U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Robertson S. X-Linked Otopalatodigital Spectrum Disorders. 2005 Nov 30 [Updated 2019 Oct 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

X-Linked Otopalatodigital Spectrum Disorders

Synonym: Otopalatodigital Spectrum Disorders (OPDSD)

Stephen Robertson, FRACP, DPhil[1]

Created: November 30, 2005; Updated: October 3, 2019.

Summary

Clinical characteristics

The X-linked otopalatodigital (X-OPD) spectrum disorders, characterized primarily by skeletal dysplasia, include the following:

- Otopalatodigital syndrome type 1 (OPD1)
- Otopalatodigital syndrome type 2 (OPD2)
- Frontometaphyseal dysplasia type 1 (FMD1)
- Melnick-Needles syndrome (MNS)
- Terminal osseous dysplasia with pigmentary skin defects (TODPD)

In OPD1, most manifestations are present at birth; females can present with severity similar to affected males, although some have only mild manifestations. In OPD2, females are less severely affected than related affected males. Most males with OPD2 die during the first year of life, usually from thoracic hypoplasia resulting in pulmonary insufficiency. Males who live beyond the first year of life are usually developmentally delayed and require respiratory support and assistance with feeding. In FMD1, females are less severely affected than related affected males. Males do not experience a progressive skeletal dysplasia but may have joint contractures and hand and foot malformations. Progressive scoliosis is observed in both affected males and females. In MNS, wide phenotypic variability is observed; some individuals are diagnosed in adulthood, while others require respiratory support and have reduced longevity. MNS in males results in perinatal lethality in all recorded cases. TODPD, seen only in females, is characterized by a skeletal dysplasia that is most prominent in the digits, pigmentary defects of the skin, and recurrent digital fibromata.

Diagnosis/testing

The diagnosis of an X-OPD spectrum disorder is established in a male proband with characteristic clinical and radiographic features and a family history consistent with X-linked inheritance. Identification of a hemizygous pathogenic variant in *FLNA* by molecular genetic testing can confirm the diagnosis if clinical features, radiographic features, and/or family history are inconclusive.

Author Affiliation: 1 Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; Email: stephen.robertson@otago.ac.nz.

The diagnosis of an X-OPD spectrum disorder is usually established in a female proband with characteristic clinical and radiographic features and a family history consistent with X-linked inheritance. Identification of a heterozygous pathogenic variant in *FLNA* by molecular genetic testing can confirm the diagnosis if clinical features, radiographic features, and/or family history are inconclusive.

Management

Treatment of manifestations: Surgical treatment may be required for hand and foot malformations. Monitoring and surgical intervention as needed for scoliosis; physiotherapy for contractures; cosmetic surgery may correct the fronto-orbital deformity; continuous positive airway pressure (CPAP) and mandibular distraction can improve airway complications related to micrognathia; hearing aids for deafness; evaluation with anesthesiology if intubation and ventilation are required due to laryngeal stenosis.

Surveillance: Annual clinical evaluation for orthopedic complications including contractures and scoliosis; monitor head size and shape with each clinical evaluation in infancy for craniosynostosis; annual clinical evaluation for apnea with somnography studies as indicated; annual audiology evaluation.

Evaluation of relatives at risk: Consider molecular genetic testing for the family-specific pathogenic variant in at-risk relatives.

Genetic counseling

The X-OPD spectrum disorders are by definition inherited in an X-linked manner. If a parent of a proband with OPD1, OPD2, or FMD1 has the *FLNA* pathogenic variant, the chance of transmitting the variant in each pregnancy is 50%.

- When the mother has an *FLNA* pathogenic variant, males who inherit the variant will be affected; females who inherit the variant have a range of phenotypic expression. If the mother of a proband with TODPD or MNS has the *FLNA* pathogenic variant, the chance of transmitting the variant in each pregnancy is 50%. Males who inherit the variant will be affected and usually exhibit embryonic lethality or die perinatally (MNS); females who inherit the variant have a range of phenotypic expression.
- Males with OPD2 do not reproduce; males with OPD1 or FMD1 transmit the pathogenic variant to all of their daughters and none of their sons.

Prenatal testing and preimplantation genetic testing are possible if the pathogenic variant in the family is known.

GeneReview Scope

X-Linked Otopalatodigital Spectrum Disorders: Included Phenotypes [1]
• Otopalatodigital syndrome type 1 (OPD1) • Otopalatodigital syndrome type 2 (OPD2) • Frontometaphyseal dysplasia type 1 (FMD1) • Melnick-Needles syndrome (MNS) • Terminal osseous dysplasia with pigmentary skin defects (TODPD)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The X-linked otopalatodigital (X-OPD) spectrum disorders, a heterogeneous group of disorders characterized primarily by a skeletal dysplasia of variable severity, include the following:

- Otopalatodigital syndrome type 1 (OPD1)

- Otopalatodigital syndrome type 2 (OPD2)
- Frontometaphyseal dysplasia type 1 (FMD1)
- Melnick-Needles syndrome (MNS)
- Terminal osseous dysplasia with pigmentary skin defects (TODPD)

Suggestive Findings

X-OPD spectrum disorders **should be suspected** in an individual with the following clinical (Table 1) and radiographic (Table 2) features.

Table 1. X-Linked Otopalatodigital Spectrum Disorders: Clinical Features

Phenotype	Craniofacial Features	Skeletal Features	Other
OPD1 (male phenotype)	Cleft palate & characteristic facies: prominent supraorbital ridges, downslanted palpebral fissures, hypertelorism, broad nasal bridge & nasal tip, hypodontia, oligodontia	Digits: short proximally placed thumbs, hypoplastic distal phalanges, great toe hypoplasia, long 2nd toe, prominent sandal gap; limited joint mobility; limbs w/mild bowing	Conductive & sensorineural hearing loss; normal intelligence
			Heterozygous females [1]: variable features; some females as affected as male relatives.
OPD2 (male phenotype)	Pierre Robin sequence; characteristic facies (more severe than OPD1)	Digits: hypoplastic thumbs & great toes, absent halluces, camptodactyly; thoracic hypoplasia; delayed closure of fontanelles; bowed limbs; short stature	Conductive & SNHL; cardiac: septal defects, obstructive lesions to the right ventricular outflow tract; omphalocele; GU: ureteric obstruction w/ hydronephrosis, hypospadias; CNS: hydrocephalus, cerebellar hypoplasia; DD; death in neonatal period
			Heterozygous females [1]: often subclinical phenotype; characteristic facies (prominent supraorbital ridges, wide nasal bridge & broad nasal tip) are most common findings. Occasionally conductive HL, cleft palate, skeletal & digital anomalies.
FMD1 (male phenotype)	Characteristic facies (more severe than OPD2)	Digits: distal phalangeal hypoplasia, progressive contractures of the hands; limited joint mobility (wrists, elbows, knees, ankles); scoliosis; bowed limbs	Conductive & SNHL; underdevelopment of musculature (shoulder girdle, intrinsic muscles of the hands); subglottic stenosis w/congenital stridor; GU: ureteric & urethral stenosis, hydronephrosis; normal intelligence
			Heterozygous females: characteristic facies similar to affected males
MNS (female phenotype)	Prominent lateral margins of the supraorbital ridges, proptosis, full cheeks, micrognathia, oligohypodontia, facial asymmetry	Digits: long w/mild distal phalangeal hypoplasia; thoracic hypoplasia; bowed limbs; joint subluxation; short stature	Conductive & SNHL; ureteric obstruction w/hydronephrosis; coloboma; normal intelligence
			Hemizygous males: phenotype ranges from lethal phenotype similar to severe OPD2 to mildly affected.

