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Bietti Crystalline Dystrophy

Synonyms: Bietti Crystalline Corneoretinal Dystrophy, Bietti Crystalline Retinopathy

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Summary

Clinical characteristics

Bietti crystalline dystrophy (BCD) is a chorioretinal degeneration characterized by the presence of yellow-white crystals and/or complex lipid deposits in the retina and (to a variable degree) the cornea. Progressive atrophy and degeneration of the retinal pigment epithelium (RPE) / choroid lead to symptoms similar to those of other forms of retinal degeneration that fall under the category of retinitis pigmentosa and allied disorders, namely: reduced visual acuity, poor night vision, abnormal retinal electrophysiology, visual field loss, and often impaired color vision. Marked asymmetry between eyes is not uncommon. Onset is typically during the second to third decade of life, but ranges from the early teenage years to beyond the third decade. With time, loss of peripheral visual field, central acuity, or both result in legal blindness in most if not all affected individuals.

Diagnosis/testing

The diagnosis of BCD is based on the finding of numerous small, glistening yellow-white retinal crystals associated with atrophy of the RPE, pigment clumps, and sclerosis of the choroidal vessels; variable crystalline deposits in the corneal limbus; varying degrees of rod and cone dysfunction on electroretinography; visual field defects; and reflective dots visualized by spectral domain optical coherence tomography. Identification of biallelic pathogenic variants in *CYP4V2* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Referral to low-vision specialists and organizations/professionals trained to work with the visually impaired.

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Surveillance: Periodic ophthalmologic examination to monitor disease progression and periodic visual field testing particularly as it relates to determination of driving eligibility and eligibility for government programs and/or disability.

Genetic counseling

BCD is 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 and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

The diagnosis of BCD, a chorioretinal degeneration, is based on the clinical findings of the typical crystalline deposits in the cornea and retina. BCD is one of few ocular diseases for which the diagnosis can be made with a high degree of confidence by careful examination alone.

Suggestive Findings

Bietti crystalline dystrophy **should be suspected** in individuals with the following clinical, electrophysiology, and optical coherence tomography (OCT) findings.

Clinical Findings

Vision impairment. Onset of impairment is typically during the second or third decade of life; however, age of onset, presenting symptoms, and disease severity vary widely. Vison impairment is progressive. Marked asymmetry between eyes is common.

- Visual field loss. Visual field defects are variable and correlate with atrophic lesions that can encroach on the central vision.
- Nyctalopia (i.e., night blindness)
- Reduction in visual acuity

Retina

- Numerous small, glistening yellow-white crystals scattered throughout the posterior pole may extend to the midperiphery; crystalline deposits may tend to diminish with advanced disease.
- Atrophy of the retinal pigment epithelium (RPE) and choriocapillaris
- Pigment clumping
- Sclerosis of the choroidal vessels
- Patchy hypofluorescent areas of RPE, choriocapillaris atrophy, and a generalized disturbance of the RPE seen on fluorescein angiography

Cornea. Crystalline deposits in the corneal limbus (~25%-33%) are usually seen on slit lamp examination but are not necessary for diagnosis.

Spectral microscopy may be appropriate if corneal crystalline deposits are too subtle to detect on slit lamp examination.

Electrophysiology

Full-field electroretinogram (ffERG) can show varying degrees of rod and cone dysfunction, ranging from normal to reduced amplitudes of scotopic and photopic responses to undetectable responses [Usui et al 2001]. Note: The ffERG can remain normal even in later stages of the disease.

Multifocal electroretinogram (mfERG) may detect regional areas of abnormal retinal function when the ffERG is normal, particularly in those regional phenotypes that predominantly affect the posterior pole.

Optical Coherence Tomography (OCT)

Crystalline deposits can be seen as hyper-reflective dots in the choriocapillaris on spectral domain OCT.

Other reflective spots of various shapes (called retinal tubulation by Zweifel et al [2009]) can be seen by OCT. Kojima et al [2012] reported the presence of spherical, hyper-refractive structures in the outer nuclear layer of the retina, in areas of RPE atrophy.

The degeneration in BCD seen by OCT is most prominent in the outer retina, including the photoreceptor layer, but the degeneration is not uniformly distributed.

Establishing the Diagnosis

The diagnosis of Bietti crystalline dystrophy **is established** in a proband with the above Suggestive Findings. Identification of biallelic pathogenic variants in *CYP4V2* by molecular genetic testing (see Table 1) can confirm the diagnosis if clinical features are inconclusive.

Molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing or multigene panel). Depending on the phenotype, **more comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) could be considered if *CYP4V2* pathogenic variants are not found by targeted testing.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Bietti crystalline dystrophy 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 chorioretinal degeneration are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *CYP4V2* 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, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *CYP4V2* 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 chorioretinal degeneration, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Bietti Crystalline Dystrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CYP4V2	Sequence analysis [3]	>93% - 97.7% [4, 5, 6]
	Gene-targeted deletion/duplication analysis [7]	2 individuals [8, 9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Pathogenic variants were identified in 95.4% (N=109) families or 93.6% of alleles [Xiao et al 2011].
5. In a study from Japan, eight probands were found to have mutation of *CYP4V2*, including seven with the c.802-8_810delinsGC (reported as IVS6-8_c.810del/insGC) variant, suggesting a founder effect.
6. *CP4V2* pathogenic variants have been detected in 97.7% of individuals of Chinese descent [Zhang et al 2018].
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. A large deletion encompassing exon 8 was reported by Zhang et al [2018].
9. A ~4-Mb deletion encompassing *CYP4V2* and several adjacent genes was identified in an individual with BCD from Germany [Astuti et al 2015].

Clinical Characteristics

Clinical Description

Bietti crystalline dystrophy (BCD) is characerized by progressive chorioretinal degeneration with onset typically during the second to third decade of life (range: early teens to >3rd decade). The symptoms, ranges of visual impairment, and disabilities are similar to those of individuals with autosomal recessive retinitis pigmentosa.

The presenting symptom, rate of disease progression, and disease severity are also highly variable in BCD, even among those of the same age, within the same family, and with the same *CYP4V2* pathogenic variants [Lee et al 2005, Lin et al 2005, Xiao et al 2011]. Some individuals have a more diffuse retinal disease presentation, whereas others present with more localized disease in the paracentral and central regions.

Vision impairment. In most affected individuals, onset of disease is during the second or third decade of life; however, age of onset, presenting symptoms, and disease severity vary widely. Marked asymmetry between eyes with respect to fundus appearance, reduction in visual acuity, and visual field loss is not uncommon.

- **Visual field loss** (progressive). Visual field loss may manifest in different individuals as peripheral field loss (ring, paracentral, or central scotoma) or central or pericentral scotomas (usually associated with atrophic lesions that encroach on the foveal region of the macula).
- **Nyctalopia** (progressive). Night blindness (i.e., difficulty seeing in low light) is a nonspecific feature of BCD in that it is typical of many forms of inherited retinal degeneration.
- **Reduction in visual acuity** (progressive). Visual acuity can range from normal to hand motion. Although the reduction in visual acuity has been reported to typically result in legal blindness by the fifth or sixth decade, central vision can sometimes be spared even in persons with severe disease. More often, loss of central visual acuity reflects atrophy or degenerative change close to or including the fovea.
- Persons with BCD may also have impaired color vision, particularly if the atrophic lesion encroaches on the fovea or cystoid macular edema is present.

In early or milder stages of disease, affected individuals can drive a car; with time, however, loss of peripheral visual field and/or central acuity results in legal blindness in most if not all affected individuals. Whereas affected individuals typically have profound vision loss by the fifth or sixth decade of life, central acuity can be spared through late stages of the disease in some [Kaiser-Kupfer et al 1994, Lee et al 2005]. A study involving 21 families with BCD showed visual acuities ranging from normal to hand motion [Xiao et al 2011].

Retina. Numerous small, glistening yellow-white crystals are scattered throughout the posterior pole and sometimes extend to the midperiphery. The crystalline deposits are associated with atrophy of the retinal pigment epithelium (RPE) and choriocapillaris, pigment clumping, and sclerosis of the choroidal vessels.

The crystalline deposits have been observed to diminish or even disappear in areas of severe chorioretinal atrophy as the disease progresses to later stages [Chen et al 2008, Xiao et al 2011]. Areas in which crystals are still present may represent retina that is still only mildly degenerated or in the process of degenerating [Kojima et al 2012].

Fluorescein angiography reveals patchy hypofluorescent areas of RPE and choriocapillaris atrophy and a generalized disturbance of the RPE.

Additional potential retinal complications of BCD include choroidal neovascularization [Atmaca et al 2007, Gupta et al 2011, Li et al 2015] and macular hole [Zhu et al 2009].

Cornea. Crystalline deposits in the corneal limbus have been estimated to occur in one quarter to one third of persons with BCD [Kaiser-Kupfer et al 1994, Halford et al 2014]. It has also been reported that corneal deposits may be more common in persons of northern European background than in Asians [Traboulsi & Faris 1987].

If present, the deposits can usually be seen on slit lamp examination. However, some crystals may be so fine as to go undetected unless specifically and carefully sought; Takikawa et al [1992] suggest that in some individuals with BCD, corneal crystalline deposits may be too subtle to detect on slit lamp examination. Spectral microscopy may be more appropriate in such individuals.

Electrophysiology. The **full-field electroretinogram (ffERG)** can show varying degrees of rod and cone dysfunction, ranging from normal to reduced amplitudes of scotopic and photopic responses to undetectable responses [Usui et al 2001]. The ffERG is more likely to be abnormal in mid- to late-stage disease, when the peripheral visual field is markedly affected. The multifocal electroretinogram (mfERG) is more likely to be abnormal when central function (e.g., visual acuity, central visual fields) are abnormal. Subnormal responses occur more often for the mfERG earlier in the course of disease than amplitudes of the ffERG. Thus, electrophysiologic studies are not as critical to establishing the diagnosis of BCD as they are to establishing the magnitude and extent of retinal degeneration and in following progression over time.

