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**NLM Citation:** Kloeckener-Gruissem B, Amstutz C. *VCAN*-Related Vitreoretinopathy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2009 Feb 3 [Updated 2016 Jan 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# *VCAN*-Related Vitreoretinopathy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Created: February 3, 2009; Updated: January 7, 2016.

## Summary

**NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.**

### Clinical characteristics

*VCAN*-related vitreoretinopathy, which includes Wagner syndrome and erosive vitreoretinopathy (ERVR), is characterized by "optically empty vitreous" on slit-lamp examination and avascular vitreous strands and veils, mild or occasionally moderate to severe myopia, presenile cataract, night blindness of variable degree associated with progressive chorioretinal atrophy, retinal traction and retinal detachment in the advanced stages of disease, and reduced visual acuity. Optic nerve inversion as well as uveitis has also been described. Systemic abnormalities are not observed. The first signs usually become apparent during early adolescence, but onset can be as early as age two years.

### Diagnosis/testing

The diagnosis of *VCAN*-related vitreoretinopathy is established in a proband with characteristic ocular findings and a family history consistent with autosomal dominant inheritance. Identification of a heterozygous *VCAN* pathogenic variant establishes the diagnosis if clinical features are inconclusive.

### Management

*Treatment of manifestations:* Refractive error is corrected by spectacles or contact lenses; visually disabling cataract is treated by cataract surgery, preferably by an experienced surgeon. Posterior capsule opacification is treated with YAG laser capsulotomy. Retinal breaks without retinal detachment are treated with laser retinopexy or cryocoagulation. Vitreoretinal surgery is indicated for retinal detachment, vitreoretinal traction involving the macula, or epiretinal membranes involving the macula.

*Surveillance:* Annual ophthalmologic examination by a vitreoretinal specialist.

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*Evaluation of relatives at risk:* For the purpose of early diagnosis and treatment of ophthalmologic complications in at-risk relatives: molecular genetic testing if the pathogenic variant has been identified in the family; otherwise, ophthalmologic evaluation.

## Genetic counseling

*VCAN*-related vitreoretinopathy is inherited in an autosomal dominant manner. Most individuals diagnosed with *VCAN*-related vitreoretinopathy have an affected parent. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant. Prenatal testing is possible for families in which the pathogenic variant is known.

# *GeneReview* Scope

| *VCAN*-Related Vitreoretinopathy: Included Phenotypes [1] |
|---|
| • Wagner vitreoretinal degeneration (Wagner syndrome)<br>• Erosive vitreoretinopathy (ERVR) |

For synonyms and outdated names see Nomenclature.
*1.* For other genetic causes of these phenotypes see Differential Diagnosis.

# Diagnosis

## Suggestive Findings

*VCAN*-related vitreoretinopathy **should be suspected** in individuals with the following characteristic features:

- "Optically empty vitreous" on slit-lamp examination and avascular vitreous strands and veils
- Mild or occasionally moderate to severe myopia
- Presenile cataract
- Night blindness of variable degree associated with progressive chorioretinal atrophy
- Retinal traction and detachment at advanced stages of the disease
- Reduced visual acuity resulting from the above manifestations
- Uveitis
- Absence of systemic abnormalities

## Establishing the Diagnosis

The diagnosis of *VCAN*-related vitreoretinopathy **is established** in a proband with the above clinical findings and a family history consistent with autosomal dominant inheritance. Not every clinical finding listed above is observed in every affected individual. The hallmark, however, is the empty vitreous. Establishing the diagnosis may be more difficult in a simplex case (i.e., a single occurrence in a family). Identification of a heterozygous pathogenic (or likely pathogenic) variant in *VCAN* by molecular genetic testing (see Table 1) establishes the diagnosis if clinical features are inconclusive.

