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FLNB Disorders

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Summary

Clinical characteristics

The *FLNB* disorders include a spectrum of phenotypes ranging from mild to severe. At the mild end are spondylocarpotarsal synostosis (SCT) syndrome and Larsen syndrome; at the severe end are the phenotypic continuum of atelosteogenesis types I (AOI) and III (AOIII) and Piepkorn osteochondrodysplasia (POCD).

SCT syndrome is characterized by postnatal disproportionate short stature, scoliosis and lordosis, clubfeet, hearing loss, dental enamel hypoplasia, carpal and tarsal synostosis, and vertebral fusions.

Larsen syndrome is characterized by congenital dislocations of the hip, knee, and elbow; clubfeet (equinovarus or equinovalgus foot deformities); scoliosis and cervical kyphosis, which can be associated with a cervical myelopathy; short, broad, spatulate distal phalanges; distinctive craniofacies (prominent forehead, depressed nasal bridge, malar flattening, and widely spaced eyes); vertebral anomalies; and supernumerary carpal and tarsal bone ossification centers. Individuals with SCT syndrome and Larsen syndrome can have midline cleft palate and hearing loss.

AOI and AOIII are characterized by severe short-limbed dwarfism; dislocated hips, knees, and elbows; and clubfeet. AOI is lethal in the perinatal period. In individuals with AOIII, survival beyond the neonatal period is possible with intensive and invasive respiratory support.

Piepkorn osteochondrodysplasia (POCD) is a perinatal-lethal micromelic dwarfism characterized by flipper-like limbs (polysyndactyly with complete syndactyly of all fingers and toes, hypoplastic or absent first digits, and duplicated intermediate and distal phalanges), macrobrachycephaly, prominant forehead, hypertelorism, and exophthalmos. Occasional features include cleft palate, omphalocele, and cardiac and genitourinary anomalies. The radiographic features at mid-gestation are characteristic.

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Diagnosis/testing

The diagnosis of SCT is established in a proband by identification of biallelic pathogenic variants in *FLNB* on molecular genetic testing. The diagnosis of other *FLNB* disorders (Larsen syndrome, AOI, AOIII, and Piepkorn osteochondrodysplasia) is established in a proband by identification of a heterozygous pathogenic variant in *FLNB* on molecular genetic testing.

Management

Treatment of manifestations: Cervical spine instability in asymptomatic infants can be successfully managed with posterior arthrodesis. Function can be stabilized (if not improved) in infants with myelopathic signs by a combination of anterior decompression and circumferential arthrodesis. Hip dislocation in individuals with Larsen syndrome usually requires operative reduction. Scoliosis and clubfeet are managed in a routine manner. Anesthetic agents that exhibit more rapid induction and recovery are preferred in those with laryngotrachiomalacia. When possible, cleft palate and hearing loss are best managed by multidisciplinary teams.

Surveillance: Annual orthopedic evaluation for progressive scoliosis. Feeding and growth assessment for those with cleft palate by a multidisciplinary team; annual audiologic and dental evaluations.

Pregnancy management: Delivery of an affected infant has the potential to be complicated by extended breech presentation due to dislocation of the hips and knees.

Genetic counseling

AOI, AOIII, Piepkorn osteochondrodysplasia, and Larsen syndrome are inherited in an autosomal dominant manner. The proportion of autosomal dominant *FLNB* disorders caused by *de novo* pathogenic variants is unknown, although the vast majority of lethal *FLNB* conditions are caused by *de novo* events. In rare instances, a parent with low-level mosaicism transmits the causative pathogenic variant to an affected offspring. Each child of an individual with an autosomal dominant *FLNB* disorder has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk for autosomal dominant *FLNB* disorders is possible if the pathogenic variant in the family is known.

SCT syndrome is inherited in an autosomal recessive manner. At conception, each sib of an individual with SCT syndrome has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for SCT syndrome are possible once the pathogenic variants have been identified in the family.

GeneReview Scope

FLNB Disorders: Included Disorders
• Atelosteogenesis type I (AOI) (includes Boomerang dysplasia) • Atelosteogenesis type III (AOIII) • Larsen syndrome [1] • Piepkorn osteochondrodysplasia • Spondylocarpotarsal synostosis (SCT) syndrome [1]

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Formal diagnostic criteria for *FLNB* disorders have not been established.