Table 1. continued from previous page.

Phenotype	Craniofacial Features	Skeletal Features	Other
TODPD (female phenotype)	Widely spaced eyes, oral frenulae, hyperpigmented lesions over the temporal region, alopecia	Digits: fibromata in infancy, camptodactyly; bowed limbs; short stature	Cardiac: septal defects; normal intelligence
			Hemizygous males: phenotype has not been described in males.

DD = developmental delay; FMD1 = frontometaphyseal dysplasia type 1; GU = genitourinary; MNS = Melnick-Needles syndrome; OPD1 = otopalatodigital syndrome type 1; OPD2 = otopalatodigital syndrome type 2; SNHL = sensorineural hearing loss; TODPD = terminal osseous dysplasia with pigmentary skin defects

1. OPD1 and OPD2 cannot be clinically differentiated in a single affected female in a family with no affected males.

Table 2. X-Linked Otopalatodigital Spectrum Disorders: Radiographic Features

Phenotype	Skull	Spine	Thorax	Long Bones	Hands/Feet	Pelvis
OPD1 (male phenotype)	Sclerosis of skull base; thickened calvarium; underdeveloped frontal sinuses; mastoids under-pneumatized	Failure of fusion of posterior vertebral arches (especially cervical)		Mild bowing; dislocation of radial heads	Thumb w/short, broad metacarpal; distal phalangeal hypoplasia; accessory proximal ossification center of 2nd metacarpal; accessory carpal bones; fusion of carpal & tarsal bones	Contracted; no iliac flaring
OPD2 (male phenotype)	Same as OPD1; large fontanelles	Same as OPD1; segmentation anomalies	Hypoplastic; thin ribs	Bowed; splayed metaphyses; absent fibulae	Broad, poorly modeled phalanges, metacarpals & metatarsals; ± duplicated terminal phalanges	Same as OPD1
FMD1 (male phenotype)	Same as OPD1; occasionally, craniosynostosis	Fusion of C2-3-4; deficiency of posterior vertebral arches	± coat-hanger shape ribs	Mild bowing; undertubulation	Carpal & tarsal fusions; later erosion of carpal bones; elongation, poor modeling of phalanges, metacarpals & metatarsals; distal phalangeal hypoplasia (thumbs & great toes)	
MNS (female phenotype)	Same as OPD1	↑ vertebral body height, especially lumbar; scoliosis	Hypoplasia; ribs irregular; wavy clavicle w/ expansion of proximal end	Bowed, sometimes ribbon-like; cortical irregularity	Elongation & undermodeling of phalanges, metacarpals & metatarsals	Supra-acetabular constriction; iliac flaring
TODPD (female phenotype)	Normal	Scoliosis	No abnormalities consistently described	Irregular ossification; cystic lesions near epiphyses; bowed; radial head dislocation	Hypoplasia, shortening, irregular ossification &/or fusions of carpals & metacarpals; irregular cortices	Narrow ilia; coxa vara

FMD1 = frontometaphyseal dysplasia type 1; MNS = Melnick-Needles syndrome; OPD1 = otopalatodigital syndrome type 1; OPD2 = otopalatodigital syndrome type 2; TODPD = terminal osseous dysplasia with pigmentary skin defects

Establishing the Diagnosis

Male proband. The diagnosis of an X-OPD spectrum disorder **is established** in a male proband with characteristic clinical (Table 1) and radiographic (Table 2) features and a family history consistent with X-linked inheritance. Identification of a hemizygous pathogenic variant in *FLNA* by molecular genetic testing can confirm the diagnosis if clinical features, radiographic features, and/or family history are inconclusive (see Table 3).

Female proband. The diagnosis of an X-OPD spectrum disorder **is usually established** in a female proband with characteristic clinical (Table 1) and radiographic (Table 2) features and a family history consistent with X-linked inheritance. Identification of a heterozygous pathogenic variant in *FLNA* by molecular genetic testing can confirm the diagnosis if clinical features, radiographic features, and/or family history are inconclusive (see Table 3).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-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 X-OPD spectrum 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 in whom the diagnosis of an X-OPD spectrum disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of an X-OPD spectrum disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Perform sequence analysis of *FLNA* to detect small intragenic deletions/insertions and missense variants.

  Note: Whole-gene deletions cause periventricular nodular heterotopia in females and are likely to be embryonic lethal in males. Partial-gene deletions or duplications have not been associated with X-OPD spectrum disorders. Whole-gene duplications (in association with neighboring genes) have been associated with intellectual disability and seizures (see Genetically Related Disorders).

  Targeted analysis for variant c.5217G>A can be performed first in individuals with a phenotype suggestive of TODPD; however, this test is not exclusionary for TODPD.

- **A multigene panel** that includes *FLNA* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 diagnosis of an X-OPD spectrum disorder is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **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 3. Molecular Genetic Testing Used in X-Linked Otopalatodigital Spectrum Disorders

Gene [1]	Method	Phenotype	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FLNA	Sequence analysis [3]	OPD1	94% (n=15) [4]
		OPD2	100% (n=19) [4]
		FMD1	71% (n=47) [5]
		MNS	100% (n=27) [4]
	Targeted analysis for c.5217G>A	TODPD	100% (n=6) [6]
	Gene-targeted deletion/duplication analysis [7]		None [8]

FMD1 = frontometaphyseal dysplasia type 1; MNS = Melnick-Needles syndrome; OPD1 = otopalatodigital syndrome type 1; OPD2 = otopalatodigital syndrome type 2; TODPD = terminal osseous dysplasia with pigmentary skin defects

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. Robertson et al [2006b]

5. Robertson et al [2006a], Wade et al [2016]

6. All reported individuals with TODPD have been heterozygous for the synonymous change c.5217G>A, which induces a splicing abnormality that results in a loss of 48 bases from the mature transcript and predicts the deletion of 16 amino acids from the resultant FLNA protein (p.Val1724_Thr1739del) [Sun et al 2010]. This pathogenic variant appears to define this disorder.

7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

8. Large deletions and duplications have been associated with allelic conditions such as myxomatous cardiac valvular dystrophy (see Genetically Related Disorders), periventricular nodular heterotopia, and intellectual disability. Partial- and whole-gene deletions do not cause an X-OPD spectrum disorder phenotype.