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 *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *VCAN* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** All *VCAN* pathogenic variants associated with Wagner syndrome and erosive vitreoretinopathy found to date have been in the splice acceptor or splice donor site of introns 7 and 8; sequence analysis of this DNA region is recommended as a first step. If targeted testing is not available, sequence analysis of *VCAN* should be done.
- **A multigene panel** that includes *VCAN* and other genes of interest (see Differential Diagnosis) may also be considered. Note (1): The genes included and sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) The presence of characteristic connective tissue abnormalities in the proband or relatives could prompt genetic testing for Stickler syndrome rather than or in addition to sequence analysis of *VCAN*.

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

**Table 1.** Molecular Genetic Testing Used in *VCAN*-Related Vitreoretinopathy

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Identified by Method |
|---|---|---|
| *VCAN* | Sequence analysis [3] | 18/20 families with *VCAN*-related vitreoretinopathy [4] |
| | Gene-targeted deletion/duplication analysis [5] | Unknown [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.* In 18 of 20 families with *VCAN*-related vitreoretinopathy, sequence analysis of the entire *VCAN* coding region and flanking introns identified pathogenic variants; in two families no pathogenic variant was found (see references in Table 2).
*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.* No data on detection rate of gene-targeted deletion/duplication analysis are available.

# Clinical Characteristics

## Clinical Description

*VCAN*-related vitreoretinopathy comprises the phenotypic continuum of Wagner vitreoretinal degeneration (Wagner syndrome) and erosive vitreoretinopathy (ERVR).

**Vitreoretinal degeneration.** The hallmark of *VCAN*-related vitreoretinopathy is progressive degenerative changes of the vitreous (syneresis) and the vitreoretinal interface beginning at a young age. Syneresis can lead to massive liquefaction of the vitreous such that on slit-lamp examination the vitreous cavity appears optically empty ("empty vitreous") with pockets of liquefied vitreous that are usually lined by avascular strands and veils. Preretinal vitreous membranes that span the whole equator of the eye are characteristic. Ocular changes show considerable inter- and intrafamilial variability.

The first signs usually become apparent during early adolescence, but onset can be as early as age two years [Miyamoto et al 2005].

No sex-specific difference in the occurrence or frequency of any particular ocular features has been observed.

The vitreous degeneration, which is assumed to be the primary pathology, leads to a number of secondary changes, including presenile cataract, degeneration and atrophy of the retina and the underlying retinal pigment epithelium (RPE) and choroid, and retinal detachment [Wagner 1938, Jansen 1962, Graemiger et al 1995, Zech et al 1999, Miyamoto et al 2005, Mukhopadhyay et al 2006, Meredith et al 2007].

## Common Ocular Features (≤60% of Affected Individuals)

**Myopic refractive error** (nearsightedness) results from axial myopia (a developmental mismatch of the refractive power and length of the globe) and/or index myopia (a change in the refractive index of the progressively cataractous lens). Axial myopia is common, although severity varies. In the family reported by Wagner, most affected members had mild myopia and only a few had moderate to severe myopia. In contrast, in the Dutch family all members had high myopia with astigmatism [Jansen 1962].

**Presenile cataract** (progressive loss of transparency of the ocular lens) is a common finding and a common cause of decline in visual acuity over time. The types of cataract vary. Small spherical opacities and posterior subcapsular cataract affected 43% of eyes in the original family reported by Wagner [Graemiger et al 1995]. In the Dutch families, cataract types included moderate cortical cataract, anterior and posterior cortical cataract, and posterior subcapsular cataract [Mukhopadhyay et al 2006]. Nuclear cataract without any posterior subcapsular opacity was described in a British family [Meredith et al 2007].

In a Japanese family, approximately 50% of affected individuals underwent cataract surgery; the oldest was age 35 years [Miyamoto et al 2005]. In a French family, cataract affected 55% of individuals [Zech et al 1999]. Of note, even after cataract extraction and correction of the refractive error, visual acuity was not normal, typically ranging from 6/12 (20/40) to 6/24 (20/80).

