Published in final edited form as:

Am J Med Genet A. 2017 March ; 173(3): 733–739. doi:10.1002/ajmg.a.38059.

Corner Fracture Type Spondylometaphyseal Dysplasia: Overlap with Type II Collagenopathies

Keren Machol¹, Mahim Jain¹, Mohammed Almannai¹, Thibault Orand¹, James T. Lu^{1,5}, Alyssa Tran¹, Yuqing Chen¹, Alan Schlesinger⁴, Richard Gibbs^{1,5}, Luisa Bonafe², Ana Belinda Campos Xavier², Sheila Unger³, Andrea Superti-Furga³, Brendan H. Lee¹, Philippe M. Campeau⁶, and Lindsay C. Burrage¹

¹Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

²Centre for Molecular Diseases and Department of Pediatrics, Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland ³Service of Medical Genetics, Lausanne University Hospital (CHUV), Lausanne, Switzerland ⁴Department of Pediatric Radiology, Texas Children's Hospital, Houston, Texas ⁵Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA ⁶Department of Pediatrics, CHU Sainte-Justine, University of Montreal, Montreal, QC, Canada

Abstract

Spondylometaphyseal dysplasia (SMD) corner fracture type (also known as SMD ‘Sutcliffe’ type, MIM 184255) is a rare skeletal dysplasia that presents with mild to moderate short stature, developmental coxa vara, mild platyspondyly, corner fracture-like lesions and metaphyseal abnormalities with sparing of the epiphyses. The molecular basis for this disorder has yet to be clarified. We describe two patients with SMD corner fracture type and heterozygous pathogenic variants in *COL2A1*. These two cases together with a third case of SMD corner fracture type with a heterozygous *COL2A1* pathogenic variant previously described suggest that this disorder overlaps with type II collagenopathies. The finding of one of the pathogenic variants in a previously reported case of spondyloepimetaphyseal dysplasia (SEMD) Strudwick type and the significant clinical similarity, suggest an overlap between SMD corner fracture and SEMD Strudwick types.

Keywords

spondylometaphyseal dysplasia; corner fracture; Sutcliffe type; developmental coxa vara; *COL2A1*; skeletal dysplasia

Correspondence to: Lindsay C. Burrage, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA, Tel:832-822-4280, Fax: 713-798-7418, Burrage@bcm.edu.

The authors have no conflict of interests to declare.

INTRODUCTION

Spondylometaphyseal dysplasias (SMD) are a heterogeneous group of disorders characterized by vertebral and metaphyseal abnormalities. According to the last Nosology of Constitutional Bone Disorders from 2015 [Bonafe et al., 2015], this group includes 8 disorders (including SMD Sedaghatian-like type) classified according to their severity, distinctive skeletal abnormalities (e.g. enchondroma-like lesions in spondyloenchondrodysplasia), the presence of extra-skeletal manifestations or according to the associated gene, if known. The molecular basis for most of these disorders is known, but the causative gene for some has not been identified yet.

SMD corner fracture type (also referred to as ‘Sutcliffe’ type by Kozlowski et al., 1992) is a rare autosomal dominant skeletal dysplasia characterized by a triad of mild vertebral abnormalities (platyspondyly), developmental coxa vara and metaphyseal irregularity with corner fracture-like lesions that can be seen through early development and tend to disappear with skeletal maturation [Langer et al., 1990]. Radiologic findings of corner fractures during the first 1-2 years of life are highly concerning for non-accidental trauma [Leaman et al., 2016]. Yet, corner fracture-like lesions can also be detected in the setting of certain skeletal dysplasias, and although considered characteristic for SMD corner fracture type, these radiological findings have been described in other disorders such as metaphyseal chondrodysplasia and spondyloepimetaphyseal dysplasia (SEMD) Strudwick type [Langer et al., 1990, Sutton et al., 2005]. Although the molecular basis for SMD corner fracture type is not yet known, one case report of SMD corner fracture type due to a heterozygous *COL2A1* pathogenic variant has been described in the literature [Walter et al., 2007].

