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MID1-Related Opitz G/BBB Syndrome

Synonyms: X-Linked Opitz Syndrome (XLOS), X-Linked Opitz G/BBB Syndrome

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Summary

Clinical characteristics

MID1-related Opitz G/BBB syndrome (*MID1*-OS) is 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 30% of affected males. Cleft lip and/or palate are present in approximately half of affected males. Other malformations (present in <50% of affected males) 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 *MID1*-OS is established in a male proband with suggestive findings and a hemizygous pathogenic variant in *MID1* identified by molecular genetic testing. Females with a heterozygous *MID1* pathogenic variant usually have isolated hypertelorism and only rarely present with other manifestations of *MID1*-OS.

Management

Treatment of manifestations: Management of anomalies by a multidisciplinary team; surgical treatment of cleft lip/palate and other craniofacial anomalies; standard treatments for hearing loss including PE tubes; speech therapy; standard dental treatments as needed for hypodontia; standard surgical management of hypospadias; surgical treatment for medically significant laryngotracheoesophageal abnormalities; anti-reflux therapy as needed; neuropsychological and educational support; surgical repair of congenital heart defects and imperforate anus; surgical treatment and/or refractive lenses as needed per ophthalmologist.

Surveillance: Follow up with craniofacial team for cleft lip/palate care; audiology evaluation annually or as needed; follow up with urologist as needed for those with significant hypospadias and/or other urinary tract

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defects; gastroenterology, pulmonology, and/or surgical team follow up for those with laryngotracheoesophageal defects; monitor developmental and educational needs at each visit; cardiology follow up per cardiologist; gastroenterology follow up as recommended for anal defects; ophthalmology evaluations as recommend by ophthalmologist; assess psychosocial and care coordination needs at each visit.

Genetic counseling

MID1-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 heterozygote. If the mother of the proband has an *MID1* 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 and will usually manifest hypertelorism only. Once the *MID1* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

Suggestive Findings

MID1-related Opitz G/BBB syndrome (*MID1*-OS) **should be suspected** in a male with the following clinical and imaging findings and family history.

Clinical findings

- Hypertelorism and/or telecanthus (present in virtually all affected individuals)
- Hypospadias
- Laryngotracheoesophageal abnormalities, primarily laryngeal cleft, resulting in swallowing difficulties and respiratory dysfunction
- Cleft lip and/or palate
- Intellectual disability and developmental delay
- Congenital heart defects (e.g., ventricular septal defect, atrial septal defect, persistent left superior vena cava, patent ductus arteriosus)
- Imperforate or ectopic anus

Imaging findings

- Urinary tract abnormalities including vesicoureteral reflux and hydronephrosis
- Midline defects of the brain including agenesis of the corpus callosum and cerebellar vermis agenesis or hypoplasia

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of *MID1*-OS **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *MID1* identified by molecular genetic testing (see Table 1).

Female proband. Females with a heterozygous *MID1* pathogenic (or likely pathogenic) variant usually have isolated hypertelorism and only rarely present with other manifestations of *MID1*-OS.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *MID1* variant of uncertain significance does not establish or rule out the diagnosis.

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). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *MID1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *MID1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of *MID1*-OS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *MID1*-Related Opitz G/BBB Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MID1	Sequence analysis [3]	90% [4]
	Gene-targeted deletion/duplication analysis [5]	10% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. 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

MID1-related Opitz G/BBB syndrome (*MID1*-OS) is characterized by facial anomalies, genitourinary abnormalities, laryngotracheoesophageal defects, and congenital heart defects. Developmental delay and intellectual disability are common. Clinical manifestations are most evident in affected males, although wide clinical variability has been described, even among members of the same family. To date, 90 individuals have been identified with a pathogenic variant in *MID1* and are reported together with their clinical synopsis [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, Maia et al 2017, Perea-Cabrera et al 2023].

Table 2. *MID1*-Related Opitz G/BBB Syndrome: Frequency of Select Features in Males

Feature	% of Males w/Feature
Hypertelorism	~100%
Hypospadias	90%
Laryngotracheoesophageal defects	70%
Cleft lip &/or palate	48%
Intellectual disability &/or developmental delay	30%
Congenital heart defects	24%
Anal abnormalities	22%
Brain abnormalities	19/41 [1]

Fontanella et al [2008], Li et al [2015], Maia et al [2017], Micale et al [2023], Perea-Cabrera et al [2023]
1. Includes males with *MID1*-related Opitz G/BBB syndrome who have undergone brain MRI examination

Affected Males

Facial appearance and head anomalies. The facial appearance of affected males is characterized by large fontanelle, prominent metopic suture, prominent forehead, widow's peak, hypertelorism (which can also be accompanied by telecanthus), a broad nasal bridge, anteverted nares, and low-set and malformed ears. Unilateral or bilateral cleft lip and/or palate is present in approximately half of affected males. Feeding issues and hearing impairment can be present due to cleft lip/palate. 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, Maia et al 2017].