**Nonspecific reactive changes of the retinal pigment epithelium and overlying retina** (pigment condensation, vascular sheathing, pigmented lattice degeneration, and later chorioretinal atrophy in the retinal periphery) occur. Affected individuals may experience nyctalopia (night blindness) and visual field constriction that are not as severe as those seen in retinitis pigmentosa. Nyctalopia may or may not progress. In some individuals the chorioretinal atrophy is so severe that it resembles choroideremia. Diffuse retinal pigmentary changes and patchy chorioretinal atrophy are observed in some (but not all) family members affected by Wagner syndrome [Meredith et al 2007, Ronan et al 2009].

The full-field electroretinogram (ERG) becomes attenuated. Typically both the amplitudes of the a-waves (response of the photoreceptor layer) and the b-waves (response of the bipolar cell layer) are reduced. The rod and cone systems (as measured by the scotopic and photopic response, respectively) are affected to varying degrees but in a family-specific manner, as demonstrated by the Swiss family originally reported by Wagner, the Japanese family, and the British family [Graemiger et al 1995, Miyamoto et al 2005, Meredith et al 2007].

**Abnormal retinal vessels or poor vascularization of the peripheral retina** were found in approximately 50% of individuals from the family reported by Wagner [Graemiger et al 1995], but only in a few individuals of the Dutch families [Mukhopadhyay et al 2006].

**Retinal detachment** was initially found to be associated with increasing age; however, a later report indicated that detachments can occur earlier (average age 9.5 years) [Ronan et al 2009]. Caused by shrinkage of the preretinal membranes and the vitreous strands and veils, retinal detachment is either tractional or rhegmatogenous.

- Tractional retinal detachment is caused by tangential shortening of the adhering membranes. The detached retina is rigid; successful surgical repair requires meticulous removal of the membranes and vitreoretinal adhesions and, most often, extensive retinotomies to relieve the traction. Tractional retinal detachment is not a particularly common feature of Wagner syndrome.

- Rhegmatogenous retinal detachment is caused by retinal breaks associated with the preretinal membranes. Liquefied vitreous fluid enters the potential subretinal space through one or more retinal tears caused by shrinking membranes. The retinal detachment is typically bullous; surgical repair primarily relies on closure of all retinal breaks. Of note, in a considerable number of young individuals, rhegmatogenous retinal detachment associated with hereditary vitreoretinal degeneration presents with only minor changes of the vitreous. Consequently, large retinal tears in young persons should raise the suspicion of a hereditary disease, and should prompt examination of other family members and eventually molecular genetic analysis.

In the original publication by Wagner the incidence of retinal detachment at age 20 years was one in four, whereas in the Dutch pedigrees published by Jansen bilateral retinal detachment was a frequent finding at a young age. Of note, follow-up publications of the original Wagner pedigree reported an incidence of retinal detachment of greater than one in two. Of the few retinal detachments described in the Swiss family reported originally by Wagner and in the Dutch families reported by Jansen, some were peripheral tractional [Graemiger et al 1995, Mukhopadhyay et al 2006]. Further tractional effects were observed as situs inversus [Wagner 1938]. Recently, affected individuals were described with inversion of the papilla as a possible consequence of tractional forces [Ronan et al 2009].

In the Japanese family reported by Miyamoto et al [2005], most of the retinal detachments were rhegmatogenous. No retinal detachments were observed in the only two affected individuals reported in a British family [Meredith et al 2007].

## Occasional Ocular Features

The following features have been reported rarely. Some may not be part of *VCAN*-related vitreoretinopathy but rather occur coincidentally.

**Spherophakia**, a spherical deformation of the ocular lens, has been observed sporadically in persons with *VCAN*-related vitreoretinopathy [Graemiger et al 1995].

**Cataract** can induce a change of the refractive index of the lens nucleus, further attenuating the myopic refractive error (index myopia).

**Posterior vitreous detachment** (PVD), detachment of the posterior vitreous membrane from the retinal surface, is caused by shrinkage of the vitreous body and the pathologic vitreoretinal interface. In contrast to the usual age-related PVD, the PVD in *VCAN*-related vitreoretinopathy initially affects the peripheral rather than the central posterior vitreous. None of the individuals from the original family described by Wagner or the French family showed PVD [Graemiger et al 1995, Zech et al 1999].

