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# Spondylometaphyseal Dysplasia, Corner Fracture Type

Synonyms: SMD, Corner Fractures Type; SMD, Sutcliffe Type

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## Summary


### Clinical characteristics

Spondylometaphyseal dysplasia, corner fracture type (SMDCF) is a skeletal dysplasia characterized by short stature and a waddling gait in early childhood. Short stature may be present at birth or develop in early infancy. Individuals may present with short limbs and/or short trunk. Radiographic features include enlargement and corner fracture-like lesions of the metaphyses, developmental coxa vara, shortened long bones, scoliosis, and vertebral anomalies. Limited joint mobility and chronic pain are common. Vision impairment and glaucoma have been reported.

### Diagnosis/testing

The diagnosis of SMDCF is established in a proband with characteristic clinical and radiographic features including short stature, corner fracture-like lesions, developmental coxa vara, and vertebral anomalies. Identification of a heterozygous pathogenic variant in *COL2A1* or *FN1* by molecular genetic testing can confirm the diagnosis if radiographic features are inconclusive.

### Management

*Treatment of manifestations:* Standard treatment for scoliosis per orthopedist; surgical treatment for coxa vara, genu valgum or varum, bowing of the tibia, leg length discrepancy, atlantoaxial instability per orthopedist; management of mobility issues and chronic joint pain by orthopedist and/or physiatrist and physiotherapist; management of vision impairment and glaucoma per ophthalmologist; management of psychosocial issues by a psychotherapist or referral to support groups.

*Surveillance:* Annual evaluation by an orthopedist and/or physiatrist for scoliosis, other orthopedic complications, and mobility issues. Annual evaluation of intraocular pressure and blood pressure in individuals with *FN1*-SMDCF. Annual screening for psychosocial issues.


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*Agents/circumstances to avoid:* Contact sports if atlantoaxial instability is present; activities that cause joint strain in those with joint pain.

## Genetic counseling

SMDCF is inherited in an autosomal dominant manner. An individual with SMDCF may have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with SMDCF has a 50% chance of inheriting the *COL2A1* or *FN1* pathogenic variant. If the SMDCF-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for SMDCF and preimplantation genetic testing are possible.

# Diagnosis

Formal diagnostic criteria for spondylometaphyseal dysplasia, corner fracture type (SMDCF) have not been established.

## Suggestive Findings

SMDCF **should be suspected** in individuals with the following clinical and radiographic features.

**Clinical features**

- Mild-to-moderate short stature (in 19/19 individuals examined) noted at birth in some individuals [Sutton et al 2005, Walter et al 2007, Lee et al 2017] with short lower extremities (5/7) and/or short trunk (4/6)
- Mild-to-severe scoliosis (15/19)
- Genu varum or valgum (12/18)
- Pectus carinatum (6/14)
- Vision impairment (3/5) (e.g., myopia, borderline increased intraocular pressure, Brown syndrome [strabismus caused by dysfunction of the superior oblique muscle])
- Normal hearing
- Normal intelligence

**Radiographic features**

- Irregular metaphyses:
  - Corner fracture-like lesions (16/17). The lesions can be asymmetric and are most often seen at the proximal and distal tibiae, distal radii, proximal humeri, and distal femora. These are thought to be irregular ossification centers and/or secondary ossification centers. They tend to enlarge in infancy and then disappear once the growth plates fuse at the time of skeletal maturation. Fusion of the growth plates occurs between age 12 and 16 years in women and age 14 and 19 years in men [Crowder & Austin 2005].
  - Enlargement of the metaphyses of the long bones
- Developmental coxa vara (i.e., varus deformity of the proximal femora that develops during early childhood) (10/18). Coxa vara was typically identified by age six years and described in one individual at birth [Costantini et al 2019].
- Scoliosis (15/19)
- Vertebral anomalies (14/18; e.g., platyspondyly, hypoplasia, ovoid vertebral bodies, biconcave vertebral bodies, anterior wedging, biconvex vertebral bodies, narrow intervertebral spaces, vertebral fusion)
- Shortening of the long bones. This finding can be detected on prenatal ultrasound in some individuals [Machol et al 2017, Costantini et al 2019].
- Leg length discrepancy (3/8) [Lee et al 2017, Machol et al 2017, Costantini et al 2019]

