



## ADAMTSL4-Related Eye Disorders

Eyvind Rødahl, MD, PhD,<sup>1</sup> Anne Elisabeth Christensen Mellgren, MD, PhD,<sup>1</sup> Nils-Erik Boonstra, MD,<sup>2</sup> and Per Morten Knappskog, PhD<sup>3</sup>

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### Summary

#### Clinical characteristics

The spectrum of *ADAMTSL4*-related eye disorders is a continuum that includes the phenotypes known as "autosomal recessive isolated ectopia lentis" and "ectopia lentis et pupillae" as well as more minor eye anomalies with no displacement of the pupil and very mild displacement of the lens. Typical eye findings are dislocation of the lens, congenital abnormalities of the iris, refractive errors that may lead to amblyopia, and early-onset cataract. Increased intraocular pressure and retinal detachment may occur on occasion. Eye findings can vary within a family and between the eyes in an individual. In general, no additional systemic manifestations are observed, although skeletal features have been reported in a few affected individuals.

#### Diagnosis/testing

The diagnosis is established in individuals with characteristic eye findings by the identification of biallelic pathogenic (or likely pathogenic) variants in *ADAMTSL4* by molecular genetic testing.

#### Management

*Treatment of manifestations:* In children, the main objective is to prevent amblyopia by early correction of refractive errors and patching. Surgery should be considered in individuals with cataracts, those at risk for complications caused by the dislocated lens, those in whom patching does not result in improvement of visual acuity, those in whom the lens edge is in the middle of the pupil, and those with insufficient correction of refractive errors, in particular large degrees of astigmatism. While lensectomy with anterior vitrectomy and correction of the aphakia with contact lenses or secondary intraocular lens (IOL) replacement has been the usual procedure in the past, capsule-sparing lens surgery has recently been introduced. Sphincterotomy can benefit individuals with small and highly displaced pupils. Increased intraocular pressure can in most cases be

**Author Affiliations:** 1 Department of Clinical Medicine, University of Bergen; Department of Ophthalmology, Haukeland University Hospital, Bergen, Norway; Email: [eyvind.rodahl@helse-bergen.no](mailto:eyvind.rodahl@helse-bergen.no); Email: [anne.christensen@uib.no](mailto:anne.christensen@uib.no). 2 Department of Ophthalmology, Haukeland University Hospital, Bergen, Norway; Email: [nils-erik.boonstra@helse-bergen.no](mailto:nils-erik.boonstra@helse-bergen.no). 3 Department of Medical Genetics, Haukeland University Hospital; Department of Clinical Science, University of Bergen, Bergen, Norway; Email: [per.morten.knappskog@helse-bergen.no](mailto:per.morten.knappskog@helse-bergen.no).

controlled by topical anti-glaucoma medication. Retinal detachment is treated in the usual manner by vitrectomy and scleral buckling if necessary.

*Surveillance:* Assessment of visual acuity, refractive error, and intraocular pressure one to three times per year; adults who are stable may be examined annually, whereas children require more frequent examinations. Ultrasonography may be necessary to evaluate for retinal detachment if the view of the fundus is limited.

*Agents/circumstances to avoid:* Care during contact sports to avoid trauma to the head. Avoid boxing and martial arts.

*Evaluation of relatives at risk:* Sibs of a proband should undergo complete ophthalmologic evaluation (determination of visual acuity, measurement of intraocular pressure, slit lamp examination, and ophthalmoscopy) to allow for early diagnosis and treatment of findings, primarily to prevent amblyopia. If the pathogenic variants in a family are known, molecular genetic testing is likely to be more helpful in clarifying the genetic status of at-risk sibs given the wide variability even within the same family.

## Genetic counseling

*ADAMTSL4*-related eye disorders are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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 for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

## GeneReview Scope

*ADAMTSL4*-Related Eye Disorders: Included Phenotypes <sup>1</sup>

- Autosomal recessive isolated ectopia lentis
- Ectopia lentis et pupillae

1. For other genetic causes of these phenotypes see Differential Diagnosis.

## Diagnosis

The spectrum of *ADAMTSL4*-related eye disorders is a continuum that includes the phenotypes known as autosomal recessive isolated ectopia lentis and ectopia lentis et pupillae as well as more minor eye anomalies with no displacement of the pupil and very mild displacement of the lens. Variability in the eye findings is observed among affected individuals in a family and between the eyes of the same individual. No formal diagnostic criteria have been published.