Suggestive Findings

The *FLNB* disorders include a spectrum of phenotypes ranging from mild to severe. At one end are spondylocarpotarsal synostosis (SCT) syndrome and Larsen syndrome and at the severe end are the phenotypic continuum of atelosteogenesis type I (AOI) and type III (AOIII) and Piepkorn osteochondrodysplasia.

Spondylocarpotarsal Synostosis Syndrome

Spondylocarpotarsal synostosis (SCT) syndrome **should be suspected** in individuals with the following clinical and radiographic features [Langer et al 1994].

Clinical features

- Postnatal disproportionate short stature
- Scoliosis, lordosis
- Clubfeet
- Other manifestations: midline cleft palate, conductive and sensorineural hearing loss, joint stiffness, dental enamel hypoplasia

Radiographic features

- Fusion of adjacent vertebrae and posterior elements that can involve noncontiguous areas of the cervical, thoracic, and lumbar spine

  Note: (1) Asymmetric fusion of the posterior elements can result in "a unilateral unsegmented vertebral bar." (2) More complex bilateral and midline-fused structures have also been reported. (3) Although frequently referred to as "segmentation defects," the process of segmentation is normal in SCT syndrome and the fusion of adjacent vertebral elements relates to a defect in a separate morphologic process that occurs later in development. (4) Basilar impression with or without foramen magnum stenosis have been recurrently observed.

- Carpal and tarsal synostosis. Carpal synostosis is usually capitate-hamate and lunate-triquetrum [Langer et al 1994].

- Delayed ossification of epiphyses (especially of carpal bones) and bilateral epiphyseal dysplasia of the femur; reported in two individuals [Honeywell et al 2002, Mitter et al 2008]

Larsen Syndrome

Larsen syndrome should be suspected in individuals with the following clinical and radiographic features [Larsen et al 1950].

Clinical features

- Congenital dislocations of the hip, knee, elbow, and (occasionally) shoulder
- Clubfeet (equinovarus or equinovalgus foot deformities). This may be the only clinically apparent sign in some individuals [Yang et al 2016].
- Scoliosis and cervical kyphosis, which can be associated with a cervical myelopathy
- Short, broad, spatulate distal phalanges, particularly of the thumb
- Craniofacial anomalies (prominent forehead, depressed nasal bridge, malar flattening, and widely spaced eyes)
- Other manifestations: midline cleft palate, hearing loss (often resulting from malformations of the ossicles)

Radiographic features in early childhood

- Vertebral anomalies: hypoplasic vertebrae, hemivertebrae, spondylolysthesis, bifid posterior processes
- Supernumerary (accessory) carpal and tarsal bone ossification centers; possibly a universal finding [Bicknell et al 2007]

Atelosteogenesis Type I

Atelosteogenesis type I (AOI) **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Perinatal lethal short-limbed dwarfism
- Severe, dislocated hips, knees, and elbows; clubfeet

Radiographic features

- Marked platyspondyly
- Hypoplastic pelvis
- Thoracic hypoplasia
- Incomplete or absent, shortened, or distally tapered humeri and femora; absent, shortened, or bowed radii; shortened and bowed ulnae and tibiae; absent fibulae
- Unossified or partially ossified metacarpals and middle and proximal phalanges
- Occasionally, extraskeletal manifestations including encephalocele and omphalocele [Bicknell et al 2005]

Note: Individuals with a diagnosis of **boomerang dysplasia** (perinatal-lethal bone dysplasia with close similarities to AOI) are probably now best subsumed under a diagnosis of AOI. Bowing of the femora was previously considered a differentiating feature between these two conditions but following the definition of their molecular pathogenesis, it is unlikely that this clinical sign adequately differentiates two distinct conditions.

Piepkorn Osteochondrodysplasia

Piepkorn osteochondrodysplasia (POCD) **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Perinatal-lethal micromelic dwarfism with flipper-like limbs
- Polysyndactyly. Complete syndactyly of all fingers and toes with missing or hypoplastic thumbs and halluces. The intermediate and distal phalanges of all fingers are duplicated, resulting in distal octodactyly.
- Pronounced cranofacial dysmorphism including macrobrachycephaly, prominant forehead, hypertelorism, and exophthalmos
- Other manifestations: Cleft palate, omphalocele, cardiac and genitourinary defects

Radiographic features (at 15-21 weeks' gestation). Absent ossification of all long bones, vertebrae, pelvis, metacarpals, and metatarsals. Some ossification of the pubic bones, pedicles, ribs, scapulae, skull, and clavicles can be observed.

