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MED12-Related Disorders

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Summary

Clinical characteristics

MED12-related disorders include the phenotypes of FG syndrome type 1 (FGS1), Lujan syndrome (LS), X-linked Ohdo syndrome (XLOS), Hardikar syndrome (HS), and nonspecific intellectual disability (NSID). FGS1 and LS share the clinical findings of cognitive impairment, hypotonia, and abnormalities of the corpus callosum. FGS1 is further characterized by absolute or relative macrocephaly, tall forehead, downslanted palpebral fissures, small and simple ears, constipation and/or anal anomalies, broad thumbs and halluces, and characteristic behavior. LS is further characterized by large head, tall thin body habitus, long thin face, prominent nasal bridge, high narrow palate, and short philtrum. Carrier females in families with FGS1 and LS are typically unaffected. XLOS is characterized by intellectual disability, blepharophimosis, and facial coarsening. HS has been described in females with cleft lip and/or cleft palate, biliary and liver anomalies, intestinal malrotation, pigmentary retinopathy, and coarctation of the aorta. Developmental and cognitive concerns have not been reported in females with HS. Pathogenic variants in *MED12* have been reported in an increasing number of males and females with NSID, with affected individuals often having clinical features identified in other *MED12*-related disorders.

Diagnosis/testing

The diagnosis of an *MED12*-related disorder is established in a male by identification of a hemizygous *MED12* pathogenic variant on molecular genetic testing. The diagnosis of an *MED12*-related disorder is established in a female with suggestive findings and a heterozygous pathogenic variant in *MED12* identified by molecular genetic testing.

Management

Treatment of manifestations: Early individualized education; physical therapy, occupational therapy, and speech therapy for developmental delays; individualized management of behavior problems; routine management of seizures, strabismus and other ocular anomalies, imperforate anus, chronic constipation, joint contractures,

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genitourinary anomalies, congenital heart defects, hearing loss, palate anomalies, and dental anomalies; social work support. Treatment of aneurysms, intestinal malrotation, and liver disease in females with HS as recommended by the appropriate specialist.

Surveillance: At each visit, assess growth, development, behavior concerns, neurologic issues, gastrointestinal functioning, and musculoskeletal manifestations. Annual eye examination with attention to retinal changes for individuals with HS. Annual audiology evaluation. Dental evaluation every six months, particularly for individuals with XLOS and LS. Females with HS should have an annual echocardiogram, carotid ultrasound, gastroenterology evaluation with liver function testing and consideration of clotting studies, serum bile acids, and liver ultrasound based on recommendations of a gastroenterologist; and MRA of the head and neck for aneurysms every two years.

Genetic counseling

MED12-related disorders are inherited in an X-linked manner. If the mother of a proband is heterozygous for a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit a pathogenic variant associated with FGS1, LS, or XLOS will typically be unaffected while females who inherit a pathogenic variant associated with HS will typically be affected. Females who inherit a *MED12* pathogenic variant associated with NSID will be at an increased risk of developing variable clinical features. Males with a *MED12*-related disorder are not known to reproduce. Once the *MED12* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing for *MED12*-related disorders are possible.

GeneReview Scope

MED12-Related Disorders: Included Phenotypes
• FG syndrome type 1 (FGS1) • Lujan syndrome (LS) • X-linked Ohdo syndrome (XLOS) • Hardikar syndrome (HS) • Nonspecific intellectual disability (NSID)

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

An *MED12*-related disorder **should be suspected** in an individual with a phenotype associated with FG syndrome type 1, Lujan syndrome, X-linked Ohdo syndrome, or Hardikar syndrome, or with nonspecific intellectual disability with overlapping features of an *MED12*-related disorder.

FG syndrome type 1 (FGS1). Formal clinical diagnostic criteria for FGS1 have not been established; however, the following clinical features would be suggestive:

- Neurodevelopmental delays
- Characteristic facial features:
  - Absolute or relative macrocephaly
  - Dolichocephaly
  - Frontal hair upsweep
  - Tall forehead
  - Downslanted palpebral fissures

    - Widely spaced eyes
    - Fullness of the upper eyelids
    - Small, simple ears (≤10th percentile)
    - Open mouth
    - Long narrow face
- Broad thumbs and halluces
- Congenital anomaly (corpus callosum, anal, cardiac, skeletal)
- Hypotonia, constipation, or feeding problems
- Characteristic behavior (affable and eager to please)
- A family history consistent with X-linked inheritance

Lujan syndrome (LS). The phenotype of individuals with the recurrent *MED12* pathogenic variant p.Asn1007Ser can be recognized by the presence of six of the following eight clinical features:

- Intellectual disability
- Hypotonia
- Large head (occipitofrontal circumference >75th percentile)
- Tall, thin body habitus (height >75th percentile)
- Long, thin face
- Prominent nasal bridge
- High narrow palate
- Short philtrum

Additional clinical features that can assist in recognition of individuals with LS:

- Hypernasal speech
- Dysphagia
- Micrognathia
- Long hands
- Hyperextensible digits
- Abnormalities of the corpus callosum
- Family history consistent with X-linked inheritance

X-linked Ohdo syndrome (XLOS). Diagnostic criteria have not been established for XLOS. Common clinical features include the following:

- Intellectual disability
- Blepharophimosis
- Ptosis
- Epicanthal folds
- Facial coarsening at an older age

Additional clinical features that can assist in recognition of individuals with XLOS:

- Triangular face
- Maxillary hypoplasia
- Sparse eyebrows
- Hypertelorism
- Strabismus
- Small low-set ears
- Thick alae nasi
- Wide nasal bridge

- Broad nasal tip
- Micrognathia
- Small mouth
- Dental anomalies
- Hypotonia
- Family history consistent with X-linked inheritance

Hardikar syndrome (HS). Diagnostic criteria have not been established for HS. The following clinical features have been described in association with HS:

- Cleft lip and/or cleft palate
- Biliary anomalies
- Liver disease
- Intestinal malrotation
- Pigmentary retinopathy
- Coarctation of the aorta

Additional clinical features that can assist in recognition of individuals with HS:

- Normal cognition
- Preauricular pit/tag
- Hydronephrosis
- Choledochal cyst
- Strabismus

Nonspecific intellectual disability (NSID). Individuals described with NSID due to *MED12* variants have variable clinical features that often overlap but are not reported to be consistent with one of the syndromic *MED12*-related disorders. Clinical features commonly described in *MED12*-related NSID include:

- Intellectual disability
- Behavior issues
- Feeding problems
- Growth delays
- Abnormalities of the corpus callosum
- Hypotonia
- Blepharophimosis
- Low-set, posteriorly rotated ears
- Prominent forehead
- Palatal anomalies
- Constipation

Establishing the Diagnosis

Male proband. The diagnosis of an *MED12*-related disorder **is established** in a male proband by identification of a hemizygous pathogenic (or likely pathogenic) variant in *MED12* by molecular genetic testing (see Table 1).