Here, we describe two additional cases of SMD corner fracture type with heterozygous pathogenic variants in *COL2A1*. These cases suggest that at least some cases of SMD corner fracture type are part of the type II collagenopathy spectrum of disorders.

MATERIAL AND METHODS

Human Subjects

Patient 1 was enrolled in a research protocol approved by the Institutional Review Board (IRB) of Baylor College of Medicine. Informed consent for whole exome sequencing (WES) and publication of medical information was obtained. WES for patient 2 was done on a clinical basis. Samples from parents of patient 2 were not available for testing.

Whole exome and Sanger sequencing

For patient 1, genomic DNA was isolated from peripheral blood monocytes and WES was done as previously described [Yang et al., 2013]. Oligonucleotide primers (forward – ACACCTCGCCATCCTCGT; reverse – CAAAGCT TGTATCGATATGCTCA) were designed to amplify exon 17 of *COL2A1* (ENST00000380518) in the patient and in his parents using polymerase chain reaction (PCR). Exon 17 was amplified using 2 ng/uL of DNA with GoTaq polymerase (Promega, Madison, WI) and was submitted for Sanger sequencing at Beckman Coulter Genomics (Danvers, MA). For patient 2, WES on genomic DNA from the affected individual and variant filtering was performed as previously

described [van Karnebeek et al., 2016]. For PCR amplification, oligonucleotide primers (forward - TAAGCTG CCTGCCCTTAGTGTG; reverse - ATGCTCTGTGAGCTCAGAAGCC) were designed to amplify exon 42 of *COL2A1* (ENST00000380518) in the patient.

CLINICAL REPORT

Patient 1

Patient 1 was born full term by spontaneous vaginal delivery. Prenatal history was remarkable for shortening of the long bones on ultrasound performed at 35 weeks of gestation. Postnatal genetic testing for achondroplasia was negative. He was first seen in the Texas Children's Hospital Skeletal Dysplasia Program at the age of 22 months. At that time, his development was reported to be age appropriate. On physical exam, his height was 75.7 cm (Z-score of -3), and his weight was at the 25th - 50th centile (12 kg). Head circumference was at the 95th centile (51.2 cm). He had accentuated lumbar lordosis. Lower extremities were markedly short with genu vara bilaterally. Fourth and fifth digit clinodactyly was noted in the hands bilaterally. Radiographs (Figure 1a-d) revealed findings of SMD. Skeletal survey from the first year of life was notable for platyspondyly as well as significant metaphyseal flaring and corner fracture-like lesions at many of the long bones. The epiphyses appeared spared. Given the findings of short stature, platyspondyly, metaphyseal irregularity and corner fracture-like lesions, a diagnosis of SMD corner fracture type was given. No coxa vara deformity was present. Surgery was later required for severe, progressive genu valgum. He had no history of joint hypermobility or dislocation, cleft palate, myopia or hearing deficit. His family history was positive for a father with unilateral slipped-capital femoral epiphysis at the age of 15 years.

Patient 2

Patient 2 was the first boy of healthy non-consanguineous Chinese parents. He was born at term with a birth weight of 2.65 kg (5th centile) and length of 49 cm (25th centile). The mother reported that his short stature was evident from the age of four years, but his first formal evaluation was at the age of 11 years. At 11 years, his height was 118.9 cm (Z score of -3.7), and he had a disproportionately short trunk. He had a mild pectus carinatum and scoliosis. He walked with a limp, and radiographs (Figure 1e-h) revealed significant dysplasia of the femoral neck with corner fracture-like lesions. The epiphyses appeared spared. Given the findings of short stature, platyspondyly, metaphyseal irregularity, right coxa-vara and corner fracture-like lesions, a diagnosis of SMD corner fracture type was given. At age 12 years, he underwent an osteotomy valgisation of the right femur. He had no history of cleft palate, myopia or hearing deficit. His parents' heights were 152 cm (mother) and 170 cm (father).