Atelosteogenesis Type III

Clinical features

- Milder than AOI; survival beyond the neonatal period is possible with intensive and invasive respiratory support [Schultz et al 1999].
- Laryngotracheobronchomalacia
- Dislocated hips, knees, and elbows; clubfeet

Radiographic features

- Mild vertebral hypoplasia
- Distal tapering of the humeri and femora
- Short and broad tubular bones of the hands and feet

Establishing the Diagnosis

The diagnosis of **SCT is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *FLNB* on molecular genetic testing (see Table 1).

The diagnosis of other *FLNB* disorders (**Larsen syndrome**, **AOI**, **POCD**, and **AOIII**) **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *FLNB* on molecular genetic testing (see Table 1).

Note: Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, 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 *FLNB* disorders 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 skeletal dysplasia and/or joint dislocations are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *FLNB* disorders, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FLNB* 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 (or only one pathogenic variant is identified in a proband with features characteristic of SCT syndrome), perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: To date, such variants have not been identified as a cause of Larsen syndrome, AOI, POCD or AOIII. Multiexon *FLNB* deletions have been identified in two individuals with SCT syndrome (see Table 1).

- **A multigene panel** that includes *FLNB* 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 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 skeletal dysplasias, **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.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

Note: To date such variants have not been identified as a cause of Larsen syndrome, AOI, POCD, or AOIII. Multiexon *FLNB* deletions have been identified in two individuals with SCT syndrome (see Table 1).

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 *FLNB* Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FLNB	Sequence analysis [3]	<100% [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. To date deletions/duplications have not been identified as a cause of **Larsen syndrome, AOI, POCD, or AOIII.** Two individuals with **SCT** have been found to have homozygous large multiexon deletions of *FLNB* [Author, unpublished data].

Clinical Characteristics

Clinical Description

To date, more than 100 individuals with a pathogenic variant(s) in *FLNB* have been identified [Daniel et al 2012, Salian et al 2018, Stenson et al 2020]. The following description of the phenotypic features associated with *FLNB* conditions is based on these reports.

Spondylocarpotarsal Synostosis (SCT) Syndrome

Individuals with SCT syndrome have normal or near-normal birth length; however, progressive vertebral fusion results in poor growth of the trunk and short stature becomes evident postnatally. Stature is typically 3-6 SD below the mean.

Scoliosis is common, but variable in severity and time of onset because of the extent and pattern of vertebral fusion. Some authors have observed deformity at birth, although the phenotype may only become evident later in childhood. The irregular nature of the vertebral anomalies can also give rise to other complications such as cervical spine instability [Seaver & Boyd 2000] and basilar impression.

Clubfeet, *pes planus*, and cleft palate have been described in a small number of individuals with SCT syndrome. Some authors have reported mild craniofacial dysmorphism as part of this condition but the majority of individuals with SCT syndrome do not exhibit these features.

SCT syndrome has been associated with retinal anomalies [Steiner et al 2000] and sensorineural deafness [Langer et al 1994, Coêlho et al 1998]. The cataracts and retinal abnormalities described in one family with SCT syndrome were not severe enough to impair vision [Steiner et al 2000] and have not been observed in subsequently described individuals and so may not represent primary manifestations of the condition.

Dental enamel hypoplasia has been reported in at least two unrelated instances [Mitter et al 2008].

Intelligence is normal.

Larsen Syndrome

Larsen syndrome is compatible with survival into adulthood [Bicknell et al 2007]. Intelligence is normal.

Intrafamilial variation in Larsen syndrome can be remarkable. In a large family segregating one of the recurring pathogenic variants leading to Larsen syndrome, some individuals had cleft palate and multiple large joint dislocations, whereas others who had no major anomalies had short stature and very mild clinical and radiographic features, such as short distal phalanges and supernumerary carpal and tarsal bones [Bicknell et al 2007]. Clinical variability can also result from the presence of somatic mosaicism for a causative pathogenic variant in a mildly affected parent and the presence of a germline pathogenic variant in more severely affected offspring.

In their study of 20 unrelated families with a total of 52 affected individuals, Bicknell et al [2007] determined that all probands had dislocations or subluxations of the large joints (80% hip, 80% knee, and 65% elbow). The most mildly affected proband had subluxation of the shoulders as her only large joint manifestation. Clubfoot was present in 75% of affected individuals.

Stature is mildly affected. In 14 of 20 probands height was below the tenth centile; height was rarely below the first centile and in one individual was above the 97th centile [Bicknell et al 2007].