Female proband. The diagnosis of an *MED12*-related disorder **is usually established** in a female proband with suggestive findings by identification of a heterozygous pathogenic (or likely pathogenic) variant in *MED12* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely

pathogenic variants. (2) Identification of a heterozygous *MED12* variant of uncertain significance does not establish or rule out a diagnosis of an *MED12*-related disorder.

Note: Female carriers of a pathogenic variant in *MED12* associated with FGS1 and LS have been unaffected. XLOS is typically seen in affected males and can be inherited from unaffected female carriers but females with clinical features associated with XLOS have been reported [Murakami et al 2020]. All reported individuals with Hardikar syndrome have been females with *MED12* frameshift or nonsense variants [Li et al 2021]. An increasing number of females have been reported with *MED12* variants that cause NSID [Polla et al 2021].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and 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. 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 *MED12*-related disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *MED12* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *MED12* and other genes of interest (see Differential Diagnosis) may also be considered. Notes: (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*; thus, clinicians need to determine which multigene panel 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. (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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *MED12*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MED12	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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.

Clinical Characteristics

Clinical Description

FG Syndrome Type 1 (FGS1)

FGS1 is an X-linked disorder associated with intellectual disability, hypotonia, relative macrocephaly, broad and flat thumbs, and imperforate anus. The clinical phenotype attributed to FGS1 has widened since the initial description. Many of the clinical features in individuals reported to have FGS1 are nonspecific and may lead to overdiagnosis [Clark et al 2009].

Craniofacial. The most characteristic craniofacial feature is small, simple ears. Other common craniofacial features in individuals with FGS1 include dolichocephaly, frontal hair upsweep, tall forehead, downslanted palpebral fissures, and widely spaced eyes [Risheg et al 2007, Clark et al 2009]. High arched palate, micrognathia, open mouth, narrow auditory canals, fullness of the upper eyelids, and craniosynostosis have also been described [Clark et al 2009].

Growth. Absolute or relative macrocephaly is frequently associated with FGS1 [Clark et al 2009]. Most individuals have a head circumference percentile greater than height percentile [Risheg et al 2007]. Although most affected individuals have normal height, short stature is not uncommon [Clark et al 2009].

Development. Although mild-to-severe cognitive impairment has been reported in the majority of individuals with FGS1, an affected individual may have a borderline to low-normal IQ if other family members have an average to above-average IQ [Clark et al 2009].

Behavior. Behavior abnormalities are commonly found in individuals with FGS1. Problems with expressive language can contribute to behavior issues including aggression, inattention, and anxiety [Clark et al 2009].

Central nervous system. Hypotonia has been described in the majority of affected individuals [Clark et al 2009]. The most common brain MRI finding is partial or complete agenesis of the corpus callosum [Risheg et al 2007, Clark et al 2009]. Seizures and EEG abnormalities have been described [Risheg et al 2007].

Ophthalmologic. Strabismus is relatively common in individuals with FGS1. Large corneas, optic atrophy, nystagmus, cataract, coloboma, phthisis bulbi, retinal detachment, and decreased visual acuity have also been reported [Clark et al 2009].

Gastrointestinal. Constipation, feeding problems in infancy, and gastroesophageal reflux disease are commonly associated with FGS1. Anal anomalies are a frequent finding and can include imperforate anus, anal stenosis, anal fistula, and anteriorly displaced anus [Risheg et al 2007, Clark et al 2009]. Pyloric stenosis and megacolon have also been identified [Clark et al 2009].

Musculoskeletal. The most characteristic musculoskeletal feature is broad thumbs and halluces. The thumbs are typically wide and flat. Single transverse palmar creases and short hands and fingers have been less commonly observed [Risheg et al 2007]. Fetal pads on the fingers and toes have been identified [Clark et al 2009]. Fingernails have been described as distally adherent to the soft tissue.

Other musculoskeletal features described in individuals with FGS1 include: cutaneous syndactyly, oligodactyly, joint hypermobility, joint contractures, limited elbow supination, ectrodactyly, clinodactyly, duplicated thumbs and halluces, spinal curvature, pectus excavatum, rib anomalies, and hip dysplasia [Clark et al 2009].

Genitourinary. Cryptorchidism and inguinal hernia are relatively common [Risheg et al 2007, Clark et al 2009]. Renal cysts and renal stones are less commonly reported [Clark et al 2009].

Cardiovascular. Congenital heart defects have been identified in approximately 60% of individuals with FGS1. Septal defects are most commonly reported. Other cardiac features include: atrioventricular canal defect, hypoplastic left heart, mitral valve prolapse, pulmonary artery hypertension, and patent ductus arteriosus [Clark et al 2009].

Morbidity and mortality. Early infant mortality and multiple miscarriages have been reported in families with FGS1. However, mortality rate is not substantially elevated following infancy, with long-term survival reported and several individuals surviving beyond age 50 years [Clark et al 2009].

Heterozygous females. Carrier females in families with FGS1 are typically unaffected [Clark et al 2009]. X-chromosome inactivation studies in females from six families with FGS1 caused by the p.Arg961Trp *MED12* pathogenic variant were markedly skewed (>90%) in three families, moderately skewed (80%-90%) in one family, and random in two families [Risheg et al 2007].

Lujan Syndrome (LS)

A pathogenic p.Asn1007Ser missense variant in *MED12* has been reported in three families with LS. A number of LS features (including intellectual disability, hypotonia, and dysgenesis of the corpus callosum) overlap with FGS1 [Schwartz et al 2007, Khan et al 2016]. Features of LS that distinguish it from FGS1 include tall and thin habitus, prominent nasal bridge, short philtrum, and high narrow palate.