- Bowing of the tibia (2/8) [Cadoff et al 2018, Costantini et al 2019]
- Epiphyses. Usually normal

## Establishing the Diagnosis

The diagnosis of SMDCF **is established** in a proband with characteristic clinical and radiographic features including short stature, corner fracture-like lesions, developmental coxa vara, and vertebral anomalies. Identification of a heterozygous pathogenic variant in *COL2A1* or *FN1* by molecular genetic testing can confirm the diagnosis if radiographic features are inconclusive (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of SMDCF is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with spondylometaphyseal dysplasia are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the clinical and radiographic findings suggest the diagnosis of SMDCF, molecular genetic testing approaches can include **concurrent gene testing** or use of a **multigene panel**:

- **Concurrent gene testing.** Sequence analysis of *COL2A1* and *FN1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Although large deletions and duplications have not been reported, deletion/duplication testing may be considered because of the possibility of single or multiexon in-frame deletion or duplication.

- **A multigene panel** that includes *COL2A1*, *FN1*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

### Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by spondylometaphyseal dysplasia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in Spondylometaphyseal Dysplasia, Corner Fracture Type

| Gene [1, 2] | Proportion of SMDCF Attributed to Pathogenic Variants in This Gene | Proportion of Pathogenic Variants [3] Detectable by This Method | |
|---|---|---|---|
| | | Sequence analysis [4] | Gene-targeted deletion/duplication analysis [5] |
| *COL2A1* | 13% [6] | 3/3 [6] | Unknown [7] |
| *FN1* | 57% [8] | 13/13 [8] | Unknown [7] |
| Unknown | 30% [9] | NA | |

*1.* Genes in alphabetic order
*2.* See Table A. Genes and Databases for chromosome locus and protein.
*3.* See Molecular Genetics for information on allelic variants detected in this gene.
*4.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*6.* Walter et al [2007], Machol et al [2017]
*7.* No data on detection rate of gene-targeted deletion/duplication analysis are available.
*8.* Lee et al [2017], Cadoff et al [2018], Costantini et al [2019]
*9.* There is evidence of locus heterogeneity (i.e., this disorder can be caused by mutation of other as-yet-unidentified genes) [Lee et al 2017].

# Clinical Characteristics

## Clinical Description

To date, approximately 45 individuals with spondylometaphyseal dysplasia, corner fracture type (SMDCF) have been reported. A heterozygous *COL2A1* or *FN1* pathogenic variant has been identified in 21 individuals with SMDCF [Walter et al 2007, Lee et al 2017, Machol et al 2017, Cadoff et al 2018, Costantini et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports. Two affected individuals had no detailed clinical description [Lee et al 2017, Costantini et al 2019].

**Table 2.** Common Physical Findings in Spondylometaphyseal Dysplasia, Corner Fracture Type

| Physical Fnding | # of Person w/Finding/ # Examined |
|---|---|
| Short stature | 19/19 |
| Short lower extremities | 5/7 |
| Short upper extremities | 3/3 |
| Short trunk | 4/6 |
| Scoliosis | 15/19 |
| Genu varum | 8/18 |
| Genu valgum | 5/17 |
| Pectus carinatum | 6/14 |
| Limited mobility [1] | 8/8 |
| Musculoskeletal pain | 5/6 |

*Table 2. continued from previous page.*

| Physical Fnding | # of Person w/Finding/<br># Examined |
|---|---|
| Vision impairment | 3/5 |
| Accentuated lumbar lordosis [2] | 2/3 |

*1.* Limited mobility was reported secondary to pain and/or limb deformity.
*2.* To date, only reported in individuals with *COL2A1*-SMDCF

**Presentation.** Individuals with SMDCF present at birth or in early childhood with short stature [Lee et al 2017], scoliosis, variable genu varum or valgum, developmental coxa vara, and pectus carinatum.

