厚生科学研究費補助金（子ども家庭総合研究事業）研究報告書

骨系統疾患および代謝性骨疾患に伴う内反膝・外反膝変形

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要約　骨系統疾患では低身長，関節変形，靱帯弛緩などさまざまな二次障害を呈する。特に膝の変形は大きな問題となり，しばしば治療対象となる。内反膝は軟骨無形成症，偽性軟骨無形成症，骨幹端異形成症Schmid型，多発性骨端異形成などがある．外反膝はMarfan症候群，Morquio病，Ollier病，一部の軟骨無形成症，偽性軟骨無形成症，くる病，先天性脊椎骨端異形成症などで見られる．

はじめに

全身の骨が罹患する本疾患群では低身長，関節変形，靱帯弛緩などさまざまな二次障害を呈する．歩行例では下肢，とくに膝の変形は大きな問題となり，しばしば治療対象となる．内反膝を呈する骨系統疾患は数多くあげられ，代表的なものとして軟骨無形成症，偽性軟骨無形成症，骨幹端異形成症Schmid型，多発性骨端異形成などがある．また代謝性骨疾患ではくる病などがある．外反膝を呈する骨系統疾患の代表的なものとしてMarfan症候群，Morquio病，Ollier病，一部の軟骨無形成症，偽性軟骨無形成症，くる病，先天性脊椎骨端異形成症などがあげられる．膝関節は足部，股関節の力学的な影響を受け，足部内反変形・内反股は外反膝を増悪させる（図1）．ここでは主な疾患の内反膝変形を主に述べ，外反膝については症例呈示程度にとどめる．

内反膝

骨系統疾患および代謝性骨疾患に伴う内反膝に共通してみられる下肢アライメントは膝外側角（FTA）の増大，膝関節および下腿での内捻，膝関節の屈曲傾向，距骨下関節での外反などであり高度な内反膝を呈する症例も，まれではない．骨系統疾患にみられる内反膝では関節弛緩，関節拘縮を伴ったものが多く，神経症状の併発などを合併していることも少なくはない．各疾患は固有の症状と経過を示し，症例数の少ないこともあって，全体像の把握が困難な場合が多い．またアライメントの変化では自然軽快していくCaffeyの四肢彎曲症から，変形矯正後再発しやすいことが知られているOllier病まで下肢変形の予後もさまざまである．下肢のアライメントの経年的変化が落ちつく小学生以上の著しい内反膝，外反膝変形に対しては荷重によるアライメントの悪化を防止する目的で早期矯正手術が奨められる場合が多い

軟骨無形成症

内軟骨性骨化障害による四肢短縮型低身長をきたす軟骨無形成症では内反膝がよく合併するが，PonsetiやKopitsによるとその原因は腓骨の過成長とそれに伴う脛骨の内反変形，反張脛骨，内捻変形としている1) 2)．安井らは本症の内反膝のX線上の特徴としてFTAは正常人に比べやや大きい秩度であることと，脛骨内反度が人きいことが本症の内反膝の原因としており，本症の外反膝では大腿骨外顆の形成不全が存在し，大腿骨骨幹軸の膝基底線に対する角度（femoral angle）が小さいことが主な原因であるとしており，その他に脛骨内反度が小さく腓骨の過成長が少ないことをあげている3)．また距腿関節面も下腿の内反に一致して傾斜していることも特徴の1つである．本症の患者会である「つくしの会」を通して，アンケート調査を行ったところ，約6割の190例からの回答を得た．12歳以上が半数を占め，15歳以上の68例の歩行についての回答は，歩行では困らない49%，ときどき疲れなどで困る41%，杖使用6%，車椅子使用3%であった．膝変形は内反膝24%，外反膝6%，変形なし70%であり，諸家の報告と同様に本症での膝変形は大きな問題となっていないと考えられた．また本症での内反膝の年齢分布をみると年齢による差は少なく進行性とはいえない．むしろ膝関節の不安定性は高頻度で30歳までの症例で約半数があると回答している．膝痛は27例14.2%にみられ，発症年齢は12歳以下が多かった．本症の内反膝の矯正手術の適応については，「つくしの会」の報告によると本症の外科的治療では約400人の会員のうち脚延長術を受けたのが67人であったのに対して，純粋に内反膝の矯正骨切り術のみを受けた者は3人と少なかった．本症の場合，上記の調査からも

わかるように下肢延長と矯正を同時に進めることが一般的である.下肢延長を行うにあたっては,単に長さのみでなくアライメントを改善することも重要である.延長に伴う合併症として既存の変形に加えて,延長中に外反,前方凸変形,トランスレーションなどの変形が起こることが知られている。そこで既存の変形や延長中に起こる変形を矯正する手段として3つの方法が考えられる.1番目は延長前の骨切り時に一期的に矯正を行う方法,2番目は延長中に徐々に矯正する方法,3番目は延長終了に一期的に矯正する方法とがある.1番目の方法は延長中の変形の予測がつきにくいことが,2番目の方法は何度も修正を要する点が実用的でない.岡崎らの報告では3番目の方法が最も安定した矯正が得られるとしており,仮骨にかかる張力をモニターリングしながら,無麻酔下で延長を行った延長仮骨の塑性を利用し矯正している.そのときの下腿矯正の目標とする下肢アライメントは,大腿骨頭中心と足関節中心を締んだ直線 (Mikulicz線) が膝関節顆間隆起の中央を通過し,膝関節面とのなす角度が87°内側下がりで,距腿関節面とは直交することである.しかし,3番目の方法も一期的矯正であるがゆえに神経麻痺のような軟部組織の障害をきたしうることを念頭にいれておくべきであろう.