Clinical Characteristics

Clinical Description

To date, more than 150 individuals with an X-OPD syndrome spectrum disorder have been identified with a pathogenic variant in *FLNA* [Robertson et al 2003, Robertson et al 2006a, Robertson et al 2006b]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 4. Features of X-Linked Otopalatodigital Spectrum Disorders

Disorder	Features	% of Persons with Feature
OPD1 in males	Digital anomalies	100%
	Deafness	100%
	Mild limb bowing	Unknown
	Cleft Palate	75%
OPD2 in males	Thoracic hypoplasia	100%
	Cleft palate	80%
FMD1 in males	Supraorbital hyperostosis	100%
	Urinary Tract obstruction	Unknown
MNS in females	Micrognathia	100%
	Limb bowing	100%
	Short stature	100%
	Thoracic hypoplasia	100%
TODPD in females	Digital fibromata	100%
	Erosive changes on radiographs	100%
	Limb bowing	Unknown

FMD1 = frontometaphyseal dysplasia type 1; MNS = Melnick-Needles syndrome; OPD1 = otopalatodigital syndrome type 1; OPD2 = otopalatodigital syndrome type 2; TODPD = terminal osseous dysplasia with pigmentary skin defects

Little is known about the natural history of the X-linked otopalatodigital (X-OPD) spectrum disorders. All manifestations can begin in childhood in both sexes.

In males, the spectrum of severity ranges from mild manifestations in otopalatodigital syndrome type 1 (OPD1) to a more severe presentation in frontometaphyseal dysplasia type 1 (FMD1) and otopalatodigital syndrome type 2 (OPD2). Prenatal lethality is the only clinical phenotype described in males with Melnick-Needles syndrome (MNS) [Spencer et al 2018].

Females exhibit variable expressivity. In OPD1, females can present with similar severity to affected males. In contrast, some females have only the mildest of manifestations [Gorlin et al 1973]. In OPD2 and FMD1, females are less severely affected than related affected males [Robertson et al 1997, Moutton et al 2016].

OPD1

Most manifestations are evident at birth. Nothing reported in the literature suggests any late-onset orthopedic complications, reduction in longevity, or reduction in fertility.

Males with OPD1 present with the following:

- A skeletal dysplasia manifest clinically by:
  - Digital anomalies including short, often proximally placed thumbs with hypoplasia of the distal phalanges. The distal phalanges of the other digits can also be hypoplastic with a squared (or "spatulate") disposition to the finger tips. The toes present a characteristic pattern of hypoplasia of the great toe, a long second toe, and a prominent sandal gap.
  - Limitation of joint movement (elbow extension, wrist abduction) in almost all affected individuals
  - Limbs that may exhibit mild bowing

- Mildly reduced final height in some, although individuals have been characterized with pathogenic variants in *FLNA* and stature greater than the 90th percentile. Pubertal development and intelligence is normal in affected individuals.
- Characteristic facial features (prominent supraorbital ridges, downslanted palpebral fissures, widely spaced eyes, wide nasal bridge and broad nasal tip)
- Deafness (secondary either to ossicular malformation, neurosensory deficit, or a combination of both). The conductive hearing loss can be caused by fused and misshapen ossicles; attempts to separate the ossicles are usually unsuccessful and can lead to formation of a perilymphatic gusher.
- Cleft palate
- Oligohypodontia
- Normal intelligence

Females with OPD1 exhibit variable expressivity. Some females can manifest a phenotype similar to that of affected, related males. Females may develop conductive or neurosensory hearing loss. Note: One cannot confidently differentiate OPD1 from OPD2 in a single affected female in a family with no affected males [Moutton et al 2016].

OPD2

Males with OPD2 present with the following [André et al 1981, Fitch et al 1983]:

- A skeletal dysplasia manifest clinically as:
  - Thoracic hypoplasia
  - Bowed long bones
  - Short stature
  - Digital anomalies (most commonly: hypoplasia of the first digit of the hands and feet or absent halluces, camptodactyly)
  - Delayed closure of the fontanelles
  - Scoliosis (occasional)
- Characteristic craniofacial features similar to but more pronounced than those in OPD1. Pierre Robin sequence is commonly observed.
- Sensorineural and conductive deafness (common)
- Cardiac septal defects and obstructive lesions to the right ventricular outflow tract in some affected individuals
- Associated omphalocele, hydronephrosis secondary to ureteric obstruction, and hypospadias [Young et al 1993, Robertson et al 1997]
- Central nervous system anomalies including hydrocephalus, cerebellar hypoplasia, and (rarely) encephalocele and meningomyelocele [Brewster et al 1985, Stratton & Bluestone 1991]
- Developmental delay (common)
- Death commonly in the neonatal period as a result of respiratory insufficiency. Survival into the third year of life has been described with intensive medical treatment [Verloes et al 2000].

Females with OPD2 usually present with a subclinical phenotype. Characteristic craniofacial features (prominent supraorbital ridges, wide nasal bridge and a broad nasal tip) are the most common findings. Occasionally, conductive hearing loss has been described. Occasionally, females can manifest a phenotype similar in severity to that of males (craniofacial dysmorphism, cleft palate, conductive hearing loss, skeletal and digital anomalies). Note: One cannot confidently differentiate OPD1 from OPD2 in a single affected female in a family with no affected males.

Frontometaphyseal Dysplasia Type 1

Frontometaphyseal dysplasia type 1 (FMD1) shares many characteristics with OPD1, with some authors considering them the same condition [Superti-Furga & Gimelli 1987].

Males with FMD1 present with the following:

- A skeletal dysplasia manifest clinically as:
  - Distal phalangeal hypoplasia
  - Progressive contractures of the hand over the first two decades resulting in marked limitation of movement at the interphalangeal and metacarpophalangeal joints
  - Joint limitation at the wrists, elbows, knees, and ankles
  - Scoliosis that may be progressive [Morava et al 2003]
  - Limb bowing
- Characteristic craniofacial features with very pronounced supraorbital hyperostosis, widely spaced eyes, and downslanted palpebral fissures [Gorlin & Cohen 1969]. Craniosynostosis, an occasional finding, can evolve postnatally.
- Oligohypodontia (frequent)
- Conductive and sensorineural hearing loss in almost all affected individuals
- Underdevelopment of the musculature, most notably around the shoulder girdle and in the intrinsic muscles of the hands (common)
- Extraskeletal anomalies including subglottic stenosis (which can present as congenital stridor [Leggett 1988, Mehta & Schou 1988]), urethral stenosis, and hydronephrosis
- Cleft palate (rare)
- Normal intelligence

Females with FMD1 present with characteristic craniofacial features similar to those of affected males [Gorlin & Winter 1980]. The digital, subglottic, and urologic anomalies observed in males with FMD1 either do not occur in females or are observed in markedly attenuated form.

Melnick-Needles Syndrome

Substantial variability is observed in females. Some individuals are diagnosed in adulthood after ascertainment of an affected family member [Kristiansen et al 2002]. Others require substantial respiratory support; several individuals have required ambulatory oxygen supplementation, typically starting in the second decade. Longevity is reduced in these individuals.