Although studies have shown that the ffERG responses appear to correlate well with stages of disease severity [Usui et al 2001, Lee et al 2005, Mansour et al 2007], this is not always the case:

- The ffERG can remain normal or near normal even in later stages of the disease. Normal ffERG responses can occur in individuals with BCD with severe atrophy of the RPE and choroid, suggesting that the neural retina may remain viable despite disruption of retinal lamination [Rossi et al 2011].
- Regional forms of BCD that may have normal ffERGs have also been described [Wilson et al 1989, Weleber & Wilson 1991, Rossi et al 2011].

A multifocal electroretinogram (mfERG) may detect regional areas of abnormal retinal function when the ffERG is normal, particularly in those regional phenotypes that predominantly affect the posterior pole [Lockhart et al 2018].

This degree of variation of electrophysiology may be the result of testing at different stages of disease progression. This variability may also reflect variation in loss of function in the gene product, with alleles with residual function associated with greater retention of ffERG amplitudes.

Fundus autofluorescence (FAF) is useful in monitoring disease extent and progression over time with regions of RPE atrophy showing relative decrease in FAF (hypo-AF). Retinal crystals have not been reported to generate an autofluorescence signal [Halford et al 2014, Li et al 2015].

Optical coherence tomography (OCT). Spectral domain OCT is of value for both diagnosis and management of BCD.

Using OCT, the integrity of the outer retinal structure can be visualized in individuals with BCD, including the hyper-reflective dots thought to represent the crystalline deposits. The majority of OCT studies report that the crystalline deposits appear to reside in the RPE-choriocapillaris complex [Pennesi & Weleber 2010, Padhi et al 2011, Kojima et al 2012].

In addition to the crystalline deposits, other reflective spots of various shapes (called retinal tubulation by Zweifel et al [2009]) can be seen by OCT. Kojima et al [2012] reported the presence of spherical, hyper-refractive structures in the outer nuclear layer of the retina, particularly located in areas of RPE atrophy. Of note, Kojima et al [2012] also observed these same circular structures, but less frequently, in retinal dystrophies other than BCD. Drusenoid deposits can be observed at the RPE early in the disease course [Li et al 2015].

The degeneration in BCD seen by OCT is most prominent in the outer retina, including the photoreceptor layer, but typically the degeneration is not uniformly distributed.

Genotype-Phenotype Correlations

A study of 125 individuals of Chinese ancestry with BCD showed that individuals who were compound heterozygous for the most common pathogenic variant c.802-8_810delinsGC had an earlier age of onset than those who did not have this pathogenic variant [Zhang et al 2018]. Individuals homozygous for c.802-8_810delinsGC also tended to have a younger age of onset than individuals with other pathogenic variants, although not to a statistically significant degree.

Another study of 18 individuals of Chinese descent with BCD showed that those who were homozygous for c.802-8_810delinsGC or compound heterozygous for variants c.802-8_810delinsGC and c.1091-2A>G had more severe disease based on electrophysiologic testing; namely, lower EOG Arden indices and higher likelihood of a nonrecordable scotopic ffERG and 30-Hz flicker ERG when compared with individuals with pathogenic variants in the coding region. The level of visual loss in BCD is related to the severity of retinal thinning [Lai et al 2007].

The variant c.332T>C (p.Ile111Thr) has only been reported in European individuals. One individual with this homozygous pathogenic variant was reported to have an unusual central and paracentral corneal distribution of crystalline deposits, without limbic involvement. Two unaffected elderly heterozygous carriers from the same family were also found to have multiple subepithelial and anterior stromal crystalline deposits in the central and

paracentral cornea. This was absent in the young heterozygous carriers. This could suggest a dose-dependent phenotype of this variant [García-García et al 2013].

Of note, individuals without two identified pathogenic *CYP4V2* variants were phenotypically indistinguishable from those found to have pathogenic variants [Astuti et al 2015].

The high degree of clinical variability in BCD suggests the influence of factors other than the primary *CYP4V2* defect. The uncommon reports of regional retinal involvement may represent disease caused by pathogenic variants that are associated with retention of either a small amount of functional gene product or other modifying factors. Inflammatory or infectious disease (e.g., sinusitis) may be associated with worsening of disease, and treatment with antibiotics, steroids, and surgery may lead to short-term improvement in visual symptoms as well as visual acuity and visual fields, suggesting the possibility of an inflammatory component to the disease [Lockhart et al 2018].