偽性軟骨無形成症

偽性軟骨無形成症は四肢短縮型低身長で顔貌正常で成長過程で椎骨の前方舌状突出と骨端および骨幹端の異形成を特徴とする疾患である.本症では関節靱帯弛緩性が強く,McKeandらによると内反膝を合併する頻度は84%,膝痛を合併する頻度は52%である4).その他にもWINDSWEPT型 (片側が外反膝と他側が内反膝) の膝変形も少数ではあるがみられる.本症の69%が平均年齢8歳時に矯正骨切り術を受けたとしており,そのうち再手術を要した者は22%であった4].この点は軟骨無形成症と大きく異なり,手術を要するほどの重度の内反膝が本疾患で多いことがうかがえる.Kopitsの報告によると本症の内反膝は歩行開始時から発症し歩行はカモ様歩行となり,5-15歳にかけて進行する5].近年まで外科的矯正が試みられているが,その成績は諸家の報告にばらつきが大きい.Kopitsは下肢矯正骨切り術は再発すると述べており,成績は一般に悪く度重なる手術を要するとしている.一方,McKeandらにより行われたアンケート調査では再手術を要した例は少ないと報告している.このように本症の内反膝に対する手術の適応,年齢,矯正角度などはこれまで不明な点であった。

自験例16例のうち15例で内反膝がみられ,うち10例20膝に平均9.8歳時に下腿矯正骨切り術を行った.骨切りは脛骨の骨幹端・骨端の移行部で行われ,Kirschner鋼線を使った固定や若年者であればギプスのみの固定が行われた.術後に膝痛,歩容の異常はほとんどの例で改善された.観察時平均年齢は16.3歳で全例に再手術を要するような明らかな再発はみられなかった.術前のFTAは約200°程度であるが,手術によりFTAは165°前後に矯正され再発傾向は2年で1度程度であった.10年以上の長期経過観察ができた症例でも同様な結果が得られた.つまり本症において早期に下肢矯正骨切り術により下肢アライメントを適正 (やや過矯正) に矯正することは将来的な再手術を防ぐだけでなく,若年発症の変形性膝関節症をも防止すると考えられる

多発性骨端異形成症

多発性骨端異形成症は偽性軟骨無形成症と同じ遺伝子 (COMP) の突然変異を原因とする疾患で長管骨骨端部の異形成を特徴とするが,偽性軟骨無形成症に比べて四肢短縮の程度も軽度であり,膝の内反膝変形も軽度な場合が多く,足関節の外反も特徴の1つにあげられている.本症の内反膝が手術の対象になることはまれである6]

骨幹端異形成症

骨幹端異形成症は成長期に長管骨骨幹端の異形成をきたすが,骨端および椎骨の変化を伴わない疾患である.最も多くみられるSchmid型は乳幼児期に出現する四肢短縮型低身長で内反股と内反膝を伴ったカモ様歩行を呈する.組織学的には成長板における軟骨細胞の成熟パターンが乱れており,変形の一原因と考えられる.下腿内反はゆっくりと進行し,本症の約半数が下肢のアライメントの異常をきたす3).しかし,偽性軟骨無形成症のような関節靱帯弛緩性は目立たない.中塚らの報告によると内反膝は3-6歳の間は改善するが,その後増悪するとしている.変形矯正手術により歩容は改善し,歩行の耐久性が増大するとされている5).初期の治療法として装具療法を行い,手術としては大腿骨の矯正骨切りや骨端線の成長抑制を目的とした大腿骨遠位骨端線外側のステープリングなどが行われている8).

低リン血症性くる病

低リン血症性くる病はリンの転送障害による低リン血症のため,成長過程の骨の石灰化障害を

生じる性染色体優性遺伝性の疾患で男性に重症である.歩行開始後の内反膝で気づかれやすい.本疾患は早期の薬物療法により変形を矯正することが期待できるが9),治療開始時期が5-6歳以降の著明な内反膝では手術が必要となりやすいこと,12-13歳以降の発育盛期の薬物服用中断で変形が再発すること,矯正骨切り術後にも適切なビタミンD投与を続けなければ変形が再発することが報告されている.またKanelらは本症の平均12歳の9例で下腿矯正骨切り後Orthofixを平均90日間装着し早期の荷重により良好な骨癒合と矯正を得ている7) .Stanitskiは平均年齢8.9歳の8例,11大腿,7下腿に下腿矯正骨切り後,平均12週のIlizarov装着にて,ほかの疾患の約1/2の速度で延長し良好な成績をあげている。またEvansらは適切なビタミンD投与と大腿骨遠位骨端線外側の成長期でのステープリングで膝外反変形は矯正できたと報告している9) .

また装具療法も試みられており,短下肢型O脚矯正装具や,歩行時側方への不安定性を呈する場合には外側楔,外足張り出しをもった足底装具が処方されているようである.

外反膝

Marfan症候群

Marfan症候群はクモ指趾,心・血管異常,水晶体脱臼を伴う常染色体優性遺伝の疾患で,靱帯弛緩性と屈曲拘縮を伴う外反膝が特徴でときに膝蓋骨脱臼を伴う場合がある。

Morquio病

Morquio病は幼児期早期 (1-3歳頃) に発症するIVA,B型のムコ多糖症で,最も骨病変が強く関節靱帯弛緩性の著明な疾患である.長管骨は短縮,沓曲し骨幹端が幅広くなり脛骨の内側に骨棘を伴う脛骨近位の骨端核の外側が骨化障害を起こすことにより重度の外反膝および反張膝を認めることが多く膝の骨端核は不整で分節化を認める.さらに外反股と扁平足も特徴である.環軸椎脱臼や胸腰椎移行部での脊髄,馬尾症状のためその歩行障害は単に膝の問題にとどまらない12]

Ollier病

Ollier病は骨発育期 (1-4歳頃) に四肢長管骨を主に片側性に侵す多発性内軟骨腫が骨幹端から骨幹部に進行するため脚長髪や片側性の外反膝をきたすことがある13).本症の外反膝は大腿骨遠位での外反と脛骨近位での角状変形による外反変形がある.本症の変形は手術による矯正には抵抗性で一般に何度も手術を要する場合が多い.下腿骨の変形再発のメカニズムとしてShapiroは1番目として骨端,骨幹端に残った内軟骨腫が再発すること,2番目として手術による矯正の不足,3番目として術後の切除した内軟骨腫部の崩壊などによる変形再発をあげている14) .

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A mild form of pseudoachondroplasia : minimal epi-metaphyseal involvement of long bones

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要約　偽性軟骨無形成症 (PSACH) の診断上の問題は、椎体の特徴的変化が10歳頃に消失し、成人例ではPSACHほど重症ではないMED Fairbank typeと鑑別が困難なことである。我々は、長管骨の骨端骨幹端障害が軽度で慎重がPSACH平均の+2SDで椎体は典型的変化を示す日本人女児を報告する。太く短い指はなく椎体の特徴的変化も消失したため、患児はPSACHのみではなくMED Fairbank typeとも診断されていなかった。分子生物学的にPSACHとMEDの重複が議論されておりPSACHの臨床像の拡がりの研究は重要である。

Introduction

Pseudoachondroplasia (PSACH) was first defined as a separate disorder among a group of spondylo-epiphyseal dysplasias in 1959 by Maroteaux and Lamy [1] . The diagnostic criteria include normal skull, disproportionate short stature with normal trunk and short limbs, anterior tongue-like protrusion and biconvexity of the vertebral bodies and epi-metaphyseal dysplasia during growth [2] .