The phenotype of four males with a pathogenic variant known to lead to conventional MNS in females has been reported. These individuals have previously described skeletal (flexed upper limbs, hypoplastic thumbs, post-axial polydactyly, bowed lower limbs, clubfeet, kyphoscoliosis and hypoplastic halluces), craniofacial (large fontanelles, malar flattening, bilateral cleft palate, bifid tongue, severe micrognathia), and visceral (fibrosis of pancreas and spleen, bilateral cystic renal dysplasia secondary to obstructive uropathy and omphalocele) findings and unusual ophthalmologic signs (exophthalmia, widely spaced eyes, sclerocornea, cataracts, retinal angiomatosis, and a cleavage defect of the anterior chambers of both eyes) [Santos et al 2010, Naudion et al 2016, Spencer et al 2018].

Males with MNS usually present with a phenotype that is indistinguishable from, or more severe than, that associated with OPD2. Several women with classic MNS have had affected male pregnancies diagnosed in utero with a lethal phenotype reminiscent of a severe form of OPD2 [Santos et al 2010, Naudion et al 2016, Spencer et al 2018].

Females with MNS present with the following:

- A skeletal dysplasia characterized by:
  - Short stature
  - Thoracic hypoplasia
  - Limb bowing
  - Joint subluxation
  - Scoliosis
  - Digits of both the hands and the feet that are typically long with mild distal phalangeal hypoplasia
- Characteristic craniofacial features (prominent lateral margins of the supraorbital ridges, proptosis, full cheeks, micrognathia, facial asymmetry) [Foley et al 2010]
- Oligohypodontia (frequent)
- Sensorineural and conductive deafness (common)
- Hydronephrosis secondary to ureteric obstruction (common)
- Bleeding diathesis [Moutton et al 2016]
- Normal intelligence
- Normal pubertal development

Terminal Osseous Dysplasia with Pigmentary Defects

The natural history for females with terminal osseous dysplasia with pigmentary skin defects (TODPD) has been documented in one large family [Brunetti-Pierri et al 2010]. A male presentation of TODPD has never been described.

Females exhibit pronounced abnormalities of the face, hands, and skin:

- The major skeletal findings are in the hands. There is variable shortening, fusion, and disorganized ossification of the carpals and metacarpals. Camptodactyly can be marked and forms no clear pattern. Additional features include cystic lesions and bowing of the long bones, radial head dislocation, short stature, and scoliosis.
- Digital fibromata appear in infancy, can grow to a large size, and may re-grow after excision – but eventually involute before age ten years.
- Cardiac septal defects
- Ureteric obstruction (occasional)
- Alopecia is a variable clinical finding.
- The most characteristic craniofacial findings are widely spaced eyes, oral frenulae, and punched out hyperpigmented lesions characteristically over the temporal region. Unlike the fibromata they do not involute with age.
- Normal intelligence
- A male presentation of TODPD has never been described and an excess of early miscarriage in affected females has been recorded but not statistically verified.

Genotype-Phenotype Correlations

Pathogenic variants associated with the X-OPD spectrum disorders are predicted to maintain the translational reading frame and to produce full-length protein. These variants are clustered in discrete regions of the gene. Genotype-phenotype correlation is strong. Two large studies have been published to date [Robertson et al 2006a]:

- **OPD1.** All males with this diagnosis had pathogenic variants in exons 3, 4, or 5.
- **OPD2.** All males with this diagnosis had pathogenic variants in exons 3, 4, or 5. Females with a phenotype similar to males with typical OPD2 had pathogenic variants in exons 28 and 29.
- **Frontometaphyseal dysplasia**

- Out of 13 males with FMD1, all had pathogenic variants in *FLNA* (exons 3-5, 22, 28-29) [Robertson et al 2006a]. Pathogenic variants in females with FMD1 (found in 68% of affected females) are more widely distributed over the gene (exons 3-5, 11, 22, 28-29, 41, 44-47) than pathogenic variants identified in males.
- One female with a combined FMD1-periventricular nodular heterotopia phenotype had a missense variant that also created an ectopic splice site [Zenker et al 2004].
- Some pathogenic variants are associated with a male-lethal phenotype caused by cardiac and urologic malformations [Stefanova et al 2005, Robertson et al 2006a].

- **Melnick-Needles syndrome.** The vast majority (>90%) of individuals with MNS have pathogenic variants in exon 22 of *FLNA,* with the two preponderant variants being p.Ala1188Thr and p.Ser1199Leu. Rare individuals have had pathogenic variants identified in exons 6 and 23.

Penetrance

Penetrance in males with an *FLNA* pathogenic variant leading to an X-OPD spectrum disorder is complete.

Some obligate heterozygote females with *FLNA* pathogenic variants leading to OPD1 have a normal clinical appearance. The proportion of heterozygous females with radiographic features of OPD1 is unknown

Nomenclature

Melnick-Needles syndrome was originally referred to as osteodysplasty.

OPD1 was also called Taybi syndrome after its first description in 1963.

Verloes et al [2000] suggested the term "fronto-otopalatodigital osteodysplasia" for the X-OPD spectrum disorders, indicative of his prediction that they would prove allelic to one another, which subsequently proved correct. This term has not gained acceptance because some of these disorders are clinically discrete, and therefore diagnosis, management, and prognostication are not served by aggregating them under one term.

Prevalence

No population-based studies have been performed to adequately assess prevalence.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *FLNA* are summarized in Table 5.

Table 5. *FLNA* Allelic Disorders

Disorder	Comment	References
Periventricular nodular heterotopia, X-linked (X-PVNH)	• Neuronal migration disorder characterized by uncalcified nodules of neurons ectopically situated along the surface of the lateral ventricles • Most affected persons are heterozygous females; males show early lethality. • Assoc w/gastrointestinal dysmotility • 1 female reported w/dual phenotype of PVNH & FMD1	*FLNA*-Related Periventricular Nodular Heterotopia, Zenker et al [2004], Hehr et al [2006], Gargiulo et al [2007], Kapur et al [2010]
Variant of X-linked periventricular nodular heterotopia	• PVNH w/marked connective tissue dysfunction (skin fragility, vascular dilatation) described in females & males • Assoc w/pathogenic variants predicted to → loss of function	Sheen et al [2005], Gómez-Garre et al [2006], Reinstein et al [2013]

Table 5. continued from previous page.

