GENEReviews

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MED12-Related Disorders

[*Includes: FG Syndrome Type 1 (FGS1, Opitz-Kaveggia Syndrome), Lujan Syndrome (Lujan-Fryns Syndrome; Mental Retardation, X-linked, with Marfanoid Habitus)*]

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Summary

Disease 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) and Lujan syndrome (LS). FGS1, caused by the recurrent mutation p.Arg961Trp, and LS, caused by the recurrent mutation p.Asn1007Ser, share the clinical findings of cognitive impairment and hypotonia. FGS1 is further characterized by constipation and/or anal anomalies, small and simple ears, tall and prominent forehead, downslanting palpebral fissures, broad thumbs and halluces, and abnormalities of the corpus callosum. LS is further characterized by large head; tall, thin body habitus; long, thin face; high nasal root; high, narrow palate; and short philtrum. Carrier females in families with FGS1 and LS are typically unaffected.

Diagnosis/testing. The diagnosis of *MED12*-related disorders relies on molecular genetic testing for the two common *MED12* mutations, followed by sequence analysis of the entire gene as indicated. Such testing is clinically available.

Management. *Treatment of manifestations:* early individualized education, physical therapy, occupational therapy, and speech therapy for developmental delays; routine management of behavior problems, seizures, chronic constipation, strabismus and other ocular anomalies, and imperforate anus. *Surveillance:* routine follow-up of growth, psychomotor development, behavior; routine attention to gastrointestinal functioning and neurologic findings; annual eye examination.

Genetic counseling. *MED12*-related disorders are inherited in an X-linked manner. If the mother of a proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and will usually not be affected. No male with a *MED12*-related disorder has reproduced. Carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutation in the family has been identified.

Diagnosis

Clinical Diagnosis

The phenotypic spectrum of *MED12*-related disorders, which is currently being defined, includes at a minimum the phenotypes associated with FG syndrome type 1 (FGS1) and Lujan syndrome (LS). The diagnosis of *MED12*-related disorders relies on molecular genetic testing.

FG syndrome type 1 (FGS1). The phenotype of individuals with the recurrent *MED12* mutation p.Arg961Trp can be recognized by the presence of six of the following eight clinical features [Risheg et al 2007; Lyons et al, submitted]:

- Mental retardation
- Hypotonia
- Constipation and/or anal anomalies
- Small and simple ears
- Tall and prominent forehead
- Downslanting palpebral fissures
- Broad thumbs and halluces
- Abnormalities of the corpus callosum

Additional clinical features that are helpful in identification of individuals with FGS1:

- Characteristic behavior (friendly, hyperactive, attention-seeking)
- Frontal hair upsweep
- Relative macrocephaly
- Ocular hypertelorism
- Family history consistent with X-linked inheritance

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

- Mental retardation
- Hypotonia
- Large head (occipitofrontal head circumference >75th percentile)
- Tall, thin body habitus (height >75th percentile)
- Long, thin face
- High nasal root
- 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

Testing

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. A recurrent p.ArgG961Trp mutation in *MED12* is the only known molecular cause of FGS1 [Risheg et al 2007]. The only known cause of LS is the *MED12* mutation p.Asn1007Ser [Schwartz et al 2007].

Clinical testing

- **Sequencing of select exons**
  - Individuals with FGS1 have a recurrent p.ArgG961Trp mutation in exon 21 of *MED12*. The mutation detection frequency in individuals clinically diagnosed with FGS is approximately 13% [Risheg et al 2007] (see Differential Diagnosis). However, subsequent data from laboratory samples on individuals clinically diagnosed with FGS have yielded a much lower mutation detection frequency [M Friez, personal communication], most likely because of the broad range of clinical features that have been associated with FGS.
  - The p.Asn1007Ser mutation in exon 22 of *MED12* has been identified in families with LS [Schwartz et al 2007]. The mutation detection frequency in individuals clinically diagnosed with LS is unknown.
- **Sequence analysis of the coding region.** Full sequencing of all 45 exons of the *MED12* cDNA is clinically available. However, full sequencing has not been a proven mechanism for identifying novel mutations in *MED12*.

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol	Phenotype	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method and Phenotype [3]	Test Availability
MED12	FGS1	Sequence analysis of select exons [1,2]	p.Arg961Trp	Unknown	Clinical Testing
	LS		p.Asn1007Ser	Unknown	

1. Sequencing of select exons 4, 5, 21, 22, 28, and 36

2. Sequencing of the entire coding region is clinically available but has not identified any additional mutations associated with these two phenotypes [M Friez, personal communication].

