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MED12-Related Disorders

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Summary

Clinical characteristics

The phenotypic spectrum of *MED12*-related disorders, which is still being defined, includes at a minimum the phenotypes of FG syndrome type 1 (FGS1), Lujan syndrome (LS), and X-linked Ohdo syndrome. 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. X-linked Ohdo syndrome (referred to as XLOS in this *GeneReview*) is characterized by intellectual disability, blepharophimosis, and facial coarsening. A number of individuals with nonsyndromic intellectual disability – including some affected females – have been described.

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 in a female would require the identification of a heterozygous pathogenic variant in *MED12* by molecular genetic testing along with clinical features consistent with an *MED12*-related disorder.

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, hearing loss, congenital heart defects, chronic constipation, and imperforate anus.

Prevention of secondary complications: Physical therapy for joint contractures in individuals with FGS1 or LS.

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Surveillance: Routine follow up of growth, development, behavior concerns, gastrointestinal functioning, and neurologic issues; annual eye examination. Annual audiology evaluation for individuals with XLOS. Regular dental evaluations for individuals with XLOS and LS.

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 the pathogenic variant will be carriers and will usually not be affected. No male with an *MED12*-related disorder has reproduced. Carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible once the pathogenic variant in the family has been identified.

GeneReview Scope

MED12-Related Disorders: Included Phenotypes
• FG syndrome type 1 • Lujan syndrome • Ohdo syndrome, X-linked

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, or X-linked Ohdo syndrome.

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
- A family history consistent with X-linked inheritance
- 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)

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

X-linked Ohdo syndrome (referred to as XLOS in this *GeneReview*). 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 ears
- Thick alae nasi
- Wide, low nasal bridge
- Broad nasal tip
- Micrognathia
- Small mouth
- Dental anomalies
- Hypotonia
- Family history consistent with X-linked inheritance

Establishing the Diagnosis

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

Female proband. The diagnosis of an *MED12*-related disorder in a female would require the identification of a heterozygous pathogenic variant in *MED12* by molecular genetic testing (see Table 1) along with clinical features consistent with an *MED12*-related disorder.

Note: Female carriers of a pathogenic variant in *MED12* have been unaffected with the exception of seven females with variable cognitive impairment in a family with a novel p.Ser1967GlnfsTer84 frameshift variant [Lesca et al 2013] and a female with a p.Gln1974His pathogenic variant who was described as having language delay [Bouazzi et al 2015].

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

- **Single-gene testing.** Sequence analysis of *MED12* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **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 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. (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.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *MED12*) fails to confirm a diagnosis in an individual with features of an *MED12*-related disorder. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). 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, 4]	22/22 families [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

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. 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. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Risheg et al [2007], Schwartz et al [2007], Graham et al [2008], Clark et al [2009], Lyons et al [2009], Rump et al [2011], Lesca et al [2013], Vulto-van Silfhout et al [2013], Isidor et al [2014], Bouazzi et al [2015], Langley et al [2015], Tzschach et al [2015], Yamamoto & Shimojima [2015]
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

FG Syndrome Type 1 (FGS1)

FGS1 was initially described by Opitz & Kaveggia [1974] as a rare X-linked disorder associated with intellectual disability, hypotonia, relative macrocephaly, broad and flat thumbs, and imperforate anus. The clinical phenotype attributed to FGS has widened since that initial description. Many of the clinical features in individuals reported to have FGS are nonspecific and may lead to over-diagnosis [Lyons 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, Lyons et al 2009]. High arched palate, micrognathia, open mouth, narrow auditory canals, fullness of the upper eyelids, and craniosynostosis have also been described in individuals with FGS1 [Clark et al 2009].

Growth. Absolute or relative macrocephaly is frequently associated with FGS1 [Clark et al 2009]. Most individuals with FGS1 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 [Risheg et al 2007, Graham et al 2008, Graham et al 2010]. Problems with expressive language can contribute to behavior issues including aggression, inattention, and anxiety [Graham et al 2008, Graham et al 2010].