Disorder	Comment	References
Myxomatous cardiac valvular dystrophy	• Not assoc w/other neurologic or skeletal manifestations • Of note, cardiac valvular anomalies are assoc w/X-PVNH & some X-OPD spectrum disorders (e.g., FMD1).	OMIM 314400, Kyndt et al [2007], Lardeux et al [2011]
Congenital intestinal obstruction, X linked	Gastrointestinal dysmotility is the prime manifestation if causative pathogenic variants lie in the 5' coding region of an alternative transcript in the *FLNA* locus.	OMIM 300048, Kapur et al [2010], Jenkins et al [2018]

FMD1 = frontometaphyseal dysplasia type 1; PVNH = periventricular nodular heterotopia; X-OPD = X-linked otopalatodigital

Differential Diagnosis

Table 6. Other Genes of Interest in the Differential Diagnosis of Otopalatodigital Spectrum Disorders

Gene	Disorder	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/X-OPD-SD	Differentiating from X-OPD-SD
AMER1	Osteopathia striata with cranial sclerosis	XL	In males: similar skeletal dysplasia to that in OPD2; occasionally, extraskeletal anomalies similar to those in OPD2	In females: striations of the long bones, macrocephaly, & deafness; in males: similar skeletal phenotype to OPD2 in males
FLNB	Larsen syndrome (LS) & atelosteogenesis type III (AOIII) (see *FLNB*-Related Disorders)	AD	Similar facial features to those in OPD1 & FMD1, cleft palate, hearing loss, spatulate fingers & toes	Large joint dislocations (in both LS & AOIII) & varying degrees of disordered ossification (in AOIII)
MAP3K7	Frontometaphyseal dysplasia type 2	AD	Very similar to FMD1	Very similar to FMD1, although persons w/*MAP3K7*-FMD are more likely to have cleft palate, scoliosis, cervical fusions, hearing loss, & keloid
NOTCH2	Serpentine fibula-polycystic kidney disease (Hajdu-Cheney syndrome) (OMIM 102500)	AD	Bowing of long bones, especially fibula	Acro-osteolysis, osteopenia, basilar indentation of the skull base. MNS does not incl cystic kidney disease.
SH3PXD2B	Frank-ter Haar syndrome (OMIM 249420)	AR	Skeletal dysplasia similar to but considerably milder than in MNS	Macrocornea w/or w/o glaucoma in Frank-ter Haar syndrome
SKI	Shprintzen-Goldberg syndrome (SGS)	AD	Skeletal dysplasia similar to MNS & FMD1 (e.g., tall, square-shaped vertebrae; bowed tibiae; occasionally, fusion of upper cervical vertebrae)	ID & craniosynostosis in SGS
TAB2	Frontometaphyseal dysplasia type 3	AD	Very similar to FMD1	Very similar to FMD1, although persons w/*TAB2*-FMD are more likely to have cleft palate, scoliosis, cervical fusions, hearing loss, & keloid

AD = autosomal dominant; AR = autosomal recessive; FMD = frontometaphyseal dysplasia; FMD1 = frontometaphyseal dysplasia type 1; ID = intellectual disability; MNS = Melnick-Needles syndrome; MOI = mode of inheritance; X-OPD-SD = X-linked otopalatodigital spectrum disorders; XL = X-linked

Possible autosomal recessive form of otopalatodigital syndrome type I. A single report of a possible autosomal recessive phenocopy of otopalatodigital syndrome type I has been described but has not been subject to molecular analysis [Zaytoun et al 2002]. The appearance of the facies and hands make this condition clinically quite distinct from the filaminopathies described here.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an X-linked otopalatodigital (X-OPD) spectrum disorder, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 7. Recommended Evaluations Following Initial Diagnosis in Individuals with X-Linked Otopalatodigital Spectrum Disorders

System/Concern	Evaluation	Comment
Musculoskeletal	• Clinical exam of extremities, joints, & spine • Complete skeletal survey w/scoliosis series if indicated	To evaluate for contractures, joint subluxations, scoliosis
Craniofacial	Clinical exam for facial or skull growth asymmetry	To evaluate for craniosynostosis
	Audiology eval	To evaluate for conduction & sensorineural hearing loss
	Clinical exam of palate & referral to ENT as necessary	To evaluate for cleft palate & subglottic stenosis
Respiratory	Referral to pulmonologist if indicated	To evaluate for respiratory complications assoc w/ thoracic hypoplasia
Cardiac	Echocardiogram	To evaluate for septal defects & right ventricular outflow tract obstructive lesions
Dental	Dental eval	To evaluate for hypodontia, oligodontia
Genitourinary	Renal tract ultrasound exam	To evaluate for ureteric & urethral obstruction & hydronephrosis
Ophthalmology	Clinical assessment for proptosis	Monitoring for proptosis
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 8. Treatment of Manifestations in Individuals with X-Linked Otopalatodigital Spectrum Disorders

Manifestation/Concern	Treatment	Considerations/Other
Hand & foot malformations	Surgical treatment may be required.	
Scoliosis	Monitoring & surgical intervention as required	Surgery for scoliosis has had satisfactory results in several persons.
Contractures	Physiotherapy	
Limb bowing		Surgical correction of limb bowing has not been reported.
Fronto-orbital deformity	Cosmetic surgery	Surgery attempted in some persons; regrowth following surgery does not appear to occur [Kung & Sloan 1998].
Thoracic hypoplasia	Chest expansion surgery	Has been attempted in several persons w/MNS w/marginal clinical benefit
Apnea	• CPAP [Lan et al 2006] • Mandibular distraction	Micrognathia & tracheobronchomalacia in severely affected persons can → airway collapse & sleep apnea that have been successfully corrected in the most severe instances of MNS.
Deafness	Hearing aids	Attempts to separate fused & misshapen ossicles are usually unsuccessful & can → formation of a perilymphatic gusher.

Table 8. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Laryngeal stenosis	Eval w/anesthesiology if intubation & ventilation are required due to laryngeal stenosis	Laryngeal stenosis rarely requires surgical intervention & is non-progressive w/growth.

CPAP = continuous positive airway pressure; MNS = Melnick-Needles syndrome

Surveillance

Table 9. Recommended Surveillance for Individuals with X-Linked Otopalatodigital Spectrum Disorders

System/Concern	Evaluation	Frequency
Orthopedic manifestations	Clinical eval for development of: • Hand contractures in FMD1 • Scoliosis in FMD1 & MNS	Annually
Craniosynostosis	Head size & shape should be monitored.	W/each clinical eval during infancy
Apnea	History &somnography studies as indicated	Annually
Deafness	Audiology evals; sensorineural component can be progressive.	

FMD1 = Frontometaphyseal dysplasia type 1; MNS = Melnick-Needles syndrome

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 early evaluations for hearing loss and orthopedic complications, including scoliosis.

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

The X-linked otopalatodigital (X-OPD) spectrum disorders – otopalatodigital syndrome type 1 (OPD1), otopalatodigital syndrome type 2 (OPD2), frontometaphyseal dysplasia type 1 (FMD1), Melnick-Needles syndrome (MNS), and terminal osseous dysplasia with pigmentary skin defects (TODPD) – are inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *FLNA* pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *FLNA* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Germline mosaicism has been reported in X-OPD spectrum disorders [Robertson et al 2006b].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo FLNA* pathogenic variant, in which case the mother is not a carrier. *De novo* pathogenic variants are common in X-OPD spectrum disorders.

Parents of a female proband

- A female proband may have inherited the *FLNA* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

  Note: If a female proband's father is asymptomatic, it is possible that he has the pathogenic variant in some cells in his body (somatic mosaicism). Somatic mosaicism for pathogenic variants leading to the X-OPD spectrum disorders has been described and has the potential to modify the expressivity of these disorders [Robertson et al 2006b].