3. Because *MED12* testing is at an early stage, the mutation detection frequency for these phenotypes is unknown [M Lyons, personal communication].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband

1 Individuals with an FGS1 or LS phenotype should have targeted mutation analysis of exons 4, 5, 20, 21, 22, 28, and 36. Such testing will detect most *MED12* mutations,

including the recurrent p.Arg961Trp mutation in exon 21 and the p.Asn1007Ser mutation in exon 22. If no mutation is identified, full sequencing of the remaining 38 exons could be considered. However, the mutation detection rate is low for individuals clinically diagnosed with FGS or LS who do not have a distinct phenotype associated with the specific mutations in *MED12* [M Friez, personal communication].

2 If a mutation in *MED12* is not identified, further genetic testing is recommended to search for an alternative diagnosis (see Differential Diagnosis).

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutation in the family.

Note: Carriers are heterozygotes for these X-linked disorders and could develop clinical findings related to the disorders.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No phenotypes other than FGS1 and LS are currently known to be associated with mutations in *MED12*.

Clinical Description

Natural History

FG Syndrome Type 1 (FGS1)

FGS was initially described by Opitz and Kaveggia [1974] as a rare X-linked disorder associated with mental retardation, 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 overdiagnosis. A recurrent p.Arg961Trp mutation in *MED12* has been reported in seven families with FGS, including the original family described by Opitz and Kaveggia [Risheg et al 2007; Lyons et al, submitted]. A distinct phenotype, termed FGS1, has been identified in individuals with the recurrent p.Arg961Trp *MED12* mutation [Lyons et al, submitted].

Craniofacial. The most characteristic craniofacial feature is small, simple ears. Other common craniofacial features in individuals with FGS1 include tall and prominent forehead, downslanting palpebral fissures, ocular hypertelorism, and frontal hair upsweep [Risheg et al 2007; Lyons et al, submitted]. High arched palate, micrognathia, dolichocephaly, and craniosynostosis have also been described in individuals with FGS1 [Opitz & Kaveggia 1974, Graham et al 1998].

Growth. Relative macrocephaly is frequently associated with FGS1. Although short stature is relatively uncommon, most individuals with FGS1 have an occipitofrontal head circumference percentile greater than height percentile [Risheg et al 2007]. Individuals with FGS1 occasionally have had failure to thrive [Opitz & Kaveggia 1974, Graham et al 1998].

Development. Mild to severe cognitive impairment has been reported in all individuals with FGS1 [Risheg et al 2007].

Behavior. Characteristic behavior consisting of a hyperactive, friendly, and attention-seeking personality was previously reported in individuals clinically diagnosed with FGS [Graham et

al 1999]. Behavior abnormalities are commonly found in individuals with FGS1 [Risheg et al 2007]. Affected individuals often have strong social skills, but behavior problems, including aggression, can be significant [Graham et al 1999].

Central nervous system. Hypotonia has been described in the majority of affected individuals. Progression to spasticity with joint contractures can occur.

Seizures and EEG abnormalities are commonly described [Risheg et al 2007].

A number of MRI abnormalities have been reported in individuals clinically diagnosed with FGS [Battaglia et al 2006]. However, the most common brain MRI finding in individuals with FGS1 is partial or complete agenesis of the corpus callosum [Risheg et al 2007].

Neuronal migration defects were identified by neuropathologic studies in an affected individual from the original FGS family that is now known to have the p.Arg961Trp mutation.

Tethered spinal cord and Chiari I malformation have been reported in individuals clinically diagnosed with FGS [Gottfried et al 2005, Wang et al 2005, Battaglia et al 2006]. However, it is unclear at this time if individuals with FGS1 have an increased risk for these two findings.

Ophthalmologic. Strabismus is relatively common in individuals with FGS1. Large corneas, optic atrophy, and decreased visual acuity have also been reported [Opitz & Kaveggia 1974, Graham et al 1998].

Gastrointestinal

- Constipation is commonly associated with FGS1.
- Anal anomalies are a frequent finding in individuals with FGS1 and can include imperforate anus as well as anteriorly displaced anus [Opitz & Kaveggia 1974, Graham et al 1998, Risheg et al 2007].
- Pyloric stenosis has been described in an affected individual from the original FGS family that is now known to have the p.Arg961Trp mutation [Opitz & Kaveggia 1974].

Genitourinary

- Inguinal hernia and cryptorchidism are relatively common in individuals with FGS1.
- Hypospadias has been reported in individuals clinically diagnosed with FGS but has not been identified in those with FGS1 [Risheg et al 2007].