Craniofacial. Individuals with LS characteristically have a tall narrow face, prominent nasal bridge, malar flattening, short philtrum, high narrow palate, dental crowding, and micrognathia. Hypotelorism is a relatively common finding. Other reported features include: dolichocephaly, prominent forehead, downslanted palpebral fissures, ptosis, narrow nose, open mouth, double row of teeth, and abnormal ears [Schwartz et al 2007].

Growth. A large head circumference (>75th percentile) has been reported in most individuals with LS. One affected male was reported with borderline microcephaly. Affected individuals are typically tall and thin with height greater than 75th percentile. Individuals have been described as having a marfanoid appearance. However, the arm span percentile was not significantly greater than the height percentile in individuals reported with the p.Asn1007Ser pathogenic variant [Schwartz et al 2007].

Development. Most individuals with LS have mild-to-moderate intellectual disability. Affected individuals with normal development and an IQ above 70 have been reported [Khan et al 2016]. Speech is often hypernasal [Schwartz et al 2007, Khan et al 2016].

Behavior. Individuals with LS are commonly hyperactive, aggressive, shy, and attention-seeking. Asperger syndrome was diagnosed in one individual [Schwartz et al 2007].

Central nervous system. Hypotonia is a characteristic feature of LS. In addition, abnormalities of the corpus callosum and seizures have been reported [Schwartz et al 2007].

Ophthalmologic. Strabismus has been identified in individuals with LS [Schwartz et al 2007].

Gastrointestinal. Dysphagia and nasal regurgitation were reported in one individual [Khan et al 2016].

Musculoskeletal. Long hands, long fingers, and hyperextensible digits are common. Broad thumbs, pectus excavatum, long second toe, pes planus, and contractures have also been reported [Schwartz et al 2007].

Genitourinary. Small testes, large testes, and varicoceles have been reported in individuals with LS [Schwartz et al 2007].

Cardiovascular. A male with LS was found to have mild aortic regurgitation and minimal mitral valve prolapse [Khan et al 2016].

Heterozygous females. Carrier females in families with LS caused by the p.Asn1007Ser pathogenic variant are typically unaffected. X-chromosome inactivation studies did not detect significant skewing [Schwartz et al 2007].

X-Linked Ohdo Syndrome (XLOS)

XLOS is characterized by blepharophimosis, intellectual disability, and coarse facial features [Vulto-van Silfhout et al 2013]. Pathogenic missense variants in *MED12* associated with XLOS have typically been described in affected males [Vulto-van Silfhout et al 2013, Isidor et al 2014, Patil et al 2017, Rubin et al 2020]. Murakami et al [2020] reported a novel *MED12* variant in a female.

Craniofacial. Individuals with XLOS characteristically have blepharophimosis, ptosis, sparse eyebrows, and epicanthal folds along with a wide and low nasal bridge, broad nasal tip, small mouth, maxillary hypoplasia, micrognathia, and triangular face [Vulto-van Silfhout et al 2013]. Less commonly reported clinical features include a high prominent forehead, frontal hair upsweep, thick arched eyebrows, hypertelorism, high narrow palate, thin vermilion of the upper lip, microdontia, small posteriorly rotated ears, low-set ears, and narrow auditory canals [Vulto-van Silfhout et al 2013, Patil et al 2017].

Growth. Although growth can be normal, short stature and microcephaly have also been reported [Vulto-van Silfhout et al 2013, Patil et al 2017].

Development. Mild-to-severe developmental delay with little to no speech is typical [Vulto-van Silfhout et al 2013, Patil et al 2017].

Behavior. Individuals with XLOS commonly have behavior issues that include hyperactivity, hand flapping, and aggression. Many are described as being friendly. Autism has been reported in one individual [Vulto-van Silfhout et al 2013].

Central nervous system. Hypotonia is common. Seizures and corpus callosum dysgenesis have also been reported [Vulto-van Silfhout et al 2013, Isidor et al 2014].

Auditory. Hearing loss is relatively common in individuals with XLOS [Vulto-van Silfhout et al 2013, Patil et al 2017].

Ophthalmologic. Strabismus, microphthalmia, and hypermetropia have been identified in individuals with XLOS [Vulto-van Silfhout et al 2013, Murakami et al 2020].

Gastrointestinal. Feeding problems, constipation, Hirschsprung disease, and anteriorly displaced anus have been reported [Vulto-van Silfhout et al 2013, Isidor et al 2014, Patil et al 2017].

Musculoskeletal. Joint hypermobility is relatively common in XLOS. Other reported musculoskeletal issues include long thin fingers, short thumbs, camptodactyly, clinodactyly, overriding toes, horizontal palmar creases, scoliosis, narrow thorax, short neck, winged scapula, short humeri with enlarged metaphyses, and hip dysplasia [Vulto-van Silfhout et al 2013, Isidor et al 2014, Patil et al 2017, Murakami et al 2020].

Genitourinary. Cryptorchidism, small penis, hypospadias, chordee, inguinal hernia, hydrocele, and shawl scrotum have been reported in individuals with XLOS [Vulto-van Silfhout et al 2013, Patil et al 2017]. Hypoplastic kidneys and renal cysts have also been reported [Isidor et al 2014].

Cardiovascular. Tetralogy of Fallot, atrioventricular canal, pulmonic stenosis, and septal defects have been reported [Isidor et al 2014, Patil et al 2017, Rubin et al 2020].

Dermatologic. A female with XLOS was reported with patchy skin hypopigmentation [Murakami et al 2020].

Immunology. Three sibs with XLOS were reported with low B-cell levels [Rubin et al 2020].

Perinatal. Oligohydramnios and hydrops have been reported in fetuses with XLOS [Vulto-van Silfhout et al 2013, Isidor et al 2014].

Heterozygous females. Carrier females in families with XLOS are typically unaffected. X-chromosome inactivation studies revealed significant (>90%) skewing in two families [Vulto-van Silfhout et al 2013]. A female reported with clinical features of XLOS was found to have moderate skewing (87%) [Murakami et al 2020].

Hardikar Syndrome (HS)

HS is characterized by cleft lip and/or cleft palate, biliary anomalies, pigmentary retinopathy, intestinal malrotation, coarctation of the aorta, and normal cognition [Li et al 2021]. Only females have been reported to have *MED12*-related HS; pathogenic frameshift or nonsense variants have been described in seven females [Li et al 2021].

