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Weill-Marchesani Syndrome

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Summary

Clinical characteristics

Weill-Marchesani syndrome (WMS) is a connective tissue disorder characterized by abnormalities of the lens of the eye, short stature, brachydactyly, joint stiffness, and cardiovascular defects. The ocular problems, typically recognized in childhood, include microspherophakia (small spherical lens), myopia secondary to the abnormal shape of the lens, ectopia lentis (abnormal position of the lens), and glaucoma, which can lead to blindness. Height of adult males is 142-169 cm; height of adult females is 130-157 cm. Autosomal recessive WMS cannot be distinguished from autosomal dominant WMS by clinical findings alone.

Diagnosis/testing

The diagnosis WMS is established in a proband with characteristic clinical features. Identification of biallelic pathogenic variants in *ADAMTS10*, *ADAMTS17*, or *LTBP2* or of a heterozygous pathogenic variant in *FBN1* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Early detection and removal of an ectopic lens to decrease the possibility of pupillary block and glaucoma. Surgical management of glaucoma can include peripheral iridectomy to prevent or relieve pupillary block and trabeculectomy in advanced chronic angle closure glaucoma; medical treatment of glaucoma is difficult because of paradoxic response to miotics and mydriatics. Consider physical therapy for joint issues. Careful evaluation prior to anesthesia because of stiff joints, poorly aligned teeth, and maxillary hypoplasia. Treatment of cardiac anomalies per cardiologist.

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Surveillance: Annual ophthalmology examinations for early detection and removal of an ectopic lens can help decrease the possibility of pupillary block and glaucoma. Annual assessment of height and joint range of motion. Regular cardiac follow up with echocardiogram and electrocardiography.

Agents/circumstances to avoid: Ophthalmic miotics and mydriatics because they can induce pupillary block; activities that increase risk of eye injury.

Genetic counseling

Autosomal dominant inheritance: FBN1-related WMS is inherited in an autosomal dominant manner. Most affected individuals have an affected parent. The proportion of individuals with autosomal dominant WMS caused by a *de novo* pathogenic variant is unknown. Each child of an individual with autosomal dominant WMS has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive inheritance: ADAMTS10-, *ADAMTS17*-, and *LTPBP2*-related WMS are inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one pathogenic variant based on family history). If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing of at-risk relatives is possible if the WMS-related pathogenic variants have been identified in the family.

Prenatal and preimplantation genetic testing are possible once the WMS-related pathogenic variant(s) have been identified in an affected family member.

Diagnosis

No consensus clinical diagnostic criteria for Weill-Marchesani syndrome (WMS) have been published.

Suggestive Findings

WMS **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Eye anomalies including microspherophakia and ectopia lentis
- Short stature
- Brachydactyly
- Progressive joint stiffness
- Thickened skin
- Pseudomuscular build
- Cardiovascular defects (e.g., patent ductus arteriosus, pulmonary stenosis, thoracic aortic aneurysm, cervical artery dissection, prolonged QTc)

Radiographic features

- Shortened long tubular bones
- Delayed bone age
- Broad proximal phalanges

Establishing the Diagnosis

The diagnosis of WMS can be **established** in a proband with characteristic Suggestive Findings and/or by identification of biallelic pathogenic (or likely pathogenic) variants in *ADAMTS10, ADAMTS17*, or *LTBP2* or of

a heterozygous pathogenic (or likely pathogenic) variant in *FBN1* by molecular genetic testing if clinical features are inconclusive (see Table 1).

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) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial 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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with short stature, ocular anomalies, and/or cardiovascular anomalies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Serial single-gene testing. In individuals suspected of having **autosomal dominant WMS**, perform sequence analysis of *FBN1* first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no pathogenic variant is detected, the next step is to perform *FBN1* deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *ADAMTS10*, *ADAMTS17*, *FBN1*, *LTBP2*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. Of note, given the rarity of WMS, some panels may not include these genes. (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 phenotype is indistinguishable from many other inherited disorders characterized by connective tissue abnormalities, **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is an option. **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 Weill-Marchesani Syndrome (WMS)

Gene [1, 2]	Proportion of WMS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ADAMTS10	<10 probands reported [6, 7]	7 probands reported [6]	See footnote 7.
ADAMTS17	6 probands reported [8]	6 probands reported [8]	None reported
FBN1	9 probands reported [9, 10]	6 probands reported [9]	3 probands reported [10]
LTBP2	1 family reported [11]	1 reported [11]	None reported