**Ectopic fovea**, manifesting as an increased angle kappa (the angle between the visual axis and the pupillary axis), has occasionally been reported [Graemiger et al 1995, Miyamoto et al 2005, Meredith et al 2007].

**Phthisis bulbi** (painful shrinking of the ocular globe as a result of loss of intraocular pressure) can occur and may require enucleation of the eye. Retinal detachment that has not been repaired successfully and retinal detachment associated with proliferative retinal vitreoretinopathy (PVR) are risk factors for phthisis bulbi. The decrease in intraocular pressure is caused by decreased aqueous production by the ciliary body epithelium, which becomes compromised by the pathologic vitreoretinal membranes because of the primary vitreal changes, the PVR, or both.

**Synchysis scintillans** (bilateral accumulation of cholesterol crystals in the vitreous, which may or may not be associated with recurrent vitreous hemorrhage), may or may not occur with increased frequency in *VCAN*-related vitreoretinopathy, as it was only observed in a few older affected individuals [Graemiger et al 1995, Zech et al 1999].

**Optic atrophy** was found in only a few of the older individuals from the original Wagner family. These individuals had advanced chorioretinal atrophy, suggesting that optic atrophy is secondary to the massive loss in retinal ganglion cells [Graemiger et al 1995].

**Glaucoma** may be an occasional feature of Wagner syndrome, or a sequela of the disease such as aphakia glaucoma or rubeotic glaucoma. In the original pedigree, ten individuals out of the sixty family members exhibited a dysgenetic chamber angle [Graemiger et al 1995]; one individual had congenital glaucoma. Three individuals with congenital glaucoma were reported by Jewsbury et al [2014].

**Exudative vitreoretinopathy** with vascular abnormalities has been reported in one French family [Brézin et al 2011]; in fact, familial exudative vitreoretinopathy (FEVR) was the initial diagnosis suspected in this family.

**Uveitis** is a rare clinical feature of *VCAN*-related vitreoretinopathy that has come to attention only recently. Uveitis was reported in a French [Brézin et al 2011] and a British [Meredith et al 2007] family as spontaneous anterior uveitis, and otherwise unexplained severe and prolonged intraocular inflammation after uneventful cataract surgery, respectively [Rothschild et al 2011, Rothschild et al 2013b]. Given versican's role in inflammation and cancer that was increasingly elucidated during the last decade, the occurrence of uveitis in individuals with *VCAN*-related vitreoretinopathy is likely related to the causative genetic defect [Du et al 2013, Wight et al 2014].

**Systemic findings.** No systemic abnormalities associated with *VCAN*-related vitreoretinopathy have been reported to date, and consequently *VCAN*-related vitreoretinopathy is considered an isolated vitreoretinal degeneration.

## Genotype-Phenotype Correlations

Because of the highly variable frequency of findings and the low number of pathogenic variants identified to date, no definite genotype-phenotype correlations have been established.

## Penetrance

Penetrance appears to be complete. Within families reported to date, no unaffected individuals had a *VCAN* pathogenic variant.

## Nomenclature

Some authors have referred to Stickler syndrome associated with pathogenic variants in exon 2 of *COL2A1* as Wagner syndrome type II. The *VCAN*-related phenotype has been referred to as vitreoretinochoroidopathy (VRCP) Wagner syndrome type I [Gupta et al 2002] or hyaloideoretinal degeneration of Wagner.

## Prevalence

Wagner syndrome is a very rare disorder. After the first Swiss pedigree reported by Wagner [1938], several additional families (some of them very large) have been reported. Including families with ERVR, not more than 50 families or simplex cases of *VCAN*-related vitreoretinopathy have been reported.

Wagner syndrome has been reported in families of various ethnic backgrounds including northern European, Japanese, and Chinese.

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *VCAN*.

# Differential Diagnosis

**Syndromes with overlapping features.** A review by Edwards [2008] summarizes the clinical features of inherited vitreoretinopathies and points out the importance of consulting an expert ophthalmologist in diagnostic assessment of the disease.