Craniofacial. Orofacial clefting was present in the following reported females with HS due to a *MED12* variant: cleft lip and palate in four females, cleft palate in two females, and cleft lip in one female [Li et al 2021]. Mild micrognathia was reported in one affected female. Preauricular pits are common with preauricular tags, abnormal helices, duplicated tragus, and posteriorly rotated ears also reported. A paranasal root pit has been reported in one individual [Li et al 2021].

Growth. Some affected females have been reported as having short stature and being underweight. Microcephaly was reported in one affected female and borderline macrocephaly in another [Li et al 2021].

Development. Females reported to have HS have not had any developmental or cognitive issues [Li et al 2021].

Auditory. Hearing loss has been reported in two females with HS [Li et al 2021].

Ophthalmologic. Pigmentary retinopathy is relatively common with retinal findings identified in five of seven females with HS and an *MED12* variant. Strabismus and ptosis have also been reported [Li et al 2021].

Gastrointestinal. Biliary anomalies, intestinal malrotation, and choledochal cysts are relatively common. Diaphragmatic hernia, absent gall bladder, Meckel diverticulum, duodenal stenosis, cholestasis, hepatic fibrosis, imperforate anus, and constipation have also been reported [Li et al 2021].

Musculoskeletal. Affected females have been reported with developmental hip dysplasia, single transverse palmar creases, clinodactyly, 2-3 toe syndactyly, hypoplastic toenails, and sacral dimple [Li et al 2021].

Genitourinary. Hydronephrosis and ectopic ureters have been reported in multiple affected females with HS. Megaureter, cloacal anomalies, bladder exstrophy, and vaginal atresia have also been reported [Li et al 2021].

Cardiovascular. Coarctation of the aorta has been reported in affected females. Ventricular septal defect, pulmonic stenosis, and patent ductus arteriosus have also been reported. Carotid artery aneurysm was reported in one female. One female reported had a fatal intracranial hemorrhage [Li et al 2021].

Nonspecific Intellectual Disability (NSID)

Both males and females have been reported with *MED12*-related NSID. Individuals with NSID can have a wide range of clinical features that often overlap with, but are not reported to be consistent with, other *MED12*-related disorders.

Craniofacial. Males and females with NSID often have craniofacial features that overlap syndromic *MED12*-related disorders. Common craniofacial features include blepharophimosis, ptosis, epicanthal folds, downslanting palpebral fissures, small ears, low-set posteriorly rotated ears, hypertelorism, and prominent forehead [Langley et al 2015, Polla et al 2021]. Additional craniofacial features reported include coarse face, triangular face, long face, brachycephaly, deep-set eyes, anteverted nares, high nasal bridge, malar hypoplasia, micrognathia, prognathism, small mouth, short philtrum, and sparse hair [Lesca et al 2013, Charzewska et al 2018, Amodeo et al 2020, Rubinato et al 2020, Polla et al 2021]. Males with NSID have been reported with hypotelorism [Langley et al 2015]. Large ears have also been reported [Yamamoto & Shimojima 2015, Charzewska et al 2018], as well as orofacial anomalies including cleft lip, cleft palate, high palate, bifid uvula, velopharyngeal insufficiency, and Pierre Robin sequence [Prescott et al 2016, Rubinato et al 2020, Wang et al 2020, Polla et al 2021]. Thin lips, preauricular pits, preauricular tags, and craniosynostosis have also been reported [Rubinato et al 2020, Riccardi et al 2021].

Dental. A variety of dental anomalies have been reported in females including crowded teeth, widely spaced teeth, and supernumerary incisor [Polla et al 2021, Riccardi et al 2021]. Large incisors have been reported in males and females [Yamamoto & Shimojima 2015, Lahbib et al 2019, Riccardi et al 2021]. Males have been reported with hypodontia [Rubinato et al 2020].

Growth. Females with NSID due to missense variants in *MED12* typically have normal growth or tall stature, while females with NSID due to truncating variants are not uncommonly reported with short stature that may become more evident over time. Microcephaly and macrocephaly have rarely been reported in females [Polla et al 2021, Gonzalez et al 2021]. Obesity has been reported in one female [Gonzalez et al 2021]. Males have been reported with tall stature and relative macrocephaly [Rubinato et al 2020]. Short stature, failure to thrive, and microcephaly have also been reported in males [Langley et al 2015, Charzewska et al 2018].

Development. Males with NSID have been reported with borderline-to-severe intellectual disability, speech delay, hypernasal speech, dyspraxia, and dysgraphia [Lesca et al 2013, Charzewska et al 2018, Rubinato et al 2020]. Females with NSID due to truncating and missense variants have been reported with mild-to-profound intellectual disability [Polla et al 2021, Riccardi et al 2021]. One female with a *de novo* missense variant was reported to have an IQ of 83 by Polla et al [2021]. Significant speech delay is common in females [Polla et al 2021].

Behavior. Autistic features and attention issues are relatively common in females [Polla et al 2021, Riccardi et al 2021]. Autism has also been reported in males [Lahbib et al 2019]. Males have also been reported with friendly personalities along with anxiety, aggression, and psychosis [Charzewska et al 2018, Rubinato et al 2020].

Central nervous system. Hypotonia is relatively common in females with NSID. Seizures have been reported more commonly in females with missense variants in *MED12* than with truncating variants. Abnormalities of the corpus callosum are relatively common in females. Affected females have also been reported with ventriculomegaly [Polla et al 2021]. White matter anomalies were reported in one female [Riccardi et al 2021].

Males with NSID have been reported with hypotonia, corpus callosum abnormalities, seizures, and mega cisterna magna [Charzewska et al 2018, Rubinato et al 2020].

Auditory. Hearing loss has been reported in males and females with NSID [Prescott et al 2016, Rubinato et al 2020, Polla et al 2021, Riccardi et al 2021]. A male was reported with inner ear anomalies [Prescott et al 2016].

Ophthalmologic. Strabismus and nystagmus are relatively common in females with NSID [Polla et al 2021]. Hypermetropia, astigmatism, lacrimal duct stenosis, and stellate irides have also been reported in affected females [Riccardi et al 2021]. Strabismus and horizontal gaze paresis have been reported in males [Prescott et al 2016, Charzewska et al 2018, Rubinato et al 2020].

Gastrointestinal. Feeding issues are relatively common in individuals with NSID [Langley et al 2015, Polla et al 2021]. Anteriorly placed anus, anal stenosis, sacral dimple, constipation, and anomalies of the larynx have also been reported in females [Polla et al 2021, Riccardi et al 2021]. Males have been reported with constipation, feeding problems, gastroesophageal reflux, anal anomaly, and Hirschsprung disease [Langley et al 2015, Yamamoto & Shimojima 2015, Charzewska et al 2018].

