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X-Linked Opitz G/BBB Syndrome

Synonyms: Opitz Syndrome, X-Linked; XLOS

Germana Meroni, PhD[1]

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Summary

Clinical characteristics

X-linked Opitz G/BBB syndrome (X-OS) is a multiple-congenital-anomaly disorder characterized by facial anomalies (hypertelorism, prominent forehead, widow's peak, broad nasal bridge, anteverted nares), genitourinary abnormalities (hypospadias, cryptorchidism, and hypoplastic/bifid scrotum), and laryngotracheoesophageal defects. Developmental delay and intellectual disability are observed in about 50% of affected males. Cleft lip and/or palate are present in approximately 50% of affected individuals. Other malformations (present in <50% of individuals) include congenital heart defects, imperforate or ectopic anus, and midline brain defects (Dandy-Walker malformation and agenesis or hypoplasia of the corpus callosum and/or cerebellar vermis). Wide clinical variability occurs even among members of the same family. Female heterozygotes usually manifest hypertelorism only.

Diagnosis/testing

The diagnosis of X-OS is established in a male proband most often by clinical findings. Identification of a hemizygous pathogenic variant in *MID1* in a male proband by molecular genetic testing establishes the diagnosis if clinical features are inconclusive. The diagnosis of X-OS can be established in a female with suggestive clinical features by identification of a heterozygous pathogenic variant in *MID1* on molecular genetic testing.

Management

Treatment of manifestations: Management of anomalies by a multidisciplinary team; surgical treatment of medically significant laryngotracheoesophageal malformations; tracheostomy as needed; standard surgical management of hypospadias, cleft lip/palate, imperforate anus, heart defects; speech therapy; neuropsychological and educational support.

Prevention of secondary complications: Antireflux measurements to minimize risk of aspiration.

Author Affiliation: 1 Department of Life Sciences, University of Trieste, Trieste, Italy; Email: gmeroni@units.it.

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Surveillance: Based on the type of malformations present; regular monitoring of hearing for those with cleft lip/palate.

Genetic counseling

X-OS is inherited in an X-linked manner. In a family with more than one affected individual, the mother of an affected male is an obligate carrier. If the mother of an affected male is a carrier, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant will be carriers and will usually manifest hypertelorism. Mildly affected males who have children will pass the pathogenic variant to all of their daughters and none of their sons. Prenatal testing is possible for pregnancies at risk if the pathogenic variant in the family has been identified.

Diagnosis

X-linked Opitz G/BBB syndrome (X-OS) is diagnosed most often on the basis of clinical findings. There is variable expressivity among affected individuals, even within the same family. The manifestations of X-OS are classified into major and minor findings based on frequency of occurrence. Formal diagnostic criteria for X-OS have not been established.

Suggestive Findings

The clinical diagnosis of X-OS **should be suspected** in a male with the following major and/or minor findings.

Major (more frequent) findings

- Hypertelorism and/or telecanthus (present in virtually all affected individuals)
- All degrees of hypospadias that, in the most severe form, can be associated with renal malformations (85%-90%)
- Laryngotracheoesophageal abnormalities, primarily laryngeal cleft, resulting in swallowing difficulties and respiratory dysfunction (60%-70%)
- A family history consistent with X-linked inheritance – although variable expressivity among affected individuals, even within the same family, should be taken into consideration

Minor findings (found in ≤50% of individuals)

- Intellectual disability and developmental delay
- Cleft lip and/or palate
- Congenital heart defects (e.g., ventricular septal defect, atrial septal defect, persistent left superior vena cava, patent ductus arteriosus)
- Imperforate or ectopic anus
- Midline defects of the brain including agenesis of the corpus callosum and cerebellar vermis agenesis or hypoplasia

Establishing the Diagnosis

Male proband. The diagnosis of X-linked Opitz G/BBB syndrome (X-OS) **is established** in a male proband with the above clinical findings. Identification of a hemizygous pathogenic variant in *MID1* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive (see Table 1).