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 finger tip pads have been described in individuals clinically diagnosed with FGS and have been identified in one individual with FGS1 [Lyons et al, submitted].
- Fingernails have been described as distally adherent to the soft tissue.
- Other musculoskeletal features described in individuals with FGS1 include: cutaneous syndactyly, joint hyperlaxity, joint contractures, ectrodactyly, clinodactyly, duplicated thumbs and halluces, spinal curvature, and pectus excavatum [Opitz & Kaveggia 1974, Graham et al 1998].

Cardiopulmonary

- Congenital heart defects were identified in 30% of affected individuals with FGS1 [Risheg et al 2007].
- Recurrent upper-respiratory infections have been reported in individuals from the original family described by Opitz and Kaveggia [1974] that is now known to have the p.Arg961Trp mutation.

Morbidity and mortality. Early mortality can occur as a result of significant cardiac malformations, pulmonary complications, or gastrointestinal malformations [Opitz & Kaveggia 1974, Graham et al 1998]. Long-term survival has been reported and several individuals with FGS1 have survived beyond age 60 years [R Stevenson, personal communication].

Heterozygous females. Carrier females in families clinically diagnosed with FGS have been reported to have manifestations [Graham et al 1998, Battaglia et al 2006]. However, carrier females in families with FGS1 are typically unaffected. X-chromosome inactivation ratios in females from six families with FGS1 caused by the p.Arg961Trp *MED12* mutation 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 p.Asn1007Ser missense mutation in *MED12* has been reported in two families with LS, including the original family described by Lujan et al [1984]. A number of features overlap with FGS1, including mental retardation, hypotonia, macrocephaly/relative macrocephaly, behavioral abnormalities, and dysgenesis of the corpus callosum.

One family with the p.Asn1007Ser mutation was originally diagnosed with FGS. Features of LS that distinguish it from FGS1 include tall and thin habitus, long and thin face, high nasal root, high and 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 and narrow face, high nasal root, maxillary hypoplasia, short philtrum, high and narrow palate, dental crowding, and micrognathia. Hypotelorism is relatively common. Other reported features include: dolichocephaly, prominent forehead, downslanting 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 occipitofrontal 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 mutation [Schwartz et al 2007].

Development. Most individuals with LS have mild-moderate mental retardation. Affected individuals with a normal IQ 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]. Psychotic disorders have been described in individuals clinically diagnosed with LS [Lerma-Carrillo et al 2006].

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.

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.

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

Cardiopulmonary. Atrial septal defect was identified in an individual with LS reported by Lujan et al [1984]. Aortic root dilation and ventricular septal defect were reported in an individual and his maternal uncle who were clinically diagnosed with LS [Wittine et al 1999].

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

Genotype-Phenotype Correlations

FG syndrome type 1 (FGS1). The only gene mutation identified in individuals with FGS1 is the recurrent p.Arg961Trp mutation in *MED12* [Risheg et al 2007]. A recognizable phenotype is associated with this mutation [Lyons et al, submitted].

Lujan syndrome (LS). Two families with LS were reported to have a p.Asn1007Ser missense mutation in *MED12* [Schwartz et al 2007].

Penetrance

Penetrance is presumed to be 100% in males with p.Arg961Trp and p.Asn1007Ser *MED12* mutations. The p.Arg961Trp and p.Asn1007Ser *MED12* mutations have not been reported in normal males.

Nomenclature

The name FG syndrome represents two surname initials in the family initially described by Opitz and Kaveggia [1974].

Prevalence

The prevalence of FGS is unknown. Clinically diagnosed FGS has been described as a common disorder [Battaglia et al 2006], but numerous nonspecific findings have led to over-diagnosis.

The prevalence of LS is unknown.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

FG Syndrome (FGS)

FGS can be a difficult clinical diagnosis because of the broadening of the phenotype since its initial description by Opitz and 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]
- FGS3 (linked to Xp22.3) (OMIM 300406) [Dessay et al 2002]
- FGS4 (linked to Xp11.4-p11.3) (OMIM 300422) [Piluso et al 2003]
- 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 comparative genomic hybridization (CGH) microarray analysis [Lyons et al, submitted].

Mutations 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, submitted]:

- *FMR1* (fragile X syndrome)
- *FLNA* (*FLNA*-related disorders)
- *UPF3B*
- *CASK*
- *MECP2* (*MECP2*-related disorders)
- *ATRX* (*ATRX* syndrome)

Thus, further genetic testing, including *FMR1* molecular analysis, chromosome analysis, and CGH microarray analysis, should be considered in individuals with features of FGS who have normal *MED12* testing.