## Autosomal Dominant Vitreoretinopathies

**Snowflake vitreoretinal degeneration (SVD)** (OMIM 193230). SVD is caused by pathogenic variants in *KCNJ13*.

- Both SVD and *VCAN*-related vitreoretinopathy exhibit vitreous abnormalities including fibrillar condensation, gel liquefaction, and marked thickening of the cortical vitreous.
- In SVD, however, membranous degeneration of the vitreous with avascular strands and veils is not observed. Retinal defects start in the superficial retinal layers, whereas in *VCAN*-related vitreoretinopathy they start in the deep retinal layers and choroid; retinal detachment is uncommon; and the retinal crystalline snowflake-like deposits that give the disease its name are common.
- Stickler syndrome, or hereditary arthroophthalmopathy, is a connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Pierre Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Variable phenotypic expression of Stickler syndrome occurs both within and among families; interfamilial variability is in part explained by locus and allelic heterogeneity. Stickler syndrome caused by mutation of *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner.
- Retinal detachment is much more common in Stickler syndrome (50%) than in *VCAN*-related vitreoretinopathy (15%).
- Abnormal dark adaptation associated with alterations in the electroretinogram (ERG) that is common in *VCAN*-related vitreoretinopathy has not been described in Stickler syndrome.
- Type 1 Stickler syndrome (in which individuals have the membranous type of vitreous abnormality) is caused by pathogenic variants in *COL2A1* encoding collagen alpha-1(II) chain. Certain pathogenic variants in *COL2A1* cause a predominantly ocular or nonsyndromic phenotype which can be readily distinguished from Wagner syndrome by the specific vitreous anomaly associated with type 1 Stickler syndrome. However, some authors have referred to this form of Stickler syndrome as Wagner syndrome type II [Gupta et al 2002].

**Autosomal dominant vitreoretinochoroidopathy (ADVIRC)** (OMIM 193220). Pathogenic variants in *BEST1*, the gene encoding bestrophin-1, are causative. Only a few families with vitreoretinochoroidopathy (VRCP) have been described. High myopia and retinal detachment do not appear to be part of VRCP [Oh & Vallar 2006]. Affected individuals show the following findings that seem to progress more slowly than those of *VCAN*-related vitreoretinopathy:

- Fibrillar condensation of the vitreous, but not optically empty vitreous
- Chorioretinal hyperpigmentation with peripheral pigmentary clumping
- Macular atrophy
- Breakdown of the blood retinal barrier (observed in one family)
- Normal full-field (Ganzfeld) ERG but altered multifocal ERG pattern
- Cataract

**Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV)** (OMIM 193235). Pathogenic variants in *CAPN5* are causative [Mahajan et al 2012]. Bennett et al [1990] reported a six-generation family with an autosomal dominant vitreoretinopathy in which the prevailing clinical features were severe anterior and

posterior segment inflammation, neovascular proliferations and related complications (in particular tractional retinal detachment and neovascular glaucoma), and a selective loss of the b-wave amplitude on the ERG early in the disease.

### Autosomal Recessive Vitreoretinopathies

**Goldmann-Favre syndrome (included in enhanced S-cone syndrome)** (OMIM 268100). Pathogenic variants in *NR2E3* (photoreceptor-specific nuclear receptor) have been identified in Goldmann-Favre syndrome, enhanced S-cone syndrome (ESCS), and clumped pigmentary retinal degeneration [Haider et al 2000]. These clinical entities are usually associated with night blindness and visual field constriction. Electroretinography characteristically reveals a severe reduction in rod function and a relatively enhanced function of the short-wavelength-sensitive cones.

- The classic Goldmann-Favre phenotype includes progressive vitreous changes (vitreous liquefaction and fibrillar strands and veils); night blindness and severe reduction in the ERG in early childhood; chorioretinal atrophy and pigmentary retinal degeneration later in the disease course resulting in marked visual field loss; retinoschisis in the periphery, macula, or both; presenile cataract; and a hyperopic rather than myopic refractive error.
- Although ESCS lacks the marked vitreous changes typical of the Goldmann-Favre phenotype, vitreous cells are a very common feature, and more prominent vitreous changes including vitreous opacities, haze, and veils can occur. Peripheral retinoschisis has been observed in ESCS, and foveal schisis, eventually associated with cystoid changes, may even be a common feature. The fundus appearance varies, and features are overlapping with clumped pigmentary retinal degeneration, in which the retinal pigmentary changes are the most prominent feature of the phenotype [Audo et al 2008].