Female proband. The diagnosis of X-OS **is established** in a female proband with suggestive clinical features and identification of a heterozygous pathogenic variant in *MID1* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of X-OS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of X-OS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *MID1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *MID1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of X-OS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in X-Linked Opitz G/BBB Syndrome

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method
MID1	Sequence analysis [3, 4]	~25% [5]
	Gene-targeted deletion/duplication analysis [6]	10 individuals [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. The detection of an *MID1* pathogenic variant in an individual without a family history of X-OS is approximately 15%. The pathogenic variant detection rate in individuals with documented X-linked inheritance is >50%. [Gaudenz et al 1998, Cox et al 2000, De Falco et al 2003, Winter et al 2003, Pinson et al 2004, So et al 2005, Fontanella et al 2008].
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. Three whole-gene deletions have been reported [Winter et al 2003, Ferrentino et al 2007, Fontanella et al 2008]. In addition, single-exon deletions and duplications have been reported [Winter et al 2003, Hüning et al 2013, Migliore et al 2013].

Clinical Characteristics

Clinical Description

Affected males. X-linked Opitz G/BBB syndrome (X-OS) is characterized by clinical abnormalities of primarily midline structures. These defects include facial anomalies, genitourinary abnormalities, laryngotracheoesophageal defects, and congenital heart defects. Developmental delay and intellectual disability are common. Wide clinical variability has been described; individuals with an *MID1* pathogenic variant may manifest only some of the clinical features with different degrees of severity, even among members of the same family.

Table 2. Incidence of Clinical Features in Males with X-OS with an Identified *MID1* Pathogenic Variant

Clinical Feature	# of Males with Clinical Feature / Total # of Males
Hypertelorism	82/82
Hypospadias	65/85
Laryngotracheoesophageal defects	46/85
Intellectual disability and/or developmental delay	28/85
Cleft lip//palate	42/85
Congenital heart defects	20/85
Anal defects	18/85
Brain abnormalities	18/35 [1]

Fontanella et al [2008], Li et al [2015]
1. Includes males with X-OS who have undergone MRI examination

Facial appearance and head anomalies. The facial appearance of affected males is characterized by hypertelorism, which can also be accompanied by telecanthus, a prominent forehead, widow's peak, broad nasal bridge, anteverted nares, low-set and malformed ears, microcephaly, large fontanelle, and/or prominent metopic

suture. Unilateral or bilateral cleft lip and/or palate is present in approximately 50% of affected individuals. Other oral manifestations include high-arched palate, ankyloglossia, micrognathia, hypodontia, and neonatal teeth [Robin et al 1996, Shaw et al 2006, Fontanella et al 2008].

Urogenital abnormalities. Hypospadias of varying severity is present in approximately 90% of males with X-linked Opitz G/BBB syndrome and is often associated with other genital anomalies such as cryptorchidism and hypoplastic/bifid scrotum. Severe hypospadias can be associated with urinary tract dysfunction (e.g., vesicoureteral reflux, hydronephrosis) [Fontanella et al 2008, Zhang et al 2011].

Laryngotracheoesophageal (LTE) defects. LTE abnormalities may result in coughing and choking with feeding, recurrent pneumonia, and life-threatening aspiration. In their most severe form, LTE defects are manifest as laryngeal and tracheoesophageal clefts and in more mild form as tracheoesophageal fistulae or LTE dysmotility. The incidence of respiratory and/or gastroesophageal symptoms is probably underestimated because mildly affected individuals may only manifest functional swallowing difficulties that improve with age and eventually disappear during infancy [Pinson et al 2004].