One problem in diagnosing PSACH is that the characteristic changes of the vertebral bodies invariably disappear around the age of 10 [3] . Subsequently, an adult case might be misdiagnosed as MED, Fairbank type, though it is generally believed that the latter is less radiologically severe and that height of the affected individual is greater than in PSACH [3]

We present a case with minimal epi-metaphyseal involvement of long bones in spite of the typical change of the vertebral bodies. Since the overlap between PSACH and MED has recently been discussed from the viewpoint of molecular biology [4,5] , study of the spectrum of clinical features of PSACH is valuable.

Case History

The propositus was a 3-year-old girl (Y.T.) referred for her short stature. There were no relatives with short stature. Her birth weight was 3075 g and she began walking at 20 months. Facial appearance and mental status were normal.

At the age of 3, she was 88 cm tall (+0.1SD of a standard Japanese girl) with an arm span / body height of 0.89. The short limb type of short stature became apparent thereafter, and at the age of 10 her height was 119 cm (-2.5SD) and arm span / body height was 0.92. Among PSACH patients, however, her short stature was not severe ; her height corresponded to +2SD on the growth curve of PSACH by Horton et al. [6] . There was general joint laxity but no gross deformity in extremities including the hands.

Radiographs at age 3 revealed an anterior tongue-like protusion and biconvexity of the vertebral bodies, which are characteristic of PSACH (Fig. 2A) . The epi-metaphyseal abnormalities of the proximal and distal femur and the proximal tibia were minimal from 3 to 10 years in comparison with those in typical PSACH patients during their growth period. Malalignment around the knee joints such as genu varus did not develop during this follow-up period .

Radiographs of the hands showed some epi-metaphyseal abnormalities and shortness of the long bones from 3 to 8 years, but the degree of the abnormalities was less than that of typical PSACH patients ; the epiphyses were not small, the metaphyses were not flared and long bones were not stubby (Fig. 2E) . There was also no delay in development of the carpal bones at the age of 3 and 8 in this case, unlike the

typical PSACH patients .

Discussion

PSACH is known to vary widely in severity. Short stature is not apparent untill 3 years of age, and thereafter the growth curve deviates from the standard. Deviation in this case was less than that of typical PSACH, the smallest among our 16 patients with this affliction from 3 to 10 years of age, and +2SD on the PSACH growth curve at 10 years. The radiological changes in this case were also milder than those of typical PSACH in spite of the typical vertebral change ; the epiphyses are not too small, the metaphyses are not too flared and shortness of the long bones is not as apparent from 3 to 10.

McKeand et al. [7] reported that 84 percent of PSACH patients have bowleg deformity, which develops after walking begins and advances between 5 and 15 years of age [8] . In this mild form, no malaligment around the knee joints was seen from 3 to 10 years.

These physical and radiological findings are less severe than those reported as mild form in the literature [9, 10] except for one reported by Maroteaux et al [11] . Although one problem in making a diagnosis of PSACH is that the mild form of an adult case might be misdiagnosed as MED, Fairbank type, the cases reported by Maroteaux et al. and this one by us might not have been diagnosed only as PSACH but also even as MED, Fairbank type after the typical changes of the vertebral bodies had disappeared.

The overlap between PSACH and MED has been discussed ; Maroteaux et al. (1980) [11] and Stanscu et al. (1982) [12] reported the accumulation of abnormal materials in rough endoplasmic reticulum in cartilage cells in patients with PSACH and similar ultrastructural findings were found in the severe form of MED, Fairbank type in 1993 [13] . More recently it has been shown that mutation in COMP gene causes both PSACH and MED [5] , and PSACH and MED, Fairbank type, were also shown to be allelic disorders [4, 5] . These molecular and genetic findings suggest the importance of determining the spectrum of clinical features of PSACH. This case is important because it shows the mildest end of the reported spectrum. The presence of such a mild form as described here also means that in evaluating the results of genetic molecular findings we should pay attention to the clinical evidence on which the diagnosis is made.

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Novel and recurrent COMP (cartilage oligomeric matrix protein) mutations in pseudoachondroplasia and multiple epiphyseal dysplasia

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要約　偽性軟骨無形成症 (PSACH) と多発性骨端異形成症 (MED) は内軟骨性骨化障害と早期の変形性関節症という共通の骨格異常がある。両者はこれまで明らかに異なる疾患単位と考えられてきたが、近年ともに cartilage oligomeric matrix protein (COMP) をコードする遺伝子の突然変異が原因であることがわかってきた。COMP突然変異を検討し表現型遺伝型の関係を調査するためにPSACHおよびMEDの15例のゲノム遺伝子を解析し８つのカルモデュリン様の繰り返しの中に10の突然変異を同定した。７つはexon 9,10,11,13,14の新たなミスセンス変異で、残る３つは。exon13の５個のGAC繰り返しの一つの欠失であった。exon13の７番目のカルモデュリン様の繰り返しのGAC繰り返しは、突然変異のhot-spotであり、その変異は重度のPSACHであり、その他では軽症型PSACHあるいはMEDであった。このような表現型遺伝型の関係を知ることは分子生物学的診断、PSACHとMEDの分類に有用でCOMP遺伝子産物の構造と機能の関係解明の端緒となる。

Introduction

Pseudoachondroplasia (PSACH) is a relatively common skeletal dysplasia characterized by short-1imbed short stature with normal facies and intelligence (Maroteaux and Lamy 1959; Hall and Dorst 1969). Its clinical features include joint laxity, limitation of the movement of joints, severe bony deformities, and early onset of osteoarthroses; radiographlc features include platyspondyly with anterior beaking of the vertebral bodies and generalized dysplasias of epiphyses and metaphyses of the long and short tubular bones (Wynne-Davies et al. 1986). This syndrome exhibits considerable clinical and genetic heterogeneity; Hall and Dorst (1969) distinguished four varieties of PSACH on the basis of severity of disease and mode of inheritance, i.e., the Maroteaux-Lamy (severe) and the Kozlowski (mild) types, each being subject to either autosomal dominant or recessive inheritance. However, recent clinical and molecular studies have demonstrated gonadal/somatic mosaicism in PSACH families that were originally considered to represent autosomal recessive inheritance, suggesting that auto-somal recessive inheritance is unlikely (Hall et al. 1 987; Hecht et al. 1995). Multiple epiphyseal dysplasia (MED) defines a group of dominantly inherited skeletal dysplasias involving epiphyses of the long and short tubular bones. MED also exhibits considerable clinical heterogeneity. This disorder appears in two forms, i.e., severe (Fairbank type; Fairbank 1947) and mild (Ribbing type; Ribbing 1 955). Although MED patients do not show the significant metaphyseal and vertebral dysplasias characteristic of PSACH, their epiphyseal mani-festations are very similar. Because of the broad phenotypic overlap between the two conditions, they are now considered to represent a continuous spectrum of disorders, being categorized as a family of skeletal dysplasias (Spranger 1988).