**Knobloch syndrome** (OMIM 267750). Knobloch syndrome is a syndromic vitreoretinopathy in which ocular changes similar to those of *VCAN*-related vitreoretinopathy are associated with occipital encephalocele. Pathogenic variants in *COL18A1* (encoding collagen, type XVIII, alpha 1) are causative [Menzel et al 2004, Keren et al 2007].

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *VCAN*-related vitreoretinopathy, the following evaluations are recommended:

- Baseline ophthalmologic examination including best corrected visual acuity, assessment of intraocular pressure, slit-lamp examination of the anterior segment, and biomicroscopy and indirect ophthalmoscopy of the posterior segment
- Visual field examination
- Photographic fundus documentation
- Optical coherence tomography (OCT), if available. While not mandatory, OCT scan is useful to assess the vitreoretinal interface, quantify atrophic changes of the central retina, and evaluate for cystoid macular edema.
- Electroretinogram
- Orthoptic assessment
- Consultation with a clinical geneticist and/or genetic counselor

### Treatment of Manifestations

**Refractive error** is corrected by spectacles or contact lenses.

**Visually disabling cataract** is treated by cataract surgery. Phacoemulsification and implantation of an intraocular lens in the capsular bag has become the widely adopted standard procedure; however, as emphasized by Edwards, cataract surgery in individuals with vitreoretinopathy and possibly preceding vitrectomy can be difficult and should be performed by an experienced surgeon [Miyamoto et al 2005, Edwards 2008].

**Posterior capsule opacification** after cataract surgery is treated with YAG laser capsulotomy.

**Retinal breaks** are treated with laser retinopexy or cryocoagulation if no retinal detachment is present.

**Vitreoretinal surgery** is indicated for retinal detachment, vitreoretinal traction involving the macula, or epiretinal membranes involving the macula.

## Surveillance

Annual ophthalmologic examination by a vitreoretinal specialist is indicated.

## Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives of an affected individual in order to reduce morbidity by early diagnosis and treatment of ophthalmologic complications. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known.
- Ophthalmologic exam 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 access to 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

*VCAN*-related vitreoretinopathy is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- Most individuals diagnosed with *VCAN*-related vitreoretinopathy have an affected parent.
- A proband with *VCAN*-related vitreoretinopathy may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is not known.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include ophthalmologic evaluation and/or molecular genetic testing of both parents.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).
- The family history of some individuals diagnosed with *VCAN*-related vitreoretinopathy may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., ophthalmologic exam and/or molecular genetic testing) have been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

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

- If a parent of the proband has *VCAN*-related vitreoretinopathy, the risk to the sibs is 50%.
- If the *VCAN* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

**Offspring of a proband.** Each child of an individual with *VCAN*-related vitreoretinopathy has a 50% chance of inheriting the pathogenic variant.

**Other family members of a proband.** The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

## 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.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

**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 or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *VCAN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *VCAN*-related vitreoretinopathy are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider 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 Eye Institute**
  **Phone:** 301-496-5248
  **Email:** 2020@nei.nih.gov
  Low Vision
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Cataracts
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  **Phone:** 301-496-5248
  **Email:** 2020@nei.nih.gov
  Retinal Detachment
- **Prevent Blindness America**
  211 West Wacker Drive
  Suite 1700
  Chicago IL 60606
  **Phone:** 800-331-2020 (toll-free)
  **Email:** info@preventblindness.org
  Cataract

## 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.** VCAN-Related Vitreoretinopathy: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *VCAN* | 5q14.2-q14.3 | Versican core protein | VCAN @ LOVD | VCAN | VCAN |