Central nervous system. Hypotonia has been described in the majority of affected individuals [Clark et al 2009].

The most common brain MRI finding in individuals with FGS1 is partial or complete agenesis of the corpus callosum [Risheg et al 2007, Clark et al 2009].

Seizures and EEG abnormalities have been described in individuals with FGS1 [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 in individuals with FGS1 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 in individuals with FGS1 [Clark et al 2009].

Genitourinary. Cryptorchidism and inguinal hernia are relatively common in individuals with FGS1 [Risheg et al 2007, Clark et al 2009]. Renal cysts and renal stones are less commonly reported [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 in affected individuals [Risheg et al 2007]. Fetal pads on the fingers and toes have been identified in individuals with FGS1 [Clark et al 2009, Lyons 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].

Cardiopulmonary. Congenital heart defects have been identified in approximately 60% of individuals with FGS1. Septal defects are most commonly reported. Other cardiac features described in individuals with FGS1 include: atrioventricular canal defect, hypoplastic left heart, mitral valve prolapse, pulmonary artery hypertension, and patent ductus arteriosus [Graham et al 2008, Clark et al 2009].

Morbidity and mortality. Early mortality and multiple miscarriages have been commonly seen in affected families but mortality is not substantially different following infancy, with long-term survival reported and several individuals with FGS1 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 ratios in females from six families with FGS1 caused by the p.Arg961Trp *MED12* pathogenic variant were markedly skewed in three families, moderately skewed in one family, and randomly inactivated in two families [Risheg et al 2007].

Lujan Syndrome (LS)

A pathogenic p.Asn1007Ser missense variant in *MED12* has been reported in two families with LS, including the original family described by Lujan et al [1984]. One individual with the p.Asn1007Ser pathogenic variant was originally diagnosed with FGS [Schwartz et al 2007]. A number of LS features (including intellectual disability, hypotonia, and dysgenesis of the corpus callosum) overlap with FGS1 [Schwartz et al 2007].

Features of LS that distinguish it from FGS1 include tall and thin habitus, prominent nasal bridge, high narrow palate, and short philtrum. Prior to the recognition that LS and FGS1 are allelic, LS was not felt to be in the differential diagnosis of FGS [Schwartz et al 2007].

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 [Lujan et al 1984, Schwartz et al 2007].

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

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

Behavior. Individuals with LS are commonly hyperactive, aggressive, shy, and attention-seeking. Asperger syndrome has been diagnosed in one individual with LS [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].

Musculoskeletal. Long hands, long fingers, and hyperextensible digits are common in LS. 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].

Cardiopulmonary. Atrial septal defect was identified in an individual with LS reported by Lujan et al [1984].

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 was initially described in two unrelated males with blepharophimosis and intellectual disability [Maat-Kievit et al 1993]. Subsequently, affected individuals were described as having blepharophimosis and mental retardation syndrome, Maat-Kievit-Brunner (BMRS, MKB) type that was distinguished from other blepharophimosis-intellectual disability syndromes by coarse facial features and X-linked inheritance [Verloes et al 2006]. Three pathogenic missense variants have since been described in four families with XLOS, including one of the original families described by Maat-Kievit et al in 1993 [Vulto-van Silfhout et al 2013, Isidor et al 2014].

Craniofacial. Individuals with XLOS characteristically have blepharophimosis, ptosis, and epicanthal folds along with a wide and low nasal bridge, broad nasal tip, small mouth, dental anomalies, 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, hypertelorism, a high narrow palate, small posteriorly rotated ears, and narrow auditory canals [Vulto-van Silfhout et al 2013].

Growth. Most individuals with XLOS have normal growth, although individuals with short stature, some of whom were underweight, have been reported.

Development. Mild to severe intellectual disability with little to no speech has been reported in all individuals with XLOS [Vulto-van Silfhout et al 2013].

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

Central nervous system. Microcephaly has also been reported [Vulto-van Silfhout et al 2013]. Hypotonia is common in XLOS. One affected individual has been reported to have seizures [Vulto-van Silfhout et al 2013]. Corpus callosum dysgenesis was reported in one individual with XLOS [Isidor et al 2014].