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *FLNA* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. Note: Male sibs of a proband with MNS or TODPD who inherit the pathogenic variant will be affected and generally die prenatally or perinatally.
  - Females who inherit the pathogenic variant will be heterozygotes and have a range of clinical manifestations.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *FLNA* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Robertson et al 2006b].

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

- If the mother of the proband has an *FLNA* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. Note: Male sibs of a proband with MNS or TODPD who inherit the pathogenic variant will be affected and generally die prenatally or perinatally.
  - Females who inherit the pathogenic variant will be heterozygotes and have a range of clinical manifestations.

- If the father of the proband has an *FLNA* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *FLNA* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Robertson et al 2006b].

Offspring of a male proband

- Males with OPD1 or FMD1 transmit the pathogenic variant to all of their daughters and none of their sons.
- Males with OPD2 do not reproduce.
- Males with MNS usually die in the pre- or perinatal period and do not reproduce.

Offspring of a female proband. Females who are heterozygous for an *FLNA* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *FLNA* pathogenic variant, his or her family members 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.

Family planning

- The optimal time for determination of genetic risk and discussion 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, are carriers, or are at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *FLNA* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for an X-OPD spectrum disorder are possible.

Ultrasound examination. Many of the manifestations of the disorder can be visualized prenatally by ultrasound examination, although the gestational age at which various anomalies can be detected differs. An omphalocele or urinary tract severely dilated by obstruction may be visible from very early in the second trimester. In contrast, the skeletal dysplasia with its associated limb bowing and thoracic hypoplasia may be visible only after 20 weeks' gestation [Naudion et al 2016].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.org
- **Human Growth Foundation**
  hgfound.org
- **MAGIC Foundation**
  Phone: 630-836-8200
  Email: contactus@magicfoundation.org
  magicfoundation.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

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. X-Linked Otopalatodigital Spectrum Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FLNA	Xq28	Filamin-A	FLNA @ LOVD	FLNA	FLNA

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 X-Linked Otopalatodigital Spectrum Disorders (View All in OMIM)

300017	FILAMIN A; FLNA
304120	OTOPALATODIGITAL SYNDROME, TYPE II; OPD2
305620	FRONTOMETAPHYSEAL DYSPLASIA 1; FMD1
309350	MELNICK-NEEDLES SYNDROME; MNS
311300	OTOPALATODIGITAL SYNDROME, TYPE I; OPD1

Molecular Pathogenesis

FLNA encodes filamin A, a member of the class of actin-binding proteins that regulate cell stability, protrusion, and motility across various organisms [Gorlin et al 1990, Cunningham et al 1992]. Filamins coordinate and integrate cell signaling and subsequent remodeling of the actin cytoskeleton. Filamin associates with integrins, which regulate such cellular processes as cell adhesion and neuronal migration [Meyer et al 1997, Loo et al 1998, Dulabon et al 2000]. The complexity of these interactions makes the implication of individual functions in the pathogenesis of these conditions difficult. Structural mechanisms that change the topology of filamin in such circumstances – and possibly alter binding interactions or post-translational modification of filamin as a result – have been described.

Filamin A may influence neuroprogenitor differentiation and migration during cortical development within the central nervous system via its interaction with the cytoskeleton. Disruption of this process could result in the formation of periventricular heterotopia [Carabalona et al 2012]. Similarly, filamins regulate signal transduction by transmembrane receptors and second messengers, the disruption of which could lead to developmental defects such as those observed in the X-linked otopalatodigital (X-OPD) spectrum disorder phenotypes.

Mechanism of disease causation. The mechanism of disease for loss-of-function variants (leading to periventricular nodular heterotopia) and of the clustered pathogenic missense variants (leading to the X-OPD spectrum disorders) are not fully understood.

This clustered distribution of pathogenic missense variants that lead to the X-OPD spectrum disorders indicates that very specific functions of filamins are being altered. Interactions with filamin or localized domains of filamin that have regulatory functions may be altered by these pathogenic variants. Some missense variants enhance the affinity of filamin A for binding actin [Clark et al 2009] while others alter the mechanically sensitive properties of filamin [Ithychanda et al 2017].

Table 10. Notable *FLNA* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_001110556.1 NP_001104026.1	c.3552C>A	p.Asp1184Glu	Melnick-Needles syndrome
	c.3562G>A	p.Ala1188Thr	
	c.3596C>T	p.Ser1199Leu	
	c.5217G>A [1]	p.Val1724_Thr1739del	Terminal osseous dysplasia w/ pigmentary skin defects

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. This variant occurs at the last base of an exon and is predicted to cause no amino acid change but does affect splicing resulting in deletion of 16 amino acids [Sun et al 2010].

References

Literature Cited

André M, Vigneron J, Didier F. Abnormal facies, cleft palate, and generalized dysostosis: a lethal X-linked syndrome. J Pediatr. 1981;98:747–52. PubMed PMID: 7229752.

Brewster TG, Lachman RS, Kushner DC, Holmes LB, Isler RJ, Rimoin DL. Oto-palato-digital syndrome, type II — an X-linked skeletal dysplasia. Am J Med Genet. 1985;20:249–54. PubMed PMID: 3976718.

Brunetti-Pierri N, Lachman R, Lee K, Leal SM, Piccolo P, Van Den Veyver IB, Bacino CA. Terminal osseous dysplasia with pigmentary defects (TODPD): Follow-up of the first reported family, characterization of the radiological phenotype, and refinement of the linkage region. Am J Med Genet A. 2010;152A:1825–31. PubMed PMID: 20583181.

Carabalona A, Beguin S, Pallesi-Pocachard E, Buhler E, Pellegrino C, Arnaud K, Hubert P, Oualha M, Siffroi JP, Khantane S, Coupry I, Goizet C, Gelot AB, Represa A, Cardoso C. A glial origin for periventricular nodular heterotopia caused by impaired expression of Filamin-A. Hum Mol Genet. 2012;21:1004–17. PubMed PMID: 22076441.

Clark AR, Sawyer GM, Robertson SP, Sutherland-Smith AJ. Skeletal dysplasias due to filamin A mutations result from a gain-of-function mechanism distinct from allelic neurological disorders. Hum Mol Genet. 2009;18:4791–800. PubMed PMID: 19773341.

Cunningham CC, Gorlin JB, Kwiatkowski DJ, Hartwig JH, Janmey PA, Byers HR, Stossel TP. Actin-binding protein requirement for cortical stability and efficient locomotion. Science. 1992;255:325–7. PubMed PMID: 1549777.

Dulabon L, Olson EC, Taglienti MG, Eisenhuth S, McGrath B, Walsh CA, Kreidberg JA, Anton ES. Reelin binds alpha3beta1 integrin and inhibits neuronal migration. Neuron. 2000;27:33–44. PubMed PMID: 10939329.

Fitch N, Jequier S, Gorlin R. The oto-palato-digital syndrome, proposed type II. Am J Med Genet. 1983;15:655–64. PubMed PMID: 6614053.