RESULTS

WES for patient 1 revealed a heterozygous missense variant in *COL2A1*. Sanger sequencing in proband and his parents revealed that this variant is de novo. This variant causes the replacement of amino acid glycine in position 345 with aspartic acid (c.1034 G>A,

p.Gly345Asp) and was reported previously once in a cohort of 71 patients with skeletal dysplasia (no detailed phenotype was published, Barat-Houari et al., 2015). WES for patient 2 revealed a heterozygous missense variant in *COL2A1*. This variant causes the replacement of amino acid glycine in position 945 with serine (c.2833G>A, p.Gly945Ser) and was reported previously in a Dutch family diagnosed with mild spondyloepiphyseal dysplasia congenita (SEDC) [Terhal et al., 2015]. Patients in this family were reported to have mildly short to normal stature, scoliosis, coxa vara and minimal bilateral cataract.

Both variants do not appear in NCBI dbSNP or in ExAc database [<http://exac.broadinstitute.org>, Lek et al., 2016]. Both changes are predicted to be pathogenic as they are predicted to disrupt COL2A1 homotrimer assembly and stability [Mouw et al., 2014], and both meet ACMG guidelines for pathogenicity [Richards et al., 2015]. PolyPhen2 [<http://genetics.bwh.harvard.edu/pph2>] and SIFT [<http://sift.jcvi.org/>], two software programs that are used to predict the functional effect of an amino acid substitution, also predict that both variants are pathogenic.

DISCUSSION

SMD is a heterogeneous group of rare skeletal dysplasias characterized by dysplastic development of the spine and generalized metaphyseal modifications of the tubular bones. The disorders in this group are diverse in their clinical presentation, and the molecular basis for six of the disorders in the SMD group is known (see table I). SMD Algerian type and dyspondyloenchondromatosis (DSC) were previously considered as distinct entities in the SMD group of disorders. However, identifying patients with *COL2A1* pathogenic variants and significant clinical overlap with SEMD Strudwick type (type II collagenopathy) changed their classification, and they are currently part of the type II collagenopathy spectrum [Bonafe et al., 2015].

Walter et al. (2007) previously described a 7-year-old female with SMD corner fracture type who was found to have a heterozygous missense pathogenic variant in *COL2A1* (p. Gly181Arg, amino acid numbering as was published, starts with the first glycine of the triple helix). As in our two patients, she presented with metaphyseal irregularities, vertebral abnormalities and corner fracture-like lesions (Table II, supplementary data). All three patients have heterozygous missense pathogenic variants in *COL2A1* that result in substitution of a glycine residue. The pathogenicity of these variants is almost certain as glycine plays a conserved and crucial role in the helical Gly-X-Y repetitive sequence of the collagen helix.

Pathogenic variants in type II collagen cause a wide spectrum of skeletal dysplasias that was reviewed previously elsewhere [Barat-Houari et al., 2015]. This wide spectrum of overlapping clinical presentations associated with pathogenic variants in type II collagen has only limited phenotype–genotype correlation. The rarity of the disorders and the difficulty in diagnosis by non skeletal dysplasia experts [Zhang et al., 2015] make it difficult to determine the phenotypic spectrum of specific skeletal dysplasias. The diagnostic challenge with SMD corner fracture type is even greater as corner fracture-like lesions tend to disappear with skeletal maturation and the severity of the metaphyseal involvement tends to

decrease with age. Although developmental coxa vara is considered to be one of the central features in SMD corner fracture type, our first patient did not have obvious femoral neck abnormality. Langer et al. in 1990 described a series of patients with SMD corner fracture type. While most of the patients had bilateral developmental coxa vara, one patient had only unilateral findings, raising the possibility of wider clinical spectrum.

Barat-Houari et al. [2015a] published a cohort of 121 patients with skeletal dysplasia. Seventy-one of these patients were found to have a *COL2A1* pathogenic variant and eight of these patients (11%) had the diagnosis of SEMD Strudwick type. Interestingly, one of the eight patients was reported to have the same pathogenic variant as our first patient (p.Gly345Asp). SMD corner fracture type shares significant clinical features with SEMD Strudwick type including metaphyseal abnormalities, coxa vara, platyspondyly and odontoid hypoplasia (table I). Moreover, corner fracture-like lesions have also been described in SEMD Strudwick type. These findings suggest clinical overlap between SMD corner fracture type and SEMD Strudwick type.