Spinal abnormalities were observed on x-rays in 16 (84%) of 19 probands. Cervical kyphosis was noted in 50%, usually from subluxation or fusion of the bodies of C2, C3, and C4, which was commonly associated with posterior vertebral arch dysraphism (i.e., dysplasia of the vertebral laminae and hypoplasia of the lateral processes of all cervical vertebrae). Individuals with Larsen syndrome and cervical spine dysplasia are at significant risk for cervical cord myelopathy and secondary tetraparesis [Bicknell et al 2007]. The incidence of myelopathy is at least 15%. Evidence suggests that preemptive posterior stabilization of the cervical spine in individuals with Larsen syndrome with cervical spine dysplasia may prevent this complication and that combined anterior and posterior stabilization can lead to clinical improvement in individuals with evidence of myelopathy [Sakaura et al 2007].

Craniofacial anomalies are found in all individuals with *FLNB* Larsen syndrome. These include a prominent forehead, depressed nasal bridge, malar flattening, and widely spaced eyes. Cleft palate occurs in 15% of affected individuals.

Deafness is common [Herrmann et al 1981, Stanley et al 1988, Maack & Muntz 1991]. Conductive deafness, often with malformation of the ossicles of the middle ear, was observed in four (21%) of 19 probands [Bicknell et al 2007].

Although laryngotracheomalacia has been reported in association with Larsen syndrome, few individuals with Larsen syndrome and a documented *FLNB* pathogenic variant are severely affected.

Short, broad, spatulate distal phalanges, particularly of the thumb, are a common (67%; Bicknell et al [2007]) but not invariable manifestation of Larsen syndrome.

Atelosteogenesis Type I (AOI) / Boomerang Dysplasia

On prenatal ultrasound examination, the findings of boomerang dysplasia and AOI consist of thoracic hypoplasia and limb shortening with delayed or absent ossification of vertebral and appendicular elements. Joint dislocations may be evident. Definitive diagnosis by ultrasound examination alone is possible [Tsutsumi et al 2012]. Polyhydramnios can complicate the pregnancy. Neonates with boomerang dysplasia or AOI die soon after birth from cardiorespiratory insufficiency. Occasionally, extraskeletal manifestations including encephalocele and omphalocele are encountered [Bicknell et al 2005].

Atelosteogenesis Type III (AOIII)

The most conspicuous finding of AOIII is joint dislocations. A specific diagnosis of AOIII is seldom possible by prenatal ultrasound examination alone.

Infants with AOIII can survive the neonatal period but may require intensive and invasive support to do so. The infant reported by Schultz et al [1999] had significant problems with respiratory insufficiency as a result of laryngotracheomalacia and thoracic hypoplasia. Her mother, who was intellectually normal, had similar but milder respiratory problems in the neonatal period. The manifestations of AOIII overlap with those of Larsen syndrome: large joint dislocations, club feet, short stature, and spinal anomalies. The observation of a distally tapering humerus on x-ray is indicative of AOIII, and of a stronger likelihood of significant laryngotracheobronchomalacia, the major differentiating feature between these two diagnoses.

Infants with AOIII have been born to parents with milder phenotypes (similar to Larsen syndrome). In these instances, the parents probably have a mild phenotype associated with somatic mosaicism, whereas their offspring with a non-mosaic germline pathogenic variant have a severe phenotype.

Neurodevelopment is mildy affected in some long-term survivors with AOIII [Schultz et al 1999], although the authors assumed this to be a secondary consequence of orthopedic and respiratory complications of the primary disorder.

Piepkorn Osteochondrodysplasia (POCD)

POCD is a form of perinatal-lethal micromelic dwarfism described in fewer than five individuals in the literature. The condition is characterized by flipper-like limbs, a characteristic form of polysyndactyly with complete syndactyly of all fingers and toes. The thumbs and halluces are either hypoplastic or absent. The intermediate and distal phalanges of all fingers are duplicated, resulting in distal octodactyly. Craniofacial features include macrobrachycephaly, prominant forehead, hypertelorism, and exophthalmos. Occasional features include cleft palate, omphalocele, cardiac anomalies, and genitourinary defects including sex reversal. The radiographic features of POCD at mid-gestation are characteristic: absent ossification of all long bones, vertebrae, pelvis, metacarpals, and metatarsals. Some ossification of the pubic bones, pedicles, ribs, scapulae, skull, and clavicles can be observed.