Urogenital abnormalities. Hypospadias of varying severity is present in approximately 90% of males with *MID1*-OS 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, Maia et al 2017].

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

Neurologic findings. Almost one third of individuals with *MID1*-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 individuals, 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 about half of males with an *MID1* pathogenic variant who underwent MRI examination [Fontanella et al 2008].

Congenital heart disease. Approximately 24% of males with *MID1*-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, and total anomalous pulmonary venous connection [Perea-Cabrera et al 2023].

Anal abnormalities are present in 22% of males with *MID1*-OS (e.g., imperforate anus, ectopic anus) [Robin et al 1996, De Falco et al 2003, Pinson et al 2004, Fontanella et al 2008, Maia et al 2017, Perea-Cabrera et al 2023].

Ophthalmologic features. Refractive error and strabismus have been reported.

Heterozygous Females

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, Perea-Cabrera et al 2023].

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 [Maia et al 2017].

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 *MID1*-OS.

Nomenclature

The title of this *GeneReview*, *MID1*-related Opitz G/BBB syndrome, is based on the dyadic naming approach proposed by Biesecker et al [2021], in which mendelian disorders are designated by combining the mutated gene and resulting phenotype.

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 became 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, *MID1*-OS is distinct from autosomal dominant Opitz G/BBB syndrome.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *MID1*-Related Opitz G/BBB Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping w/*MID1*-OS	Distinguishing from *MID1*-OS
22q11.2 deletion	22q11.2 deletion syndrome [1]	AD	• Facial dysmorphism • Cleft lip/palate • Congenital heart defects • Laryngotracheoesophageal defects • DD • Genitourinary defects	• Skeletal anomalies • Autoimmune disorders • Hypotonia, polymicrogyria
CASK	*CASK*-related FG syndrome / XL ID ± nystagmus [2] (See *CASK* Disorders.)	XL	• Facial dysmorphism • Cryptorchidism • DD • Feeding problems	• Joint hyperlaxity • Short stature • Hypotonia
EFNB1	Craniofrontonasal dysplasia (OMIM 304110)	XL	• Facial dysmorphism • Cleft lip/palate • Hypospadias • DD • Hypoplasia or agenesis of corpus callosum	• Skeletal, chest, skin, nail, & hair defects • Short stature • Hypotonia

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping w/*MID1*-OS	Distinguishing from *MID1*-OS
MED12	*MED12*-related FG syndrome (See *MED12*-Related Disorders.)	XL	• Facial dysmorphism • Congenital heart defects • Cryptorchidism • DD/ID	• Congenital hypotonia w/joint hyperlaxity evolving into spasticity • Chronic constipation • Characteristic behavior (affable & eager to please)
SPECC1L	*SPECC1L* syndrome [3] (also referred to as AD Opitz G/BBB syndrome & Teebi hypertelorism syndrome 1 [OMIM 145420])	AD	• Facial dysmorphism • Cleft lip/palate • Congenital heart defects • DD/ID	• Short stature • Congenital diaphragmatic hernias • Bicornuate uterus • Absence of hypospadias
ZEB2	Mowat-Wilson syndrome	AD	• Facial dysmorphism • Cardiovascular defects • Hypospadias • DD • Hypoplasia or agenesis of corpus callosum	• Ocular & gastrointestinal abnormalities • Short stature • Pectus excavatum • Hypotonia

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. It is now recognized that 22q11.2 deletion syndrome encompasses the phenotypes previously described as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, some cases of autosomal dominant Opitz G/BBB syndrome, and Cayler cardiofacial syndrome (see 22q11.2 Deletion Syndrome).

2. An FG syndrome (FGS)-like phenotype has been suggested as a distinct *CASK*-related phenotype based on findings in affected males from two families (see *CASK* Disorders). However, with the exception of *MED12*-related FGS, FGS is not clearly defined, and *CASK*-related FGS is not discernible as a phenotype. Thus, it seems more appropriate to subsume the phenotype described in these families under X-linked intellectual disability with or without nystagmus.

3. Bhoj et al [2019]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MID1*-related Opitz G/BBB syndrome (*MID1*-OS), the evaluations summarized in Table 4 by a multidisciplinary team (including craniofacial surgeon, ophthalmologist, pediatrician, pediatric urologist, cardiologist, pulmonologist, speech-language pathologist, and clinical geneticist) are recommended if they have not already been performed.