**Growth.** SMDCF is typically associated with short stature which persists throughout life. Some individuals present with short trunk and others with short limbs. The expected adult height is more than two standard deviations (SD) below the mean, with half of individuals 3 SD below the mean. In two individuals with *COL2A1*-SMDCF head circumference was above the 90th percentile.

**Progression.** Coxa vara (a smaller angle between the head and the shaft of the femur) in individuals with SMDCF can cause significant morbidity that can require surgery. The involvement of the long bones, knees, and spine can also lead to significant morbidity. Leg length discrepancy and bowing of the tibia were reported in some individuals [Lee et al 2017, Machol et al 2017, Cadoff et al 2018, Costantini et al 2019]. There is a report of chronic pain especially in the legs in individuals with SMDCF. All individuals described were ambulatory except for one individual who became wheelchair bound in adulthood because of painful joint limitations [Lee et al 2017, Machol et al 2017, Cadoff et al 2018, Costantini et al 2019]. In one affected individual, pain restricted activity and necessitated physiotherapy [Costantini et al 2019].

Individuals with *FN1*-SMDCF often require scoliosis surgery. Because of the association of SMDCF with scoliosis and short stature, there is a risk for chest deformity.

**Ocular manifestations.** Most individuals have normal vision, with the exception of two individuals with myopia [Walter et al 2007, Costantini et al 2019] and one with Brown syndrome (strabismus caused by dysfunction of the superior oblique muscle) [Machol et al 2017]. One child with myopia also had borderline elevated intraocular pressure [Costantini et al 2019].

Hearing impairment has not been reported.

Intelligence is normal.

**Nonspecific dysmorphic features.** The following nonspecific dysmorphic features have been reported in one or more individuals with *FN1*-SMDCF: flat facial profile, facial asymmetry, prominent eyes, ear anomalies (posteriorly rotated ears, underfolded helix with prominent ears, hypoplastic lobe and antitragus, preauricular tag), high palate, pointed chin, and micrognathia [Lee et al 2017, Costantini et al 2019].

**Other**

- ***COL2A1*-SMDCF.** To date, the following manifestations have been reported in only one affected individual: short neck, odontoid hypoplasia, clinodactyly, small and round iliac wings, epiphyses reduced in size, Brown syndrome, and left myopia [Walter et al 2007, Machol et al 2017]. In two individuals with *COL2A1*-SMDCF accentuated lumbar lordosis was reported.
- ***FN1*-SMDCF.** To date, the following manifestations have been reported in only one affected individual: hypertension, osteoarthrosis, atlantoaxial instability, intradural lipoma, megacisterna magna, dental anomalies (missing teeth), bicuspid aortic valve, avascular necrosis of capitulum, short distal phalanges, glaucoma, low bone mineral density with fractures, elevation of osteocalcin and N-terminal telopeptide, and iron deficiency [Lee et al 2017, Cadoff et al 2018, Costantini et al 2019].

## Phenotype Correlations by Gene

***COL2A1***. Some distinguishing features reported in individuals with *COL2A1*-SMDCF include biconcave vertebral bodies and milder scoliosis [Walter et al 2007, Machol et al 2017].

***FN1.*** Some distinguishing features reported in individuals with *FN1*-SMDCF include nonspecific dysmorphic facial features, and low bone mineral density with fractures. Scoliosis in individuals with *FN1*-SMDCF tends to be more severe and abnormalities of the vertebrae are frequent (e.g., ovoid-shaped vertebral bodies, anterior wedging, narrow intervertebral spaces, vertebral fusion, vertebral hypoplasia) [Lee et al 2017, Cadoff et al 2018, Costantini et al 2019]. Developmental coxa vara is less frequent in individuals with *FN1*-SMDCF.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations for *FN1* and *COL2A1* have been identified given the relatively small number of individuals reported to date.

## Penetrance

Penetrance is 100%.

## Nomenclature

See Bonafe et al [2015] for a complete nosology of constitutional bone disorders.

SMDCF has also been called spondylometaphyseal dysplasia, Sutcliffe-type.