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

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

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 humeri with enlarged metaphyses, and hip dysplasia [Vulto-van Silfhout et al 2013, Isidor et al 2014].

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

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

Cardiopulmonary. An atrial septal defect was identified in one individual with XLOS [Isidor et al 2014].

Perinatal. Oligohydramnios and hydrops have been reported in 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].

Genotype-Phenotype Correlations

FG syndrome type 1 (FGS1). The p.Arg961Trp and p.Gly958Glu pathogenic variants in *MED12* are associated with a recognizable phenotype which 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, Lyons et al 2009, Rump et al 2011].

Lujan syndrome (LS). Two families with LS were reported to have the pathogenic missense variant p.Asn1007Ser in *MED12* [Schwartz et al 2007]. Features of LS that distinguish it from FGS1 include tall and thin habitus, prominent nasal bridge, high narrow palate, and short philtrum.

X-linked Ohdo syndrome (XLOS). Three families with XLOS have been reported with p.Arg1148His, p.Ser1165Pro, and p.His1729Asn hemizygous pathogenic variants in *MED12* associated with intellectual disability, hypotonia, behavior issues, blepharophimosis, ptosis, facial coarsening, and thick alae nasi [Vulto-van Silfhout et al 2013]. An additional family with the p.Arg1148His hemizygous pathogenic variant was described with a more severe presentation that included blepharophimosis and short humeri [Isidor et al 2014]. 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].

Nonspecific intellectual disability (NSID). A family with a novel p.Ser1967GlnfsTer84 frameshift pathogenic variant in *MED12* was reported to have ten affected males with profound intellectual disability along with seven females with variable cognitive impairment [Lesca et al 2013]. The only other affected female had three brothers with NSID and a mother with a history of language delay caused by a p.Gln1974His pathogenic variant – located in the same exon as in the other family with affected females [Bouazzi et al 2015]. A p.Ile1023Val pathogenic variant was described in a male with NSID [Yamamoto & Shimojima 2015]. NSID and microcephaly were reported in a family with a p.Ala1383Thr pathogenic variant and a family with a p.Arg815Gln pathogenic variant [Langley et al 2015, Tzschach et al 2015]. The recent identification of multiple affected families with NSID caused by novel *MED12* pathogenic variants not consistent with FGS1, LS, or XLOS indicates that the clinical spectrum of *MED12*-related disorder is wider than previously reported and the genotype-phenotype correlations will likely evolve over time as additional families are reported.

Penetrance

Penetrance is presumed to be 100% in males with *MED12* pathogenic variants associated with FGS1, LS, and XLOS. *MED12* pathogenic variants associated with FGS1, LS, and XLOS have not been reported in unaffected males [Risheg et al 2007, Schwartz et al 2007, Graham et al 2008, Clark et al 2009, Lyons et al 2009, Rump et al 2011, Vulto-van Silfhout et al 2013, Isidor et al 2014]. Penetrance is presumed to be 100% in males with *MED12* pathogenic variants associated with nonspecific intellectual disability; however, recent reports involve unique variants, and incomplete penetrance may be identified in the future as additional families are described. Affected females with variable clinical expression have been described in two families with nonspecific intellectual disability [Lesca et al 2013, Bouazzi et al 2015].

Nomenclature

The name FG syndrome represents two surname initials in the family initially described by Opitz & Kaveggia [1974]. FG syndrome type 1 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 [Hackmann et al 2016]. X-linked Ohdo syndrome has been referred to as blepharophimosis and mental retardation syndrome, Maat-Kievit-Brunner type [Verloes et al 2006].

Prevalence

The prevalence of FGS 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, Graham et al 2008, Clark et al 2009, Lyons et al 2009, Rump et al 2011]. Clinically diagnosed FGS has been described as a common disorder [Battaglia et al 2006], but numerous nonspecific findings have led to over-diagnosis [Lyons et al 2009].