Genotype-Phenotype Correlations

SCT syndrome. Homozygosity or compound heterozygosity for pathogenic frameshift or nonsense variants in *FLNB* causes SCT syndrome [Krakow et al 2004]. Pathogenic variants associated with SCT syndrome are associated with loss of protein expression and hence constitute true null alleles [Farrington-Rock et al 2006].

Larsen syndrome, AOI, and AOIII. The pathogenic variants associated with Larsen syndrome, AOI, and AOIII are either missense variants or small in-frame deletions and are predicted to encode full-length filamin B protein.

- Larsen syndrome-associated pathogenic variants are spread predominantly over exons 2-5 and 27-33 [Bicknell et al 2007, Daniel et al 2012].
- Atelosteogenesis type III-causing pathogenic variants occur in exons 2-5, 13, and 27-33 [Farrington-Rock et al 2006].
- The large majority of pathogenic variants reported in boomerang dysplasia and AOI are in exons 2-5 [Bicknell et al 2005, Daniel et al 2012].

In some instances the same pathogenic variant is associated with different phenotypes (e.g., c.502G>A (p.Gly168Ser) is associated with both AOI and AOIII).

Recurrent pathogenic variants:

- c.5071G>A (p.Gly1691Ser) is the most common recurrent substitution, associated with phenotypes ranging from mild Larsen syndrome (isolated bilateral dislocation of the knees and digital and craniofacial anomalies) to AOIII [Bicknell et al 2005, Farrington-Rock et al 2006].
- c.679G>A (p.Glu227Lys) is associated with Larsen syndrome.

Peipkorn dysplasia. Three individuals with Peipkorn dysplasia have had pathogenic variants in exons 28 and 29.

Mosaicism

Clinical evidence suggests that somatic mosaicism can complicate the presentation of these conditions [Petrella et al 1993, Bicknell et al 2007, Bernkopf et al 2017]. Most notably, somatic mosaicism for an *FLNB* pathogenic variant can be associated with Larsen syndrome, whereas the same pathogenic variant in the germline state can be associated with AOIII.

Penetrance

Germline *FLNB* pathogenic variants are fully penetrant but show variable expressivity, leading to the range of phenotypes described in this *GeneReview*.

Nomenclature

Larsen syndrome. Some authors described what appeared to be autosomal recessive Larsen syndrome [Clayton-Smith & Donnai 1988, Bonaventure et al 1992, Laville et al 1994, Yamaguchi et al 1996]. Some of these families had sib recurrence of Larsen syndrome as a result of germline mosaicism in an unaffected parent [Petrella et al 1993].

In contrast, other recessive disorders with multiple joint dislocations called Larsen syndrome in the past but not sharing other clinical characteristics of Larsen syndrome are best not referred to as Larsen syndrome [Topley et al 1994]. These conditions include a variety of chondrodysplasias with multiple joint dislocations and include: the "Reunion Island form of Larsen syndrome" [Bonaventure et al 1992, Laville et al 1994], which is clinically and radiographically distinct from *FLNB* Larsen syndrome and caused by pathogenic variants in *B4GALT7*

[Cartault et al 2015]; *CHST3*-type chondrodysplasia; and two different forms of Desbuquois dysplasia caused by pathogenic variants in *CANT1* and *XYLT1*.

Atelosteogenesis types I and III were so named because the major manifestation is disordered and incomplete ossification of the skeleton [Maroteaux et al 1982, Sillence et al 1982, Stern et al 1990].

Note: Atelosteogenesis type II, one of the sulfate transporter-related osteochondrodysplasias caused by pathogenic variants in *SLC26A2* (*DTDST*), is genetically distinct from AOI and AOIII.

Piepkorn osteochondrodysplasia, although formerly considered to be the same as boomerang dysplasia, has been readdressed by Rehder et al [2018]. A case series of four indicates that a phenotype distinct from boomerang dysplasia and AOI constituting flipper-like limbs, a characteristic form of synpolydactyly, and completely absent ossification of many skeletal elements at mid-gestation defines this entity, a suggestion that is supported by a different distribution of pathogenic variants compared to those underlying boomerang dysplasia and AOI.

Prevalence

No prevalence figures are available for any of the *FLNB* conditions.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *FLNB*.