Disorders with common clinical features include the following:

- **Alpha-thalassemia X-linked mental retardation (ATRX) syndrome**. Ocular hypertelorism, genitourinary anomalies, hypotonia, and mental retardation are features of ATRX syndrome that can also be seen in FGS. 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 FGS are X-linked mental retardation syndromes with common craniofacial features including broad forehead, ocular hypertelorism, and downslanting palpebral fissures. Individuals with FGS 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 FGS include large occipitofrontal head circumference, prominent forehead, hypotonia, and mental retardation. FXS is associated with large ears whereas FGS is distinguished by small and simple ears. In addition, individuals with FGS commonly have constipation with or without anal anomalies. FXS is caused by a loss-of-function mutation in *FMR1* that most commonly results from an expansion of CGG trinucleotide repeats.
- **22q13.3 deletion syndrome**. Common features seen in both FGS and 22q13 deletion syndrome include hypotonia, mental retardation, and delayed speech. FGS can be

distinguished by the presence of constipation, small and simple ears, and characteristic behavior. 22q13 deletion syndrome can often be detected by chromosome analysis but may require further testing (e.g., FISH).

- **Mowat-Wilson syndrome (MWS).** Features seen in both MWS and FGS include constipation, abnormalities of the corpus callosum, ocular hypertelorism, and mental retardation. Individuals with MWS have characteristic facial features distinct from FGS including prominent chin, prominent columella, and uplifted earlobes with a central depression. In addition, microcephaly is associated with MWS whereas relative macrocephaly is commonly described in individuals with FGS. MWS is caused by mutations and deletions in *ZEB2*.
- **X-linked Opitz G/BBB syndrome**. Ocular hypertelorism 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. Mental retardation is seen in only about half of affected males. Craniofacial features associated with FGS 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, downslanting palpebral fissures, and mental retardation are commonly associated with RSTS and FGS. Individuals with FGS often have thumbs and halluces that are broad, but not angulated as in RSTS. RSTS is more commonly associated with microcephaly as opposed to the relative macrocephaly described in FGS. The craniofacial features and head size of FGS are distinct from RSTS and should allow clinical differentiation. *CREBBP* and *EP300* are the only genes associated with RSTS.
- **Greig cephalopolysyndactyly syndrome (GCPS)** is characterized by preaxial polydactyly but can be associated with broad thumbs and halluces. In addition, ocular hypertelorism and macrocephaly are common. The head circumference is typically greater than the 97th percentile, which is uncommon in individuals with FGS [Risheg et al 2007]. Mental retardation is uncommon in GCPS. Other craniofacial features of FGS, including small and simple ears, are not associated with GCPS. *GLI3* is the only gene associated with GCPS.
- **Townes-Brocks syndrome (TBS)** is characterized by imperforate anus, dysplastic ears, and thumb malformations. Congenital heart defects and genitourinary anomalies are commonly described. Mental retardation is uncommon. Craniofacial features of FGS are distinct from TBS and should allow clinical differentiation. The only gene associated with TBS is *SALL1*.

Lujan Syndrome (LS)

LS was clinically diagnosed in an individual with a terminal deletion of chromosome 5p [Stathopulu et al 2003].

Disorders with common clinical features 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 mental retardation 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: mental retardation, 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 mutations 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 mutations in *TGFBR1* or *TGFBR2* [Loeys et al 2005]. Inheritance is autosomal dominant.
- **Shprintzen-Goldberg syndrome (SGS)** and LS are both associated with mental retardation, pectus deformity, and high arched palate. SGS is associated with craniosynostosis, which has not been described in LS. Although mutations in *FBN1* and *TGFBR2* have been reported in a minority of individuals with clinically diagnosed SGS [Kosaki et al 2006, van Steensel et al 2008], the underlying cause is unknown. The mode of inheritance is unknown.
- **Fragile X syndrome (FXS)** findings commonly found in individuals with LS include large occipitofrontal head circumference, prominent forehead, hypotonia, and mental retardation. FXS is caused by a loss-of-function mutation in *FMR1* that most commonly results from an expansion of CGG trinucleotide repeats. Inheritance is X-linked.
- **Snyder-Robinson syndrome (SRS)** is characterized by mental retardation, 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 mutations in *SMS* [Cason et al 2003]. Inheritance is X-linked.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with FG syndrome type 1 (FGS1) or Lujan syndrome (LS), the following are recommended:

- Measurement of height, weight, and head circumference
- Developmental and behavioral assessment
- Examination for evidence of genitourinary anomalies
- Examination for evidence of anal anomalies in individuals with FGS1
- Cardiac evaluation with echocardiogram
- Neurologic history and examination for evidence of seizures and hypotonia
- Evaluation for evidence of spasticity in individuals with FGS1
- Consider brain imaging studies
- Ophthalmologic evaluation for evidence of abnormalities including strabismus and visual deficits

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 and consideration of need for further testing (e.g., EEG, brain MRI)
- Standard management of chronic constipation for individuals with FGS1
- Ophthalmologic management of strabismus and other ocular anomalies, if present
- 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.