Foley C, Roberts K, Tchrakian N, Morgan T, Fryer A, Robertson SP, Tubridy N. Expansion of the spectrum of FLNA mutations associated with Melnick-Needles syndrome. Mol Syndromol. 2010;1:121–6. PubMed PMID: 21031081.

Gargiulo A, Auricchio R, Barone MV, Cotugno G, Reardon W, Milla PJ, Ballabio A, Ciccodicola A, Auricchio A. Filamin A is mutated in X-linked chronic idiopathic intestinal pseudo-obstruction with central nervous system involvement. Am J Hum Genet. 2007;80:751–8. PubMed PMID: 17357080.

Gómez-Garre P, Seijo M, Gutiérrez-Delicado E, Castro del Río M, de la Torre C, Gómez-Abad C, Morales-Corraliza J, Puig M, Serratosa JM. Ehlers-Danlos syndrome and periventricular nodular heterotopia in a Spanish family with a single FLNA mutation. J Med Genet. 2006;43:232–7. PubMed PMID: 15994863.

Gorlin JB, Yamin R, Egan S, Stewart M, Stossel TP, Kwiatkowski DJ, Hartwig JH. Human endothelial actin-binding protein (ABP-280, nonmuscle filamin): a molecular leaf spring. J Cell Biol. 1990;111:1089–105. PubMed PMID: 2391361.

Gorlin RJ, Cohen MM Jr. Frontometaphyseal dysplasia. A new syndrome. Am J Dis Child. 1969;118:487–94. PubMed PMID: 5807657.

Gorlin RJ, Winter RB. Frontometaphyseal dysplasia — evidence for X-linked inheritance. Am J Med Genet. 1980;5:81–4. PubMed PMID: 7395904.

Gorlin RJ, Poznanski AK, Hendon I. The oto-palato-digital (OPD) syndrome in females. Oral Surg Oral Med Oral Pathol. 1973;35:218–24. PubMed PMID: 4513067.

Hehr T, Classen J, Welz S, Ganswindt U, Scheithauer H, Koitschev A, Bamberg M, Budach W. Hyperfractionated, accelerated chemoradiation with concurrent mitomycin-C and cisplatin in locally advanced head and neck cancer, a phase I/II study. Radiother Oncol. 2006;80:33–8. PubMed PMID: 16875750.

Ithychanda SS, Dou K, Robertson SP, Qin J. Structural and thermodynamic basis of a frontometaphyseal dysplasia mutation in filamin A. J Biol Chem. 2017;292:8390–400. PubMed PMID: 28348077.

Jenkins ZA, Macharg A, Chang CY, van Kogelenberg M, Morgan T, Frentz S, Wei W, Pilch J, Hannibal M, Foulds N, McGillivray G, Leventer RJ, García-Miñaúr S, Sugito S, Nightingale S, Markie DM, Dudding T, Kapur RP, Robertson SP. Differential regulation of two FLNA transcripts explains some of the phenotypic heterogeneity in the loss-of-function filaminopathies. Hum Mutat. 2018;39:103–13. PubMed PMID: 29024177.

Kapur RP, Robertson SP, Hannibal MC, Finn LS, Morgan T, van Kogelenberg M, Loren DJ. Diffuse abnormal layering of small intestinal smooth muscle is present in patients with FLNA mutations and X-linked intestinal pseudo-obstruction. Am J Surg Pathol. 2010;34:1528–43. PubMed PMID: 20871226.

Kristiansen M, Knudsen GP, Soyland A, Westvik J, Orstavik KH. Phenotypic variation in Melnick-Needles syndrome is not reflected in X inactivation patterns from blood or buccal smear. Am J Med Genet. 2002;108:120–7. PubMed PMID: 11857561.

Kung DS, Sloan GM. Cranioplasty in frontometaphyseal dysplasia. Plast Reconstr Surg. 1998;102:1144–6. PubMed PMID: 9734434.

Kyndt F, Le Scouarnec S, Jaafar P, Gueffet JP, Legendre A, Trochu JN, Jousseaume V, Chaventré A, Schott JJ, Le Marec H, Probst V. Genetic aspects of valvulopathies. Arch Mal Coeur Vaiss. 2007;100:1013–20. PubMed PMID: 18223515.

Lan CC, Hung KF, Liao YF, Lin SW, Chen NH. Melnick-Needles syndrome with obstructive sleep apnea successfully treated with nasal continuous positive airway pressure ventilation. J Formos Med Assoc. 2006;105:77–9. PubMed PMID: 16440074.

Lardeux A, Kyndt F, Lecointe S, Marec HL, Merot J, Schott JJ, Le Tourneau T, Probst V. Filamin-a-related myxomatous mitral valve dystrophy: genetic, echocardiographic and functional aspects. J Cardiovasc Transl Res. 2011;4:748–56. PubMed PMID: 21773876.

Leggett JM. Laryngo-tracheal stenosis in frontometaphyseal dysplasia. J Laryngol Otol. 1988;102:74–8. PubMed PMID: 3343570.

Loo DT, Kanner SB, Aruffo A. Filamin binds to the cytoplasmic domain of the beta1-integrin. Identification of amino acids responsible for this interaction. J Biol Chem. 1998;273:23304–12. PubMed PMID: 9722563.

Mehta Y, Schou H. The anaesthetic management of an infant with frontometaphyseal dysplasia (Gorlin-Cohen syndrome). Acta Anaesthesiol Scand. 1988;32:505–7. PubMed PMID: 3176838.

Meyer U, Meyer T, Jones DB. No mechanical role for vinculin in strain transduction in primary bovine osteoblasts. Biochem Cell Biol. 1997;75:81–7. PubMed PMID: 9192077.

Morava E, Illés T, Weisenbach J, Kárteszi J, Kosztolányi G. Clinical and genetic heterogeneity in frontometaphyseal dysplasia: severe progressive scoliosis in two families. Am J Med Genet A. 2003;116A:272–7. PubMed PMID: 12503106.

Moutton S, Fergelot P, Naudion S, Cordier MP, Solé G, Guerineau E, Hubert C, Rooryck C, Vuillaume ML, Houcinat N, Deforges J, Bouron J, Devès S, Le Merrer M, David A, Geneviève D, Giuliano F, Journel H, Megarbane A, Faivre L, Chassaing N, Francannet C, Sarrazin E, Stattin EL, Vigneron J, Leclair D, Abadie C, Sarda P, Baumann C, Delrue MA, Arveiler B, Lacombe D, Goizet C, Coupry I. Otopalatodigital spectrum disorders: refinement of the phenotypic and mutational spectrum. J Hum Genet. 2016;61:693–9. PubMed PMID: 27193221.

Naudion S, Moutton S, Coupry I, Sole G, Deforges J, Guerineau E, Hubert C, Deves S, Pilliod J, Rooryck C, Abel C, Le Breton F, Collardeau-Frachon S, Cordier MP, Delezoide AL, Goldenberg A, Loget P, Melki J, Odent S, Patrier S, Verloes A, Viot G, Blesson S, Bessières B, Lacombe D, Arveiler B, Goizet C, Fergelot P. Fetal phenotypes in otopalatodigital spectrum disorders. Clin Genet. 2016;89:371–7. PubMed PMID: 26404489.