Musculoskeletal. Syndactyly, scoliosis, pectus anomalies, and rhizomelia have been reported in females with *MED12*-related NSID [Polla et al 2021, Riccardi et al 2021]. Vertebral anomalies, wide neck, long hands, camptodactyly, joint contractures, pes planus, short feet, sandal gap, single palmar creases, and joint hypermobility have been reported in males [Prescott et al 2016, Charzewska et al 2018, Amodeo et al 2020, Rubinato et al 2020].

Genitourinary. Cryptorchidism, chordee, genital hypoplasia, inguinal hernia, and urinary incontinence have been reported in males [Langley et al 2015, Charzewska et al 2018, Rubinato et al 2020].

Cardiovascular. Tetralogy of Fallot, atrioventricular septal defect, pulmonic stenosis, narrow aortic arch, patent ductus arteriosus, ventricular septal defect, atrial septal defect, and tricuspid valve insufficiency have been reported in females [Wang et al 2020, Polla et al 2021, Riccardi et al 2021]. Wolff-Parkinson-White syndrome has been reported in one female [Polla et al 2021]. Males have been reported with truncus arteriosus, ventricular septal defect, aortopulmonary window, and tricuspid regurgitation [Amodeo et al 2020].

Dermatologic. Females with NSID have been reported to have anomalies of pigmentation [Polla et al 2021, Riccardi et al 2021].

Genotype-Phenotype Correlations

FGS1. The p.Arg961Trp and p.Gly958Glu pathogenic variants in *MED12* are associated with a recognizable phenotype that includes characteristic facial features (tall forehead, frontal hair upsweep, long narrow face, open mouth), small simple ears, absolute or relative macrocephaly, congenital anomalies (corpus callosum, heart, anus, skeleton), behavior issues, and relatively nonspecific features of hypotonia, constipation, and feeding problems [Risheg et al 2007, Clark et al 2009, Rump et al 2011]. A male with suspected FGS1 was found to have a p.Asn898Asp variant in *MED12* that was also identified in a male reported with NSID [Donnio et al 2017, Srivastava et al 2019].

LS. Males from three families have been reported with LS due to a p.Asn1007Ser variant in *MED12* [Schwartz et al 2007, Khan et al 2016]. Two families with males who have clinical features that overlap LS have been reported with a p.Arg1295His variant in *MED12* [Donnio et al 2017, Srivastava et al 2019]. Two male sibs with a p.Arg1214Cys variant in *MED12* were reported with clinical features felt to overlap LS and FGS1 [Srivastava et al 2019]. A female with a p.Trp1557Arg variant in *MED12* was described with clinical features felt to overlap with LS including intellectual disability, prominent nose, and short philtrum [Gonzalez et al 2021]. Features of LS that distinguish it from FGS1 include tall and thin habitus, prominent nasal bridge, high narrow palate, and short philtrum.

XLOS. Males from two families have been reported with XLOS due to a p.Arg1148His hemizygous pathogenic variant in *MED12* [Vulto-van Silfhout et al 2013, Isidor et al 2014]. Two females with NSID were found to have the p.Arg1148His variant, inherited from their unaffected mother [Charzewska et al 2018]. A *de novo* p.Glu172Gln variant was reported in a female with XLOS and a female with NSID [Murakami et al 2020, Polla et al 2021]. XLOS and NSID have been reported in males with a p.Arg296Glu variant [Patil et al 2017, Amodeo et al 2020]. Individuals with XLOS share clinical features of intellectual disability, hypotonia, and behavior issues with FGS1 and LS but can be distinguished by the presence of blepharophimosis, ptosis, facial coarsening, and thick alae nasi [Vulto-van Silfhout et al 2013]. Corpus callosum dysgenesis and macrocephaly are not common in XLOS [Vulto-van Silfhout et al 2013, Isidor et al 2014].

HS. Seven females have been reported with unique *de novo* nonsense and frameshift variants in *MED12*. One of the affected females was reported with 15% mosaicism and no reported eye findings [Li et al 2021].

NSID. Truncating variants have been reported to cause more severe clinical features than missense variants in both males and females with NSID [Lesca et al 2013, Polla et al 2021].

Penetrance

Penetrance is presumed to be 100% in males with *MED12* pathogenic variants associated with FGS1, LS, XLOS, and NSID; however, recent reports involve unique variants, and incomplete penetrance in males may be identified in the future as additional families are described.

Females with *MED12* variants associated with FGS1 and LS are typically unaffected [Schwartz et al 2007, Clark et al 2009, Rump et al 2011]. Unaffected heterozygous females have been described in families with XLOS [Vulto-van Silfhout et al 2013]. However, a female was reported with XLOS [Murakami et al 2020] and two affected females and their unaffected mother were found to have the p.Arg1148His variant previously reported in males with XLOS [Charzewska et al 2018]. All females reported to have HS due to a *MED12* variant have characteristic clinical features [Li et al 2021]. Affected females with variable clinical expression have been described in families with NSID [Lesca et al 2013, Bouazzi et al 2015].

Nomenclature

The name FG syndrome represents two surname initials in the originally reported family. FGS1 is also referred to as Opitz-Kaveggia syndrome [Risheg et al 2007].

Lujan syndrome is also referred to as Lujan-Fryns syndrome or intellectual disability, X-linked, with marfanoid habitus [Schwartz et al 2007].

X-linked Ohdo syndrome has been referred to as blepharophimosis and mental retardation syndrome, Maat-Kievit-Brunner type [Vulto-van Silfhout et al 2013].

Prevalence

The prevalence of **FGS1** is unknown, but FGS1 appears to be an uncommon condition as only 11 families with clinical features of FGS1 have been found with a pathogenic variant in *MED12* [Risheg et al 2007, Clark et al 2009, Rump et al 2011]. An additional male with suspected FGS1 was reported to have a p.Asn898Asp variant in *MED12* [Srivastava et al 2019].

The prevalence of **LS** is unknown; it appears to be uncommon, as only three families with clinical features of LS have been found to have the p.Asn1007Ser pathogenic variant in *MED12* [Schwartz et al 2007, Khan et al 2016]. Additional individuals have been reported with clinical features that overlap LS [Donnio et al 2017, Srivastava et al 2019, Gonzalez et al 2021].