Genetic linkage of mild (Briggs et al. 1993) and severe (Hecht et al. 1993) forms of PSACH, respectively, has been demonstrated to a locus in the pericentromeric region of chromosome 19. A subsequent candidate-gene approach revealed that mutations of the gene encoding cartilage oligomeric matrix protein (COMP) were responsible for PSACH (Briggs et al. 1995; Hecht et al. 1995). Furthermore, COMP mutations were also identified in patients with Fairbank (Briggs et al. 1995) and Ribbing (Ballo et al. 1 997) types of MED. These findings indicated that PSACH and MED are allelic, and that mutations of the COMP gene can produce a wide spectrum of manifestations from severe PSACH to mild MED. However, the full extent of COMP mutations, and possible phenotype-genotype relationships, are unclear because so few mutations have been identified; we are aware of only 15 previously documented COMP mutations, ten of them in PSACH patients (Briggs et al. 1995, 1998; Hecht et al. 1995; Susic et al. 1997) and five in MED patients (Briggs et al. 1995, 1998; Ballo et al. 1997; Susic et al. 1997) .

To characterize additional COMP mutations and investigate possible phenotype-genotype correlations, we screened the COMP gene in 15 patients with PSACH or MED, by direct sequencing. We report here the identification of ten mutations, seven of them novel, and pro-

vide ev-idence to indicate a correlation of genotypes with phenotypic manifestations.

Materials and methods

Patients

Patients were identified and followed at special clinics for skeletal dysplasias in the National Rehabilitation Center for Disabled Chil-dren, the Saitama Children's Medical Center, or the Dokkyo University Hospital. Diagnosis of PSACH was made on the basis of clinical and radiographic examinations. Criteria were (1) short-limbed short stature, not identifiable at birth but recognized in early childhood; (2) normal facies and intelligence; (3) joint laxity, Iimitation of the movement of joints, and severe bony deformities; (4) platyspondyly with anterior beaking; and (5) generalized dysplasias of epiphyses and metaphyses of the long and short tubular bones. Diagnosis of MED was also made on the basis of clinical and radiographic criteria, including generalized dysplasias of epiphyses of the long and short tubular bones and the absence of spinal dysplasia.

Fifteen patients were included in the study; ten of them were diag-nosed as having PSACH, and five as MED. None had family histories of the disease except for two of the MED patients. On the basis of the severity of the disease, the PSACH patients could be divided into the severe and mild types. Four PSACH patients were classified as the se-vere type, six the mild type. The heights of PSACH patients of the se-vere type were below -6 SD, and those of the mild type, between -4SD and -2SD. Limitation of the movement, and the deformities of the joints were more severe in the severe type. However, radiographs showed no significant qualitative difference between the two types.

DNA samples and polymerase chain reaction (PCR)

Blood samples were obtained from patients and members of their families with informed consent. Genomic DNA samples were extracted by standard procedures and amplified by the PCR. For exons lO and 13 of the COMP gene, primers were as described previously (Briggs et al. 1995; Hecht et al. 1995). Other exons were amplified by sets of primers designed according to the published COMP cDNA sequence (L32137 in GCG) and its genomic structure reported by Briggs et al. (1995). Primer sequences for exon 9 were i7i9/F (sense): 5'-TTGAGGCCGGCTTGGGTG-3' and i7i9/R (anti-sense): 5'-CCCGTAGATCTACCTTTTCATTGGG-3'. Primer sequences for exon Il were i lOil l/F (sense): 5'-CATCCTAATGAAGTCATTCTGGC-3' and ilOill/R (anti-sense): 5'-ATCCAACTTGCAGTTCACCC-3'. Primer sequences for exon 14 were e 14/F (sense): 5'-GACGTGTGCCAGGA-CGACTT-3' and el4/R (anti-sense): 5'-CCCACCTGGTrGAGCAC-CAC-3'. The PCRs were performed with the Takara exTaq system (Takara Shuzo, Otsu, Japan) according to the instructions of the manufacturer, in a total volume of 25 μl using as templates 50 - 100 ng of each genomic DNA sample. The PCR conditions were as follows: initial de-naturation (94°C, 2 min) followed by 35 cycles of denaturation (94°C, 30 s), annealing (55°-63°C according to the Tm of the primers, 30 s), extension (72°C, 30 s), and final extension (72°C, 5 min).

Nucleotide sequence analysis

The PCR products were purified by Ultrafree-MC (Millipore) and sequenced directiy by means of the AB1377 automated sequencer and the Prism Ready Reaction DyeDeoxy Terminator Cycle Sequencing Kit (ABI). For confirmation of mutations, PCR products were subcloned to T-vector (Invitrogen) and sequenced by the automated sequencer using M 13 universal primers. Nucleotide sequences were determined on both strands.

Restriction digestion of PCR products

The PCR products were digested for 6-8 h with l0-20 U of each appropriate restriction enzyme per microgram of DNA, at the optimal temperature for each enzyme, then electrophoresed on 3% or 4% NuSieve GTG agarose gels (EMC, Rockland, Me., USA).

Results

Ten COMP mutations were identified, nine for PSACH and one for MED. Three mutations comprised a 3-bp deletion, and the remaining seven were all missense mutations.