Differential Diagnosis

Spondylocarpotarsal Synostosis (SCT) Syndrome

Table 2. Genes of Interest in the Differential Diagnosis of Spondylocarpotarsal Synostosis (SCT) Syndrome

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features	
			Overlapping	Differentiating
DLL3 *HES7* *LFNG* *MESP2* *RIPPLY2* *TBX6*	Spondylocostal dysplasia (See Spondylocostal Dysostosis, AR.)	AR (AD) [1]	Vertebral dysplasia	Rib anomalies in spondylocostal dysplasia
FGF9 *GDF5* *NOG*	Multiple synostosis (OMIM PS186500)	AD	Vertebral dysplasia	Progressive symphalangism & distinct facial findings in multiple synostosis
GDF6	Klippel-Feil syndrome 1 (OMIM 118100)	AD	Vertebral, carpal, & tarsal fusions similar to findings in SCT syndrome	No carpal or tarsal fusions. Isolated cervical fusions do not occur in SCT syndrome.
MYH3	Contractures, pterygia, & variable skeletal fusions syndrome 1A (OMIM 178110)	AD	Vertebral, carpal, & tarsal fusions similar to findings in SCT syndrome	Pterygia can be present in persons w/ *MYH3* pathogenic variant(s).
	Contractures, pterygia, & variable skeletal fusions syndrome 1B (OMIM 618469)	AR	Vertebral, carpal, & tarsal fusions similar to findings in SCT syndrome	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. TBX6-related spondylocostal dysplasia can be inherited in an autosomal dominant or autosomal recessive manner.

Larsen Syndrome

Table 3. Genes of Interest in the Differential Diagnosis of Larsen Syndrome

Gene	Differential Diagnosis Disorder	MOI	Clinical Features	
			Overlapping	Differentiating
B3GAT3	B3GAT3 deficiency (OMIM 245600)	AR	Joint dislocations	Brachydactyly & cardiac defects (incl bicuspid aortic valve & dilatation of the aorta) in B3GAT3 deficiency
B4GALT7	Ehlers-Danlos syndrome, spondylodysplastic type 1 (OMIM 130070)	AR	Joint dislocations	Short stature (< -3 SD) in Ehlers-Danlos syndrome, spondylodysplastic type 1
CANT1	Desbuquois dysplasia (OMIM 251450)	AR	Joint dislocations	Short stature (< -3 SD); advanced carpal bone age; & characteristic radiographic manifestations in hips, pelvis, & hands in Desbuquois dysplasia
CHST3	*CHST3* skeletal dysplasia [1]	AR	Joint dislocations	Epiphyseal dysplasia; progressive spondylodysplasia in early & mid-childhood; rhizomelic shortening of limbs; & short stature in *CHST3* skeletal dysplasia
FLNA	Otopalatodigital syndrome type 1 (OPD1) (See XL Otopalatodigital Spectrum Disorders.)	XL	Spatulate fingers; craniofacial dysmorphism	OPD1 is not assoc w/: dislocation of the large joints (except of the radial heads), cervical spine dysplasia, or radiologically supernumerary ossification centers w/in the carpus &/or tarsus.
GZF1	Joint laxity, short stature, & myopia (JLSM) (OMIM 617662)	AR	Joint dislocations	Myopia, short stature, & excessive joint laxity in *GZF1*-JLSM (seldom a characteristic of *FLNB* Larsen syndrome)
BPNT2 (IMPAD1)	Chondrodysplasia w/joint dislocations, GPAPP type (GPAPP deficiency) (OMIM 614078)	AR	Joint dislocations	Pronounced brachydactyly, asymmetry in the hands, & short stature in GPAPP deficiency

AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Also known as spondyloepiphyseal dysplasia, Omani type.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *FLNB* disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *FLNB* Disorders

System/Concern	Evaluation	Comment
Orthopedic	Lateral cervical spine films in flexion & extension	• To evaluate for cervical dysplasia, which can → cervical cord myelopathy • Evaluate cervical spine for instability prior to general anesthesia.
	Spine films	To evaluate for vertebral abnormalities that predispose to scoliosis
	Clinical & ultrasound assessment of hips for dislocation	Development of dislocations postnatally has not been described.
	Clinical exam for joint dislocation, club foot	
ENT	Eval for cleft palate	
Pulmonology	Respiratory exam	For evidence of laryngotracheobronchomalacia

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Audiology	Audiologic eval	To assess for sensorineural &/or conductive hearing loss
Ophthalmology	Ophthalmologic exam	In those w/SCT syndrome to evaluate for retinal anomalies
Dental	Eval for enamel hypoplasia & need for sealants	
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *FLNB* Disorders

