive joint and skin laxity, and progressive multisystem fragility-related manifestations, including recurrent large subcutaneous hematomas and other cardiac, respiratory, gastrointestinal, ophthalmological complications [Yasui et al., 2003; Kosho et al., 2005, 2010].

Very recently, Malfait et al. [2010] have independently found mutations in *CHST14* in three patients from two families, who were diagnosed with kyphoscoliosis type EDS without lysyl hydroxylase deficiency (EDS VIB). They concluded that their series and ATCS, as well as EDSKT, formed a phenotypic continuum based on their clinical observations and identification of an identical mutation in both conditions, and proposed to coin the disorder as "musculocontractural EDS" (MCEDS) [Malfait et al., 2010]. However, it is still an unsolved problem whether ATCS, EDSKT, and MCEDS would be distinct clinical entities or a single clinical entity with variable inter- and intrafamilial expressions and with different presentations depending on the patients' ages at diagnosis [Miyake et al., 2010], because detailed clinical information are lacking in ATCS from later childhood to adulthood and in EDSKT and MCEDS from birth to early childhood.

Here, we present detailed clinical findings and courses of two additional unrelated patients, aged 2 years and 6 years, with EDSKT, which would contribute to delineate comprehensive phenotypic spectrum of D4ST1 deficiency.

CLINICAL REPORTS

Patient 1

The patient, a Japanese boy, was the second child of a healthy 31-year-old mother and a healthy 33-year-old nonconsanguineous father. He was born by cesarean for breech presentation at 38 weeks and 3 days of gestation. His birth weight was 3,092 g (+0.2 SD), length 46 cm (−1.3 SD), and OFC 34 cm (+0.4 SD). At age 15 days, he was referred to our hospital for the treatment of bilateral talipes equinovarus. He had a round face with a large fontanelle, hypertelorism, short palpebral fissures, blue sclerae, strabismus, a short nose with a hypoplastic columella, low-set and rotated ears, a high palate, a long philtrum, a thin upper lip vermillion, a small mouth, and microretrognathia (Fig. 1A, B). He had arachnodactyly, flexion-adduction contractures of bilateral thumbs, flexion contractures of the interphalangeal (IP) joints in the other fingers, flexion contractures of bilateral elbows and knees, and rigidity of bilateral hip joints (Fig. 1C). He also had widely spaced nipples, a redundant and translucent skin, an umbilical hernia, and bilateral cryptorchidism (Fig. 1C). Talipes equinovarus was treated with incision of bilateral Achilles' tendons at age 2 months, followed by serial plaster casts and braces. Skin fragility was observed at the procedure. It was surgically corrected at age 1 year and 11 months. Gross motor development was delayed: He raised his head at 6 months, sat without support at age 1 year, stood up assisted at age 1 year and 6 months, and walked assisted after surgical correction of talipes equinovarus. He had bruises easily on the occiput

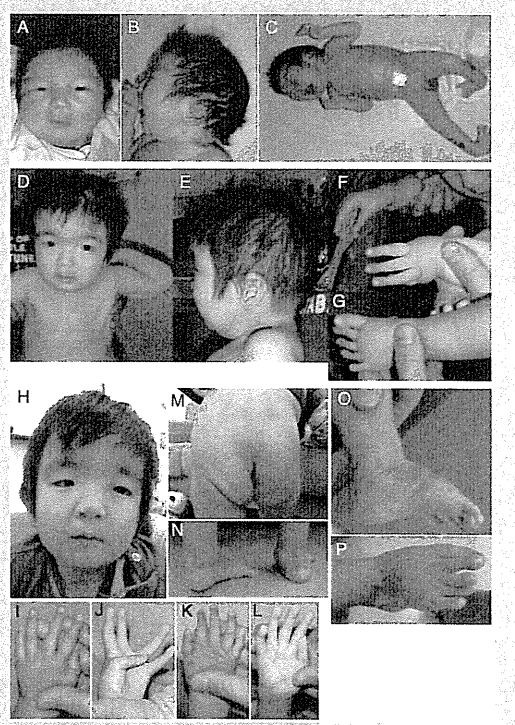

FIG. 1. Clinical photographs of Patient 1 at age 15 days (A–C), at age 1 year and 3 months (D–G), and at age 2 years and 10 months (H–P).

and buttocks after falling, which were absorbed spontaneously. Bleeding time was 1.3 min (normal values, 1–5 min), prothrombin time-international normalized ratio (PT-INR) 1.00 (normal values, 0.81–1.38 sec), and activated partial thromboplastin time (APTT) 27.9 sec (normal values, 23–36 sec).