## Prevalence

SMDCF is a rare disorder. Approximately 45 individuals have been described in the literature [Langer et al 1990, Kozlowski et al 1992, Kozlowski et al 1993, Currarino et al 2000, Sutton et al 2005, Walter et al 2007, Nair et al 2016, Lee et al 2017, Machol et al 2017, Cadoff et al 2018, Costantini et al 2019].

# Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *COL2A1* (see Type II Collagen Disorders Overview) and *FN1* are summarized in Tables 3a and 3b. *COL2A1*-related disorders included in Table 3a have overlapping phenotypic features with spondylometaphyseal dysplasia, corner fracture type (SMDCF) and should be considered in the differential diagnosis.

Note: All disorders included in Tables 3a and 3b are inherited in an autosomal dominant manner.

**Table 3a.** *COL2A1* Allelic Disorders to Consider in the Differential Diagnosis of Spondylometaphyseal Dysplasia, Corner Fracture Type (SMDCF)

| Allelic Disorder | Features of Allelic Disorder | |
|---|---|---|
| | Overlapping w/SMDCF | Not Observed in SMDCF |
| Spondyloepimetaphyseal dysplasia, Strudwick type | • Odontoid hypoplasia<br>• Myopia<br>• Pectus carinatum<br>• Platyspondyly<br>• Scoliosis<br>• Short trunk<br>• Metaphyseal irregularity: corner fracture-like lesions<br>• Coxa vara<br>• Genu valgum | • Cleft palate<br>• Splayed ribs<br>• Epiphyseal delay |
| Kniest dysplasia | • Myopia<br>• Platyspondyly<br>• Short trunk<br>• Coxa vara | • Cataracts<br>• Retinal detachment<br>• Cleft palate<br>• Conductive hearing loss<br>• Delayed epiphyseal ossification<br>• Abnormal epiphyses |
| Spondyloperipheral dysplasia | • Pectus carinatum<br>• Platyspondyly<br>• Short stature | • Sensorineural hearing loss<br>• Absent styloid processes<br>• Hand & foot abnormalities<br>• Short ulna |
| Spondyloepiphyseal dysplasia congenita | • Myopia<br>• Odontoid hypoplasia<br>• Pectus carinatum<br>• Ovoid vertebral bodies<br>• Platyspondyly<br>• Scoliosis<br>• Short trunk<br>• Coxa vara | • Retinal detachment<br>• Vitreoretinal degeneration<br>• Cleft palate<br>• Cervical myelopathy<br>• Hypotonia<br>• Flattened epiphyses<br>• Talipes equinovarus |
| Spondyloepiphyseal dysplasia w/ metatarsal shortening (Czech dysplasia) | • Platyspondyly<br>• Scoliosis<br>• Coxa vara | • Normal stature<br>• Short metacarpals<br>• Hypoplastic/dysplastic toes & metatarsals |

**Table 3b.** Other Allelic Disorders (not in the Differential Diagnosis of SMDCF)

| Gene | Disorder |
|---|---|
| *COL2A1* [1] | Achondrogenesis type II |
| | Hypochondrogenesis |
| | Legg-Calve-Perthes disease (avascular necrosis of the femoral head) |
| | Mild spondyloepiphyseal dysplasia w/premature-onset arthrosis |
| | Osteoarthritis w/mild chondrodysplasia |
| | Platyspondylic dysplasia, Torrance type |
| | Spondyloepiphyseal dysplasia, Stanescu type (OMIM 616583) |
| | Stickler syndrome |
| *FN1* | Glomerulopathy with fibronectin deposits 2 (OMIM 601894) |
| | Plasma fibronectin deficiency (OMIM 614101) |

*1.* See Type II Collagen Disorders Overview.