Prevalence

While BCD is generally considered to be a rare disease, it may be underdiagnosed. For example, in a study done by Mataftsi et al [2004], approximately 10% of persons with autosomal recessive retinitis pigmentosa (RP) were also diagnosed with BCD. Furthermore, it has been estimated that up to 3% of individuals initially diagnosed with RP can be accounted for by BCD [Mataftsi et al 2004]. According to Hartong et al [2006], worldwide prevalence of RP was one in 4,000, with autosomal recessive RP accounting for 50%-60% of the affected individuals. This implies a prevalence of BCD of up to 1:67,000, representing almost 5,000 individuals in the US alone.

BCD appears to be more common in people of East Asian descent, particularly the Chinese and Japanese [Hu 1983, Tian et al 2015]; however, individuals of European, Middle Eastern, African, and North and South American origin have also been reported [Mataftsi et al 2004, Lin et al 2005, Lai et al 2007, Zenteno et al 2008, García-García et al 2013, Astuti et al 2015].

Genetically Related (Allelic) Disorders

A single report identified pathogenic variants in *CYP4V2* and *CTNNA1* in individuals with Leber congenital amaurosis [Jinda et al 2017]; however, this association requires further elucidation in larger cohorts.

A novel homozygous *CYP4V2* variant (c.362C>A:Ser121Tyr) in exon 3 has been reported with a choroideremia-like phenotype in an individual of Japanese descent [Katagiri et al 2017].

A common single-nucleotide variant (SNV) of *CYP4V2*, c.775C>A (p.Gln259Lys), has emerged as a risk factor in deep venous thromboembolism (DVT) [Bezemer et al 2008, Li et al 2009, Trégouët et al 2009]. The association was confirmed in a recent meta-analysis of five replication cohorts [Austin et al 2011]. c.775C>A is in linkage disequilibrium with SNVs in *F11* (encoding factor XI) and *KLKB1* (encoding pre-kallikrein), proteins known to be involved in coagulation. Initially this was thought to explain, at least in part, the observed association of c.775C>A with DVT; however, more detailed genetic analysis indicated that persons possessing the A-C-T haplotype corresponding to *CYP4V2* c.775C>A, *F11* rs2036914, and *F11* rs2289252 were at highest risk for DVT (odds ratio: 1.55-1.57) [Li et al 2009], indicating an essential modulating influence of *CYP4V2* c.775C>A variant on the two more directly acting *F11* SNVs.

Differential Diagnosis

Retinitis pigmentosa. The clinical symptoms and findings on visual field testing and electrophysiologic studies in Bietti crystalline dystrophy (BCD) are similar to those of other forms of retinal degeneration that fall under the category of retinitis pigmentosa and allied disorders.

Crystalline deposits in the retina may be associated with the following:

- Primary hyperoxaluria type 1 and primary hyperoxaluria type 2
- Cystinosis, particularly the more benign adolescent presentation
- Sjögren-Larsson syndrome (OMIM 270200)
- Drug toxicity (e.g., tamoxifen, the anesthetic methoxyflurane, the oral tanning agent canthaxanthine)
- Drug abuse (talc retinopathy)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with Bietti crystalline dystrophy (BCD), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Fundoscopic examination
- Full-field electroretinogram (ffERG) to establish a baseline
- Visual field testing (perimetry) to evaluate the degree of visual field constriction or presence of scotomas and to establish a baseline
- Optical coherence tomography to evaluate for complications such as choroidal neovascularization (CNV) or macular hole formation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific treatment for BCD currently exists; however, affected individuals should be referred to services specific to those with vision impairment:

- Low-vision specialists can prescribe low-vision aids/devices to optimize remaining vision.
- State services for the blind or organizations/professionals trained to work with the visually impaired provide access to services related to employment, education, and counseling regarding the psychosocial adaptation to visual loss.

Note: CNV is uncommon in BCD. Laser photocoagulation is not usually considered for CNV in inherited forms of retinal degeneration and has recently been superseded by the use of antivascular endothelial growth factor (anti-VEGF) therapy in a fashion similar to its use in age-related macular dystrophy.

Surveillance

Ophthalmologic examination is recommended every one to two years to monitor disease progression. Examination should include visual field testing particularly as it relates to determination of driving eligibility and eligibility for government programs and/or disability.

Affected individuals should be aware of the possibility of CNV and the option of self-monitoring using an Amsler grid under direction of their primary care ophthalmologist.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Bietti crystalline dystrophy (BCD) is 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 *CYP4V2* 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. Unless an individual with Bietti crystalline dystrophy has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *CYP4V2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CYP4V2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CYP4V2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CYP4V2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Bietti crystalline dystrophy 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 Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Bietti's Crystalline Dystrophy

- **American Council of the Blind (ACB)**
  2200 Wilson Boulevard
  Suite 650
  Arlington VA 22201
  Phone: 800-424-8666 (toll-free); 202-467-5081
  Fax: 202-467-5085
  Email: info@acb.org
  www.acb.org

- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org

- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org

- **Prevent Blindness America**
  211 West Wacker Drive
  Suite 1700
  Chicago IL 60606
  Phone: 800-331-2020
  Email: info@preventblindness.org
  www.preventblindness.org