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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.
6. Dagoneau et al [2004], Morales et al [2009], Kutz et al [2011], Pimienta et al [2013], Li et al [2014]
7. A whole-gene deletion has been reported as a founder variant in the Amish population [Strauss & Puffenberger 2009].
8. Morales et al [2009], Shah et al [2014], Yi et al [2019], Karoulias et al [2020]
9. Faivre et al [2003b], De Backer et al [2007], Sengle et al [2012], Cecchi et al [2013], Lerner-Ellis et al [2014], Wang et al [2014], Newell et al [2017], Groth et al [2017]
10. De Backer et al [2007], Groth et al [2017]
11. Haji-Seyed-Javadi et al [2012]

Clinical Characteristics

Clinical Description

Weill-Marchesani syndrome (WMS) is a connective tissue disorder that usually presents in childhood with short stature and/or ocular problems. The autosomal recessive and autosomal dominant forms of WMS share clinical manifestations in the following systems [Faivre et al 2003a].

Eyes. The mean age of recognition of an ocular problem is 7.5 years. Microspherophakia (small spherical lens) is the most important manifestation of WMS. Microspherophakia results in lenticular myopia (i.e., myopia primarily resulting from abnormal shape of the lens), ectopia lentis (abnormal position of the lens), and glaucoma (elevation of the intraocular pressure).

- Lenticular myopia is usually the first ophthalmologic finding.
- Ectopia lentis usually results in downward displacement of the lens.
- Glaucoma is the most serious complication because it can lead to blindness. In most individuals glaucoma results from pupillary block resulting from forward movement of the lens or dislocation of the lens into the anterior chamber. Increased central corneal thickness has been recognized as a pathologic feature of WMS that may lead to overestimation of intraocular pressure by applanation tonometers [Razeghinejad & Safavian 2006].

Loss of vision occurs earlier in WMS and is more severe than in other lens dislocation syndromes. In some individuals, lens dislocation and pupillary block appear after blunt trauma to the eye weakens the zonular fibers.

Presenile vitreous liquefaction has been described in a large family with autosomal dominant WMS [Evereklioglu et al 1999].

Retinal vascular tortuosity in the absence of congenital heart disease has been described in one affected individual [Gallagher et al 2011].

Retinitis pigmentosa has been reported in an affected female age 14 years [Jethani et al 2007].

Advanced glaucoma and corneal endothelial dysfunction have recently been reported in an affected female age 30 years [Guo et al 2015].

Growth. Short stature is reported in all affected individuals. The growth rate falls below the standard growth curve in the first years of life. An adult male with WMS is expected to achieve a height of 142-169 cm and an adult female a height of 130-157 cm. No information is available about growth hormone efficacy in individuals with WMS.

Musculoskeletal. The skeletal features include brachydactyly and short metacarpals. The metacarpophalangeal and interphalangeal joints may be prominent. Joint stiffness of the digits, wrists, shoulders, hips, knees, and ankles may be progressive.

Heart abnormalities are frequently seen and include patent ductus arteriosus, pulmonary stenosis, aortic stenosis, and mitral valve prolapse [Haji-Seyed-Javadi et al 2012]. Thoracic aortic aneurysm and cervical artery dissection was recently reported in a three-generation family with *FBN1*-related WMS [Cecchi et al 2013, Newell et al 2017]. Systematic electrocardiogram revealed prolonged QT in individuals with WMS [Kojuri et al 2007].

Skin. Taut skin with thickened skin folds is seen.

Intellectual disability has been reported in 11%-17% of individuals and is always mild.

Phenotype Correlations by Gene

Table 2. Weill-Marchesani Syndrome Phenotype Correlations by Gene

Gene	Phenotypic Feature				
	Eye anomalies	Short stature	Brachydactyly	Joint stiffness	Other
ADAMTS10	+	+	+	+	Heart defects, mild ID
ADAMTS17	+	+	±	+	Heart defects
FBN1	+	+	+	+	Heart defects
LTBP2	+	+	+	+	Heart defects

ID = intellectual disability

Genotype-Phenotype Correlations

Given the limited number of individuals with WMS in the literature, no genotype-phenotype correlations for *ADAMTS10*, *ADAMTS17*, *FBN1*, or *LTBP2* have been identified.