# Differential Diagnosis

**Table 4.** Genes of Interest in the Differential Diagnosis of Spondylometaphyseal Dysplasia, Corner Fracture Type (SMDCF)

| Gene | Differential Disorder | MOI | Clinical Features of Differential Disorder | | Radiographic Features of Differential Disorder | |
|---|---|---|---|---|---|---|
| | | | Like SMDCF | Unlike SMDCF | Like SMDCF | Unlike SMDCF |
| *ATP7A* | Menkes disease (See *ATP7A*-Related Copper Transport Disorders.) | XL | Short stature | Microcephaly, kinky sparse hair, skin hypopigmentation, skin/joint laxity, neurologic degeneration, ↓ copper & ceruloplasmin | Corner fractures, osteoporosis | Wormian bones |
| *COL10A1* | Metaphyseal chondrodysplasia, Schmid type | AD | Short stature | | Platyspondyly, corner fracture-like lesions, metaphyseal abnormalities, coxa vara, genu varum | Endplate irregularity, metaphyseal abnormalities of phalanges & metacarpals |
| *PTH1R* | Metaphyseal chondrodysplasia, Jansen type (OMIM 156400) | AD | Short stature, facial dysmorphism | Choanal stenosis, deafness, nephrocalcinosis, hypercalcemia, hypophosphatemia | Corner fracture-like lesions, osteopenia | |
| *TRPV4* | Spondylometaphyseal dysplasia, Kozlowski type (OMIM 184252) | AD | Short trunk, pectus carinatum, scoliosis | | Odontoid hypoplasia, irregular metaphyses, coxa vara | Marked platyspondyly & kyphoscoliosis, severe involvement of short tubular bones, hand/carpal/foot abnormalities; not assoc w/corner fractures |
| *GALNS* | Mucopolysaccharidosis type IVA | AR | Short stature, scoliosis, short trunk, pectus carinatum, joint pain, normal intelligence | Coarse facial features, corneal opacities, hearing loss, hepatomegaly, hypermobile joints, abnormal glycosaminoglycan excretion in urine | Odontoid hypoplasia, platyspondyly, widened metaphyses, genu valgum | Cervical subluxation, rib abnormalities, compression of spinal cord, epiphyseal involvement, coxa valga, hip dislocation, ulnar deviation of wrists |
| *PCYT1A* | Spondylometaphyseal dysplasia w/cone-rod dystrophy (OMIM 608940) | AR | Short stature, scoliosis, short limbs | Cone-rod dystrophy, macular involvement, nystagmus | Ovoid vertebral bodies, platyspondyly, coxa vara, metaphyseal involvement, tibial & femoral bowing | Rib cupping, flat acetabuli, hypoplastic inferior ilia, narrow sacrosciatic notch, brachydactyly, short metacarpals |

*Table 4. continued from previous page.*

| Gene | Differential Disorder | MOI | Clinical Features of Differential Disorder | | Radiographic Features of Differential Disorder | |
|---|---|---|---|---|---|---|
| | | | Like SMDCF | Unlike SMDCF | Like SMDCF | Unlike SMDCF |
| *CFAP410* | Spondylometaphyseal dysplasia, axial (OMIM 602271) | AR | Short stature, short limbs | Retinal abnormalities, progressive retinal degeneration, optic atrophy, cone-rod dystrophy, nystagmus, splenomegaly | Platyspondyly, coxa vara, metaphyseal dysplasia, short metacarpals | Small thorax & thoracic deformation, lacy iliac wings, narrow sacrosciatic notch, short femoral neck |
| *SBDS* [1] | Shwachman-Diamond syndrome | AR | Short stature | Small head circumference, failure to thrive, exocrine pancreatic deficiency, bone marrow failure, DD, ID | Ovoid vertebral bodies, coxa vara, metaphyseal dysplasia of long bones, osteoporosis | Narrow thorax & costal abnormalities, narrow sacroiliac notch, delayed skeletal maturation |

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

*1.* Mutation of *EFL1*, *DNAJC21*, or *SRP54* may also be associated with Shwachman-Diamond syndrome (SDS) in rare cases. Note: SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner.

**Disorders of unknown genetic cause**

- **Spondyloepimetaphyseal dysplasia Duetting type** (SMD, type A4) (OMIM 609052), an autosomal recessive disorder, shares the following features with SMDCF: corner fractures, irregular metaphyses, ovoid vertebral bodies, pectus carinatum, platyspondyly, short limbs, short stature, and small iliac wings.