The prevalence of **LS** is unknown; it appears to be uncommon, as only two families with clinical features of LS have been found to have the p.Asn1007Ser pathogenic variant in *MED12* [Schwartz et al 2007]. The clinical diagnosis of LS has broadened since the initial description but pathogenic variants in *MED12* are rare [Hackmann et al 2016].

The prevalence of **XLOS** is unknown but it appears to be uncommon: only four families with clinical features of XLOS caused by *MED12* pathogenic variants have been described [Vulto-van Silfhout et al 2013, Isidor et al 2014].

Novel pathogenic variants in *MED12* have recently been reported in families with nonspecific intellectual disability [Lesca et al 2013, Bouazzi et al 2015, Langley et al 2015, Tzschach et al 2015, Yamamoto & Shimojima 2015]. The prevalence of the broader *MED12*-related disorder clinical spectrum is unknown but is expected to increase as additional families are identified.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are currently known to be caused by *MED12* pathogenic variants.

Differential Diagnosis

FG Syndrome (FGS)

FGS can be a difficult clinical diagnosis because of the broadening of the phenotype since its initial description by Opitz & Kaveggia [1974].

Individuals reported to have FGS have been linked to four additional loci on the X chromosome:

- FGS2 (linked to Xq28) (OMIM 300321) [Briault et al 1999, Briault et al 2000]. A hemizygous p.Pro1291Leu variant was identified in *FLNA* in one male reported to have FGS2 [Unger et al 2007].
- FGS3 (linked to Xp22.3) (OMIM 300406) [Dessay et al 2002]
- FGS4 (linked to Xp11.4) (OMIM 300422) [Piluso et al 2003]. A hemizygous p.Arg28Leu variant was identified in *CASK* in one family reported to have FGS4 [Piluso et al 2009].
- FGS5 (linked to Xq22.3) (OMIM 300581) [Jehee et al 2005]

However, identification of the underlying molecular etiology has been difficult because of the wide range of features reported in individuals clinically diagnosed with FGS. Various alternative diagnoses have been detected, most commonly by chromosome analysis or chromosomal microarray analysis (CMA) [Lyons et al 2009].

Pathogenic variants in the following genes have been reported in individuals clinically diagnosed with FGS [Piussan et al 1996, de Vries et al 2000, Piluso et al 2007, Tarpey et al 2007, Unger et al 2007, Lyons et al 2009]:

- *FMR1* (fragile X syndrome)
- *FLNA* (OMIM 300321)
- *UPF3B* (OMIM 300676)
- *CASK* (*CASK*-related disorders)
- *MECP2* (Rett syndrome)
- *ATRX* (ATRX syndrome)

Thus, further genetic testing including *FMR1* molecular analysis, chromosome analysis, CMA, and next-generation sequencing should be considered in individuals with features of FGS who have normal *MED12* testing.

Disorders with clinical features that overlap those of FGS include the following.