Manifestation/ Concern	Treatment	Considerations/Other
Cervical spine instability	• Asymptomatic infants: Early intervention to improve cervical spine stability using posterior arthrodesis is successful. • Infants w/myelopathic signs: Function can be stabilized &/or improved by combination of anterior decompression & circumferential arthrodesis. [1]	Care must be taken to minimize extension of cervical spine intraoperatively.
Scoliosis	Medical treatment per orthopedist	No effective surgical intervention has been described.
Large joint dislocations	Operative reduction is usually required.	Conservative, nonsurgical mgmt of hip dislocation in Larsen syndrome is often unsuccessful.
Clubfeet	Routine mgmt per orthopedist	
Laryngotrach-eomalacia	Anesthetic agents that exhibit more rapid induction & recovery are preferred.	Due to ↑ risk for airway complications in persons w/Larsen syndrome
Cleft palate	Treated by multidisciplinary craniofacial team when possible	
Hearing loss	Possible treatments incl: hearing aids, vibrotactile devices, & cochlear implantation (See Hereditary Hearing Loss and Deafness Overview).	• Ideally, by ENT & audiologist w/expertise in early-childhood otologic disorders • The expertise of an educator of the Deaf may be required. An important part of eval is determining appropriate habilitation option.

1. Johnston et al [1996], Sakaura et al [2007], Madera et al [2008]

Surveillance

Table 6. Recommended Surveillance for Individuals with *FLNB* Disorders

System/Concern	Evaluation	Frequency
Vertebral anomalies	Orthopedic eval for development of progressive scoliosis	Annually from birth
Feeding for those w/cleft	Feeding & growth assessment	Per multidisciplinary craniofacial team
Audiologic	Audiologic exam	Annually
Enamel hypoplasia	Dental eval	

Evaluation of Relatives at Risk

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

Pregnancy Management

Delivery of an affected infant has the potential to be complicated by extended breech presentation due to dislocation of the hips and knees.

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

The following *FLNB* disorders are inherited in an autosomal dominant manner:

- Atelosteogenesis type I (AOI)
- Atelosteogenesis type III (AOIII)
- Boomerang dysplasia
- Larsen syndrome

Spondylocarpotarsal synostosis (SCT) syndrome is inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The parents of some individuals diagnosed with an autosomal dominant *FLNB* disorder are heterozygous for the *FLNB* pathogenic variant.
- Alternatively, a proband with an autosomal dominant *FLNB* disorder may have the disorder as the result of a *de novo* pathogenic variant.

  Although the vast majority of lethal *FLNB* conditions are the result of *de novo* events; a proband with AOI, AOIII, or boomerang dysplasia may have the disorder as the result of a pathogenic variant inherited from a mosaic parent with a milder phenotype [Meira et al 2018].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo FLNB* pathogenic variant include molecular genetic testing and a detailed clinical examination, which may include radiographic examination where indicated.
- 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 somatic and/or germline mosaicism in a parent. Parental somatic and germline mosaicism has been reported [Meira et al 2018].

- The family history of some individuals diagnosed with an autosomal dominant *FLNB* disorder may appear to be negative because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

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

- If a parent of the proband is affected and/or is known to have the *FLNB* pathogenic variant identified in the proband, the risk to the sibs is 50%. Note: Significant intrafamilial clinical variability is observed in Larsen syndrome; a heterozygous sib may have milder or more severe manifestations of the disorder than the proband.
- Clinical evidence suggests that both germline and somatic mosaicism can complicate the presentation and recurrence risks associated with autosomal dominant *FLNB* disorders [Bernkopf et al 2017]. Most notably, the presentation of a typical Larsen syndrome phenotype in a parent can result from mosaicism for a pathogenic variant which, when present as a germline pathogenic variant in a child, leads to the AOIII phenotype.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent and/or the parents appear to be clinically unaffected, recurrence risk to sibs is slightly greater than that of the general population because of the risk of parental somatic and/or germline mosaicism [Meira et al 2018].

Offspring of a proband

- Each child of a proband who is heterozygous for an autosomal dominant *FLNB* pathogenic variant has a 50% chance of inheriting the pathogenic variant.
- Clinical evidence suggests that both germline and somatic mosaicism can complicate the presentation and recurrence risks associated with autosomal dominant *FLNB* disorders. Most notably, the presentation of a typical Larsen syndrome phenotype in a proband can result from mosaicism for a pathogenic variant which, when present as a germline pathogenic variant in offspring, leads to the AOIII phenotype. One approach for the assessment of recurrence risk in offspring of a male proband who is known to have somatic mosaicism for a dominant *FLNB* pathogenic variant is to measure the degree of gonadal mosaicism in sperm [Bernkopf et al 2017].