Identification of a recurrent COMP mutation in patients with severe PSACH

Direct sequencing of exon 13 of the COMP gene identified 3-bp deletions in three patients IPS-SI (M), PS-S2(H), PS-S3(O)]; each deletion had eliminated one of the five copies of GAC from the trinucleotide repeat region at nucleotides 1405-1419 (nucleotides are numbered from the translation start site). This mutation, confirmed by sequencing the subcloned PCR products, had been describeci previously in patients with severe PSACH (Hecht et al. i995), It resulted in loss of an aspartic acid residue (D473del) within the 7th calmodulin-like repeat of the gene product. The phenotype of all three of our patients with this mutation was also severe, their adult heights being less than 110 cm. They were all sporadic cases.

Identification of a novel COMP mutation
in a patient with severe PSACH

One patient [PS-S4(1)] was heterozygous for a single-base change at nucleotide 1418 (A 141 8~,G) . This novel missense mutation, which also occurred within the GAC repeat in the 7th calmodulin-like repeat encoded in exon 13, would cause replacement of a conserved aspartic acid residue with glycine at codon 473 (D473G). Direct sequencing of DNA samples from the patient's clinically unaffected parents failed to find this mutation, nor was it detected in normal controls or any other PSACH or MED patients. The patient was a sporadic case. His height at the age of 17 years was 108 cm (-l0 SD).

Identification of novel COMP mutations i
n mild PSACH cases

Five of the six patients with mild PSACH carried novel missense mutations elsewhere than in exon 13 of the COMP gene. These mutations occurred at sites encoding conserved amino acids in the calmodulin-like repeats of the protein. Patient PS-M1 (O) was heterozygous for G868->A (D290N) in exon 9; patient PS-M2(D) for AI046->G (D349V) in exon 10; patient PS-M3(W) for Tl 159->G (C387G) in exon 11 ; patient PS-M4(1) for G1552->A (D518N) in exon 14; and patient PS-M5(K) for G895->A (G299R) in exon 9. These mutations were confirmed by PCR-RFLP (restric-tion fragment length polymorphism) analyses : the D349V and C387G mutations created Fnu4HI and Sau961 sites respectively, and the D290N , D518N, and G299R mutations abolished Mval, Taql and DdeI sites, respectively. None of these sequence changes were present among 50 unrelated, unaffected individuals or in other PSACH or MED patients of our panel. All patients were sporadic cases.

Identification of a novel COMP mutation in MED

We found a novel missense mutation in exon 10, A 1082->T (D361V), in a patient [MED-1 (M)] with Fairbank-type MED The aspartic acid at codon 361 is a highly conserved amino acid in the 3rd calmodulin-like repeat. This mutation was confirmed by PCR-RFLP analysis, as the change had created a Tsp451 site. The mutation was not detected in 50 unrelated, unaffected individuals or in other PSACH or MED patients. The patient had an affected mother and an affected younger sister, who also had the mutation.

Sequence variations

In all patients examined, nucleotides 766-767 and 854-855 were GC, not CG as in the published sequence (L32137). This difference would mean substitution of an arginine residue for alanine at codon 256 (CGC->GCC) and a phenylalanine residue for arginine at codon 285 (CCG->CGC). However, neither of these sites represents a conserved amino acid. We also found two patients who were heterozygous for C279->A, but this change did not cause an amino acid substitution.

Discussion

COMP is an extracellular matrix protein specific to cartilage; it is localized mainly in the territorial matrix surrounding chondrocytes. The COMP monomer is a 110-kDa glycoprotein containing an amino-terminal domain, four contiguous epidermal growth factor-like repeats, eight contiguous calmodulin-like repeats, and a carboxy-terminal domain (Newton et al. 1994; Briggs et al. 1995). Calmodulin-like repeats are thought to bind calcium by means of aspartic acid residues lining calcium-binding pockets. The consensus sequence of the calmodulin-like repeats of COMP is N-(D)Q-D-D-DG-GDAC(D)-D-D-D...DNPC- (DiCesare et al. 1994). Because the amino acids in the repeats are highly conserved, replacement would alter the conformation and function of the COMP gene product. All COMP mutations reported in the previous and present studies have involved calmodulin-like repeats, except for two cases (Briggs et al. 1998), underscoring the

functional importance of this domain. If one includes the results of the present study, a total of 22 different COMP mutations have been identified in 37 patients, 19 of them with severe PSACH, 12 with mild PSACH, and 6 with MED . All 19 patients with severe PSACH carried mutations in the 7th calmodulin-like repeat encoded in exon 13, 17 of them within the GAC repeat sequence at nucleotides 1405-1419; 15 of these reflected deletion of one trinucleotide. Hence, the GAC repeat is a mutational hotspot of the COMP gene; more than one-third of the identified mutations, and almost half of mutations in PSACH comprised this delption. Mutations in the 7th calmodulin-like repeat in exon 13 produce the severe PSACH phenotype except one at the top of the repeat. In contrast, patients with mutations in exons other than 13 showed mild PSACH or MED phenotypes. These genotype-phenotype correlations should facilitate molecular diagnosis and classification of PSACH and MED, and provide insight into the function of COMP and the physiological consequences of different mutations. Among the 22 COMP mutations documented here and elsewhere, 18 were missense mutations and 4 were inframe deletions; most of them substituted or deleted conserved aspartic acid or cysteine residues. The type of mutation is unlikely to be related to phenotype, however, because although missense mutations such as D473G could produce a severe PSACH phenotype, the most drastic change among the reported mutations, a four amino acid deletion (V513-K516del), resulted in mild PSACH (Susic et al. 1997). To date, no mutations producing truncated gene products, for example nonsense mutations or insertion/deletions causing frameshifts, have been identified so far. It remains to be determined whether these kinds of mutation would produce phenotypes within the PSACH-MED spectrum of skeletal dysplasias, or cause syndromes belonging to a completely different category. The molecular mechanism by which COMP mutations cause PSACH and MED remains unclear. Haplo-insufficiency is unlikely, in view of the wide spectrum of disease phenotypes associated with known mutations. No individuals with a karyotypic deletion of 19p have shown pheno-types similar to PSACH and MED; no case of PSACH or MED with deletion of the COMP Iocus has been reported. A dominant-negative mechanism has been postulated, on the ground that COMP forms a pentamer (Morgelin et al. 1992). However, incorporation of mutant monomers into the COMP pentamer has not been proven. COMP belongs to the thrombospondin family of extra-cellular calcium-binding proteins. Thrombospondins participate in calcium-dependent interactions with a number of extracellular matrix proteins, including type V collagen, laminin, and heparin (Mumby et ai. 1984; Takagi et al. 1 993). Chondrocytes from PSACH and MED patients show cytoplasmic inclusion bodies that stain with antibodies against core protein of proteoglycan (Stanescu et al. 1982). Patients carrying mutations in the type IX collagen gene (COL9A2) also exhibit a MED phenotype (Muragaki et al. 1996). These lines of evidence suggest that COMP might interact with these molecules. If so, dysfunction of COMP would likely result in structural and functional disintegration of the extracellular matrix. Identification and charac-terization of additional COMP mutations in PSACH and MED patients would improve our understanding of the molecular pathogenesis of these diseases and provide more information about the relationship between the structure and function of the COMP gene product.