## Suggestive Findings

*ADAMTSL4*-related eye disorders **should be suspected** in individuals with the following characteristics:

- Mild-to-severe dislocation of the lens due to loss of zonular fibers without any preceding trauma. The lens may be displaced in any direction. Spherophakia, lens coloboma, and iridodonesis may be present.
- Mild-to-severe displacement of the pupil; in some instances the pupils are normal. If the pupil is displaced, the lens is usually displaced in the opposite direction.
- Enlarged iris processes; seen in most affected individuals, causing an anomalous iridocorneal angle
- A deep anterior chamber and a thin and flat iris with loss of iris crypts accompanied by iris transillumination; seen in individuals with prominent displacement of the pupil
- Fibrosis of iris tissue surrounding the pupil resulting in poor dilation of the pupil in response to mydriatics

- Presence of a pupillary membrane, with small strands extending from the pupillary margin visible after dilation of the pupil. A fibrous membrane, visible on ultrasound biomicroscopy, may cover the posterior part of the iris.
- Family history consistent with autosomal recessive inheritance

## Establishing the Diagnosis

The diagnosis of an *ADAMTSL4*-related eye disorder is **established** in a proband with characteristic eye findings by the identification of biallelic pathogenic (or likely pathogenic) variants in *ADAMTSL4* on molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

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 an *ADAMTSL4*-related eye disorder 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 with a phenotype indistinguishable from many other inherited disorders with ectopia lentis and/or pupillary displacement or those in whom the diagnosis of an *ADAMTSL4*-related eye disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the phenotypic findings suggest the diagnosis of an *ADAMTSL4*-related eye disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ADAMTSL4* 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 only one or no pathogenic variant is found gene-targeted deletion/duplication analysis can be considered; however, to date no large deletions or complex rearrangements involving *ADAMTSL4* have been reported.
- **A multigene panel** that includes *ADAMTSL4* 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*. (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 ectopia lentis and/or pupillary displacement or if the diagnosis of an *ADAMTSL4*-related eye disorder 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 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 *ADAMTSL4*-Related Eye Disorders

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
<i>ADAMTSL4</i>	Sequence analysis <sup>3</sup>	100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	None reported <sup>4</sup>

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 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. Overwater et al [2017]

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.

## Clinical Characteristics

### Clinical Description

The spectrum of *ADAMTSL4*-related eye disorders is a continuum that includes the phenotypes known as autosomal recessive isolated ectopia lentis and ectopia lentis et pupillae as well as more minor eye anomalies with no displacement of the pupil and very mild displacement of the lens. Variability in the eye findings described in detail in Diagnosis is observed among affected individuals in a family and even between eyes in the same individual.

**Presentation.** The diagnosis of ectopia lentis is usually made in early childhood although dislocation of the lens may be present at birth [Neuhann et al 2011]. When ectopia lentis is accompanied by severe ectopia pupillae, the diagnosis is usually made at birth; in mild cases, the findings may not be recognized until adulthood. The clinical presentation in *ADAMTSL4*-related eye disorders is considered to be more severe than that seen in individuals with other nonsyndromic forms of ectopia lentis [Chandra et al 2012].

**Refractive errors** are common:

- Hyperopia (+5 D to +15 D) occurs when the lens is dislocated out of the visual axis resulting in a functionally aphakic eye.
- Myopia (-5 D to >-15 D) may result from increased axial growth of the eye, or because of abnormalities like spherophakia and lens coloboma.
- Various degrees of astigmatism, sometimes quite large, are frequently observed.

In children, uncorrected refractive errors and anisometropia (unequal refractive errors between the two eyes) may lead to amblyopia. One study found that the risk for amblyopia was highest when the lens was still covering the visual axis and the edge of the lens was within 0.3-2.3 mm of the center of the pupil [Romano et al 2002].

**Cataract** can be seen at an early age. In the study by Christensen et al [2010], all affected individuals older than age 45 years had undergone cataract surgery.