Neurologic findings. More than one third of individuals with X-OS show developmental delay and intellectual disability; they frequently manifest delay in onset of walking, short attention span, learning difficulties, and speech problems. In some cases, these delays are secondary to surgical interventions. Midline brain anatomic defects including agenesis or hypoplasia of the corpus callosum and/or cerebellar vermis and Dandy-Walker malformations were identified in 50% of individuals with an *MID1* pathogenic variant who underwent MRI examination [Fontanella et al 2008].

Congenital heart disease. Approximately 20% of individuals with X-OS present with congenital heart anomalies (e.g., ventricular septal defect, atrial septal defect, coarctation of the aorta, persistent left superior vena cava, patent ductus arteriosus, patent foramen ovale) [Robin et al 1996, Fontanella et al 2008].

Anal abnormalities are present in approximately 20% of individuals with X-OS (e.g., imperforate anus, ectopic anus) [Robin et al 1996, De Falco et al 2003, Pinson et al 2004, Fontanella et al 2008].

Ophthalmologic features. Refractive error and strabismus have been reported.

Heterozygous females usually have hypertelorism only, and rarely other manifestations (e.g., characteristic facial features [anteverted nares, short nose, short uvula, high arched palate, micrognathia], tracheoesophageal cleft or esophageal stenosis, anal malformations) [So et al 2005].

Genotype-Phenotype Correlations

In general, no genotype-phenotype correlations have been observed. Pathogenic missense, nonsense, splice site, and frameshift variants, insertions, and deletions all result in highly variable phenotypes even within the same family [Pinson et al 2004].

Two possible exceptions are:

- An association between truncating variants and the presence of anatomic brain abnormalities, in particular cerebellar defects [Fontanella et al 2008];
- Possible correlation of a mild phenotype with pathogenic variants in the fibronectin type III domain of the protein [Mnayer et al 2006].

Penetrance

Usually the presence of an *MID1* pathogenic variant is associated with clinical findings of X-OS; however, recently an instance of reduced penetrance has been reported [Ruiter et al 2010].

Nomenclature

Opitz G/BBB syndrome was first reported as two separate entities, BBB syndrome [Opitz et al 1969b] and G syndrome [Opitz et al 1969a]. Subsequently, it has become apparent that the two syndromes identified in 1969 are in fact a single entity, now named Opitz G/BBB syndrome.

Other names, no longer used, include hypospadias-dysphagia syndrome, Opitz-Frias syndrome, telecanthus with associated abnormalities, and hypertelorism-hypospadias syndrome.

Of note, X-linked Opitz G/BBB syndrome (X-OS; OSX; type I) is distinct from autosomal dominant Opitz G/BBB syndrome (ADOS; type II).

Prevalence

The prevalence of X-linked Opitz G/BBB syndrome ranges from 1:50,000 to 1:100,000 males.

Genetically Related (Allelic) Disorders

No other phenotype is known to be associated with pathogenic variants in *MID1*.

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of X-OS

Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of This Disorder	
			Overlapping with X-OS	Distinguishing from X-OS
AD Opitz G/BBB syndrome (ADOS; Opitz G/BBB syndrome, type II)	*SPECC1L* 22q11.2 deletion [1]	AD	• Hypertelorism • Swallowing difficulties • Hypospadias • DD	• MOI • More complex phenotype in females w/ADOS
FG syndrome [2]	*MED12* *FLNA* *CASK*	XL	• Facial dysmorphism • Congenital heart defects • Hypospadias • DD/ID	• Congenital hypotonia w/ joint hyperlaxity evolving into spasticity • Chronic constipation • Characteristic personality
Craniofrontonasal dysplasia (OMIM 304110)	*EFNB1*	XL	• Facial dysmorphism • Cleft lip/palate • Hypospadias • DD • Hypoplasia or agenesis of corpus callosum	• Skeletal, skin, nail, & hair defects • Chest defects • Short stature • Hypotonia

Table 3. continued from previous page.

Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of This Disorder	
			Overlapping with X-OS	Distinguishing from X-OS
Mowat-Wilson syndrome	*ZEB2*	AD	• Facial dysmorphism • Cardiovascular defects • Hypospadias • DD • Hypoplasia or agenesis of corpus callosum	• Ocular and gastrointestinal abnormalities • Short stature • Microcephaly • Pectus excavatum • Hypotonia

MOI = mode of inheritance
AD = autosomal dominant
XL = X-linked
DD = developmental delay
ID = intellectual disability
1. AD Opitz G/BBB syndrome can be caused either by a heterozygous pathogenic variant in *SPECC1L* [OMIM 145410] or by deletion on the chromosome region 22q11.2.
2. FG syndrome is genetically heterogeneous and includes several X-linked forms: FGS1, caused by pathogenic variants in *MED12* (see *MED12*-Related Disorders); FGS2 (OMIM 300321), associated with pathogenic variants in *FLNA* (locus Xq28); FGS3 (linked to Xp22.3) (OMIM 300406); FGS4 (OMIM 300422), caused by pathogenic variants in *CASK* (locus Xp11.4); FGS5 (linked to Xq22.3) (OMIM 300581).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked Opitz G/BBB syndrome, the following evaluations by a multidisciplinary team (including craniofacial surgeon, ophthalmologist, pediatrician, pediatric urologist, cardiologist, pulmonologist, speech pathologist, and clinical geneticist) are recommended if they have not already been performed:

- Past medical history and physical examination with attention to palate, heart, genitourinary system, and lower respiratory system
- Assessment of hypospadias by a urologist, including ultrasound examination to evaluate for renal/urinary tract abnormalities in males with severe hypospadias
- Laryngoscopy and chest x-ray in individuals who have choking with feeding, recurrent pneumonia, and/or aspiration
- Developmental evaluation
- Referral of individuals with cleft lip/palate to a craniofacial surgeon
- Echocardiogram
- Assessment of anal position and patency
- Complete ophthalmology evaluation including assessment of visual acuity, refractive error, and ocular alignment for possible strabismus

Treatment of Manifestations

Management of anomalies by a multidisciplinary team (including craniofacial surgeon, ophthalmologist, pediatrician, pediatric urologist, cardiologist, pulmonologist, speech pathologist, and clinical geneticist) to help assure coordination of care is indicated.

- Surgical intervention as needed for hypospadias

- Surgical treatment of medically significant laryngotracheoesophageal (LTE) abnormalities. Often tracheostomy is necessary initially to assure an adequate airway.
- Neuropsychological support. Many males with X-linked Opitz G/BBB syndrome require special educational programs.
- Surgical management for cleft lip/palate and other craniofacial anomalies; therapy for speech problems secondary to the cleft lip and palate
- Surgical repair as needed for heart defects
- Surgical intervention for imperforate anus
- Treatment as needed by an ophthalmologist

Prevention of Secondary Complications

Antireflux pharmacologic therapy minimizes the risk for aspiration until laryngeal competence is assured.

Surveillance

Regular follow up depending on the type of malformations present:

- Urology follow up for those with significant hypospadias and/or renal defects
- Gastroenterology, pulmonary, and/or surgical follow up for those with LTE defects
- Craniofacial team follow up for those with cleft lip/palate, including regular monitoring of hearing
- Cardiac follow up for those with cardiac defects
- Gastroenterology and/or surgical follow up for those with anal defects

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 www.ClinicalTrialsRegister.eu in Europe for 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

X-linked Opitz G/BBB syndrome (X-OS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the 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). Note: If a woman has more than one affected child and no other affected relatives

and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- 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* pathogenic variant. *De novo* pathogenic variants have been detected in several affected males [Pinson et al 2004, Ferrentino et al 2007, Fontanella et al 2008].

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

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be carriers and will usually manifest hypertelorism only.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in DNA extracted from the leukocytes of the mother, the risk to sibs is low but slightly greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Mildly affected males transmit the pathogenic variant to:

- All of their daughters, who will be heterozygotes (carriers) and will usually manifest hypertelorism only;
- None of their sons.