Table 4. *MID1*-Related Opitz G/BBB Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
General	Past medical history & physical exam w/attention to palate, heart, genitourinary system, & lower respiratory system	
Cleft lip &/or palate	• Referral of persons w/cleft lip/palate to craniofacial surgeon • Assessment of feeding & speech • Dental assessment	
	Audiology eval in those at risk for hearing loss due to cleft lip/palate	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Urogenital abnormalities	Assessment of hypospadias by urologist, incl ultrasound exam to evaluate for urinary tract dysfunction in males w/severe hypospadias	
LTE defects	Laryngoscopy & chest x-ray in persons who have choking w/feeding, recurrent pneumonia, &/or aspiration	
Developmental delay	Developmental eval	
Congenital heart disease	Echocardiogram	
Anal abnormalities	Assessment of anal position & patency	
Ophthalmologic manifestations	Complete ophthalmology eval incl assessment of visual acuity, refractive error, & ocular alignment for possible strabismus	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *MID1*-OS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

LTE = laryngotracheoesophageal; *MID1*-OS = *MID1*-related Opitz G/BBB syndrome; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves management of anomalies by a multidisciplinary team (including craniofacial surgeon, ophthalmologist, pediatrician, pediatric urologist, cardiologist, pulmonologist, speech-language pathologist, and clinical geneticist) to help assure coordination of care (see Table 5).

Table 5. *MID1*-Related Opitz G/BBB Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cleft lip &/or palate	• Surgical mgmt for cleft lip/palate & other craniofacial anomalies • Standard treatments for hearing loss incl PE tubes for recurrent otitis • Speech therapy for speech problems secondary to cleft lip/palate • Standard dental treatments as needed for hypodontia	
Urogenital abnormalities	Surgical intervention as needed for hypospadias	
LTE defects	• Surgical treatment of medically significant LTE abnormalities • Anti-reflux pharmacologic therapy minimizes risk for aspiration until laryngeal competence is assured.	Often tracheostomy is necessary initially to assure an adequate airway.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Development	Neuropsychological & educational support	Many males w/*MID1*-OS require special educational programs.
Congenital heart disease	Surgical repair as needed for congenital heart defects	
Anal abnormalities	Surgical intervention for imperforate anus	
Ophthalmologic manifestations	Surgical treatment as needed by an ophthalmologist &/or refractive lenses	

LTE = laryngotracheoesophageal; PE = pressure equalization

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *MID1*-Related Opitz G/BBB Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cleft lip/palate	Craniofacial team follow up for those w/cleft lip/palate	Per craniofacial specialists
Hearing	Audiology eval	Annually or as needed
Urogenital abnormalities	Urology follow up for those w/significant hypospadias &/or other urinary tract abnormalities	Per urologist &/or nephrologist
LTE defects	Gastroenterology, pulmonology, &/or surgical team follow up for those w/LTE defects	As needed
Development	Monitoring of developmental progress & educational needs	At each visit
Congenital heart disease	Cardiac follow up for those w/cardiac defects	Per cardiologist
Anal abnormalities	Gastroenterology &/or surgical follow up for those w/anal defects	Per gastroenterologist or surgical team
Ophthalmologic manifestations	Ophthalmology assessment	Per ophthalmologist
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

LTE = laryngotracheoesophageal

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 information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The

following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

MID1-related Opitz G/BBB syndrome (*MID1*-OS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *MID1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *MID1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo MID1* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism. *De novo* pathogenic variants have been detected in several affected males [Pinson et al 2004, Ferrentino et al 2007, Fontanella et al 2008, Maia et al 2017].
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

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 *MID1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. (Note: Wide variability in clinical manifestations has been described among affected members of the same family.)
  - Females who inherit the pathogenic variant will be heterozygotes and will usually manifest hypertelorism only (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the *MID1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but slightly greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Mildly affected males transmit the *MID1* pathogenic variant to:

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

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having an *MID1* pathogenic variant.

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

Heterozygote Detection

Heterozygote testing for at-risk female relatives requires prior identification of the *MID1* pathogenic variant in the family.

Note: Females who are heterozygous for this X-linked disorder will usually manifest hypertelorism only.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygotes, or are at risk of being heterozygotes.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MID1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Opitz G/BBB syndrome
- **American Cleft Palate-Craniofacial Association**
  Phone: 919-933-9044
  acpa-cpf.org
- **Face Equality International**
  United Kingdom
  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. MID1-Related 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 MID1-Related Opitz G/BBB Syndrome (View All in OMIM)

300000	OPITZ GBBB SYNDROME; GBBB
300552	MIDLINE 1; MID1

Molecular Pathogenesis

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]. *MID1* encodes 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 fully clarified, and possible roles in common non-genetic diseases have also been reported; the findings available are reviewed in Baldini et al [2020].

The pathogenic variants are missense and nonsense variants, small deletions, intronic splicing variants, 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, Micale et al 2023].

Mechanism of disease causation. 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.

Chapter Notes

Author Notes

Germana Meroni, PhD, focuses on basic research on the molecular basis of X-linked Opitz syndrome, including functional studies of *MID1* and proteins belonging to the TRIM/RBCC family.

Contact Dr Meroni to inquire about review of *MID1* variants of uncertain significance.

Acknowledgments

This chapter is dedicated to the memory of Dr John M Opitz, whose passion and dedication for children and families affected by *MID1*-related Opitz G/BBB syndrome has inspired the work of many geneticists, including Dr Germana Meroni.

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