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

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *FLNB* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *FLNB* pathogenic variant and allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders.)
- Heterozygotes (carriers) are generally asymptomatic. One report described a parent of a child with typical SCT syndrome who had a height 2.2 SD below the mean and mild unilateral hip dysplasia.

Sibs of a proband

- If both parents are known to be heterozygous for an *FLNB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Heterozygotes (carriers) are generally asymptomatic. One report described a parent of a child with typical SCT syndrome who had a height 2.2 SD below the mean and mild unilateral hip dysplasia.

Offspring of a proband. The offspring of an individual with SCT syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *FLNB*.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of an *FLNB* pathogenic variant.

Carrier (heterozygote) detection. Carrier testing for at-risk family members requires prior identification of the pathogenic variants in the family.

Note: SCT syndrome is inherited in an autosomal recessive manner; heterozygotes for *FLNB* pathogenic variants causing SCT syndrome are usually asymptomatic. One report described a parent of a child with typical SCT syndrome who had a height 2.2 SD below the mean and mild unilateral hip dysplasia. All other *FLNB* disorders are inherited in an autosomal dominant manner and, thus, carrier testing is not an issue.

Related Genetic Counseling Issues

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 or at risk.

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

A Priori High-Risk Pregnancies

Molecular genetic testing. Once the *FLNB* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

A Priori Low-Risk Pregnancies

Routine prenatal ultrasound examination may identify skeletal findings such as limb changes consistent with multiple joint dislocations that raise the possibility of Larsen syndrome in a fetus not known to be at increased risk. Detection of fetuses with AOI and POCD by ultrasound examination during the second trimester is possible because of the multiple anomalies present including shortening of the limbs and thoracic hypoplasia [Ueno et al 2002].

Consideration of molecular genetic testing for mutation of *FLNB* in these situations is appropriate.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather

than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Helping After Neonatal Death (HAND)**
  PO Box 341
  Los Gatos CA 95031
  Phone: 888-908-HAND (4263)
  www.handonline.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **Medline Plus**
  Scoliosis
- **Medline Plus**
  Clubfoot
- **National Scoliosis Foundation (NSF)**
  5 Cabot Place
  Stoughton MA 02072
  Phone: 800-673-6922 (toll-free)
  Fax: 781-341-8333
  Email: nsf@scoliosis.org
  www.scoliosis.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. FLNB Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FLNB	3p14.3	Filamin-B	FLNB database	FLNB	FLNB

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 FLNB Disorders (View All in OMIM)

108720	ATELOSTEOGENESIS, TYPE I; AO1
108721	ATELOSTEOGENESIS, TYPE III; AO3
112310	BOOMERANG DYSPLASIA; BOOMD
150250	LARSEN SYNDROME; LRS
272460	SPONDYLOCARPOTARSAL SYNOSTOSIS SYNDROME; SCT
603381	FILAMIN B; FLNB

Molecular Pathogenesis

FLNB encodes filamin-B, which connects cell membrane compoments, including transmembrane proteins, to the actin skeleton. Features of filamin-B:

- An N-terminal actin-binding domain
- 24 filamin repeats
- Two "hinge" regions between filamin repeats 15 and 16 and 23 and 24, which are thought to confer flexibility to the protein

Filamin-B is expressed by endothelial cells and chondrocytes during development, playing an important role in embryonal skeletal development. *FLNB* disorders can occur either by loss of filamin-B binding to or enhanced filamin-B avidity for actin (see **Mechanism of disease causation**).

Mechanism of disease causation

- The cause of SCT syndrome is loss of function, which exerts a pathogenic effect at least in part through de-repression of transforming growth factor beta signaling.
- For Larsen syndrome, AOI, POCD, and AOIII, it is not known whether the pathogenic variants disrupt protein interactions or facilitate novel interactions with filamin B.

Table 7. Notable *FLNB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001457.4 NP_001448.2	c.502G>A	p.Gly168Ser	Assoc w/both AOI & AOIII [1]
	c.679G>A	p.Glu227Lys	Recurrent pathogenic variant assoc w/Larsen syndrome [1]
	c.5071G>A	p.Gly1691Ser	Recurrent variant assoc w/a range of *FLNB* phenotypes [1]

Variants listed in the table have been provided by the author. *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. See Genotype-Phenotype Correlations.

Chapter Notes

Author Notes

University of Otago Clinical Genetics Group website

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- 13 February 2020 (sw) Comprehensive update posted live
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