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 VCAN-Related Vitreoretinopathy (View All in OMIM)

| | |
|---|---|
| 118661 | VERSICAN; VCAN |
| 143200 | WAGNER VITREORETINOPATHY; WGVRP |

## Molecular Pathogenesis

Since *VCAN* is expressed in many human tissues, pathogenic variants in *VCAN* could be expected to interfere with functions in tissues and organs other than the eye; the cardiovascular system in particular would seem a likely candidate, as versican, the protein product of *VCAN*, is a component of the extracellular matrix of the blood vessels [Yao et al 1994, Lemire et al 1999]. A possible explanation for the absence of consequences of *VCAN* pathogenic variants in nonocular tissues is that splicing of the *VCAN* transcripts may be tissue specific.

**Gene structure.** The genomic region (109,399 nucleotides) of *VCAN* includes 15 exons (NM_004385.4, splice variant V0). The two largest exons, 7 (2961 nucleotides) and 8 (5262 nucleotides), are subject to alternative splicing, yielding four naturally occurring splice variants (named V0, 1, 2, and 3; see Figure 1) that exhibit a tissue-specific expression pattern. The respective exon-intron boundaries show the consensus sequences for splice acceptor and splice donor sites. For a detailed summary of gene, splice variants, and protein information, see Table A, **Gene**.

**Pathogenic variants.** Eleven different single nucleotide variants, all located in conserved splice consensus sites of introns 7 and 8, were identified in 17 families with vitreoretinopathy. In some cases, identical pathogenic variants have been found in different, unrelated families (Table 2). In several individuals, it was shown that the pathogenic variants can lead to aberrant splice products and/or to quantitative changes of the naturally occurring splice variants lacking exon 8. No pathogenic exon variants have been found.

**Table 2.** Selected *VCAN* Pathogenic Variants

| DNA Nucleotide Change | Intron Location | # of Families w/ Pathogenic Variant | Reference | Reference Sequences |
|---|---|---|---|---|
| c.9265+1G>A | Intron 8 splice donor site | 1 | Rothschild et al [2013a] | NM_004385.4 NP_004376.2 |
| c.9265+1G>T | | 2 | Kloeckener-Gruissem et al [2006], Meredith et al [2007], Ronan et al [2009] | |
| c.9265+2T>A | | 2 | Kloeckener-Gruissem et al [2013] | |
| c.4004-1G>A | IVS 7 splice acceptor site | 1 | Mukhopadhyay et al [2006] | |
| c.4004-1G>C | | 1 | Kloeckener-Gruissem et al [2013] | |
| c.4004-1G>T | | 1 | Chen et al [2013] | |
| c.4004-2A>G | | 1 | Miyamoto et al [2005], Brézin et al [2011] | |
| c.4004-2A>T | | 1 | Brézin et al [2011] | |
| c.4004-5T>C | | 4 | Mukhopadhyay et al [2006] | |
| c.4004-5T>A | | 2 | Mukhopadhyay et al [2006] | |
| c.4004-6T>A | | 2 | Rothschild et al [2013b] | |

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). See Quick Reference for an explanation of nomenclature.

**Normal gene product.** The extracellular matrix proteoglycan (chondroitin sulfate proteoglycan type 2), also named versican core protein, is found in many different tissues in the human body, including the eye [White & Bruzzone 2000]. Four naturally occurring protein isoforms accumulate tissue-specifically. They are products of alternative splicing of exons 7 and 8 (see Figure 1). A central domain of the protein, encoded by both exons 7

and 8, carries glycosaminoglycan (GAG) residue modifications, which may be involved in preventing collagen fibrils from adhering, thus ensuring the gel-like properties of the vitreous content. Versican appears to have a central role in the outflow resistance through the trabecular meshwork, and splicing variant patterns in the trabecular meshwork extracellular matrix are altered in glaucoma [Keller et al 2007, Keller et al 2011].