The finding of three patients with clinical diagnosis of SMD corner fracture type and pathogenic variants in *COL2A1*, two of which had been previously described in patients with type II collagenopathies, may suggest that this type of SMD is a heterogeneous disorder with a subset of patients showing overlap with type II collagenopathies. Thus, *COL2A1* molecular testing should be considered in patients with the finding of corner fracture-like lesions in the settings of SMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank the patients and their families. We thank Dr. Magdalena Walkiewicz for her technical assistance. This work was supported by the Baylor College of Medicine Intellectual and Developmental Disabilities Research Center (HD024064) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development, NIH U54HG003273 (R.A.G.), NIH U54 U54HG006542 (R.A.G.), NIH T32 GM07526 (M.J.), NIH K08DK106453 (L.C.B), and NICHD P01 HD070394 (B.L).

REFERENCES

- Barat-Houari M, Dumont B, Fabre A, Them FT, Alembik Y, Alessandri J-L, Amiel J, Audebert S, Baumann-Morel C, Blanchet P, Bieth E, Brechard M, Busa T, Calvas P, Capri Y, Cartault F, Chassaing N, Ciorca V, Coubes C, David A, Delezoide A-L, Dupin-Deguine D, Chehadeh S El, Faivre L, Giuliano F, Goldenberg A, Isidor B, Jacquemont M-L, Julia S, Kaplan J, Lacombe D, Lebrun M, Marlin S, Martin-Coignard D, Martinovic J, Masurel A, Melki J, Mozelle-Nivoix M, Nguyen K, Odent S, Philip N, Pinson L, Plessis G, Quélin C, Shaeffer E, Sigaudy S, Thauvin C, Till M, Touraine R, Vigneron J, Baujat G, Cormier-Daire V, Le Merrer M, Geneviève D, Touitou I. The expanding spectrum of COL2A1 gene variants IN 136 patients with a skeletal dysplasia phenotype. *Eur J Hum Genet.* 2015; 24(7):992–1000. [PubMed: 26626311]
- Barat-Houari M, Sarabay G, Gatinois V, Fabre A, Dumont B, Genevieve D, Touitou I. Mutation update for *COL2A1* gene variants associated with type II Collagenopathies. *Hum Mutat.* 2015; 37:7–15. [PubMed: 26443184]
- Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, Nishimura G, Sangiorgi L, Savarirayan R, Sillence D, Spranger J, Superti-Furga A, Warman M, Unger S. Nosology and

classification of genetic skeletal disorders: 2015 revision. *Am J Med Genet A*. 2015; 167:2869–2892.