Penetrance

The penetrance in those with autosomal recessive and dominant WMS is thought to be 100%. Intrafamilial and interfamilial variable expressivity is observed in WMS.

Nomenclature

Other terms previously used to refer to Weill-Marchesani syndrome:

- Spherophakia-brachymorphia syndrome
- Mesodermal dysmorphodystrophy, congenital

Prevalence

WMS is described as being very rare. Prevalence has been estimated at 1:100,000 population.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ADAMTS10* or *ADAMTS17*.

Other phenotypes associated with pathogenic variants in *FBN1* and *LTBP2* are summarized in Tables 3a and 3b, respectively. Disorders included in Table 3a have overlapping phenotypic features with Weill-Marchesani syndrome and should be considered in the differential diagnosis.

Table 3a. Allelic Disorders to Consider in the Differential Diagnosis of Weill-Marchesani Syndrome

Gene	Disorder	MOI	Reference
FBN1	Acromicric dysplasia	AD	See Table 5. Other Acromelic Dysplasias to Consider in the Differential Diagnosis of Weill-Marchesani Syndrome.
	Geleophysic dysplasia	AR AD	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Table 3b. Other Allelic Disorders

Gene	Disorder
FBN1	Isolated ectopia lentis (OMIM 129600)
	Marfan syndrome
	MASS syndrome (OMIM 604308)
	Stiff skin syndrome (OMIM 184900)
	Thoracic aortic aneurysms & aortic dissections
LTBP2	Congenital glaucoma (OMIM 613086)
	Isolated microspherophakia [Ben Yahia et al 2009, Kumar et al 2010]
	Microspherophakia &/or megalocornea w/ectopia lentis w/ or w/o secondary glaucoma (OMIM 251750)

MASS = *m*itral valve prolapse, *a*ortic root dilatation, *s*kin striae, *s*keletal features

Differential Diagnosis

Ectopia Lentis

Ectopia lentis may occur in the conditions listed in Table 4. All, however, are clinically distinct from Weill-Marchesani syndrome (WMS).

Table 4. Other Genes and Disorders Associated with Ectopia Lentis

Gene(s)	Disorder	MOI	Clinically Distinctive Features
AASS	Hyperlysinemia type I (OMIM 238700)	AR	Mild ID
ADAMTSL4	Ectopia lentis et pupilae (OMIM 225200)	AR	Ectopic pupil, flat-appearing iris, cataracts

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinically Distinctive Features
CBS	Classic homocystinuria [1]	AR	• DD/ID • Tall & slender w/asthenic habitus ("marfanoid") • Biochemical features [1] • Thromboembolism
FBN1	Marfan syndrome	AD	• Skeletal manifestations: bone overgrowth & joint laxity; extremities disproportionately long for trunk size (dolichostenomelia) • Cardiovascular manifestations: dilatation of aorta at the level of sinuses of Valsalva, predisposition for aortic tear & rupture, mitral valve prolapse w/or w/o regurgitation, tricuspid valve prolapse, & enlargement of proximal pulmonary artery
SUOX	Isolated sulfite oxidase deficiency [2]	AR	Severe neurologic symptoms: untreatable seizures, opisthotonus, attenuated growth of the brain, & ID [2]

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

1. Homocystinuria 1 is a metabolic disorder caused by cystathionine β-synthase deficiency. The cardinal biochemical features of homocystinuria are markedly increased concentrations of plasma homocystine, total homocysteine, and methionine; increased concentration of urine homocystine; and reduced cystathionine β-synthase (CBS) enzyme activity.

2. Sulfite oxidase deficiency results from an isolated deficiency in the enzyme sulfite oxidase (which is responsible for the oxidation of sulfite to sulfate) or from molybdenum cofactor deficiency.

Acromelic Dysplasia

The acromelic dysplasia group includes four rare disorders: Weill-Marchesani syndrome, geleophysic dysplasia, acromicric dysplasia, and Myhre syndrome. The clinical overlap between the four disorders is striking. Overlapping and distinguishing clinical features are summarized in Table 5.