- **Alpha-thalassemia X-linked intellectual disability (ATRX) syndrome.** Widely spaced eyes, genitourinary anomalies, hypotonia, and intellectual disability are features of ATRX syndrome that can also be seen in FGS1. Individuals with ATRX syndrome have characteristic craniofacial features including microcephaly, small nose, tented upper lip, prominent lower lip, and coarsening of facial features. The only gene associated with ATRX syndrome is *ATRX* (*XNP*).
- **Coffin-Lowry syndrome(CLS)** and FGS1 are X-linked intellectual disability syndromes with common craniofacial features including broad forehead, widely spaced eyes, and downslanted palpebral fissures. Individuals with FGS1 can be distinguished by the presence of small and simple ears, relative macrocephaly, constipation with or without anal anomalies, and broad thumbs and halluces. The only gene associated with CLS is *RPS6KA3* (*RSK2*).
- **Fragile X syndrome(FXS)** findings commonly found in individuals with FGS1 include large head circumference, prominent forehead, hypotonia, and intellectual disability. FXS is associated with large ears whereas FGS1 is distinguished by small and simple ears. In addition, individuals with FGS1 commonly have constipation with or without anal anomalies. In more than 99% of affected individuals, FXS is caused by an *FMR1* allele with greater than 200 CGG repeats. Inheritance is X-linked.
- **Phelan-McDermid syndrome.** (22q13.3 deletion syndrome) Common features seen in both FGS1 and 22q13.3 deletion syndrome include hypotonia, intellectual disability, and delayed speech. FGS1 can be distinguished by the presence of constipation, small and simple ears, and characteristic behavior. 22q13.3 deletion syndrome can often be detected by chromosome analysis but may require further testing (e.g., FISH, CMA).
- **Mowat-Wilson syndrome(MWS).** Features seen in both MWS and FGS1 include constipation, abnormalities of the corpus callosum, widely spaced eyes, and intellectual disability. Individuals with MWS have characteristic facial features distinct from FGS1 including prominent chin, prominent columella, and uplifted earlobes with a central depression. In addition, microcephaly is associated with MWS whereas absolute or relative macrocephaly is commonly described in individuals with FGS1. MWS is typically the result of a *de novo* dominant pathogenic variant in *ZEB2*.
- **X-linked Opitz G/BBB syndrome.** Widely spaced eyes and genitourinary abnormalities, including hypospadias and cryptorchidism, are commonly associated with X-linked Opitz G/BBB syndrome. Imperforate anus, abnormalities of the corpus callosum, and congenital heart defects are also relatively common. Intellectual disability is seen in about half of affected males. Craniofacial features associated with

FGS1 help distinguish the two conditions. *MID1* is the only gene associated with X-linked Opitz G/BBB syndrome.

- **Rubinstein-Taybi syndrome(RSTS).** Broad thumbs and halluces, downslanted palpebral fissures, and intellectual disability are commonly associated with RSTS and FGS1. Individuals with FGS1 often have thumbs and halluces that are broad, but not angulated as in RSTS. RSTS is more commonly associated with microcephaly as opposed to absolute or relative macrocephaly in FGS1. The craniofacial features and head size of FGS1 are distinct from RSTS and should allow clinical differentiation. *CREBBP* and *EP300* are the only genes associated with RSTS. RSTS is expressed in an autosomal dominant manner and typically occurs as the result of a *de novo* pathogenic variant.
- **Greig cephalopolysyndactyly syndrome(GCPS)** is characterized by preaxial polydactyly but can be associated with broad thumbs and halluces. In addition, widely spaced eyes and macrocephaly are common. The head circumference is typically greater than the 97th percentile, which is uncommon in individuals with FGS1. Intellectual disability is uncommon in GCPS. Other craniofacial features of FGS1, including small and simple ears, are not associated with GCPS. GCPS either is inherited in an autosomal dominant manner (as a pathogenic variant in *GLI3* or as a deletion of 7p13 involving *GLI3*) or occurs as the result of a *de novo* or inherited chromosome rearrangement.
- **Townes-Brocks syndrome(TBS)** is characterized by imperforate anus, dysplastic ears, and thumb malformations. Congenital heart defects and genitourinary anomalies are commonly described. Intellectual disability is uncommon. Craniofacial features of FGS1 are distinct from TBS and should allow clinical differentiation. The only gene associated with TBS is *SALL1*. TBS is inherited in an autosomal dominant manner.

Lujan Syndrome (LS)

The clinical diagnosis of LS has broadened since the initial description by Lujan et al [1984]. Pathogenic variants in *UPF3B* were reported in two individuals with a clinical diagnosis of LS [Tarpey et al 2007]. Three families with features that overlap LS were found to have pathogenic variants in *ZDHHC9* [Raymond et al 2007].

The evaluation of 28 individuals with clinical features of LS did not identify pathogenic variants in *MED12*, *UPF3B*, or *ZDHHC9* but did find multiple chromosome and single-gene abnormalities [Hackmann et al 2016]. As a result, further genetic testing including chromosome analysis, CMA, and next-generation sequencing should be considered in individuals with features of LS who have normal *MED12* testing.