- **Retina International**
  Ireland
  Phone: 353 1 961 9259
  Email: info@retina-International.org
  www.retina-international.org

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. Bietti Crystalline Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CYP4V2	4q35.1-q35.2	Cytochrome P450 4V2	CYP4V2 @ LOVD	CYP4V2	CYP4V2

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 Bietti Crystalline Dystrophy (View All in OMIM)

210370	BIETTI CRYSTALLINE CORNEORETINAL DYSTROPHY; BCD
608614	CYTOCHROME P450, FAMILY 4, SUBFAMILY V, POLYPEPTIDE 2; CYP4V2

Molecular Pathogenesis

Though the biochemical basis of BCD remains unknown, findings suggest that BCD may result from a systemic abnormality in lipid metabolism. There also have been reports of a missing 32-kd fatty-acid binding protein with a high affinity for fatty acids: docosahexaenoic acid (DHA; 22:6n-3), α-linolenic acid (18:3n-3), and palmitic acid (16:0) in the lymphocytes of persons with BCD compared to controls [Lee et al 1998]. Metabolic studies of fibroblasts and lymphocytes cultured from individuals with BCD exhibited altered lipid metabolism, with decreased synthesis of ω-3 polyunsaturated fatty acids (PUFAs) (e.g., eicosapentaenoic acid [EPA; 20:5n-3] and DHA) from α-linolenic acid compared to controls [Lee et al 2001]. *CYP4V2* has been proposed to play a role in ocular inflammation [Nakano et al 2014] and worsening of disease has been associated with extraocular infection (e.g., severe sinusitis) [Lockhart et al 2018].

Free fatty acid profiling revealed significantly altered fatty acid concentrations in the serum of persons with BCD: stearic acid (18:0) was elevated and oleic acid (18:1n-9) was lowered in persons with BCD compared to controls [Lai et al 2010].

In addition to ocular tissues, transmission electron microscopy showed crystalline material of unknown lipid composition in lymphoblasts and fibroblasts of persons with BCD [Welch 1977].

Gene structure. *CYP4V2* spans 19 kb and comprises 11 exons [Li et al 2004]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A wide range of *CYP4V2* pathogenic variants (nearly 100) have now been described in individuals with BCD.

Several common variants are specific to geographic or ethnic backgrounds, such as c.802-8_810delinsGC in East Asian individuals, p.Met66Arg in individuals of South Asian ancestry, and p.Ile111Thr in European individuals [Halford et al 2014]. These variations have been attributed to a founder effect [Zhang et al 2018].

The most frequent *CYP4V2* pathogenic variant found in affected individuals, c.802-8_810delinsGC, results in the skipping of exon 7 due to deletion of the 3' splicing acceptor site of intron 6. Eight nucleotides of the 3' end of intron 6 and nine from the 5' end of exon 7 are deleted along with an insertion of GC [Lee et al 2005, Shan et al 2005, Wada et al 2005, Lai et al 2007, Chung et al 2013, Zhang et al 2018].

Two other disease-associated variants, c.1091-2A>G and c.1226-6_1235del16 (a deletion spanning the splice acceptor site for exon 9), result in skipping of exons 9 and 10, respectively [Li et al 2004, Shan et al 2005].

Numerous disease-associated variants have been described. The majority of described variants are missense variants, while the remaining variants include nonsense variants, small insertions or deletions, and splicing defects. One large deletion encompassing exon 8 and an additional deletion including all of *CYP4V2* and several other genes has been reported [Li et al 2004, Lee et al 2005, Lin et al 2005, Shan et al 2005, Wada et al 2005, Lai et al 2007, Hardwick 2008, Zenteno et al 2008, Xiao et al 2011, Astuti et al 2015, Tian et al 2015, Zhang et al 2018].

Table 2. *CYP4V2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.197T>G	p.Met66Arg	NM_207352.3 NP_997235.3
c.327+1G>A (IVS2+1G>A)	See footnote 2.	
c.332T>C	p.Ile111Thr	
c.802-8_810delinsGC [3] (IVS6-8del/insGC)	See footnote 3.	
c.1091-2A>G (IVS8-2A>G)	See footnote 4.	
c.1226-6_1235del16 [5] (IVS9-6del)	See footnote 5.	

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.
1. Variant designation that does not conform to current naming conventions
2. Skipping of exon 2, resulting in a frameshift in which the exon 1 sequence is followed by four novel amino acids and a premature terminating [Li et al 2004]
3. Skipping of exon 7, which encodes 62 amino acids [Wada et al 2005]
4. Skipping of exon 9, which encodes 62 amino acids
5. Skipping of exon 10, which encodes 60 amino acids [Shan et al 2005]

Normal gene product. The cytochrome P450 4V2 protein (CYP4V2) is 525 amino acids. This protein is a member of the CYP superfamily of heme-containing monooxygenases. CYP4V2 is a fatty acid oxidase, with preferential activity for ω-hydroxylation of saturated, medium-chain fatty acids [Nakano et al 2009]. Homology modeling predicts that the CYP4V2 structure contains a transmembrane segment located near the amino terminus with a globular structural domain following that is typical of cytochrome P450 enzymes. The globular domain of CYP4V2 comprises 18 helices and β structural elements [Li et al 2004].