- Briggs TA, Rice GI, Daly S, Urquhart J, Gornall H, Bader-Meunier B, Baskar K, Baskar S, Baudouin V, Beresford MW, Black GCM, Dearman RJ, de Zegher F, Foster ES, Francès C, Hayman AR, Hilton E, Job-Deslandre C, Kulkarni ML, Le Merrer M, Linglart A, Lovell SC, Maurer K, Musset L, Navarro V, Picard C, Puel A, Rieux-Laucat F, Roifman CM, Scholl-Bürgi S, Smith N, Szykiewicz M, Wiedeman A, Wouters C, Zeef LAH, Casanova J-L, Elkon KB, Janckila A, Lebon P, Crow YJ. Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat Genet*. 2011; 43:127–131. [PubMed: 21217755]
- Hoover-Fong J, Sobreira N, Jurgens J, Modaff P, Blout C, Moser A, Kim O-H, Cho T-J, Cho SY, Kim SJ, Jin D-K, Kitoh H, Park W-Y, Ling H, Hetrick KN, Doheny KF, Valle D, Pauli RM. Mutations in *PCYT1A*, Encoding a key regulator of Phosphatidylcholine metabolism, cause SMD with cone-rod dystrophy. *Am J Hum Genet*. 2014; 94:105–112. [PubMed: 24387990]
- Kozlowski K, Napiontek M, Beim ER. Spondylometaphyseal dysplasia, Sutcliffe type: a rediscovered entity. *Can Assoc Radio J*. 1992; 43(5):364–368.
- Krakow D, Vriens J, Camacho N, Luong P, Deixler H, Funari TL, Bacino CA, Irons MB, Holm IA, Sadler L, Okenfuss EB, Janssens A, Voets T, Rimoin DL, Lachman RS, Nilius B, Cohn DH. Mutations in the Gene Encoding the calcium-permeable ion channel TRPV4 produce SMD, Kozlowski type and Metatropic dysplasia. *Am J Hum Genet*. 2009; 84:307–315. [PubMed: 19232556]
- Langer L, Brill P, Ozonoff M, Pauli R, Wilson W, Alford B, Pavlov H, Drake D. SMD, corner fracture type: A heritable condition associated with coxa vara. *Radiology*. 1990; 3:761–766.
- Lausch E, Janecke A, Bros M, Trojandt S, Alanay Y, De Laet C, Hübner CA, Meinecke P, Nishimura G, Matsuo M, Hirano Y, Tenoutasse S, Kiss A, Machado Rosa RF, Unger SL, Renella R, Bonafé L, Spranger J, Zabel B, Superti-Furga A. Genetic deficiency of tartrate-resistant acid phosphatase associated with skeletal dysplasia, cerebral calcifications and autoimmunity. *Nat Genet*. 2011; 43:132–137. [PubMed: 21217752]
- Leaman LA, Hennrikus WL, Bresnahan JJ. Identifying non-accidental fractures in children aged <2 years. *J Child Orthop*. 2016; 10:335–341. [PubMed: 27339476]
- Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won H-H, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG. Analysis of protein-coding genetic variation in 60, 706 humans. *Nature*. 2016; 536:285–291. [PubMed: 27535533]
- Mouw JK, Ou G, Weaver VM. Extracellular matrix assembly: A multiscale deconstruction. *Nat Rev Mol Cell Biol*. 2014; 15:771–785. [PubMed: 25370693]
- Nishimura G, Nakashima E, Hirose Y, Cole T, Cox P, Cohn DH, Rimoin DL, Lachman RS, Miyamoto Y, Kerr B, Unger S, Ohashi H, Superti-Furga A, Ikegawa S. The Shwachman-Bodian-Diamond syndrome gene mutations cause a neonatal form of spondylometaphyseal dysplasia (SMD) resembling SMD Sedaghatian type. *J Med Genet*. 2007; 44:e73–e73. [PubMed: 17400792]
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehml HL. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American college of medical genetics and Genomics and the association for molecular pathology. *Genet Med*. 2015; 17:405–423. [PubMed: 25741868]
- Smith AC, Mears AJ, Bunker R, Ahmed A, MacKenzie M, Schwartzentruber JA, Beaulieu CL, Ferretti E, Majewski J, Bulman DE, Celik FC, Boycott KM, Graham GE. Mutations in the enzyme