Disorders with clinical features that overlap those of LS include the following:

- **Marfan syndrome(MS).** Individuals with LS have been described as having a marfanoid habitus as they may have musculoskeletal features overlapping MS: tall and thin habitus, long hands and fingers, pectus excavatum, narrow palate with dental crowding, and joint hypermobility. LS can be distinguished from MS by the presence of intellectual disability and the absence of significant heart and eye involvement characteristic of MS. The only gene associated with MS is *FBN1*. Inheritance is autosomal dominant.
- **Homocystinuria.** Individuals with homocystinuria have features that overlap LS: intellectual disability, tall and thin habitus, pectus deformity, and high-arched palate. Ectopia lentis is a characteristic feature of homocystinuria not found in individuals with LS. Homocystinuria is caused by pathogenic variants in *CBS*. Inheritance is autosomal recessive.
- **Loeys-Dietz syndrome(LDS)** and LS have overlapping features including long face, high-arched plate, micrognathia, and pectus deformity. Learning disability has also been described in LDS. LDS has a number of distinguishing features including cleft palate, bifid uvula, hydrocephalus, arterial tortuosity and aneurysms, and easy bruising. LDS is caused by pathogenic variants in *TGFBR1*, *TGFBR2*, *SMAD3*, or *TGFB2*. Inheritance is autosomal dominant.
- **Shprintzen-Goldberg syndrome(SGS)** and LS are both associated with intellectual disability, pectus deformity, and high-arched palate. SGS is associated with craniosynostosis, which has not been described

in LS. *SKI* is the only gene in which pathogenic variants are known to cause SGS. SGS is expressed in an autosomal dominant manner and typically occurs as the result of a *de novo* pathogenic variant.

- **Fragile X syndrome (FXS)** findings commonly found in individuals with LS include large head circumference, prominent forehead, hypotonia, and intellectual disability. In more than 99% of affected individuals, FXS is caused by an *FMR1* allele with greater than 200 CGG repeats. Inheritance is X-linked.
- **Snyder-Robinson syndrome (SRS)** is characterized by intellectual disability, hypotonia, thin habitus, narrow palate, and nasal speech. Affected individuals have an unsteady gait and movement disorder that is not associated with LS. SRS is caused by pathogenic variants in *SMS* and inherited in an X-linked manner.

X-linked Ohdo syndrome (XLOS)

XLOS was first clinically described by Maat-Kievit et al [1993] in two unrelated males with blepharophimosis and intellectual disability. XLOS has also been called blepharophimosis and mental retardation syndrome, Maat-Kievit-Brunner type to distinguish it from other syndromes that have blepharophimosis and intellectual disability [Verloes et al 2006].

Disorders with clinical features that overlap those of XLOS include the following:

- **Say-Barber-Biesecker-Young-Simpson (SBBYS) syndrome** (see *KAT6B*-Related Disorders). Features in common with XLOS include intellectual disability and blepharophimosis. Individuals with SBBYS have a mask-like face and can have thyroid issues and cleft palate. SBBYS is caused by pathogenic variants in *KAT6B* and inherited in an autosomal dominant manner.
- **Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES)** is characterized by blepharophimosis, ptosis, and epicanthus inversus but the lack of intellectual disability distinguishes BPES from XLOS. The only gene associated with BPES is *FOLX2*. Deletions of chromosome 3q23 which include *FOXL2* along with contiguous genes can present with blepharophimosis and intellectual disability. Inheritance is autosomal dominant.
- **Dubowitz syndrome (DS)** (OMIM 223370). Affected individuals typically have overlapping features of blepharophimosis, ptosis, and intellectual disability. Microcephaly and eczema are characteristic for DS but are not typically seen in individuals with XLOS. A homozygous variant in *NSUN2* was identified in one family with features that overlapped with DS.
- **Fetal alcohol spectrum disorders (FASD)** are caused by in utero exposure to alchol. They are characterized by short palpebral fissures and intellectual disability. Affected individuals typically have a smooth philtrum and thin upper lip.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with FG syndrome type 1 (FGS1), Lujan syndrome (LS), or X-linked Ohdo syndrome (XLOS) the following are recommended:

- Measurement of height, weight, and head circumference
- Developmental and behavioral assessment
- Neurologic history and examination for evidence of seizures and hypotonia
- Evaluation for evidence of spasticity in individuals with FGS1
- Consideration of brain imaging studies in individuals with FGS1 and LS
- Ophthalmologic evaluation for strabismus, visual deficits, and other ophthalmologic features
- Examination for evidence of anal anomalies in individuals with FGS1
- Examination for evidence of genitourinary anomalies
- Cardiology evaluation with echocardiogram

- Audiology evaluation in individuals with XLOS
- Dental evaluation to evaluate for dental anomalies in individuals with XLOS and LS
- Consultation with a clinical geneticist

Treatment of Manifestations

The following measures are appropriate:

- Early individualized education planning and therapies, including physical therapy, occupational therapy, and speech therapy
- Individualized management of behavior problems
- Neurologic management of seizures
- Ophthalmologic management of strabismus and other ocular anomalies, if present
- Standard management of chronic constipation for individuals with FGS1
- Surgical intervention for imperforate anus, congenital heart defects, and other major malformations, if needed

Prevention of Secondary Complications

Physical therapy can help prevent and manage joint contractures for individuals with FGS1 or LS.

Surveillance

The following are appropriate:

- Growth parameters followed on a regular basis and plotted on age-appropriate curves
- Regular follow up to monitor developmental progress, behavior concerns, gastrointestinal functioning, and neurologic issues
- Annual ophthalmologic evaluation for evidence of strabismus and any visual issues
- Annual audiology evaluation for evidence of hearing loss in XLOS
- Regular dental evaluations for individuals with XLOS and LS

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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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 disease 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 (carrier). 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 may have germline mosaicism. Germline mosaicism has not been described in the mothers of individuals with an *MED12* pathogenic variant.
- If a male is the only affected family member, the mother may be a heterozygote (carrier) or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier. The only reported *de novo* pathogenic variant in an individual with an *MED12*-related disorder is a male with XLOS who had a *de novo*p.His1729Asn pathogenic variant [Vulto-van Silfhout et al 2013]

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

- If the mother of the proband has an *MED12* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and will usually not be affected.
- 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 (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. No male with an *MED12*-related disorder has reproduced.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their gender, may be at risk of being heterozygotes (carriers) for the pathogenic variant or of being affected.

Heterozygote (Carrier) 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.

Note: Females who are heterozygous (carriers) for an *MED12* pathogenic variant are typically unaffected but may have clinical manifestations (see Clinical Description).

Related Genetic Counseling Issues

Assisted reproduction technologies (ART). Donor eggs may be utilized by carrier females to avoid the risk of transmitting an *MED12* pathogenic variant.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal 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 (carriers) or are at risk of being carriers.

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

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 an *MED12*-related disorder are possible.

Fetal ultrasonography. A level II ultrasound to evaluate for congenital anomalies including congenital heart defects, renal cysts, gastrointestinal anomalies, and skeletal defects may be considered in pregnancies at risk for an *MED12*-related disorder.

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)**
  501 3rd Street Northwest
  Suite 200
  Washington DC 20001
  Phone: 202-387-1968
  Fax: 202-387-2193
  Email: sis@aaidd.org
  www.aaidd.org
- **Medline Plus**
  Intellectual Disability
- **National Center on Birth Defects and Developmental Disabilities**
  Phone: 800-232-4636 (toll-free)
  Email: cdcinfo@cdc.gov
  Facts About Intellectual Disability

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

Table B. continued from previous page.

300895	OHDO SYNDROME, X-LINKED; OHDOX
305450	OPITZ-KAVEGGIA SYNDROME; OKS
309520	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, LUJAN-FRYNS TYPE; MRXSLF

Gene structure. *MED12* was initially described as having 25 kb and 44 exons [Philibert et al 1999]. Risheg et al [2007] later reported that the gene has 45 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table 2. The most common pathogenic variant identified in individuals with a distinct FG syndrome (FGS) phenotype is a recurrent pathogenic p.Arg961Trp missense variant in exon 21, identified in ten families [Risheg et al 2007, Clark et al 2009]. A pathogenic p.Gly958Glu missense variant in exon 21 of *MED12* has been reported in three male cousins with features of FGS1 [Rump et al 2011].