  Unlike SMDCF, SMD Duetting type is also characterized by bipartite trochlea, brachydactyly, coxa valga, dolichocephaly, irregular patellar margins, osteoporotic tarsals and metatarsals, sclerotic costochondral joints, severe metaphyseal changes of the femoral neck, and tongue-like deformity of the vertebral bodies.
- **Blount disease** (OMIM 188700, 259200). Like SMDCF, Blount disease is characterized by corner fracture-like lesions. Unlike SMDCF, Blount disease is also characterized by osteochondritis dissecans (knee), sloping proximal tibial epiphysis, bowleg, and tibia vara.

**Other.** Corner fractures can also be caused by non-accidental injuries [Leaman et al 2016], congenital contractures, rickets, and scurvy [Lee et al 2017].

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spondylometaphyseal dysplasia, corner fracture type (SMDCF), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with Spondylometaphyseal Dysplasia, Corner Fracture Type

| System | Evaluation | Comment |
|---|---|---|
| **Musculoskeletal** | Referral to orthopedic surgeon, physiatrist, & PT depending on local practices | To evaluate for scoliosis, other skeletal manifestations, mobility issues |
| | Flexion-extension radiographs of the cervical spine | To evaluate for cervical instability; [1] if atlantoaxial instability is present, eval by anesthesiologist & pulmonary assessment (when indicated) prior to any surgery [White et al 2017] |
| **Ophthalmology** | Referral to ophthalmologist for vision assessment | Incl eval of intraocular pressure in persons w/*FN1*-SMDCF [1] |
| **Cardiovascular** | Eval of blood pressure | In persons w/*FN1*-SMDCF [1] |
| **Other** | Consultation w/clinical geneticist &/or genetic counselor | |
| | Psychology or other resources for support | Issues related to short stature, joint pain, limited mobility |
| | Eval by pulmonologist | Recommended for those w/*COL2A1*-SMDCF [2] |

PT = physical therapist
*1.* Recommendations are based on a single individual reported with this feature.
*2.* Recommendations based on the best practice guidelines regarding diagnosis and management of patients with type II collagen disorders [Savarirayan et al 2019]

## Treatment of Manifestations

**Table 6.** Treatment of Manifestations in Individuals with Spondylometaphyseal Dysplasia, Corner Fracture Type

| Manifestation/Concern | Treatment | References |
|---|---|---|
| **Scoliosis** | Treatment per orthopedist | |
| **Coxa vara** | Surgical treatment per orthopedist | Currarino et al [2000] |
| **Genu valgum or genu varum** | Surgical treatment per orthopedist | Lee et al [2017], Machol et al [2017] |
| **Bowing of the tibia** | Surgical treatment per orthopedist | Machol et al [2017], Cadoff et al [2018], Costantini et al [2019] |
| **Leg-length discrepancy** | Surgical treatment per orthopedist | Lee et al [2017, Machol et al [2017], Costantini et al [2019] |
| **Atlantoaxial instability** | Surgical treatment per orthopedist | Costantini et al [2019] |
| **Joint pain / Limited mobility** | Management per physiatrist & physiotherapist; surgical treatment by orthopedist | |
| **Vision impairment &/or glaucoma** | Mgmt per ophthalmologist | |
| **Psychosocial issues** | Mgmt by psychotherapist or referral to support groups | |

For individuals with *COL2A1*-SMDCF, there is no evidence that treatment with human growth hormone supplementation increases final height [Savarirayan et al 2019]; therefore, it is not recommended.

## Surveillance

**Table 7.** Recommended Surveillance for Individuals with Spondylometaphyseal Dysplasia, Corner Fracture Type

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Musculoskeletal** | Eval by orthopedic surgeon & physiatrist depending on local practices | Annually for scoliosis, other skeletal manifestations, mobility issues, & chronic joint pain |
| **Glaucoma** | Eval of intraocular pressure [1] | Annual eval in those w/*FN1*-SMDCF |

*Table 7. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Hypertension** | Eval of blood pressure [1] | Annual eval in those w/*FN1*-SMDCF |
| **Psychosocial issues** | Screening for psychosocial issues | Annually |
| **Possible hearing loss** | Routine eval for hearing loss | Recommended in those w/a *COL2A1* pathogenic variant [2] (not reported to date in SMDCF) |
| **Possible respiratory complications** | Routine lung capacity assessment & respiratory health status | Recommended in those w/a *COL2A1* pathogenic variant [2] |

*1.* Recommendations are based on a single individual reported with this feature.
*2.* Recommendations based on the best practice guidelines regarding diagnosis and management of patients with type II collagen disorders [Savarirayan et al 2019].