Table 5. Other Acromelic Dysplasias to Consider in the Differential Diagnosis of Weill-Marchesani Syndrome (WMS)

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/WMS	Distinguishing from WMS
ADAMTSL2 *FBN1* *LTBP3*	Geleophysic dysplasia	AD AR	Short stature; brachydactyly; stiff joints; delayed bone age; cone-shaped phalangeal epiphyses; thickened skin; heart disease	Hepatomegaly; no lens abnormalities
FBN1 *LTBP3* [1]	Acromicric dysplasia (OMIM 102370)	AD		No lens abnormalities
SMAD4	Myhre syndrome	AD [2]	IUGR; short stature; brachydactyly; joint stiffness; thickened skin; heart disease	Hearing loss; characteristic facial features; variable degree of cognitive impairment; no lens abnormalities

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; IUGR = intrauterine growth restriction; MOI = mode of inheritance

1. McInerney-Leo et al [2016]

2. All probands with Myhre syndrome reported to date have had a *de novo SMAD4* pathogenic variant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Weill-Marchesani syndrome (WMS), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Weill-Marchesani Syndrome

System/Concern	Evaluation	Comment
Ophthalmology	Complete ophthalmologic exam	
Musculoskeletal	• Growth assessment • Assessment of joint range of motion by orthopedist/PT	
Cardiology	• Echocardiography • Electrocardiogram	To evaluate for: • Patent ductus arteriosus, valvular stenosis, &/or arterial narrowing • Prolonged QT
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of WMS to facilitate medical & personal decision making

MOI = mode of inheritance; PT = physical therapist
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Ocular complications. It is not possible to generalize the management of the ocular complications of WMS.

- The medical treatment of glaucoma is difficult because of paradoxic response to miotics and mydriatics.
- A peripheral iridectomy should be performed to prevent or relieve pupillary block [Chang et al 2002, Ritch et al 2003].
- Lens extraction and/or trabeculectomy may be necessary in some persons with advanced chronic angle closure glaucoma [Harasymowycz & Wilson 2004].
- Individuals with WMS were recently reported to have increased central corneal thickness, which needs to be considered in the diagnosis and follow up of glaucoma because increased central corneal thickness may lead to overestimation of intraocular pressure by applanation tonometers [Razeghinejad & Safavian 2006].

Table 7. Treatment of Manifestations in Individuals with Weill-Marchesani Syndrome (WMS)

Manifestation/Concern	Treatment	Considerations/Other
Ocular complications	See above.	
Joint stiffness	Consider PT to maintain joint mobility.	No study has been done on efficacy of passive range-of-motion exercises to help maintain flexibility.
Airway management during anesthesia	Careful eval prior to anesthesia	Anesthesia can be difficult in persons w/WMS because of stiff joints, poorly aligned teeth, & maxillary hypoplasia [Dal et al 2003, Karabiyik 2003, Riad et al 2006].
Cardiac anomalies	Treatment per cardiologist	

PT = physical therapy

Surveillance

Table 8. Recommended Surveillance for Individuals with Weill-Marchesani Syndrome

System/Concern	Evaluation	Frequency
Ophthalmology	Ophthalmology exams for early detection & removal of ectopic lens can help ↓ possibility of pupillary block & glaucoma.	Annually
Growth	Assessment of height	
Joint stiffness	Assessment of joint range of motion by orthopedist/physiotherapist	
Cardiac anomalies	• Echocardiogram for evidence of valvular stenosis, arterial narrowing, &/or aneurysm • Electrocardiography to evaluate QT interval	Periodic if normal; otherwise, specific follow up according to cardiac defect

Agents/Circumstances to Avoid

Use of ophthalmic miotics and mydriatics should be avoided as they can induce pupillary block.

Potential increased risk of WMS-related ocular complications associated with contact sports should be discussed with the ophthalmologist.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing for the pathogenic variant(s) in the family in order to identify as early as possible those who would benefit from ophthalmology and cardiology evaluations. Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Ophthalmologic examination for detection of possible microspherophakia and detailed examination by a clinical geneticist if the pathogenic variant in the family is not known.

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

Weill-Marchesani syndrome (WMS) caused by pathogenic variants in *FBN1* is inherited in an autosomal dominant manner.