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付録：骨系統疾患国際分類表（1992年）

Osteochondrodysplasias

A. **Defects of the tubular (and flat) bones and/or axial skeleton**

1. **Achondroplasia group**
   Thanatophoric dysplasia
   Thanatophoric dysplasia-straight femur/cloverleaf skull type
   Achondroplasia
   Hypochondroplasia
2. **Achondrogenesis**
   Type IA
   Type IB
3. **Spondylodysplastic group** (Perinatally lethal)
   San Diego type
   Torrance type
   Luton type
4. **Metatropic dysplasia group**
   Fibrochondrogenesis
   Schneckenbecken dysplasia
   Metatropic dysplasia
5. **Short rib dysplasia group** (with/without polydactyly)
   SR (P) Type I Saldino Noonan
   SR (P) Type II Majewski
   SR (P) Type III Verma-Naumoff
   SR (P) Type IV Beemer-Langer
   Asphyxiating thoracic dysplasia
   Ellis-van Creveld dysplasia
6. **Atelosteogenesis/Diastrophic dysplasia group**
   Boomerang dysplasia
   Atelosteogenesis type 1
   Atelosteogenesis type 2 (de la Chapelle)
   Omodysplasia I (Maroteaux)
   Omodysplasia II (Borochowitz)
   Oto-palato-digital syndrome type 2
   Diastrophic dysplasia
   Pseudodiastrophic dysplasia
7. **Kniest-Stickler dysplasia group**
   Dyssegmental dysplasia-Silverman Handmaker type
   Dyssegmental dysplasia-Rolland-Desbuquois type
   Kniest dysplasia
   Oto-spondylo-megaepiphyseal dysplasia
   Stickler dysplasia (heterogeneous, some not linked to Coll CoL 2 A1)
8. **Spondyloepiphyseal dysplasia congenita group**
   Langer-Saldino dysplasia (Achondrogenesis type II)

骨軟骨異形成症

A. **管状(扁平)骨・軸性骨格の障害**

1. **軟骨無形成症グループ**
   致死性骨形成症 AD 187.600
   致死性骨異形成症ー非弯曲大腿骨・クローバ頭蓋型 AD 187.600
   軟骨無形成症 AD 100.800
   軟骨低形成症 AD 146.000
2. **軟骨無発生症**
   IA 型 AR 200.600
   IB 型 AR 200.600
3. **脊椎異形成グループ（周産期致死性）**
   San Diego 型 Sp 151.210
   Torrance 型 Sp 151.210
   Luton 型 Sp 151.210
4. **変容性骨形成症グループ**
   線維性軟骨発生症 AR 228.520
   蝸牛様骨盤骨異形成症 AR 269.250
   変容性骨異形成症 AD 156.530
   AR 250.600
5. **短肋骨異形成症グループ（多指症を伴う，または伴わない）**
   SR (P) I型 (Saldino Noonan 型) AR 263.530
   SR (P) II型 (Majewski 型) AR 263.520
   SR (P) III型 (Verma-Naumoff 型) AR 263.510
   SR (P) IV型 (Beemer-Langer 型) AR 269.860
   窒息性胸郭異形成症 AR 208.500
   Ellis-van Creveld 骨異形成症 AR 225.500
6. **骨不全発生症・捻曲性骨異形成症グループ**
   ブーメラン骨異形成症 Sp-
   骨不全発生症 I 型 Sp 108.720
   骨不全発生症II型 (de la Chapelle 型) AR 256.050
   上腕骨異形成症 I 型 (Maroteaux 型) AD-
   上腕骨異形成症II型 (Borochowitz 型) AR-
   耳・口蓋・指症候群II型 XLR 304.120
   捻曲性骨異形成症 AR 222.600
   偽性捻曲性骨異形成症 AR 264.180
7. **Kniest-Stickler 骨異形成症グループ**
   分節異常骨異形成症-Silverman Handmaker 型 AR 224.410
   分節異常骨異形成症-Rolland-Desbuquois 型 AR 224.400
   Kniest 骨異形成症 AD 156.550
   耳・脊椎・巨大骨端異形成症 AR 215.150
   Stickler 骨異形成症（異質性，一部は Coll CoL 2 A1 に関連せず）AD 108.300
8. **先天性脊椎・骨端異形成症グループ**
   Langer-Saldino 骨異形成症（軟骨無発生症II型）AD 120.140.02

Hypochondrogenesis
Spondyloepiphyseal dysplasia congenita

9. Other spondyloepi-(meta)-physeal dysplasias
X-linked spondyloepiphyseal dysplasia tarda
Other late onset spondyloepi-(meta)-physeal dysplasias (ie. Namaqualand d.. Irapa D.)
Progressive pseudorheumatoid dysplasia
Dyggve-Melchior-Clausen dysplasia
Wolcott-Rallison dysplasia
Immunoosseous dysplasia
Pseudoachondroplasia
Opsismodysplasia

10. Dysostosis multiplex group
Mucopolysaccharidosis I-H
I-S
Mucopolysaccharidosis II
Mucopolysaccharidosis III-A
III-B
III-C
III-D
Mucopolysaccharidosis IV-A
IV-B
Mucopolysaccharidosis VI
Mucopolysaccharidosis VII
Fucosidosis
α-Mannosidosis
β-Mannosidosis
Aspartylglucosaminuria
gM1 Gangliosidosis, several forms
Sialidosis, several forms
Sialic storage disease
Galactosialidosis, several forms
Mucosulfatidosis
Mucolipidosis II
Mucolipidosis III
Mucolipidosis IV

11. Spondylometaphyseal dysplasias
Spondylometaphyseal dysplasia-Kozlowski type
Spondylometaphyseal dysplasia-corner fracture type (Sutcliffe)
Spondyloenchondrodysplasia