## Agents/Circumstances to Avoid

Avoid contact sports if atlantoaxial instability is present.

For individuals with joint pain, avoid activities that strain joints and favor joint-friendly activities (e.g., swimming, cycling).

## Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt treatment for orthopedic and ophthalmologic complications. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Measurement of height, physical examination, and x-ray examination of the spine and limbs if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Spondylometaphyseal dysplasia, corner fracture type (SMDCF) is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- An individual diagnosed with *COL2A1*- or *FN1*-SMDCF may have the disorder as the result of a *de novo* pathogenic variant [Machol et al 2017]. In fourteen families in which the parents of the proband underwent molecular genetic testing, the causative pathogenic variant occurred *de novo* in ten probands:
  - *FN1-SMDCF*. In nine of thirteen evaluated families, the *FN1* pathogenic variant occurred *de novo* in the proband.
  - *COL2A1*-SMDCF. In a single evaluated family, the *COL2A1* pathogenic variant occurred *de novo* in the proband [Machol et al 2017].
- Somewhat less frequently, an individual with a clinical and/or genetic diagnosis of SMDCF has an affected parent. Intrafamilial clinical variability is observed in SMDCF [Currarino et al 2000, Lee et al 2017, Costantini et al 2019].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with SMDCF may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation [Machol et al 2017]. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. Phenotypic variability within families has been reported [Currarino et al 2000, Lee et al 2017, Machol et al 2017].
- If the proband has a known SMDCF-causing pathogenic variant that cannot be detected in the leukocyte DNA of either parent and/or the parents have not been tested for the causative pathogenic variant but are unaffected based on appropriate clinical evaluation, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

**Offspring of a proband**

- Each child of an individual with SMDCF has a 50% chance of inheriting the causative pathogenic variant.
- Because many individuals with short stature have reproductive partners with short stature, offspring of individuals with SMDCF may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals are distinct from those of the parents, and the affected individuals may suffer from serious sequelae and poor outcomes [Krakow 2015].

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has an SMDCF-causing pathogenic variant, members of the parent's family may be at risk.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the SMDCF-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be hlepful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Genetic and Rare Diseases Information Center (GARD)**
  PO Box 8126
  Gaithersburg MD 20898-8126
  **Phone:** 888-205-2311 (toll-free)
  **Email:** GARDinfo@nih.gov
  Spondylometaphyseal dysplasia corner fracture type

- **Dwarfism Support Organizations and Groups**
  www.lpaonline.org/dwarfism-support-organizations

- **Little People of America**
  **Phone:** 888-LPA-2001; 714-368-3689
  **Fax:** 707-721-1896
  **Email:** info@lpaonline.org
  lpaonline.org

- **Little People UK**
  United Kingdom
  **Phone:** 07925893398
  **Email:** admin@littlepeopleuk.org
  littlepeopleuk.org

- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  **Phone:** 310-825-8998
  International Skeletal Dysplasia Registry

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Spondylometaphyseal Dysplasia, Corner Fracture Type: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *COL2A1* | 12q13.11 | Collagen alpha-1(II) chain | COL2A1 database | COL2A1 | COL2A1 |
| *FN1* | 2q35 | Fibronectin | FN1 database | FN1 | FN1 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Spondylometaphyseal Dysplasia, Corner Fracture Type (View All in OMIM)

| | |
|---|---|
| 120140 | COLLAGEN, TYPE II, ALPHA-1; COL2A1 |
| 135600 | FIBRONECTIN 1; FN1 |
| 184255 | SPONDYLOMETAPHYSEAL DYSPLASIA, CORNER FRACTURE TYPE; SMDCF |

## Molecular Pathogenesis

The formation of fibronectin depends on *FN1*. Fibronectin is a major component of the extracellular matrix and is the foundation of collagen, glycosaminoglycans, and other constituents [Cadoff et al 2018]. By its role in the extracellular matrix, fibronectin is essential for the formation of cartilaginous tissues and bones [Cadoff et al 2018, Costantini et al 2019].