The prevalence of **XLOS** is unknown but it appears to be uncommon with fewer than ten families reported to have XLOS due to a *MED12* pathogenic variant [Vulto-van Silfhout et al 2013, Isidor et al 2014, Patil et al 2017, Murakami et al 2020, Rubin et al 2020].

The prevalence of **HS** is unknown with only seven affected females reported with unique frameshift and nonsense variants in *MED12* [Li et al 2021].

The overall prevalence of *MED12*-related disorders appears to be higher than suggested by the prevalence associated with specific syndromic forms, as there are an increasing number of reported cases of **NSID** due to *MED12* variants affecting both males and females [Charzewska et al 2018, Rubinato et al 2020, Polla et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are currently known to be associated with germline *MED12* pathogenic variants.

Differential Diagnosis

Disorders with features overlapping those of FG syndrome type 1 (FGS1), Lujan syndrome (LS), X-linked Ohdo syndrome (XLOS) and/or Hardikar syndrome (HS) are summarized in Table 2.

Table 2. Disorders to Consider in the Differential Diagnosis of FG Syndrome Type 1, Lujan Syndrome, X-Linked Ohdo Syndrome, and Hardikar Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Clinical Overlap with:			
			FGS1	LS	XLOS	HS
CBS	Homocystinuria	AR		+		
CHD7	CHARGE syndrome (See *CHD7* Disorder.)	AD				+
CREBBP *EP300*	Rubinstein-Taybi syndrome	AD	+			
FBN1	Marfan syndrome	AD		+		
FLNA	FG syndrome 2 (OMIM 300321)	XL	+			
FMR1	Fragile X syndrome	XL	+	+		
FOLX2 3q23 rearrangements	Blepharophimosis, ptosis, epicanthus inversus syndrome	AD (AR)			+	
GLI3 7p14.1 deletion	Greig cephalopolysyndactyly syndrome	AD	+			
JAG1 *NOTCH2*	Alagille syndrome	AD				+
KAT6B	Say-Barber-Biesecker variant of Ohdo syndrome (See *KAT6B* Disorders.)	AD			+	
KMT2D *KDM6A*	Kabuki syndrome	AD XL				+
MID1	XL Opitz G/BBB syndrome	XL	+			
NSUN2	Dubowitz-like syndrome (OMIM 223370)	AR			+	
RPS6KA3	Coffin-Lowry syndrome	XL	+			
SALL1	Townes-Brocks syndrome	AD	+			

Table 2. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Clinical Overlap with:			
			FGS1	LS	XLOS	HS
SHANK3 22q13.3 deletion	Phelan-McDermid syndrome	AD	+			
SKI	Shprintzen-Goldberg syndrome	AD		+		
SMAD2 *SMAD3* *TGFB2* *TGFB3* *TGFBR1* *TGFBR2*	Loeys-Dietz syndrome	AD		+		
SMS	Snyder-Robinson syndrome	XL		+		
TBX1	22q11.2 deletion syndrome	AD				+
UPF3B	XL ID syndrome 14 (OMIM 300676)	XL	+	+		
ZDHHC9	XL ID syndrome, Raymond type (OMIM 300799)	XL		+		
ZEB2	Mowat-Wilson syndrome	AD	+			

AD = autosomal dominant; AR = autosomal recessive; FGS1 = FG syndrome type 1; HS = Hardikar syndrome; ID = intellectual disability; LS = Lujan syndrome; MOI = mode of inheritance; XL = X-linked; XLOS = X-linked Ohdo syndrome

Fetal alcohol spectrum disorders (FASD) are caused by in utero exposure to alcohol and may have phenotypic overlap with XLOS. FASD are characterized by short palpebral fissures and intellectual disability. Affected individuals typically have a smooth philtrum and thin upper lip.

Nonspecific intellectual disability (NSID). All genes known to be associated with intellectual disability (see OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series) should be included in the differential diagnosis of individuals with NSID (i.e., isolated ID or ID with additional clinical features that do not closely correlate with FGS1, LS, or XLOS).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *MED12*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *MED12*-Related Disorders

System/Concern	Evaluation	Comment
Growth	Measure height, weight, & head circumference.	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screen for behavior concerns

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval for evidence of seizures & hypotonia • Consider EEG if seizures are a concern. • Consider brain imaging studies in persons w/seizures.	
Eyes	Ophthalmologic eval	To assess for strabismus, visual deficits, & other ophthalmologic features
	Eval for retinal issues	In persons w/HS
Gastrointestinal/ Feeding	• Assessment for feeding problems, constipation & gastroesophageal reflux • Exam for evidence of anal anomalies	
	Evaluate for orofacial clefting & velopharyngeal insufficiency.	In persons w/HS & NSID
	• Gastroenterology eval for liver disease & intestinal malrotation • Liver function testing, clotting studies, & liver ultrasound	In persons w/HS
Musculoskeletal	Eval for evidence of joint contractures or hypermobility	
Genitourinary	Exam for genitourinary anomalies	
Cardiovascular	Cardiology eval w/echocardiogram	
	MRA of head & neck for vascular malformations	In persons w/HS
Hearing	Audiologic eval	
Dental	Dental eval for dental anomalies	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *MED12*-related disorders in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

HS = Hardikar syndrome; MOI = mode of inheritance; NSID = nonspecific intellectual disability
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *MED12*-Related Disorders

Manifestation/Concern	Treatment	Considerations/Other
DD/ID/Behavioral concerns	See Developmental Delay / Intellectual Disability Management Issues.	
Seizures	Standardized treatment w/ASM by experienced neurologist.	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Aneurysms	Treatment as recommended by surgeon	In persons w/HS
Strabismus & other ocular anomalies	Standard treatment(s) as recommended by ophthalmologist	
Imperforate anus	Surgical intervention	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Bowel dysfunction	Standard management of chronic constipation	
Intestinal malrotation	Mgmt as recommended by surgeon	
Liver disease	Treatment as recommended by gastroenterologist	In persons w/HS
Joint contractures	PT can help prevent & manage contractures.	
Genitourinary anomalies	Treatment as recommended by urologist	
Congenital heart defects	Treatment as recommended by cardiologist & cardiothoracic surgeon	
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Palatal issues	Treatment as recommended by otolaryngologist	
Dental anomalies	Treatment per dentist &/or orthodontist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; HS = Hardikar syndrome; ID = intellectual disability; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *MED12*-Related Disorders