**Abnormal gene product.** Pathogenic variants in splice consensus sites result in skipping of exon 8 and in the production of aberrant splice products [Miyamoto et al 2005, Kloeckener-Gruissem et al 2006, Mukhopadhyay et al 2006]. One consequence is increased accumulation of splice variant V2 (no exon 8; NP_001157570.1) and V3 (no exon 7 and 8; NP_001119808.1) [Mukhopadhyay et al 2006] and most likely their respective protein isoforms. This may result in severe reduction of GAG modification, which will render the physical properties of the vitreous, leading to a process of premature liquefaction.

# Chapter Notes

## Acknowledgments

The authors would like to thank Drs Wolfgang Berger and John Neidhardt for critical reading of the manuscript.

## Revision History

- 16 May 2024 (ma) Chapter retired: outdated; qualified authors not available for update
- 7 January 2016 (me) Comprehensive update posted live
- 16 August 2012 (me) Comprehensive update posted live
- 3 February 2009 (me) Review posted live
- 18 April 2008 (bkg) Original submission

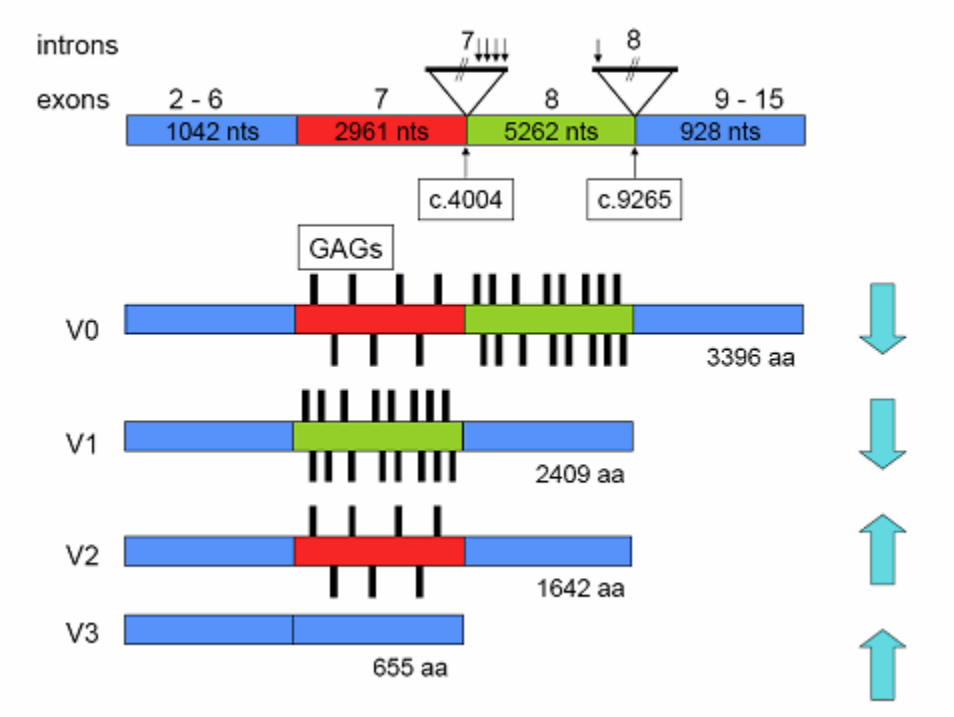


**Figure 1.** Vitreoretinopathy-associated pathogenic variants in *VCAN* and their effects on naturally occurring splice variants and protein isoforms. Under normal conditions, differential splicing leads to four transcript variants and protein isoforms V0, V1, V2, or V3, depending on the presence of exon 7 (red) and/or exon 8 (green). Attachment of glycosaminoglycan residues (GAGs; black vertical lines) modifies the protein to function in water inclusion. Pathogenic variants (black single-line vertical arrows pointing downward) lead to skipping of exon 8 and yielding increased amounts of variants V2 and V3. The effects of the variants on isoform expression (decrease or increase) are displayed by vertical turquoise arrows. An imbalanced quantitative ratio of these variants is a result of the pathogenic variants. Schematic lines are not drawn to scale. Exon sizes are given in nucleotides (nt). Protein isoform length is given by number of amino acid (aa) residues beneath each isoform. c.4004 and c.9265 are the first and last nucleotide of exon 8.

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