12. Epiphyseal dysplasias
Multiple epiphyseal dysplasia Fairbank/Ribbing

13. Chondrodysplasia punctata (Stippled epiphyses) group
Rhizomelic type
Conradi-Hünermann type
X-linked recessive type
MT-type
Others including CHILD syndrome,
Zellweger syndrome, Warfarin embryopathy, Chromosomal abnormalities, Fetal alchohol syndrome

14. Metaphyseal dysplasias
Jansen type
Schmid type
Spahr type

軟骨低発生症 AD 120.140.02
先天性脊椎・骨端異形成症 AD 183.900

9. その他の脊椎・骨端・(骨幹端)・異形成症
伴性遅発性脊椎・骨端異形成症 XLD 313.400
その他の遅発性脊椎・骨端・(骨幹端)・異形成症（例 Namaqualand d.. Irapa D.)
進行性偽性リウマチ様骨異形成症 AR 208.230
Dyggve-Melchior-Clausen 骨異形成症 AR 223.800
Wolcott-Rallison 骨異形成症 AR 226.980
免疫不全性骨異形成症 AR-
偽性軟骨無形成症 AD 177.150
成熟遅延骨異形成症 AR 258.480

10. 多発性異骨症グループ
ムコ多糖症 I-H 型 AR 252.800
I-S 型 AR 252.800
ムコ多糖症II型 XLR 309.900
ムコ多糖症III-A 型 AR-
III-B 型 AR-
III-C 型 AR-
III-D 型 AR 252.940
ムコ多糖症IV-A 型 AR-
IV-B 型 AR 230.500
ムコ多糖症VI型 AR 253.200
ムコ多糖症VII型 AR 253.220
フコシドーシス AR 230.000
α-マンノシドーシス AR 248.500
β-マンノシドーシス AR 248.510
アスパラチルグルコサミン尿症 AR 208.400
gM1 ガングリオシドーシス，各型 AR 230.500
シアリドーシス，各型 AR 256.550
シアリン酸蓄積病 AR 269.920
ガラクトシアリドーシス，各型 AR 256.540
ムコスルファチドーシス AR 272.200
ムコ脂質症II型 AR 252.500
ムコ脂質症III型 AR 252.600
ムコ脂質症IV型 AR 252.650

11. 脊椎・骨幹端異形成症
脊椎・骨幹端異形成症-Kozlowski 型 AD 271.660
脊椎・骨幹端異形成症-骨幹端分節型 (Sutcliffe 型) AD-
脊椎・内軟骨異形成症 AR 271.550

12. 骨端異形成症
多発性骨端異形成症-Fairbank・Ribbing 型 AD 132.400

13. 点状軟骨異形成症（点状骨端）グループ
近位肢型 AR 215.100
Conradi-Hünermann 型 XLD 302.950
伴性劣性型 XLR 302.940
脛骨・中手骨型 Sp-
その他 CHILD 症候群，Zellweger 症候群，ワーファリン胎芽病，染色体異常症，胎児性アルコール症候群

14. 骨幹端異形成症
Jansen 型 AD 156.400
Schmid 型 AD 156.500
Spahr 型 AR 250.400

McKusick type (CHH)
Metaphyseal anadysplasia
Shwachman type
Adenosine deaminase deficiency

15. Brachyrachia (Short spine dysplasia)
Brachyolmia, several types

16. Mesomelic dysplasias
Dyschondrosteosis
Langer type
Nievergelt type
Robinow type

17. Acro/acro-mesomelic dysplasias
Acromicric dysplasia
Geleophysic dysplasia
Acrodysostosis
Tricho-rhino-phalangeal dysplasia type 1
Tricho-rhino-phalangeal dysplasia type 2
Saldino-Mainzer dysplasia
Pseudohypoparathyroidism several types

Cranioectodermal dysplasia
Acromesomelic dysplasia
Grebe dysplasia

18. Dysplasias with significant (but not exclusive) membraneous bone involvement
Cleidocranial dysplasia
Osteodysplasty, Melnick-Needles

19. Bent bone dysplasia group
Campomelic dysplasia
Kyphomelic dysplasia
Stüve-Wiedemann dysplasia

20. Multiple dislocations with dysplasias
Larsen syndrome
Desbuquois syndrome
Spondylo-epi-metaphyseal dysplasia with joint laxity

21. Osteodysplastic primordial dwarfism group
Type 1
Type 2

22. Dysplasias with decreased bone density
Osteogenesis imperfecta (several types)

Osteoporosis with pseudoglioma
Idiopathic juvenile osteoporosis
Bruck syndrome
Homocystinuria
Singleton-Merten syndrome
Geroderma osteodysplastica
Menkes syndrome

23. Dysplasias with defective mineralization
Hypophosphatasia

Hypophosphatemic rickets
Pseudodeficiency rickets, several types

Neonatal hyperparathyroidism

McKusick 型 (CHH) AR 250.250
回復性骨幹端異形成症 XLA?-
Shwachman 型 AR 264.400
アデノシンデアミナーゼ欠損症 AR 102.700

15. 短脊柱症（短脊椎異形成症）
短体幹症，各型 113.500，271.530

16. 中間肢異形成症
異軟骨・骨症 AD 127.300
Langer 型 AR 249.700
Nievergelt 型 AD 163.400
Robinow 型 AD 180.700

17. 遠位・中間肢異形成症
先端短肢異形成症 Sp 102.370
幸福顔貌骨異形成症 AR 231.050
先(肢)端異骨症 AD 101.800
毛髪・鼻・指節異形成症 I 型 AD 190.350
毛髪・鼻・指節異形成症II型 AD 150.230
Saldino-Mainzer 骨異形成症（症候群）AR 266.920
偽性上皮小体機能低下症，各型 AD 103.580，AR? 139.320，XLD? 203.330
頭蓋・外胚葉異形成症 AR 218.330
遠位中間肢異形成症 AR 201.250
Grebe 骨異形成症 AR 200.700

18. 膜性骨稟患を伴う異形成症

鎖骨・頭蓋異形成症 AD 119.600
Melnick-Needles 骨異形成症 XLD 309.350

19. 弯曲骨異形成症グループ
屈曲肢異形成症 AR 211.970
後弯肢異形成症 AR 211.350
Stüve-Wiedemann 骨異形成症 AR-

20. 骨異形成を伴った多発性脱臼症候群
Larsen 症候群 AD 150.250
Desbuquois 症候群 AR 215.200
関節弛緩を伴う脊椎・骨端・骨幹端異形成症 AR 271.640