System/Concern	Evaluation	Frequency
Growth	Measure height, weight, & head circumference.	At each visit throughout childhood
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures & changes in tone.	
Eyes	Ophthalmologic eval for evidence of strabismus & other visual issues; eval for retinal issues in those w/HS	Annually
Gastrointestinal	Assess for feeding problems, constipation & gastroesophageal reflux	At each visit
Liver disease	Gastroenterology eval w/liver function testing & consideration of clotting studies, serum bile acids, & liver ultrasound per recommendations of gastroenterologist in persons w/HS	Annually
Musculoskeletal	Assess for joint contractures, joint hypermobility, scoliosis.	At each visit
Cardiovascular	Echocardiogram & carotid ultrasound in persons w/HS	Annually
	MRA of head & neck for development of aneurysms in those w/HS	Biannually
Hearing	Audiology eval	Annually
Dental	Dental eval	Every 6 mos

HS = Hardikar syndrome

Evaluation of Relatives at Risk

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

MED12-related disorders 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 *MED12* pathogenic variant; therefore, he does not require further evaluation/testing.
- 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 *MED12* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo MED12* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Parents of a female proband

- Because there have been no instances reported to date of a male with a pathogenic *MED12* variant reproducing, an affected female proband would not be expected to have inherited the *MED12* pathogenic variant from her father.
- A female proband may have inherited the *MED12* pathogenic variant from her mother (who may be unaffected or have variable clinical features depending on the pathogenic variant and X-chromosome inactivation) or the pathogenic variant may be *de novo*. (Note: An increasing number of female probands have been reported with *MED12*-related nonspecific intellectual disability (NSID), with most affected female probands having the disorder as the result of a *de novo* pathogenic variant.)
- 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.

Sibs of a proband

- The risk to sibs of a male proband depends on the genetic status of the mother; the risk to sibs of a female proband is also expected to depend on the genetic status of the mother as there are no reports to date of a male with a pathogenic *MED12* variant reproducing.
- If the mother of the proband has a *MED12* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
    - Males who inherit a *MED12* pathogenic variant will be affected.

- Females who inherit a pathogenic variant associated with FG syndrome type 1 (FGS1) or Lujan syndrome (LS) will be heterozygotes and will typically be unaffected but may have clinical manifestations (see Clinical Description).
- Both males and females have been reported with X-linked Ohdo syndrome (XLOS) [Vulto-van Silfhout et al 2013, Murakami et al 2020]. Females who inherit a pathogenic variant may be unaffected or have clinical features with variable expression based on the pathogenic variant and X-chromosome inactivation.
- Hardikar syndrome (HS) has only been reported in females [Li et al 2021]. Females who inherit the pathogenic variant may have clinical features with variable expression based on the pathogenic variant and X-chromosome inactivation.
- Females with specific pathogenic variants associated with NSID may have clinical features with variable expression based on the pathogenic variant and X-chromosome inactivation.

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *MED12* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the theoretic possibility of maternal germline mosaicism or, if the proband is female, paternal transmission.

Offspring of a male proband. Affected males are not known to reproduce.

Offspring of a female proband

- Females with a *MED12* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy (see **Sibs of a proband**).
- Female probands with NSID due to specific *MED12* pathogenic variants have been reported to have both affected male and female offspring [Lesca et al 2013].

Other family members. The maternal aunts and maternal cousins of a proband may be at risk of having a *MED12* pathogenic variant; to date, transmission of a *MED12* pathogenic variant through male family members has not been reported.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the *MED12* pathogenic variant in the proband.

Females who are heterozygous for an *MED12* pathogenic variant associated with FGS1 or LS are typically unaffected but may have clinical manifestations. Females have been reported with clinical features consistent with XLOS. HS is caused by pathogenic *MED12* variants in females who have characteristic clinical findings. *MED12* variants reported to cause NSID can result in clinical findings in heterozygous females with significant variability related to the specific variant as well as X-chromosome inactivation (see Clinical Description).

Related Genetic Counseling Issues

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 heterozygotes or are at risk of being heterozygotes.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MED12* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *MED12*-related disorders are possible.

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

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability
- **Human Disease Gene Website Series – Registry**
  Email: info@humandiseasegenes.com
  MED12-related disorders

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. MED12-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MED12	Xq13.1	Mediator of RNA polymerase II transcription subunit 12	MED12 @ LOVD	MED12	MED12

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 MED12-Related Disorders (View All in OMIM)

300188	MEDIATOR COMPLEX SUBUNIT 12; MED12
300895	OHDO SYNDROME, X-LINKED; OHDOX
305450	OPITZ-KAVEGGIA SYNDROME; OKS
309520	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, LUJAN-FRYNS TYPE; MRXSLF

Table B. continued from previous page.

612726	none found

Molecular Pathogenesis

MED12 encodes MED12, a subunit of a protein complex called Mediator. Mediator serves as an interface between transcription factors and RNA polymerase II and comprises multiple subunits organized into a head, middle, and tail module. A fourth module (Cdk8 module), which contains MED12, can also be included in Mediator. Mediator can activate or repress transcription through specific action of the MED12 protein when the CdK8 module is present [Plassche & Brouwer 2021].

The MED12 protein contains an N-terminal MED12 domain involved in Cdk8 activation and a C-terminal Pro-, Gln-, and Leu-rich (PQL) domain which plays an important role in gene regulation through interaction with the Wnt, sonic hedgehog, REST, and SOX9 pathways [Plassche & Brouwer 2021]. The LCEWAV, LS, and OPA domains do not have known functions but the majority of reported *MED12* variants involve the LS domain [Srivastava et al 2019, Plassche & Brouwer 2021].

Mechanism of disease causation. Females with Hardikar syndrome have been reported with loss-of-function variants that are predicted to be degraded by nonsense-mediated decay [Li et al 2021]. It has been suggested that males and females with nonspecific intellectual disability (NSID) due to nonsense and frameshift variants in *MED12* have intellectual disability due to loss of function, with variants in the C-terminal part of the gene escaping nonsense-mediated decay [Li et al 2021, Polla et al 2021]. Splice variants with overlapping clinical features are also felt to be due to loss of function [Polla et al 2021]. Missense variants that disrupt *MED12* function have been identified across the gene and can result in variable severity in males and females [Plassche & Brouwer 2021].