Recent studies support a role for CYP4V2 function in controlling intracellular lipid metabolisms [Li et al 2017].

Abnormal gene product. Variants predicted to be loss-of-function resulting in loss of enzyme activity have been associated with disease. Similarly, several amino acid deletions and substitutions would be predicted to be deleterious based on conservation studies with other CYP4 enzymes [Li et al 2004].

Exon-skipping pathogenic variants, namely c.802-8_810delinsGC, are associated with more severe forms of the disease than are pathogenic missense variants [Lai et al 2007, Zhang et al 2018].

Defects in the catalytic function of this enzyme lead to altered fatty acid metabolism; the endogenous substrate(s) have yet to be identified.

References

Literature Cited

Astuti GDN, Sun V, Bauwens M, Zobor D, Leroy BP, Omar A, Jurklies B, Lopez I, Ren H, Yazar V, Hamel C, Kellner U, Wissinger B, Kohl S, Baere ED, Collin RWJ, Koenekoop RK. Novel insights into the molecular pathogenesis of CYP4V2-associated Bietti's retinal dystrophy. Mol Genet Genomic Med. 2015;3:14–29. PubMed PMID: 25629076.

Atmaca LS, Muftuoglu O, Atmaca-Sonmez P. Peripapillary choroidal neovascularization in Bietti crystalline retinopathy. Eye (Lond). 2007;21:839–42. PubMed PMID: 17173010.

Austin H, De Staercke C, Lally C, Bezemer ID, Rosendaal FR, Hooper WC. New gene variants associated with venous thrombosis: a replication study in white and black Americans. J Thromb Haemost. 2011;9:489–95. PubMed PMID: 21232005.

Bezemer ID, Bare LA, Doggen CJ, Arellano AR, Tong C, Rowland CM, Catanese J, Young BA, Reitsma PH, Devlin JJ, Rosendaal FR. Gene variants associated with deep vein thrombosis. JAMA. 2008;299:1306–14. PubMed PMID: 18349091.

Chen H, Zhang M, Huang S, Wu D. Functional and clinical findings in 3 female siblings with crystalline retinopathy. Doc Ophthalmol. 2008;116:237–43. PubMed PMID: 17962988.

Chung JK, Shin JH, Jeon BR, Ki CS, Park TK. Optical coherence tomographic findings of crystal deposits in the lens and cornea in Bietti crystalline corneoretinopathy associated with mutation in the CYP4V2 gene. Jpn J Ophthalmol. 2013;57:447–50. PubMed PMID: 23793346.

García-García GP, López-Garrido MP, Martínez-Rubio M, Moya-Moya MA, Belmonte-Martínez J, Escribano J. Genotype-phenotype analysis of Bietti crystalline dystrophy in a family with the CYP4V2 Ile111Thr mutation. Cornea. 2013;32:1002–8. PubMed PMID: 23538635.

Gupta B, Parvizi S, Mohamed MD. Bietti crystalline dystrophy and choroidal neovascularisation. Int Ophthalmol. 2011;31:59–61. PubMed PMID: 20972604.

Halford S, Liew G, Mackay DS, Sergouniotis PI, Holt R, Broadgate S, Volpi EV, Ocaka L, Pobson AG, Holder GE, Moore AT, Michaelides M, Webster AR. Detailed phenotypic and genotypic characterization of Bietti crystalline dystrophy. Ophthalmology. 2014;121:1174–84. PubMed PMID: 24480711.

Hardwick JP. Cytochrome P450 omega hydroxylase (CYP4) function in fatty acid metabolism and metabolic diseases. Biochem Pharmacol. 2008;75:2263–75. PubMed PMID: 18433732.

Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368:1795–809. PubMed PMID: 17113430.

Hu DN. Ophthalmic genetics in China. Ophthal Paediat Genet. 1983;2:39–45.

Jinda W, Taylor TD, Suzuki Y, Thongnoppakhun W, Limwongse C, Lertrit P, Trinavarat A, Atchaneeyasakul LO. Whole exome sequencing in eight Thai patients with Leber congenital amaurosis reveals mutations in the CTNNA1 and CYP4V2 genes. Invest Ophthalmol Vis Sci. 2017;58:2413–20. PubMed PMID: 28453600.

Kaiser-Kupfer MI, Chan CC, Markello TC, Crawford MA, Caruso RC, Csaky KG, Guo J, Gahl WA. Clinical biochemical and pathologic correlations in Bietti's crystalline dystrophy. Am J Ophthalmol. 1994;118:569–82. PubMed PMID: 7977570.