21. 骨異形成性原発性小人症グループ
I 型 AR 210.710
II型 AR 210.720

22. 骨密度低下を伴う骨異形成症
骨形成不全症（各型）AD 120.150, 120.160, 166.210-60, AR 259.110, 259.420
偽性神経膠腫を伴う骨粗鬆症 AR 259.770
特発性若年性骨粗鬆症 Sp 259.750
Bruck 症候群 AR 259.450
ホモシスチン尿症 AR 236.200
Singleton-Merten 症候群 Sp 182.250
骨異形成性老人様皮膚症 AR 231.070
Menkes 症候群 XLR 309.400

23. 石灰化障害を伴う骨異形成症
低フォスファターゼ症 AD 146.300, 171.760, 241.500, 241.510
低リン血症性くる病 XLR 370.800
ビタミンD偽欠乏性くる病，各型 AR 264.700, 277.420, 277.400
新生児上皮小体機能亢進症 AR 239.200

24. Dysplasins with increased bone density

Osteopetrosis
a) precocious type
b) delayed type
c) intermediate type
d) with renal tubular acidosis
Dysosteosclerosis
Pycnodysostosis
Osteosclerosis-Stanescu type
Axial osteosclerosis including
a) Osteomesopycnosis
b) with bamboo hair (Netherton syndrome)
c) Tricho-thiodystrophy
Osteopoikilosis
Melorheostosis
Osteopathia striata
Osteopathia striata with cranial sclerosis
Diaphyseal dysplasia, Camurati-Engelmann
Craniodiaphyseal dysplasia
Lenz-Majewski dysplasia
Craniometadiaphyseal dysplasia
Endosteal hyperostosis
a) van Buchem disease
b) Sclerosteosis
c) Worth disease
d) with cerebellar hypoplasia
Pachydermoperiostosis
Fronto-metaphyseal dysplasia
Craniometaphyseal dysplasia
a) severe type
b) mild type
Pyle (disease) dysplasia
Osteoectasia with hyperphosphatasia
Oculo-dento-osseous dysplasia
a) severe type
b) mild type
Familial infantile cortical hyperostosis-Caffey

B. Disorganized development of cartilage and fibrous components of the skeleton

Dysplasia epiphysealis hemimelica
Multiple cartilaginous exostoses
Enchondromatosis (Ollier)
Enchondromatosis with hemangiomata (Maffucci)
Metachondromatosis
Osteoglophonic dysplasia
Fibrous dysplasia (Jaffe-Lichtenstein)
Fibrous dysplasia with pigmentary skin changes and precocious puberty (McCune-Albright)
Cherubism
Myofibromatosis (Generalized fibromatosis)

24. 骨密度増加を伴う骨異形成症

大理石骨病
a) 早発型 AR 259.700
b) 遅発型 AD 166.600
c) 中間型 AR 259.710
d) 尿細管性アシドーシスを伴う型 AR 259.730
異骨性骨硬化症 AR 224.300
濃化異骨症 AR 265.800
Stanescu 型骨硬化症 AD 122.900
軸性骨硬化症，下記を含む
a) 骨中間濃化症 AD 166.450
b) 竹様毛髪を伴う (Netherton 症候群) AR 256.500
c) 毛髪・チオ異栄養症 AR 242.170
骨斑紋症 AD 166.700
メロレオストーシス，流蠟骨症 Sp 155.950
線条性骨症 Sp-
頭蓋骨硬化を伴う線条性骨症 AD 166.500
骨幹異形成症 (Camurati-Engelmann 病) AD 131.300
頭蓋骨・骨幹異形成症 AD 122.860, AR 218.300
Lenz-Majewski 骨異形成症 Sp 151.050
頭蓋・骨幹端・骨幹異形成症 Sp-
骨内性骨増殖症
a) van Buchem 病 AR 239.100
b) 骨硬化症 AR 269.500
c) Worth 病 AD 144.750
d) 小脳低形成を伴うもの AR-
皮膚骨膜肥厚症 AD 167.100
前頭・骨幹端異形成症 XLR 309.620
頭蓋・骨幹端異形成症
a) 重症型 AR 218.400
b) 軽症型 AD 123.000
Pyle (病) 骨異形成症 AR 265.900
高アルカリフォスファターゼを伴う骨肥大症 AR 239.000
眼・歯・骨異形成症
a) 重症型 AR 257.850
b) 軽症型 AD 164.200
家族性乳児皮質骨増殖症-Caffey 病 AD 114.000

B. 骨格の軟骨性および線維性成分の発生異常

片肢性骨端異形成症 Sp 127.800
多発性軟骨性外骨腫症 AD 133.700
内軟骨腫症 (Ollier 病) Sp 166.000
血管腫を伴う内軟骨腫症 (Maffucci 症候群) Sp 166.000
メタコンドロマトーシス AD 156.250
骨空洞性異形成症 Sp 166.250
線維性骨異形成症 (Jaffe-Lichtenstein 病) Sp 174.800
皮膚色素沈着と早発性思春期症を伴う線維性骨異形成症 (McCune-Albright 症候群) Sp 174.800
ケルビム症 AD 118.400
筋線維腫症 (汎発性線維腫症) AR 228.550

C. Idiopathic osteolyses
1. Predominantly phalangeal
Hereditary acrosteolysis, several forms
Hajdu-Cheney type
2. Predominantly carpal/tarsal
Carpal-tarsal osteolysis with nephropathy
François syndrome (Dermo-chondro-corneal dystrophy)
3. Multicentric
Winchester syndrome
Torg type
Mandibulo-acral dysplasia
4. Other
Familial expansile osteolysis

C. 特発性骨溶解症
1. 特発性指節骨溶解症
遺伝性先(肢)端骨溶解症，各型-102.400
Hajdu-Cheney 型 AD 102.500
2. 特発性手根・足根骨溶解症
腎疾患を伴う手根・足根骨溶解症 AD 166.300
François 症候群（皮膚・軟骨・角膜異栄養症）
AR 221.800
3. 多中心性特発性骨溶解症
Winchester 症候群 AR 27.950
Torg 型 AR 259.600
下顎・先(肢)端異形成症 AR 248.370
4. その他
家族性拡張性骨溶解症 AD 174.810

AD＝常染色体優性，AR＝常染色体劣性，XLD＝伴性優性，XLR＝伴性劣性，Sp＝散発性，数字＝McKusick カタログナンバー