- glutathione peroxidase 4 cause Sedaghatian-type spondylometaphyseal dysplasia. *J Med Genet*. 2014; 51:470–474. [PubMed: 24706940]
- Sutton VR, Hyland JC, Phillips WA, Schlesinger AE, Brill PW. A dominantly inherited spondylometaphyseal dysplasia with Corner Fractures and congenital scoliosis. *Am J Med Genet A*. 2005; 133A:209–212. [PubMed: 15666313]
- Terhal PA, Nievelstein RJA, Verver EJJ, Topsakal V, van Dommelen P, Hoornaert K, Le Merrer M, Zankl A, Simon MEH, Smithson SF, Marcelis C, Kerr B, Clayton-Smith J, Kinning E, Mansour S, Elmslie F, Goodwin L, van der Hout AH, Veenstra-Knol HE, Herkert JC, Lund AM, Hennekam RCM, Megarbane A, Lees MM, Wilson LC, Male A, Hurst J, Alanay Y, Anneren G, Betz RC, Bongers EMHF, Cormier-Daire V, Dieux A, David A, Elting MW, van den Ende J, Green A, van Hagen JM, Hertel NT, Holder-Espinasse M, den Hollander N, Homfray T, Hove HD, Price S, Raas-Rothschild A, Rohrbach M, Schroeter B, Suri M, Thompson EM, Tobias ES, Toutain A, Vreeburg M, Wakeling E, Knoers NV, Coucke P, Mortier GR. A study of the clinical and radiological features in a cohort of 93 patients with a COL2A1 mutation causing spondyloepiphyseal dysplasia congenita or a related phenotype. *Am J Med Genet Part A*. 2015; 167:461–475.
- Tiller GE, Polumbo PA, Weis MA, Bogaert R, Lachman RS, Cohn DH, Rimoin DL, Eyre DR. Dominant mutations in the type II collagen gene, COL2A1, produce spondyloepimetaphyseal dysplasia, Strudwick type. *Nat Genet*. 1995; 11:87–89. [PubMed: 7550321]
- van Karnebeek CDM, Bonafé L, Wen X-Y, Tarailo-Graovac M, Balzano S, Royer-Bertrand B, Ashikov A, Garavelli L, Mammi I, Turolla L, Breen C, Donnai D, Cormier V, Heron D, Nishimura G, Uchikawa S, Campos-Xavier B, Rossi A, Hennet T, Brand-Arzamendi K, Rozmus J, Harshman K, Stevenson BJ, Girardi E, Superti-Furga G, Dewan T, Collingridge A, Halparin J, Ross CJ, Van Allen MI, Engelke UF, Kluijtmans LAJ, van der Heeft E, Renkema H, de Brouwer A, Huijben K, Zijlstra F, Heisse T, Boltje T, Wasserman WW, Rivolta C, Unger S, Lefeber DJ, Wevers RA, Superti-Furga A. NANS-mediated synthesis of sialic acid is required for brain and skeletal development. *Nat Genet*. 2016; 48:777–784. [PubMed: 27213289]
- Walter K, Tansek M, Tobias ES, Ikegawa S, Coucke P, Hyland J, Mortier G, Iwaya T, Nishimura G, Superti-Furga A, Unger S. COL2A1-related skeletal dysplasias with predominant metaphyseal involvement. *Am J Med Genet A*. 2007; 143A:161–167. [PubMed: 17163530]
- Wang Z, Iida A, Miyake N, Nishiguchi KM, Fujita K, Nakazawa T, Alswaid A, Albalwi MA, Kim O-H, Cho T-J, Lim G-Y, Isidor B, David A, Rustad CF, Merckoll E, Westvik J, Stattin E-L, Grigelioniene G, Kou I, Nakajima M, Ohashi H, Smithson S, Matsumoto N, Nishimura G, Ikegawa S. Axial Spondylometaphyseal dysplasia is caused by C21orf2 mutations. *PLOS ONE*. 2016; 11:e0150555. [PubMed: 26974433]
- Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM. Clinical Whole-Exome Sequencing for the diagnosis of Mendelian disorders. *N Engl J Med*. 2013; 369:1502–1511. [PubMed: 24088041]
- Zhang H, Yang R, Wang Y, Ye J, Han L, Qiu W, Gu X. A pilot study of gene testing of genetic bone dysplasia using targeted next-generation sequencing. *J Hum Genet*. 2015; 60:769–776. [PubMed: 26377240]

Figure 1.

Radiographs of patient 1 (a-d) and patient 2 (e-h). For patient 1, note the platyspondyly and the exaggerated lumbar lordosis at age 5 years (a), hypoplastic odontoid process at age 3 years (b). Note leg length discrepancy prior to surgery (radiograph was obtained with a 1.5 cm block under the right foot), 'corner fracture' type lesion (arrow) at the right proximal tibia and irregular flared metaphyses with sparing of the epiphyses at age 5 years (c). At the age of 9 years (d), note the wide metaphyses with resolution of the 'corner fracture' like lesion. For patient 2, spine radiographs (e) show platyspondyly (age 11 years and 7 months). Right knee radiographs (f) reveal metaphyseal irregularity on the medial side of right proximal tibia and distal femur with small 'corner fracture' like lesion on the medial distal femur (arrow). Pelvis radiographs (g) reveal right coxa vara and metaphyseal irregularity. Following surgery for right femoral joint correction (at the age of 12 years and 9 months), radiographs (h) reveal a 'corner fracture' like metaphyseal lesion (arrow) in the femoral neck.