**Elevated intraocular pressure (IOP)** is seen in up to 20%-25% of affected individuals [Christensen et al 2010, Neuhann et al 2011]. In the event of anterior subluxation of the lens, an acute rise in intraocular pressure may occur. Of note, the central corneal thickness can be increased (median value 589  $\mu\text{m}$ ; range 528-630  $\mu\text{m}$ ) [Christensen et al 2010], which may explain, to some extent, why some individuals have moderately elevated intraocular pressure, but few have glaucomatous damage of the optic nerve head.

**Retinal detachment** occurs more frequently than in the general population; in some individuals retinal detachment as well as elevated IOP could be the consequence of lensectomy or cataract surgery [Christensen et al 2010, Neuhann et al 2015, Overwater et al 2017].

**Progression** of the lens displacement and development of cataract may occur over time, whereas the pupillary displacement is fairly stable.

**Visual acuity** varies from light perception to 20/20 depending on the degree of amblyopia, the presence of cataract, or sequelae after retinal detachment or glaucoma. Surprisingly, some individuals with highly displaced pupils may have normal visual acuity.

**Nonocular findings.** Individuals with *ADAMTSL4*-related eye disorders have, in general, no additional systemic manifestations although there have been some reports of skeletal features including craniosynostosis, *pes planus*, *pectus carinatum*, scoliosis, and/or joint laxity in a few affected individuals [Christensen et al 2010, Chandra et al 2013a, Overwater et al 2017].

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been noted.

- The phenotype may vary significantly from one individual to another within a family.
- The phenotype may vary significantly between eyes in the same individual.
- The same pathogenic variant can be associated with ectopia lentis and ectopia lentis et pupillae.

## Prevalence

In studies of individuals with nonsyndromic ectopia lentis, the proportion of those having a pathogenic variant in *ADAMTSL4* ranges from 0% in a group of Chinese individuals to 50% in several groups of European individuals [Aragon-Martin et al 2010, Chandra et al 2012, Li et al 2014, Overwater et al 2017, van Bysterveldt et al 2017].

Pathogenic variants frequently associated with *ADAMTSL4*-related eye disorders vary across populations. The *ADAMTSL4* c.767\_786del pathogenic variant is common across Europe and probably represents a founder variant. In western Norway, three of 190 blood donors were heterozygous for this variant, suggesting that the frequency of homozygous individuals in this population is around 1:16,000 (with wide confidence intervals) [Christensen et al 2010].

In a German study, two of 360 ethnically matched anonymous individuals were heterozygous for this pathogenic variant [Neuhann et al 2011].

In Polynesians (Maori) the c.2237G>A (p.Arg746His) variant is common with an observed frequency in carriers of 1:132 [van Bysterveldt et al 2017]. In Bukharian Jews originating from Kazakhstan and Tajikistan, the most common variant is c.2594G>A (p.Arg865His) (reported as c.2663G>A [p.Arg888His]) with a carrier frequency of 1:48 predicting a frequency of homozygous individuals around 1:9,000 [Reinstein et al 2016].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *ADAMTSL4*.

## Differential Diagnosis

**Table 2.** Disorders with Ectopia Lentis and/or Iris Anomalies to Consider in the Differential Diagnosis of *ADAMTSL4*-Related Eye Disorders