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 issues, gastrointestinal issues, and neurologic issues
- Annual ophthalmologic evaluation for evidence of strabismus and any visual issues

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

MED12-related disorders are inherited in an X-linked manner.

Risk to Family Members

Parents of the proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If a woman has more than one son with a *MED12* mutation and the disease-causing mutation cannot be detected in her DNA, she may have germline mosaicism. Germline mosaicism has not been described in the mothers of individuals with a *MED12* mutation.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a de novo gene mutation, in which case the mother is not a carrier. The frequency of de novo mutations is unknown.
- When an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
  - He has a de novo disease-causing mutation in *MED12* and his mother is not a carrier.
  - His mother has a de novo disease-causing mutation in *MED12* either (a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or (b) as "germline mosaicism" (i.e., present in some of her germ cells only).
  - His mother has a disease-causing mutation that she inherited from a maternal female ancestor.

Sibs of the proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
- If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

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

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

Carrier Detection

Carrier testing of at-risk female relatives is possible if the disease-causing mutation has been identified in the family.

Related Genetic Counseling Issues

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

Family planning. The optimal time for determination of genetic risk, clarification of carrier 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 carriers or 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

If the *MED12* mutation has been identified in a family member, prenatal testing is possible for pregnancies at increased risk. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

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

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of *MED12*-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
MED12	Xq13	Mediator of RNA polymerase II transcription subunit 12

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot

Table B. OMIM Entries for MED12-Related Disorders

300188	MEDIATOR OF RNA POLYMERASE II TRANSCRIPTION, SUBUNIT 12, S. CEREVISIAE, HOMOLOG OF; MED12
305450	OPITZ-KAVEGGIA SYNDROME; OKS
309520	LUJAN-FRYNS SYNDROME

Table C. Genomic Databases for MED12-Related Disorders

Gene Symbol	Entrez Gene
MED12	9968 (MIM No. 300188)

For a description of the genomic databases listed, click here.

Normal allelic variants: *MED12* was initially described as being 25 kb with 44 exons [Philibert et al 1999]. Risheg et al [2007] later reported that the gene has 45 exons. A polymorphism involving a four-amino acid insertion in the Opa domain has been associated with an increased risk for psychosis [Philibert & Madan 2007].

Pathologic allelic variants: See Table 2. The only mutation identified in individuals with a distinct FG syndrome (FGS) phenotype is a recurrent p.Arg961Trp missense mutation in exon 21 [Risheg et al 2007]:

- Lujan syndrome (LS) is caused by a recurrent p.Asn1007Ser missense mutation in exon 22 [Schwartz et al 2007].
- Other *MED12* mutations associated with alternative phenotypes have occurred in a select number of exons.

Table 2. *MED12* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.2881C>T	p.Arg961Trp	NM_005120.2 NP_005111.2
c.3020A>G	p.Asn1007Ser	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

Normal gene product: *MED12* encodes a subunit of the mediator complex, which serves as an interface between transcription factors and RNA polymerase II. The mediator complex comprises 25 subunits organized into four modules. The protein encoded for by *MED12* (MED12) is part of the CdK8 module. The CdK8 module is needed for repression of transcription. MED12 consists of 2212 amino acids and has four domains: Leu-rich (L); Leu-Ser (LS); Pro-, Gln-, and Leu-rich (PQL); and Opa. Transcriptional repression occurs 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].

Abnormal gene product: The p.Arg961Trp and p.Asn1007Ser missense mutations associated with FGS1 and LS are located in the Leu-Ser (LS) domain, which has an unclear function [Philibert & Madan 2007].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

FG Syndrome Family Alliance, Inc.
946 NW Circle Boulevard #290
Corvallis OR 97330
Phone: 617-577-9050
Email: info@fg-syndrome.org
www.fg-syndrome.org

American Association on Intellectual and Developmental Disabilities (AAIDD)
444 North Capitol Street NW Suite 846
Washington DC 20001-1512
Phone: 800-424-3688; 202-387-1968

Fax: 202-387-2193
Email: anam@aaidd.org
www.aaidd.org

Medline Plus
Mental retardation

National Center on Birth Defects and Developmental Disabilities
Mental retardation

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Reading

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Chapter Notes

Author Notes

Web: www.ggc.org

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