Lujan syndrome (LS) is caused by a recurrent pathogenic p.Asn1007Ser missense variant in exon 22 of *MED12* [Schwartz et al 2007].

X-linked Ohdo syndrome (XLOS) has been reported to be caused by p.Arg1148His, p.Ser1165Pro, and p.His1729Asn hemizygous pathogenic variants in *MED12* [Vulto-van Silfhout et al 2013, Isidor et al 2014].

Nonspecific intellectual disability distinct from FGS1, LS, or XLOS has been reported to be caused by p.Ser1967GlnfsTer84, p.Gln1974His, p.Ala1383Thr, p.Arg815Gln, and p.Ile1023Val hemizygous pathogenic variants in *MED12* [Lesca et al 2013, Bouazzi et al 2015, Langley et al 2015, Tzschach et al 2015, Yamamoto & Shimojima 2015].

Table 2. *MED12* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2444G>A	p.Arg815Gln	NM_005120.2 NP_005111.2
c.2873G>A	p.Gly958Glu	
c.2881C>T	p.Arg961Trp	
c.3020A>G	p.Asn1007Ser	
c.3067A>G	p.Ile1023Val	
c.3443G>A	p.Arg1148His	
c.3493T>C	p.Ser1165Pro	
c.4147G>A	p.Ala1383Thr	
c.5185C>A	p.His1729Asn	
c.5898dupC	p.Ser1967GlnfsTer84	
c.5922G>T	p.Gln1974His	

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.

Normal gene product. *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 [Conaway & Conaway 2011]. Mediator can repress transcription through specific

action of the MED12 protein when the CdK8 module is present [Ding et al 2008] and can also be involved in transcription activation [Conaway & Conaway 2011].

MED12 consists of 2212 amino acids and has four domains: Leu-rich (L); Leu-Ser-rich (LS); Pro-, Gln-, and Leu-rich (PQL); and Opa. Transcriptional repression can occur through direct interaction of the PQL domain with a number of transcription factors, including SOX9, GLI3, and β-catenin [Zhou et al 2006, Philibert & Madan 2007]. MED12 can also be associated with repression of gene expression by repressor element-1 silencing transcription factor [Ding et al 2008].

Abnormal gene product. The pathogenic p.Arg961Trp missense variant most commonly associated with FGS1 is located in the Leu-Ser (LS) domain, the function of which is unclear [Philibert & Madan 2007]. The p.Arg961Trp pathogenic variant leads to conformational changes in MED12 [Risheg et al 2007]. The p.Gly958Glu pathogenic variant reported in one family with FGS1 is also located in the LS domain and is predicted to result in the replacement of a highly conserved glycine residue with a larger, charged glutamic acid which is hydrophilic [Rump et al 2011].

The pathogenic p.Asn1007Ser missense variant associated with LS is also located in the LS domain and is predicted to affect MED12 folding [Schwartz et al 2007].

The p.Arg1148His, p.Ser1165Pro, and p.His1729Asn pathogenic variants in *MED12* associated with XLOS involve highly conserved amino acids with the variants predicted to damage protein function [Vulto-van Silfhout et al 2013]. Variants p.Arg1148His and p.Ser1165Pro are in the LS domain while the p.His1729Asn is in the PQL domain of MED12 [Vulto-van Silfhout et al 2013]. The p.Arg961Trp, p.Asn1007Ser, p.Arg1148His, and p.Ser1165Pro pathogenic variants in *MED12* have been shown to disturb the role of MED12 in repression by disrupting how Mediator is recruited to RE1 elements directed by REST [Ding et al 2008, Vulto-van Silfhout et al 2013].

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Chapter Notes

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- 23 June 2008 (me) Review posted live
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