Disorder	Gene(s)	MOI	Distinguishing Clinical Features of Disorder
Ectopia lentis (OMIM 129600)	<i>FBN1</i> <sup>1</sup>	AD	May incl the systemic features of <a href="#">Marfan syndrome</a>
Homocystinuria caused by cystathionine beta-synthase deficiency	<i>CBS</i>	AR	<ul style="list-style-type: none"> <li>• Tall, thin stature</li> <li>• High-arched feet</li> <li>• Chest anomalies</li> <li>• Intellectual disability</li> <li>• Seizures</li> <li>• Arterial atheroma formation</li> </ul>
Isolated sulfite oxidase deficiency	<i>SUOX</i>	AR	<ul style="list-style-type: none"> <li>• Seizures</li> <li>• Ataxia</li> <li>• Dystonia</li> <li>• Choreoathetotic movements</li> </ul>
Weill-Marchesani syndrome (WMS)	<i>ADAMTS10</i> <i>FBN1</i> <i>LTPBP2</i>	AD <sup>2</sup> AR <sup>2</sup>	<ul style="list-style-type: none"> <li>• Proportionate short stature</li> <li>• Brachydactyly</li> <li>• Joint stiffness</li> </ul>
WMS-like syndrome (OMIM 613195)	<i>ADAMTS17</i>	AR	Brachydactyly
MSPKA (OMIM 251750)	<i>LTPBP2</i>	AR	<ul style="list-style-type: none"> <li>• Megalocornea</li> <li>• Glaucoma</li> <li>• Microspherophakia</li> <li>• Axial myopia</li> <li>• Marfanoid features</li> </ul>
Aniridia	<i>PAX6</i>	AD	<ul style="list-style-type: none"> <li>• Iris hypoplasia</li> <li>• Foveal dysplasia</li> <li>• Optic nerve hypoplasia</li> <li>• Nystagmus</li> </ul>
Axenfeld-Rieger syndrome type 1 (OMIM 180500)	<i>PITX2</i>	AD	<ul style="list-style-type: none"> <li>• Embryotoxon posterior</li> <li>• Iridocorneal adhesions</li> <li>• Iris anomalies</li> </ul>
Iridocorneal endothelial syndrome <sup>3</sup>	NA <sup>4</sup>	NA <sup>4</sup>	<ul style="list-style-type: none"> <li>• Corneal edema</li> <li>• Corneal endothelial irregularities</li> <li>• Polycoria</li> <li>• Iris nevus</li> </ul>
Iris coloboma	>30	AD AR XL	Variable <sup>5</sup>

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Distinguishing Clinical Features of Disorder
Anterior segment dysgeneses (OMIM PS107250)	<i>CPAMD8</i> <i>CYP1B1</i> <i>FOXC1</i> <i>FOXE3</i> <i>PAX6</i> <i>PITX2</i> <i>PITX3</i> <i>PXDN</i>	AD AR	<ul style="list-style-type: none"> <li>• Microphthalmia</li> <li>• Embryotoxon posterior</li> <li>• Corneal opacities</li> <li>• Sclerocornea</li> <li>• Iris hypoplasia</li> <li>• Iridocorneal adhesions</li> <li>• Glaucoma</li> </ul>
Posterior polymorphous corneal dystrophy (OMIM PS122000)	<i>COL8A2</i> <i>OVOL2</i> <i>ZEB1</i>	AD	<ul style="list-style-type: none"> <li>• Posterior corneal opacities</li> <li>• Iridocorneal adhesions</li> <li>• Glaucoma</li> </ul>

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; MSPKA = microspherophakia and/or megalocornea, with ectopia lentis and with or without secondary glaucoma; XL= X-linked

1. Ectopia lentis most frequently occurs as an autosomal dominant disorder in association with pathogenic variants in *FBN1* (OMIM 134797) that may (OMIM 154700) or may not (OMIM 129600) be accompanied by the systemic features of [Marfan syndrome](#).
2. Pathogenic variants in *ADAMTSL10* are known to cause autosomal recessive WMS. Biallelic pathogenic variants in *LTPBP2* have been reported in one family with autosomal recessive inheritance [Haji-Seyed-Javadi et al 2012]. A heterozygous pathogenic variant in *FBN1* has been identified in one family with autosomal dominant WMS [Faivre et al 2003].
3. Silva et al [2018]
4. This is an acquired disorder and rarely seen in children.
5. There are many genes associated with iris coloboma, and accompanying features can be quite complex.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs of an individual diagnosed with an *ADAMTSL4*-related eye disorder, routine ophthalmologic examination that includes the following is recommended if it has not already been completed:

- Determination of visual acuity and refractive error
- Measurement of intraocular pressure

Note: Affected individuals may have increased central corneal thickness that could explain, to some extent, why some individuals have moderately elevated intraocular pressure, but few have glaucomatous damage of the optic nerve head.