When seen by us at age 1 year and 3 months, his craniofacial shape became square with a broad, bossed forehead, and hypertelorism with downslanting palpebral fissures became evident (Fig. 1D, E). Skin redundancy and tapering fingers and toes were noted (Fig. 1D, F, G). Ear rotation and flexion contractures of fingers improved (Fig. 1E, F).

When last seen by us at age 2 years and 10 months, he weighed 9.86 kg (−2.4 SD), height 84.9 cm (−2.1 SD), and OFC 45.5 cm (−2.4 SD). His face was slender, and was characterized by an unclosed fontanelle, hypertelorism, short and downslanting palpebral fissures, blue sclerae, strabismus, a short nose with a hypoplastic columella, low-set ears, a high palate, a long philtrum, a thin upper lip vermillion, a small mouth, and microretrognathia (Fig. 1H). He had a Marfanoid habitus, generalized joint laxity, a flat and thin thorax, and distinctive fingers (tapering with enlargement of distal phalanges) (Fig. 1I–L), and talipes valgus and planus with extremely soft subcutaneous tissues at the heels (Fig. 1N–P). The distal IP joints in bilateral index to little fingers and the IP/metacarpophalangeal (MP) joints in bilateral thumbs could hardly be flexed or extended. The MP joints in bilateral index to little fingers could be moved with poor flexion and hyperextension (see Supplementary Video 1 online). He had hyperextensible to redundant skin with bruisability and fine palmer creases (Fig. 1J, L, M). He suffered from constipation (defecation twice a week), treated with oral magnesium oxide. Ophthalmological examinations showed mild esotropia, and amblyopia due to severe hyperopic astigmatism. A cardiac ultrasonography showed no defects or valve abnormalities but mild dilation of the ascending aorta at the sinus of Valsalva. A brain CT showed no ventricular enlargement (Fig. 3O, P). G-banded chromosomes were normal. The Kinder Infant Developmental Scale [Cheng et al., 2010] showed mild developmental delay with the overall developmental quotient as 65 (physical/motor, 35; manipulation, 58; receptive language, 77; expressive language, 103; conceptual thinking, 77; social relationships with children, 68; social relationships with adults, 116; home training, 68; feeding, 42). He had orchiopexy and a surgical correction of an umbilical hernia at age 2 years and 7 months.

Patient 2

The patient, a Japanese boy, was the first child of a healthy 25-year-old mother and a healthy 28-year-old nonconsanguineous father. He was born by normal vaginal delivery at 38 weeks of gestation. His birth weight was 2940 g (+0.3 SD), length 49.1 cm (+0.3 SD), and OFC 32 cm (−0.5 SD). He was admitted for the treatment of bilateral adducted thumbs and talipes equinovarus. His craniofacial features included a large fontanelle, a high forehead, hypertelorism, short and downslanting palpebral fissures, blue sclerae, strabismus, a short nose with a hypoplastic columella, low-set and rotated ears, a high palate, a long philtrum, a thin upper lip vermillion, a small mouth, and microretrognathia (Fig. 2A). He had arachnodactyly, flexion-adduction contractures of bilateral thumbs, flexion contractures of the IP joints in the other fingers, rigidity of bilateral hip joints, and mild pectus excavatum (Fig. 2A, B). He also had widely spaced nipples, a redundant skin, and bilateral cryptorchidism (Fig. 2A). He suckled poorly and hated to be hugged tightly, suggesting hyperalgesia to pressure. Talipes equinovarus was treated with serial plaster casts. Gross motor development was delayed: He raised his head at 7 months, sat without support at age 1 year and 2 months, crawled at age 1 year and 6 months, pulled himself up by holding to something at age 1 year and 6 months, and walked unassisted at age 2 years and 6 months. His fontanelle was closed at age 3 years.