Katagiri S, Hayashi T, Gekka T, Tsuneoka H. A novel homozygous CYP4V2 variant (p.S121Y) associated with a choroideremia-like phenotype. Ophthalmic Genet. 2017;38:286–7. PubMed PMID: 27348340.

Kojima H, Otani A, Ogino K, Nakagawa S, Makiyama Y, Kurimoto M, Guo C, Yoshimura N. Outer retinal circular structures in patients with Bietti crystalline retinopathy. Br J Ophthalmol. 2012;96:390–3. PubMed PMID: 21803923.

Lai TY, Chu KO, Chan KP, Ng TK, Yam GH, Lam DS, Pang CP. Alterations in serum fatty acid concentrations and desaturase activities in Bietti crystalline dystrophy unaffected by CYP4V2 genotypes. Invest Ophthalmol Vis Sci. 2010;51:1092–7. PubMed PMID: 19797200.

Lai TY, Ng TK, Tam PO, Yam GH, Ngai JW, Chan WM, Liu DT, Lam DS, Pang CP. Genotype phenotype analysis of Bietti's crystalline dystrophy in patients with CYP4V2 mutations. Invest Ophthalmol Vis Sci. 2007;48:5212–20. PubMed PMID: 17962476.

Lee J, Jiao X, Hejtmancik JF, Kaiser-Kupfer M, Chader GJ. Identification, isolation, and characterization of a 32-kDa fatty acid-binding protein missing from lymphocytes in humans with Bietti crystalline dystrophy (BCD). Mol Genet Metab. 1998;65:143–54. PubMed PMID: 9787106.

Lee J, Jiao X, Hejtmancik JF, Kaiser-Kupfer M, Gahl WA, Markello TC, Guo J, Chader GJ. The metabolism of fatty acids in human Bietti crystalline dystrophy. Invest Ophthalmol Vis Sci. 2001;42:1707–14. PubMed PMID: 11431432.

Lee KY, Koh AH, Aung T, Yong VH, Yeung K, Ang CL, Vithana EN. Characterization of Bietti crystalline dystrophy patients with CYP4V2 mutations. Invest Ophthalmol Vis Sci. 2005;46:3812–6. PubMed PMID: 16186368.

Li A, Jiao X, Munier FL, Schorderet DF, Yao W, Iwata F, Hayakawa M, Kanai A, Shy Chen M, Alan Lewis R, Heckenlively J, Weleber RG, Traboulsi EI, Zhang Q, Xiao X, Kaiser-Kupfer M, Sergeev YV, Hejtmancik JF. Bietti crystalline corneoretinal dystrophy is caused by mutations in the novel gene CYP4V2. Am J Hum Genet. 2004;74:817–26. PubMed PMID: 15042513.

Li Q, Li Y, Zang X, Xu Z, Zhu X, Ma K, She H, Peng X. Utilization of fundus autofluorescence, spectral domain optical coherence tomography, and enhanced depth imaging in the characterization of Bietti crystalline dystrophy in different stages. Retina. 2015;35:2074–84. PubMed PMID: 25978730.

Li S, Li Q, Kong Y, Wu S, Cui Q, Zhang M, Zhang SO. Specific regulation of thermosensitive lipid droplet fusion by a nuclear hormone receptor pathway. Proc Natl Acad Sci U S A. 2017;114:8841–6. PubMed PMID: 28760992.

Li Y, Bezemer ID, Rowland CM, Tong CH, Arellano AR, Catanese JJ, Devlin JJ, Reitsma PH, Bare LA, Rosendaal FR. Genetic variants associated with deep vein thrombosis: the F11 locus. J Thromb Haemost. 2009;7:1802–8. PubMed PMID: 19583818.

Lin J, Nishiguchi KM, Nakamura M, Dryja TP, Berson EL, Miyake Y. Recessive mutations in the CYP4V2 gene in East Asian and Middle Eastern patients with Bietti crystalline corneoretinal dystrophy. J Med Genet. 2005;42:e38. PubMed PMID: 15937078.

Lockhart CM, Smith TB, Yang P, Naidu M, Rettie AE, Nath A, Weleber R, Kelly EJ. Longitudinal characterisation of function and structure of Bietti crystalline dystrophy: report on a novel homozygous mutation in CYP4V2. Br J Ophthalmol. 2018;102:187–94. PubMed PMID: 28698241.

Mansour AM, Uwaydat SH, Chan CC. Long-term follow-up in Bietti crystalline dystrophy. Eur J Ophthalmol. 2007;17:680–2. PubMed PMID: 17671952.

Mataftsi A, Zografos L, Millá E, Secrétan M, Munier FL. Bietti's crystalline corneoretinal dystrophy: a cross-sectional study. Retina. 2004;24:416–26. PubMed PMID: 15187665.