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

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 (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder will usually manifest hypertelorism only. (2) Identification of female heterozygotes requires either (a) prior identification of the pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

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 affected, are 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 Diagnosis

Once the *MID1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for X-OS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **Cleft Palate Foundation (CPF)**
  1504 East Franklin Street
  Suite 102
  Chapel Hill NC 27514-2820
  Phone: 800-242-5338 (toll-free); 919-933-9044
  Fax: 919-933-9604
  Email: info@cleftline.org
  www.cleftline.org
- **Face Equality International**
  United Kingdom
  Email: info@faceequalityinternational.org
  www.faceequalityinternational.org
- **Medline Plus**
  Hypospadias repair

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Opitz G/BBB Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MID1	Xp22.2	E3 ubiquitin-protein ligase Midline-1	MID1 @ LOVD	MID1	MID1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Opitz G/BBB Syndrome (View All in OMIM)

300000	OPITZ GBBB SYNDROME, TYPE I; GBBB1
300552	MIDLINE 1; MID1

Gene structure. *MID1* is composed of nine coding exons and variable and alternative 5' untranslated regions [Quaderi et al 1997, Gaudenz et al 1998, Perry et al 1998, Van den Veyver et al 1998, Cox et al 2000, Landry & Mager 2002]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, pathogenic variants in *MID1* have been found in approximately 85 individuals with X-linked Opitz G/BBB syndrome (X-OS) [Gaudenz et al 1998, Cox et al 2000, De Falco et al 2003, Winter et al 2003, Pinson et al 2004, So et al 2005, Mnayer et al 2006, Ferrentino et al 2007, Fontanella et al 2008, Hu et al

2012, Hüning et al 2013, Migliore et al 2013, Ji et al 2014, Li et al 2015]. Several pathogenic variants predicted to result in arginine to stop changes, including p.Arg277Ter, p.Arg368Ter and p.Arg495Ter, are recurrent variants [Cox et al 2000, Pinson et al 2004, Preiksaitiene et al 2015]. The other pathogenic variants are missense and nonsense variants, small deletions, or insertions located along the entire length of the gene – the majority in the most 3' portion of the gene.

MID1 whole-gene deletions as well as single-exon deletions and duplications have been reported [Winter et al 2003, Ferrentino et al 2007, Fontanella et al 2008, Hüning et al 2013, Migliore et al 2013].

Table 4. *MID1* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.829C>T	p.Arg227Ter	NM_000381.3 NP_000372.1
c.1102C>T	p.Arg368Ter	
c.1483C>T	p.Arg495Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *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. The normal gene product is E3 ubiquitin-protein ligase Midline-1, which is anchored to the microtubules [Cainarca et al 1999, Schweiger et al 1999, Cox et al 2000] and acts as an E3 ubiquitin ligase that regulates the degradation of phosphatase 2A [Liu et al 2001, Trockenbacher et al 2001, Short et al 2002]. The role of this protein function within the cell and during development is yet to be clarified.

Abnormal gene product. The missense and truncated forms lower their affinity for the microtubular apparatus. The pathogenic mechanism is likely to be caused by the loss of E3 ubiquitin-protein ligase Midline-1 function on the microtubules.

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Chapter Notes

Author Notes

Focus. Basic research on the molecular basis of X-linked Opitz syndrome, functional study of *MID1* and proteins belonging to the TRIM/RBCC family

Revision History

- 5 April 2018 (sw) Comprehensive update posted live
- 28 July 2011 (me) Comprehensive update posted live
- 20 June 2007 (cd) Revision: deletion/duplication analysis available clinically
- 18 January 2007 (me) Comprehensive update posted to live Web site
- 17 December 2004 (me) Review posted to live Web site
- 30 June 2004 (gm) Original submission

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