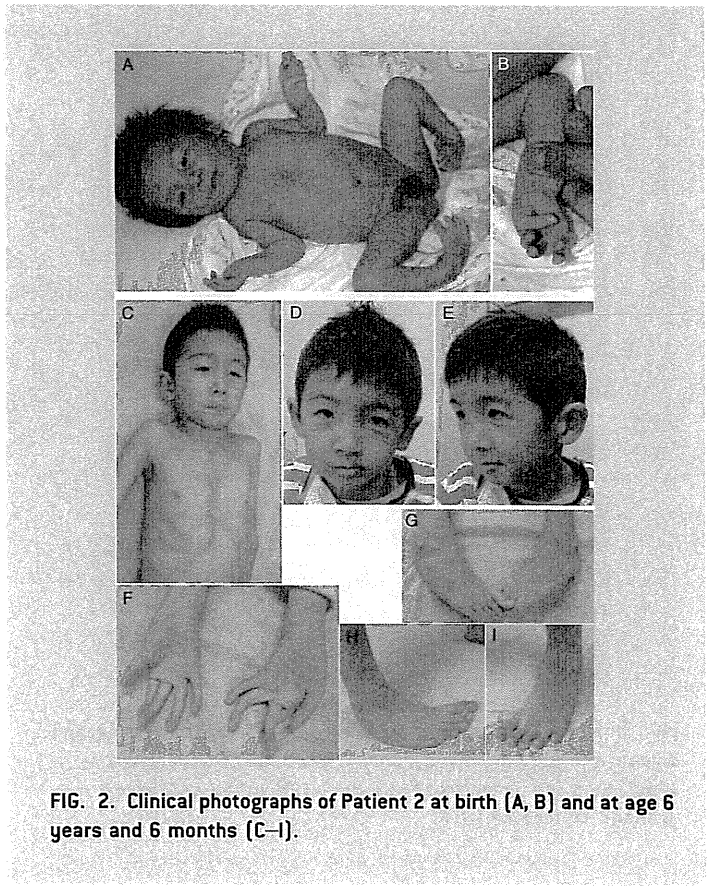

FIG. 2. Clinical photographs of Patient 2 at birth (A, B) and at age 6 years and 6 months (C–I).

At age 3 years, he developed a large subcutaneous hematoma over the skull after falling. Hematomas on the lower legs frequently occurred. He had recurrent dislocations of bilateral shoulders.

When last seen by us at age 6 years and 6 months, he weighed 16.4 kg (−1.4 SD), height 112 cm (−1.0 SD), and OFC 51.5 cm (−0.2 SD). He could jump unassisted. His craniofacial features included hypertelorism, short and downslanting palpebral fissures, blue sclerae, strabismus, a short nose with a hypoplastic columella, low-set ears, a high palate, a long philtrum, a thin upper lip vermillion, a small mouth, and microretrognathia (Fig. 2D, E). He had a Marfanoid habitus, generalized joint laxity, and pectus excavatum (Fig. 2C). His fingers were cylindrical and slender (Fig. 2F). He showed talipes equinovarus when lying down (Fig. 2G) and talipes planus when standing (Fig. 2H, I). The subcutaneous tissues at the heels were extremely soft. The distal IP joints in bilateral index to little fingers and the IP joints in bilateral thumbs

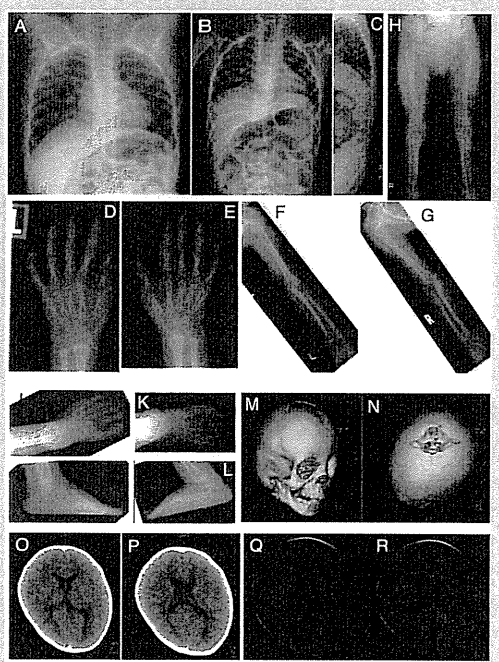

FIG. 3. Radiographs of Patient 1 at age 1 year and 10 months (A) and 2 years and 6 months (B–L). Cranial and brain CT of Patient 1 at age 2 years and 6 months (M–P). Brain MRI of Patient 2 at age 1 year and 10 months (Q, R).

could hardly be flexed or extended. The proximal IP joints in bilateral index to little fingers and the MP joints in all fingers could be flexed and extended, but could not be moved separately and smoothly. His skin was hyperextensible and bruisable. Fine palmar creases were also noted (Fig. 2F). He occasionally had constipation and abdominal pain. A cardiac ultrasonography showed trivial mitral valve prolapse, patent ductus arteriosus, and dextrocardia. A brain MRI showed bilateral ventricular enlargement (Fig. 3Q, R). G-banded chromosomes were normal. His intelligence was normal.