Table 6. Notable *MED12* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005120.3 NP_005111.2	c.322C>T	p.Arg108Ter	*De novo* variant w/15% mosaicism in a female w/HS [Li et al 2021]
	c.514G>C	p.Glu172Gln	*De novo* variant in a female w/XLOS [Murakami et al 2020] & a female w/NSID [Polla et al 2021]
	c.617G>A	p.Arg206Gln	Reported in males w/NSID [Donnio et al 2017, Srivastava et al 2019]
	c.887G>A	p.Arg296Gln	Reported in persons w/XLOS [Patil et al 2017] & NSID [Amodeo et al 2020]
NM_005120.3	c.1249-1G>C	--	*De novo* variant in 3 females w/NSID; leads to exon 9 skipping [Wang et al 2020, Polla et al 2021]
NM_005120.3 NP_005111.2	c.1547G>A	p.Arg516His	*De novo* variant in a female w/NSID [Riccardi et al 2021]
	c.1862G>A	p.Arg621Gln	Reported in male sibs w/NSID [Prescott et al 2016]
	c.2207_2210del	p.Thr736IlefsTer43	*De novo* variant in a female w/HS [Li et al 2021]
	c.2312T>C	p.Ile771Thr	Reported in male sibs & their niece w/NSID [Prontera et al 2016]
	c.2444G>A	p.Arg815Gln	Reported in male sibs w/NSID [Charzewska et al 2018]
	c.2661_2662insG	p.Leu889ProfsTer11	*De novo* variant in a female w/HS [Li et al 2021]
	c.2669T>A	p.Ile890Asn	*De novo* variant in a female w/NSID [Riccardi et al 2021]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.2692A>G	p.Asn898Asp	Reported in a male w/FGS1 [Srivastava et al 2019] & a male w/NSID [Donnio et al 2017]
	c.2735C>T	p.Ser912Leu	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.2786T>A	p.Val929Asp	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.2861T>G	p.Val954Gly	Reported in male sibs w/NSID [Charzewska et al 2018]
	c.2873G>A	p.Gly958Glu	Reported in a family w/FGS1 [Rump et al 2011]
	c.2881C>T	p.Arg961Trp	Most common pathogenic variant in persons w/FGS1 [Risheg et al 2007, Clark et al 2009]
	c.3020A>G	p.Asn1007Ser	Recurrent variant in persons w/LS [Schwartz et al 2007, Khan et al 2016]
	c.3067A>G	p.Ile1023Val	Reported in a male w/NSID [Yamamoto & Shimojima 2015]
	c.3271G>A	p.Glu1091Lys	Reported in male cousins w/NSID [Charzewska et al 2018]
	c.3412C>T	p.Arg1138Trp	*De novo* variant in 4 females w/NSID [Polla et al 2021, Riccardi et al 2021, Gonzalez et al 2021]
	c.3443G>A	p.Arg1148His	Reported in males w/XLOS [Vulto-van Silfhout et al 2013, Isidor et al 2014] & females w/NSID [Charzewska et al 2018]
	c.3493T>C	p.Ser1165Pro	Reported in a male w/XLOS [Vulto-van Silfhout et al 2013]
	c.3640C>T	p.Arg1214Cys	Reported in male sibs w/features of FGS1 & LS [Srivastava et al 2019]
	c.3646G>A	p.Val1216Met	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.3653G>A	p.Gly1218Glu	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.3883C>T	p.Arg1295Cys	Reported in a family w/NSID [Rubinato et al 2020]
	c.3884G>A	p.Arg1295His	Reported in persons w/NSID [Charzewska et al 2018] & features of LS [Donnio et al 2017] & in male sibs w/ features of FGS1 & LS [Srivastava et al 2019]
	c.3932T>A	p.Val1311Glu	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.3935T>C	p.Leu1312Ser	*De novo* variant in a female w/NSID [Riccardi et al 2021]
	c.4070G>A	p.Arg1357His	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.4111C>T	p.Pro1371Ser	Reported in a male w/NSID [Charzewska et al 2018]
	c.4147G>A	p.Ala1383Thr	Reported in male sibs w/NSID [Langley et al 2015]
	c.4400G>A	p.Arg1467Gln	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.4669T>C	p.Trp1557Arg	*De novo* variant in a female w/LS [Gonzalez et al 2021]
	c.4832G>A	p.Arg1611His	Reported in a male w/NSID [Narayanan & Phadke 2017]
	c.4903_4906delinsCCAGCA	p.Val1635ProfsTer61	Presumed *de novo* variant in a female w/HS [Li et al 2021]
	c.5111G>A	p.Trp1704Ter	*De novo* variant in a female w/HS [Li et al 2021]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.5185C>A	p.His1729Asn	Reported in a male w/XLOS [Vulto-van Silfhout et al 2013]
	c.5622C>A	p.Tyr1874Ter	*De novo* variant in a female w/HS [Li et al 2021]
	c.5898dupC	p.Ser1967GlnfsTer84	Reported in males & females w/NSID [Lesca et al 2013]
	c.5919C>A	p.Tyr1973Ter	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.5922G>T	p.Gln1974His	Reported in male sibs w/NSID [Bouazzi et al 2015]
	c.6169C>T	p.Gln2057Ter	*De novo* variant in a female w/HS [Li et al 2021]
	c.6231C>A	p.Tyr2077Ter	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.6250_6258delCAGCAGCAG	p.Gln2084_Gln2086del	Reported in male sibs w/NSID & their unaffected mother [Lahbib et al 2019]
	c.6268C>T	p.Gln2090Ter	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.6280C>T	p.Gln2094Ter	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.6448C>T	p.Gln2150Ter	*De novo* variant in a female w/NSID [Polla et al 2021]
	c.6476A>C	p.Gln2159Pro	Reported in 3 male sibs w/XLOS [Rubin et al 2020]

FGS1 = FG syndrome type 1; HS = Hardikar syndrome; LS = Lujan syndrome; NSID = nonspecific intellectual disability; XLOS = X-linked Ohdo syndrome

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.

Chapter Notes

Author Notes

Greenwood Genetic Center

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- 12 August 2021 (sw) Comprehensive update posted live
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- 14 July 2009 (cd) Revision: targeted mutation analysis for p.Arg961Trp mutation available clinically
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- 25 April 2008 (mjl) Original submission

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