- Slit lamp examination
- Dilated fundus examination

The following may also provide important information:

- Orthoptic examination, particularly in children
- Measurement of axial length
- Anterior segment examination with optical coherence tomography and in selected individuals ultrasound biomicroscopy
- Corneal topography including measurement of corneal diameter and central corneal thickness
- Gonioscopy

Consultation with a clinical geneticist and/or genetic counselor is also recommended.

## Treatment of Manifestations

**Refractive errors.** In children, the main objective is to prevent amblyopia by early correction of refractive errors. Patching is necessary when correction of the refractive error is insufficient in restoring vision.

**Lens abnormality.** Surgery should be considered in individuals with cataracts, those at risk for complications caused by the dislocated lens (e.g., endocorneal contact, pupillary block), those in whom patching does not result in improvement of visual acuity, those in whom the lens edge is in the middle of the pupil, and those with insufficient correction of refractive errors, in particular large degrees of astigmatism [Anteby et al 2003, Wu-Chen et al 2005]. Surgery is rarely needed in children. Most individuals undergoing surgery are adolescents or young adults. Following lens removal, improvement of visual acuity has been observed even in individuals older than age seven years [Speedwell & Russell-Eggitt 1995].

In the past, lensectomy with anterior vitrectomy and correction of the aphakia with contact lenses or secondary intraocular lens (IOL) replacement has been the usual procedure. More recently, capsule-sparing lens surgery has been introduced. "Bag in the lens" (BIL) IOL implantation combined with capsular rings or lasso suture is an efficient procedure for the treatment of lens dislocation [Boonstra 2019]. Should BIL fail, the authors suggest removing the capsule and implanting a three-piece IOL by the technique described by Yamane et al [2017], at least in individuals from age four to five years and older.

Surgical treatment must be weighed against loss of accommodation and the risk for secondary glaucoma and retinal detachment. Aphakia correction in children imposes challenges with respect to the use of contact lenses and IOL implantation, particularly in individuals with unilateral involvement. Special care should be taken in the youngest children (age <2 years) as the growth of the eye will give a myopic shift. All surgical procedures should therefore be planned individually by an experienced ophthalmic surgeon [Hoffman et al 2013].

**Pupil displacement.** Sphincterotomy (widening of the pupil by incision of the iris at the pupillary margin) can benefit individuals with small and highly displaced pupils.

**Increased intraocular pressure** can in most cases be controlled by topical anti-glaucoma medication.

**Retinal detachment.** It is not clear if pathogenic variants in *ADAMTSL4* increase the risk for retinal detachment. However, after lensectomy or cataract surgery, retinal detachment may occur. If typical signs (e.g., floaters, lightning, a diminished visual field) appear, evaluation by an ophthalmologist should be sought as soon as possible. Treatment of retinal detachment is by standard techniques using vitrectomy and scleral buckling if necessary. It is important to examine the fellow eye for retinal degeneration.

## Surveillance

Assess visual acuity, refractive error, and intraocular pressure one to three times per year: adults who are stable may be examined yearly, whereas children require more frequent examinations. Ultrasonography may be necessary to evaluate for retinal detachment if the view of the fundus is limited.

## Agents/Circumstances to Avoid

Care must be taken during contact sports to avoid blunt trauma to the eye and head. Affected individuals should not participate in activities like boxing or martial arts.

## Evaluation of Relatives at Risk

Sibs of a proband with an *ADAMTSL4*-related eye disorder should undergo complete ophthalmologic evaluation (determination of visual acuity, measurement of intraocular pressure, slit lamp examination, and ophthalmoscopy) to allow for early diagnosis and treatment of findings, primarily to prevent amblyopia.