SKELETAL INVESTIGATIONS

Radiographs of Patient 1 were reviewed. At age 2 years and 6 months, he had mild scoliosis (Fig. 3B), which was not noted at age 1 year and 10 months (Fig. 3A). Physiological lumbar lordosis was not present (Fig. 3C). The left hip joint was dislocated (Fig. 3H). Long bones of the legs and arms showed over modeling, with narrowing diaphysis and widening metaphysis (Fig. 3F–H). Bilateral tibiae and fibulae were medially curved (Fig. 3H). Short bones of the hands (Fig. 3D, E) and feet (Fig. 3I–L) also showed over modeling, as well as osteoporotic changes in the feet (Fig. 3I–L).

MUTATION ANALYSIS

Genomic DNA was extracted from peripheral blood leukocytes of the patients and their parents, and was amplified with PCR using four primer sets for *CHST14* (sequences available on request). Through direct sequencing of the PCR products, compound heterozygous mutations were detected in both patients: c.842 C > T causing p. Pro281Leu (p.P281L) and c.878 A > G causing p.Tyr293Cys (p.Y293C) in Patient 1; c.626 T > C causing p.Phe209Ser (p.F209S) and c.842 C > T causing p.Pro281Leu (p.Y293C) in Patient 2 (data not shown). The parents had one of the two heterozygous mutations observed in their children.

DISCUSSION

We have presented detailed clinical characteristics and courses of two new unrelated pediatric patients with compound heterozygous *CHST14* mutations. The features showed striking resemblance to those of patients with EDSKT in their infancy to early childhood [Kosho et al., 2005, 2010]. *CHST14* mutations (P281L/Y293C) in Patient 1 were identical to those found in two patients with EDSKT [Miyake et al., 2010]. F209S found in Patient 2, which was not listed on a database of common gene variations in the Japanese population (JSNP) [Haga et al., 2002], was the mutation that has never found in previous patients with ATCS, EDSKT, or MCEDS.

To date, 22 patients (12 males, 10 females) from 14 families, including present patients, have been reported to have homozygous or compound heterozygous mutations in *CHST14* (Tables I and II) [Dündar et al., 1997; Sonoda and Kouno, 2000; Dündar et al., 2001; Janecke et al., 2001; Yasui et al., 2003; Kosho et al., 2005; Dündar et al., 2009; Kosho et al., 2010; Malfait et al., 2010; Miyake et al., 2010]. Eight families were of Japanese origin, three of Turkish origin, one of Austrian origin, and one of Indian origin. The median patients' age at their initial publication was 4 years and 1 month (range, 0 day–32 years): 7 months (range, 0 day–6 years) in ATCS, 12.5 years in EDSKT (range, 2 years–32 years), and 21 years (range, 12 years–22 years) in MCEDS.

CHST14 mutations included V49X in two families (ATCS, MCEDS), K69X in one (EDSKT), R135G in one (ATCS), L137Q in one (ATCS), F209S in one (EDSKT), R213P in one (ATCS), P281L in eight (EDSKT), C289S in one (EDSKT), Y293C in four (one ATCS, three EDSKT), and E334GfsX107 in one (MCEDS). Sulfotransferase activity of COS-7 cells transfected with *CHST14* containing K69X, P281L, C289S, or Y293C mutation was decreased at almost the same level, suggesting that loss-of-function mutations in *CHST14*, that is to say D4ST1 deficiency, would cause these disorders [Miyake et al., 2010].

Characteristic craniofacial features at birth to early infancy (large fontanelle, hypertelorism, short and downslanting palpebral fissures, blue sclerae, short nose with hypoplastic columella, low-set and rotated ears, high palate, long philtrum, thin upper lip vermilion, small mouth, and micro-retrognathia) were noted in most patients with ATCS, EDSKT, and MCEDS. Slender and asymmetrical facial shapes with protruding jaws from school age, commonly observed in patients with EDSKT, were also described in ATCS2 at age 15 years, ATCS3 at age 6 years, ATCS7 at age 8 years [Dündar et al., 2009], and in MCEDS1 at age 21 years [Malfait et al., 2010]. A pair of ATCS siblings had palatal defects: ATCS4 with cleft lip and palate, which was surgically repaired, and ATCS5 with cleft soft palate [Sonoda and Kouno, 2000].

Congenital multiple contractures, most specifically adduction–flexion contractures of thumbs and talipes equinovarus,