Reinstein E, Frentz S, Morgan T, García-Miñaúr S, Leventer RJ, McGillivray G, Pariani M, van der Steen A, Pope M, Holder-Espinasse M, Scott R, Thompson EM, Robertson T, Coppin B, Siegel R, Bret Zurita M, Rodríguez JI, Morales C, Rodrigues Y, Arcas J, Saggar A, Horton M, Zackai E, Graham JM, Rimoin DL, Robertson SP. Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A. Eur J Hum Genet. 2013;21:494–502. PubMed PMID: 23032111.

Robertson S, Gunn T, Allen B, Chapman C, Becroft D. Are Melnick-Needles syndrome and oto-palato-digital syndrome type II allelic? Observations in a four-generation kindred. Am J Med Genet. 1997;71:341–7. PubMed PMID: 9268106.

Robertson SP, Jenkins ZA, Morgan T, Adès LA, Aftimos S, Boute O, Fiskerstrand T, Garcia-Minãur S, Grix A, Green A, Der Kaloustian V, Lewkonia R, McInnes B, van Haelst MM, Mancini G, Illés T, Mortier G, Newbury-Ecob R, Nicholson L, Scott CI, Ochman K, Brożek I, Shears DJ, Superti-Furga A, Suri M, Whiteford M, Wilkie AO, Krakow D. Frontometaphyseal dysplasia: mutations in FLNA and phenotypic diversity. Am J Med Genet A. 2006a;140:1726–36. PubMed PMID: 16835913.

Robertson SP, Thompson S, Morgan T, Holder-Espinasse M, Martinot-Duquenoy V, Wilkie AO, Manouvrier-Hanu S. Postzygotic mutation and germline mosaicism in the otopalatodigital syndrome spectrum disorders. Eur J Hum Genet. 2006b;14:549–54. PubMed PMID: 16538226.

Robertson SP, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D, Kenwrick SJ, Kim CA, Morava E, Newbury-Ecob R, Orstavik KH, Quarrell OW, Schwartz CE, Shears DJ, Suri M, Kendrick-Jones J, Wilkie AO, et al. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet. 2003;33:487–91. PubMed PMID: 12612583.

Santos HH, Garcia PP, Pereira L, Leão LL, Aguiar RA, Lana AM, Carvalho MR, Aguiar MJ. Mutational analysis of two boys with the severe perinatally lethal Melnick-Needles syndrome. Am J Med Genet A. 2010;152A:726–31. PubMed PMID: 20186808.

Sheen VL, Jansen A, Chen MH, Parrini E, Morgan T, Ravenscroft R, Ganesh V, Underwood T, Wiley J, Leventer R, Vaid RR, Ruiz DE, Hutchins GM, Menasha J, Willner J, Geng Y, Gripp KW, Nicholson L, Berry-Kravis E, Bodell A, Apse K, Hill RS, Dubeau F, Andermann F, Barkovich J, Andermann E, Shugart YY, Thomas P, Viri M, Veggiotti P, Robertson S, Guerrini R, Walsh CA. Filamin A mutations cause periventricular heterotopia with Ehlers-Danlos syndrome. Neurology. 2005;64:254–62. PubMed PMID: 15668422.

Spencer C, Lombaard H, Wise A, Krause A, Robertson SP. A recurrent mutation causing Melnick-Needles syndrome in females confers a severe, lethal phenotype in males. Am J Med Genet A. 2018;176:980–4. PubMed PMID: 29575627.

Stefanova M, Meinecke P, Gal A, Bolz H. A novel 9 bp deletion in the filamin a gene causes an otopalatodigital-spectrum disorder with a variable, intermediate phenotype. Am J Med Genet A. 2005;132A:386–90. PubMed PMID: 15654694.

Stratton RF, Bluestone DL. Oto-palatal-digital syndrome type II with X-linked cerebellar hypoplasia/hydrocephalus. Am J Med Genet. 1991;41:169–72. PubMed PMID: 1785627.

Sun Y, Almomani R, Aten E, Celli J, van der Heijden J, Venselaar H, Robertson SP, Baroncini A, Franco B, Basel-Vanagaite L, Horii E, Drut R, Ariyurek Y, den Dunnen JT, Breuning MH. Terminal osseous dysplasia is caused by a single recurrent mutation in the FLNA gene. Am J Hum Genet. 2010;87:146–53. PubMed PMID: 20598277.

Superti-Furga A, Gimelli F. Fronto-metaphyseal dysplasia and the oto-palato-digital syndrome. Dysmorph Clin Genet. 1987;1:2–5.

Verloes A, Lesenfants S, Barr M, Grange DK, Journel H, Lombet J, Mortier G, Roeder E. Fronto-otopalatodigital osteodysplasia: clinical evidence for a single entity encompassing Melnick-Needles syndrome, otopalatodigital syndrome types 1 and 2, and frontometaphyseal dysplasia. Am J Med Genet. 2000;90:407–22. PubMed PMID: 10706363.

Wade EM, Daniel PB, Jenkins ZA, McInerney-Leo A, Leo P, Morgan T, Addor MC, Adès LC, Bertola D, Bohring A, Carter E, Cho TJ, Duba HC, Fletcher E, Kim CA, Krakow D, Morava E, Neuhann T, Superti-Furga A, Veenstra-Knol I, Wieczorek D, Wilson LC, Hennekam RC, Sutherland-Smith AJ, Strom TM, Wilkie AO, Brown MA, Duncan EL, Markie DM, Robertson SP. Mutations in MAP3K7 that alter the activity of the TAK1 signaling complex cause frontometaphyseal dysplasia. Am J Hum Genet. 2016;99:392–406. PubMed PMID: 27426733.

Young K, Barth CK, Moore C, Weaver DD. Otopalatodigital syndrome type II associated with omphalocele: report of three cases. Am J Med Genet. 1993;45:481–7. PubMed PMID: 8465856.

Zaytoun GM, Harboyan G, Kabalan W. The oto-palato-digital syndrome: variable clinical expressions. Otolaryngol Head Neck Surg. 2002;126:129–40. PubMed PMID: 11870342.

Zenker M, Rauch A, Winterpacht A, Tagariello A, Kraus C, Rupprecht T, Sticht H, Reis A. A dual phenotype of periventricular nodular heterotopia and frontometaphyseal dysplasia in one patient caused by a single FLNA mutation leading to two functionally different aberrant transcripts. Am J Hum Genet. 2004;74:731–7. PubMed PMID: 14988809.

Chapter Notes

Acknowledgments

The author is supported by Curekids New Zealand.

Revision History

- 3 October 2019 (sw) Comprehensive update posted live
- 2 May 2013 (me) Comprehensive update posted live
- 28 April 2009 (cd) Revision: Deletion/duplication analysis available clinically
- 25 July 2008 (me) Comprehensive update posted live
- 30 November 2005 (me) Review posted live
- 14 March 2005 (sr) Original submission

License