If the pathogenic variants in a family are known, molecular genetic testing is likely to be more helpful than clinical examination in clarifying the genetic status of at-risk sibs, given the wide phenotypic variability even within the same family.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://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, 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

ADAMTSL4-related eye disorders are inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one ADAMTSL4 pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with an ADAMTSL4-related eye disorder are obligate heterozygotes (carriers) for a pathogenic variant in ADAMTSL4.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a ADAMTSL4 pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the ADAMTSL4 pathogenic variants 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, clarification of carrier status, 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.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *ADAMTSL4* pathogenic variants 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**  
[Isolated ectopia lentis](#)

## 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.** ADAMTSL4-Related Eye Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>ADAMTSL4</i>	1q21.2	ADAMTS-like protein 4	ADAMTSL4 @ LOVD	ADAMTSL4	ADAMTSL4

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 ADAMTSL4-Related Eye Disorders ([View All in OMIM](#))

225100	ECTOPIA LENTIS 2, ISOLATED, AUTOSOMAL RECESSIVE; ECTOL2
225200	ECTOPIA LENTIS ET PUPILLAE
610113	ADAMTS-LIKE 4; ADAMTSL4

**Gene structure.** *ADAMTSL4* has alternate transcriptional splice variants, encoding different isoforms.

[NM\\_019032.4](#) is the longer transcript that encodes the longer protein isoform. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** Several pathogenic *ADAMTSL4* variants have been reported (summarized in Overwater et al [2017]). Some occur more frequently in certain populations and are most likely founder variants, like the c.767\_786del variant in individuals of western European descent [Aragon-Martin et al 2010, Christensen et al 2010, Neuhaus et al 2011, Chandra et al 2012, Neuhaus et al 2015], the c.2237G>A (p.Arg746His) variant in Polynesians (Maori) [van Bysterveldt et al 2017], and the c.2594G>A (p.Arg865His; reported as c.2663G>A; p.Arg888His) variant in Bukharian Jews (originating from Kazakhstan and Tajikistan) [Reinstein et al 2016].

**Table 3.** ADAMTSL4 Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.767_786del	p.Gln256ProfsTer38	NM_019032.4 NP_061905.2
c.2237G>A	p.Arg746His	
c.2594G>A	p.Arg865His	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

**Normal gene product.** ADAMTSL proteins lack the metalloproteinase domain found in ADAMTS proteins (ADAM [*a disintegrin and metalloproteinase*] with *thrombospondin* domains) and are therefore thought to be catalytically inactive. ADAMTSL4 contains the following:

- Seven predicted thrombospondin type 1 repeats. Proteins with this domain have diverse biologic functions including cell adhesion, angiogenesis, and patterning of the central nervous system. Within each repeat are several protein binding sites that may anchor the protein to components of the extracellular matrix.
- Cysteine-rich module
- ADAMTS-spacer 1 domain
- PLAC (*protease and lacunin*) domain

Several splice variants encoding different isoforms have been described [Apte 2009]. The longest isoform is predicted to consist of 1,097 amino acids.

ADAMTSL4 is a secreted glycoprotein that is both N- and O-glycosylated [Gabriel et al 2012]. In cell culture ADAMTSL4 colocalizes with fibrillin-1 and the presence of ADAMTSL4 enhances the deposition of fibrillin-1. ADAMTSL4 is expressed in many tissues including the eye [Buchner & Meisler 2003, Gabriel et al 2012]. In the eye, it is found in the iris, ciliary body, and retinal pigment epithelium [Chandra et al 2013b]. In mice, *in situ* hybridization revealed a strong expression at the lens equator suggesting a role for *Adamtsl4* in anchoring the zonular fibers to the lens [Collin et al 2015].

**Abnormal gene product.** Most pathogenic ADAMTSL4 variants introduce a premature stop codon [Overwater et al 2017], while some cause single amino acid substitutions in critical parts of the protein. For example, the p.Arg746His substitution affects the first thrombospondin 1 repeat domain.

*Adamtsl4*-negative mice show zonular fiber detachment and dedifferentiation of the retinal pigment epithelium. Disruption of zonular fibers is a key event in the pathogenesis of ectopia lentis and could be explained by impaired assembly of fibrillin-1 into microfibrils and most importantly deficient attachment of microfibrils to the lens caused by reduced function of ADAMTSL4.

## Chapter Notes

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### Author History

Helge Boman, MD, PhD; University of Bergen (2012-2020)

Nils-Erik Boonstra, MD (2020-present)

Torunn Fiskerstrand, MD, PhD; University of Bergen (2012-2020)

Per Morten Knappskog, PhD (2012-present)

Anne Elisabeth Christensen Mellgren, MD, PhD (2012-present)

Eyvind Rødahl, MD, PhD (2012-present)

## Revision History

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