Table I

The Spondylometaphyseal Dysplasias.

		Kozlowski	Sedaghatian	Severe SMD (Sedaghatian- like)	ODCD	SMD- CRD	SMD with retinal degeneration, axial type	SPENCD	Corner fracture	SEMD Strudwick type
	OMIM #	184252	250220	None	184260	608940	602271	271550	184255	184250
	2015 Nosology group (#)	TRPV4 (8)	Severe SDD (14)	Severe SDD (14)	SMD (12)	SMD (12)	SMD (12)	SMD (12)	SMD (12)	Type 2 collagen (2)
Inheritance		AD	AR	AR	AR	AR	AR	AR	AD	AD
	Short stature	+	+	+	+	+	+	+	+	+
	Short trunk	+	+				+	+	+	+
	Short limbs		+	+	+	+	+	+		+
Metaphyseal changes	Irregular metaphysis	+	+	+	+	+	+	+	+	+
	Corner fracture type lesions								+	+
Epiphyseal involvement			+	+	+					+
Other bone abns.	Enchondroma-like lesions							+		
Vertebral abns.	Scoliosis	+			+	+			+	+
	Platyspondyly	+	+	+	+	+	+	+	+	+
	Odontoid hypoplasia	+							+	+
Hip abns.	Coxa vara	+				+	+		+	+
	Iliac bone abnormality	+	+	+	+	+	+			
Chest	Pectus carinatum	+			+			+		+
	Small chest			+			+			
	Rib abnormalities		+	+		+	+			+
Leg abns					+	+				+

		Kozlowski	Sedaghatian	Severe SMD (Sedaghatian- like)	ODCD	SMD- CRD	SMD with retinal degeneration, axial type	SPENCD	Corner fracture	SEMD Strudwick type
Hands	Irregular carpal/metacarpal bones	+	+		+					
	Brachydactyly		+		+	+		+ (short distal phalanges)		+
Feet	Short and thick feet/Clubfeet	+	+							
Joints	Hyper extensible joints				+					
Skull	Skull abnormalities	+	+							
Face	Facial dysmorphism		+		+			+		+ (cleft palate)
Dental	Dentinogenesis imperfecta				+					
Eyes	Vision impairment					+	+			+ (myopia)
Hearing	Hearing impairment			+						
Skin			+ (Redundant skin)					+ (Pigmentati on absns)		
Systemic involvement	Respiratory problems		+ (Pulmonary hemorrhage)	+	+		+ (Recurrent pneumonia)	+ (Neonatal period, interstitial fibrosis)		
	Hypotonia		+	+						
	Cardiac		+ (conduction defects)							
	CNS		+	+ (Seizures)				+		
	Immunodeficiency with autoimmunity			+ (Neutropenia)				+		
	Intellectual disability							+		
Lethality			+							
Molecular basis		TRPV4	GPX4	SBDS	Unknown	PCYT1A	C21orf2	ACP5	COL2A1	COL2A1

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Kozlowski	Sedaghatian	Severe SMD (Sedaghatian-like)	ODCD	SMD-CRD	SMD with retinal degeneration, axial type	SPENCD	Corner fracture	SEMD Strudwick type
Reference	Krakow et al., 2009	Smith et al., 2014	Nishimura et al., 2007		Hoover-Fong et al., 2014	Wang et al., 2016	Lausch et al., 2011; Briggs et al., 2011	Walter et al., 2007	Tiller et al., 1995

SEMD included (gray column) for comparison purposes. SMD=spondylometaphyseal dysplasia; SDD=spondylodysplastic dysplasias; ODCD=odontochondrodysplasia; SPENCD=spondyloenchondrodysplasia; SEMD=spondyloepimetaphyseal dysplasia; M=mesomelic; R=rhizomelic; SMD-CRD=SMD with cone-rod dystrophy; AD=autosomal dominant; AR=autosomal recessive; abis=abnormalities; CNS=central nervous system