*COL2A1* encodes type II collagen. This collagen is synthetized by chondrocytes and is an important component of the extracellular matrix (OMIM 120140). Alterations in this gene can lead to multiple skeletal dysplasia and ocular abnormalities since it is the main constituent of cartilage and vitreous humor [Walter et al 2007]. The most recent nosology includes a group of disorders related to *COL2A1* and referred to as the type 2 collagen group [Bonafe et al 2015].

**Mechanism of disease causation.** Pathogenic variants in *FN1*, which occur throughout different domains, often affect cysteine residues that form disulfide bonds in the fibronectin type I domain. Those bonds create the three-dimensional structure of fibronectin and their perturbation leads to instability and possible risk of degradation by metalloproteinases (MMP9 and MMP13) [Costantini et al 2019].

- Pathogenic variants in the N-terminal assembly domain, necessary for fibronectin interaction to form fibrils, affect the assembly on the cell and lower the number of fibrils in the cell matrix [Lee et al 2017, Cadoff et al 2018].
- Pathogenic variants in the III-2 domain, necessary for the assembly of fibronectin, result in similar levels of mutated mRNA and wild type mRNA but greatly reduced secretion of the abnormal protein [Cadoff et al 2018] and accumulation of abnormal fibronectin within the cells [Lee et al 2017].
- Fibronectin is secreted by the liver; levels in the plasma of affected individuals is reduced [Cadoff et al 2018]. Circulating fibronectin in the plasma deposits in the bones. It has a role in the mineralization, density, and assembly of the collagen fibers [Bentmann et al 2010, Costantini et al 2019].

Since mutated fibronectin is not secreted, its accumulation in chondrocytes could be deleterious to their function. This remains to be tested.

*COL2A1*-related diseases generally occur through dominant-negative mechanisms. Pathogenic variants in *COL2A1*, typically resulting in a substitution of a glycine residue [Machol et al 2017], alter the homotrimer assembly and stability of the collagen type II. Those residues play an essential role in the collagen helix and assembly into fibrils, their disruption can lead to manifestation of the disease [Walter et al 2007, Machol et al 2017]. However, misfolding could also affect secretion and the accumulation in chondrocytes could be deleterious to their function.

**Table 8.** Spondylometaphyseal Dysplasia, Corner Fracture Type: Notable Pathogenic Variants by Gene

| Gene [1] | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *COL2A1* | NM_001844.5<br>NP_001835.3 | c.541G>C | p.Gly181Arg | Glycine substitutions are implicated in 1/3 of persons w/type II collagenopathies & are more frequent w/more severe phenotypes [Walter et al 2007, Barat-Houari et al 2016, Machol et al 2017]. |
| | | c.1034G>A | p.Gly345Asp | |
| | | c.2833G>A | p.Gly945Ser | |
| *FN1* | NM_212482.3<br>NP_997647.1 | c.260G>T | p.Cys87Phe | Impairs fibronectin secretion [Lee et al 2017] |
| | | c.718T>G | p.Tyr240Asp | Impairs fibronectin secretion [Lee et al 2017]. This tyrosine residue was shown to be important for fibronectin binding to fibroblasts [Sottile et al 1991]. |
| | | c.2425_2427del | p.Thr809del | Only amino acid deletion reported [Lee et al 2017] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Genes in alphabetic order

# Chapter Notes

## Author Notes

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Dr Campeau focuses on studying new skeletal dysplasias, new forms of epilepsy, and chromatin remodeling disorders. His lab identifies disease-causing genes, studies the pathologic basis of disease in cells and mice, and strives to improve the management of children affected by these conditions, notably through clinical trials.

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