Nakano M, Kelly EJ, Rettie AE. Expression and characterization of CYP4V2 as a fatty acid omega-hydroxylase. Drug Metab Dispos. 2009;37:2119–22. PubMed PMID: 19661213.

Nakano M, Lockhart CM, Kelly EJ, Rettie AE. Ocular cytochrome P450s and transporters: roles in disease and endobiotic and xenobiotic disposition. Drug Metab Rev. 2014;46:247–60. PubMed PMID: 24856391.

Padhi TR, Kesarwani S, Jalali S. Bietti crystalline retinal dystrophy with subfoveal neurosensory detachment and congenital tortuosity of retinal vessels: case report. Doc Ophthalmol. 2011;122:199–206. PubMed PMID: 21611771.

Pennesi ME, Weleber RG. High-resolution optical coherence tomography shows new aspects of Bietti crystalline retinopathy. Retina. 2010;30:531–2. PubMed PMID: 20139800.

Rossi S, Testa F, Li A, Iorio VD, Zhang J, Gesualdo C, Corte MD, Chan CC, Fielding Hejtmancik J, Simonelli F. An atypical form of Bietti crystalline dystrophy. Ophthalmic Genet. 2011;32:118–21. PubMed PMID: 21385027.

Shan M, Dong B, Zhao X, Wang J, Li G, Yang Y, Li Y. Novel mutations in the CYP4V2 gene associated with Bietti crystalline corneoretinal dystrophy. Mol Vis. 2005;11:738–43. PubMed PMID: 16179904.

Takikawa C, Miyake Y, Yamamoto S. Re-evaluation of crystalline retinopathy based on corneal findings. Folia Ophthalmol Jpn. 1992;43:969–78.

Tian R, Wang SR, Wang J, Chen YX. Novel CYP4V2 mutations associated with Bietti crystalline corneoretinal dystrophy in Chinese patients. Int J Ophthalmol. 2015;8:465–9. PubMed PMID: 26085992.

Traboulsi EI, Faris BM. Crystalline retinopathy. Ann Ophthalmol. 1987;19:156–8. PubMed PMID: 3619268.

Trégouët DA, Heath S, Saut N, Biron-Andreani C, Schved JF, Pernod G, Galan P, Drouet L, Zelenika D, Juhan-Vague I, Alessi MC, Tiret L, Lathrop M, Emmerich J, Morange PE. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood. 2009;113:5298–303. PubMed PMID: 19278955.

Usui T, Tanimoto N, Takagi M, Hasegawa S, Abe H. Rod and cone a-waves in three cases of Bietti crystalline chorioretinal dystrophy. Am J Ophthalmol. 2001;132:395–402. PubMed PMID: 11530054.

Wada Y, Itabashi T, Sato H, Kawamura M, Tada A, Tamai M. Screening for mutations in CYP4V2 gene in Japanese patients with Bietti's crystalline corneoretinal dystrophy. Am J Ophthalmol. 2005;139:894–9. PubMed PMID: 15860296.

Welch RB. Bietti's tapetoretinal degeneration with marginal corneal dystrophy crystalline retinopathy. Trans Am Ophthalmol Soc. 1977;75:164–79. PubMed PMID: 306693.

Weleber RG, Wilson DJ. Bietti's crystalline dystrophy of the cornea and retina. In: Heckenlively JR, Arden GB, eds. *Principles and Practice of Clinical Electrophysiology of Vision.* St Louis, MO: Mosby Year Book; 1991:683-91.

Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR. Bietti's crystalline dystrophy. A clinicopathologic correlative study. Arch Ophthalmol. 1989;107:213–21. PubMed PMID: 2783846.

Xiao X, Mai G, Li S, Guo X, Zhang Q. Identification of CYP4V2 mutation in 21 families and overview of mutation spectrum in Bietti crystalline corneoretinal dystrophy. Biochem Biophys Res Commun. 2011;409:181–6. PubMed PMID: 21565171.

Zenteno JC, Ayala-Ramirez R, Graue-Wiechers F. Novel CYP4V2 gene mutation in a Mexican patient with Bietti's crystalline corneoretinal dystrophy. Curr Eye Res. 2008;33:313–8. PubMed PMID: 18398705.

Zhang X, Xu K, Dong B, Peng X, Li Q, Jiang F, Xie Y, Tian L, Li Y. Comprehensive screening of CYP4V2 in a cohort of Chinese patients with Bietti crystalline dystrophy. Mol Vis. 2018;24:700–11. PubMed PMID: 30429639.

Zhu Z, Ji X, Zhang J, Ke G. Posterior scleral reinforcement in the treatment of macular retinoschisis in highly myopic patients. Clin Exp Ophthalmol. 2009;37:660–3. PubMed PMID: 19788661.

Zweifel SA, Engelbert M, Laud K, Margolis R, Spaide RF, Freund KB. Outer retinal tubulation: a novel optical coherence tomography finding. Arch Ophthalmol. 2009;127:1596–602. PubMed PMID: 20008714.

Chapter Notes

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