WMS caused by pathogenic variants *ADAMTS10*, *ADAMTS17*, or *LTPBP2* is inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant WMS have an affected parent.
- A proband with autosomal dominant WMS may have the disorder as the result of a *de novo FBN1* pathogenic variant. The proportion of individuals with autosomal dominant WMS caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member, molecular genetic testing (if a molecular diagnosis has been established in the proband) is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling. Recommendations may also include ophthalmologic examination for detection of possible microspherophakia and detailed examination by a clinical geneticist.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

      * A parent with somatic and germline mosaicism for a *FBN1* pathogenic variant may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *FBN1* pathogenic variant identified in the proband, the risk to the sibs is 50%. Intrafamilial variable expressivity is observed in WMS.
- If the proband has a known WMS-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *FBN1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for WMS because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant WMS has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *ADAMTS10, ADAMTS17,* or *LTPBP2* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents to confirm that both parents are heterozygous for an *ADAMTS10*, *ADAMTS17*, or *LTPBP2* pathogenic variant and to allow reliable recurrence risk assessment. (In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband or (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ADAMTS10*, *ADAMTS17*, or *LTPBP2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial variable expressivity is observed in WMS.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive WMS are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a WMS-related pathogenic variant.

Carrier Detection

Carrier testing of at-risk relatives is possible if the WMS-related pathogenic variants have been identified in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the WMS-related pathogenic variant(s) have 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.

- **National Library of Medicine Genetics Home Reference**
  Weill-Marchesani syndrome
- **Children's Glaucoma Foundation**
  Phone: 617-227-3011
  Email: info@childrensglaucomafoundation.org
  childrensglaucoma.org
- **Human Growth Foundation**
  hgfound.org
- **MAGIC Foundation**
  Phone: 630-836-8200
  Email: contactus@magicfoundation.org
  magicfoundation.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision

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. Weill-Marchesani Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ADAMTS10	19p13.2	A disintegrin and metalloproteinase with thrombospondin motifs 10	ADAMTS10 @ LOVD	ADAMTS10	ADAMTS10
ADAMTS17	15q26.3	A disintegrin and metalloproteinase with thrombospondin motifs 17	ADAMTS17 database	ADAMTS17	ADAMTS17
FBN1	15q21.1	Fibrillin-1	FBN1 @ LOVD	FBN1	FBN1
LTBP2	14q24.3	Latent-transforming growth factor beta-binding protein 2	LTBP2 database	LTBP2	LTBP2

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 Weill-Marchesani Syndrome (View All in OMIM)

134797	FIBRILLIN 1; FBN1
277600	WEILL-MARCHESANI SYNDROME 1; WMS1
602091	LATENT TRANSFORMING GROWTH FACTOR-BETA-BINDING PROTEIN 2; LTBP2
607511	A DISINTEGRIN-LIKE AND METALLOPROTEINASE WITH THROMBOSPONDIN TYPE 1 MOTIF, 17; ADAMTS17
608328	WEILL-MARCHESANI SYNDROME 2; WMS2
608990	A DISINTEGRIN-LIKE AND METALLOPROTEINASE WITH THROMBOSPONDIN TYPE 1 MOTIF, 10; ADAMTS10
613195	WEILL-MARCHESANI SYNDROME 4; WMS4
614819	WEILL-MARCHESANI SYNDROME 3; WMS3

Molecular Pathogenesis

Weill-Marchesani syndrome (WMS) is a genetic disorder of the connective tissue caused by pathogenic variants in four genes, *ADAMTS10*, *ADAMTS17*, *LTBP2*, and *FBN1*, which encode extracellular matrix components.

ADAMS10 and *ADAMTS17* belong to the *ADAMTS (*disintegrin-like and metalloprotease with thrombospondin type 1 motif) gene superfamily which codes for proteases. These zinc metalloendopeptidases have diverse roles in the formation, remodeling, and destruction of the extracellular matrix [Yi et al 2019].

A direct interaction between the protein products encoded by *ADAMTS10* and *FBN1* has been demonstrated; the ADAMTS10 protein promotes fibrillin-1 deposition in the extracellular matrix of cultured fibroblasts [Kutz et al 2011].

Latent transforming growth factor beta-binding protein 2 (LTBP2) is an extracellular matrix protein that associates with fibrillin-1 containing microfibrils. *LTBP2* pathogenic variants are responsible for disruptions of the microfibrillar network in the extracellular matrix in fibroblasts of individuals with WMS [Haji-Seyed-Javadi et al 2012].

Mechanism of disease causation. The precise mechanism of WMS-related pathogenic variants remains unclear.

Chapter Notes

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