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Variable phenotype of congenital corneal opacities in biallelic *CYP1B1* pathogenic variants

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Abstract

Introduction: To describe the variable phenotype of congenital corneal opacities (CCO) occurring in patients with biallelic *CYP1B1* pathogenic variants.

Methods: A retrospective chart review was conducted to identify patients with CCO and *CYP1B1* pathogenic variants seen at UPMC Children's Hospital of Pittsburgh. Ophthalmic examination, high frequency ultrasound, anterior segment optical coherence tomography, histopathology images and details of genetic testing were reviewed.

Results: Three children were identified. All presented with raised intraocular pressure (IOP). Two patients showed bilateral limbus-to-limbus avascular corneal opacification which did not resolve with IOP control; one showed unilateral avascular corneal opacity with a crescent of clear cornea, irido-corneal adhesions (ICA), irido-lenticular adhesions (ILA), and classical features of congenital glaucoma in the fellow eye (enlarged corneal diameter, Haab striae, and clearing of the corneal clouding with appropriate IOP control). The first 2 patients were visually rehabilitated with penetrating keratoplasty. Histopathology revealed distinct features: a variably keratinized epithelium; a thick but discontinuous Bowman-like layer with areas of disruption and abnormal cellularity; Descemet's membrane, when observed, showed reduced endothelial cells; no pathological changes of Haab striae were identified. Two patients had compound heterozygous pathogenic variants in *CYP1B1* causing premature stop codons, whilst one was homozygous for a pathogenic missense variant.

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Conclusion: Congenital corneal opacities seen in biallelic *CYP1B1* pathogenic variants have a variable phenotype. One is that commonly termed as Peters Anomaly type 1 (with ICA, with or without ILA); the other is a limbus-to-limbus opacity, termed *CYP1B1* cytopathy. Clinicians should be aware of this phenotypic variability.

Keywords

CYP1B1 cytopathy; *CYP1B1* ; congenital glaucoma; secondary congenital corneal opacity; irido-corneal adhesions

Introduction

Pathogenic variants of *CYP1B1* are the commonest molecular cause of primary congenital glaucoma.[1] However, changes in *CYP1B1* have also been reported in association with other anterior segment developmental anomalies (ASDA), including congenital corneal opacities (CCO).

Three previous reports have found *CYP1B1* pathogenic variants in patients with Peters Anomaly (PA), proposing that primary congenital glaucoma and PA may share a common molecular pathophysiology. Peters Anomaly cases with *CYP1B1* variants were not phenotypically different from the ones without involvement of this gene and were namely due to irido-corneal adhesions (ICA) with or without irido-lenticular adhesions (PA type 1).[2–4]

CYP1B1 has been also linked to a particular phenotype of CCO, described as "*CYP1B1* cytopathy".[5,6] The term refers to a phenotype characterized by raised intraocular pressure (IOP) and limbus-to-limbus avascular corneal opacity, which do not resolve with glaucoma control. The histopathology was reported as showing central absence of Bowman layer, Descemet membrane, and endothelium, with no Haab striae. This latter feature is important to distinguish this condition from CCO secondary to uncontrolled congenital glaucoma. Corneal transparency in these patients can be obtained with penetrating keratoplasty (PK), but the graft survival may be threatened by the difficult glaucoma management.

We herein report three patients with biallelic *CYP1B1* pathogenic variants and a spectrum of phenotypic presentation of ASDA.

Material and methods

A retrospective chart review was conducted to identify patients with *CYP1B1* variants and corneal opacity seen in the Division of Pediatric Ophthalmology, Strabismus, and Adult Motility at UPMC Children's Hospital of Pittsburgh.

Ocular examination under anesthesia was performed in all patients, including high frequency ultrasonography (HFU), and anterior segment optical coherence tomography (AS-OCT). Surgical interventions were performed when indicated and histopathology was reviewed when available.

Results

Three children were included. Details about the ophthalmic examination are reported in Table 1, and clinical pictures in Figure 1.

Case *1*

A 2-month-old boy was referred for CCO and glaucoma, previously managed with trabeculotomies, which failed to resolve the corneal clouding. At examination, he had diffused corneal opacities extending from limbus to limbus with corneal edema (Figure 1 A); in the left eye, the central area was relatively less opaque. The eyes were soft to moderate on palpation. The corresponding AS-OCT findings showed corneal thickening with subepithelial edema in the right eye and a relative central thinning in the left. The child was treated with bilateral PK, and the grafts remained clear at the one-year-follow-up visit. Six weeks after surgery, the cup-to-disc ratios were 0.1 and 0.2 in the right and left eye, respectively, but axial length was increased (20.24 mm and 20.04 mm, respectively), thus cyclodiode laser was performed.

Histopathological examination of the right cornea showed a thickened Bowman's-like layer extending across the specimen (Figure 2 A, B), with central regions of attenuation associated with abnormal cellularity within the layer (Figure 2 C). The left cornea showed similar fragments of thickened Bowman's-like tissue at the periphery (Figure 2 D, F) that was nearly absent centrally (Figure 2 E, G). High resolution composite images in comparison to a normal infant cornea showed disruption of the lamellar architecture of the stroma with an anterior condensed region and myxoid expansion of mid-corneal to posterior lamellae (Supplemental Figure S1). Both eyes exhibited corneal edema with keratinization of the corneal epithelium. Descemet's membrane was thin and prone to disruption but was present across the majority of the left corneal profile. A corneal endothelial layer was not observed.

Of note, neither of patient's parents have anterior segment abnormalities and there was no known family history of congenital ocular anomalies or glaucoma. The child showed an umbilical hernia, inguinal hernia and hypospadias, therefore genetic testing to rule out Axenfeld-Rieger syndrome were performed. Whole Exome Sequencing (WES) revealed compound heterozygosity for two *CYP1B1* pathogenic variants, specifically: c.171G>A (p.Trp57X), which was maternally inherited, and c.1064_1076del (p.Arg355HisfsX69), which was paternally inherited.

CYP1B1 c.171G>A (p.Trp57X) was interpreted as pathogenic (ACMG criteria PVS1, PP5, PM2) and is a well-established variant in the medical literature having been previously detected in a homozygous or compound heterozygous state in individuals with glaucoma and Peter's anomaly.[3,7–12] *CYP1B1* c.1064_1076del (p.Arg355Hisfs*69) was interpreted as pathogenic (ACMG criteria PVS1, PP5, PM2), representing a well-established variant in the medical literature detected in a homozygous or compound heterozygous state in individuals with glaucoma.[7,10,13–15]

Case 2

A 3-year-old male with a history of bilateral congenital glaucoma and dense corneal clouding extending to the limbus was referred to our clinic for consideration of PK. He was diagnosed as affected by congenital glaucoma at 10 days of life. The high IOP was initially managed pharmacologically, but it was necessary to proceed with numerous cyclodiode laser procedures and tube placement in both eyes. These procedures were effective for IOP control but did not lead to resolution or even reduction of the CCO.

The ophthalmic examination at our institution was significant for moderate-to-high IOP, bilaterally enlarged corneas with dense avascular opacities extending to the limbus, and bilateral aniridia. AS-OCT and HFU revealed that iris was absent bilaterally and lenses were present and not attached to the cornea. He underwent bilateral PK. Two months after surgery, the cup-to-disc ratio were 0.4-0.5 and 0.1 in the right and left eye, respectively. Axial length remained stable, but there appeared to be some corneal bulging within the sutures in the right eye, and an epithelial defect in the left eye, therefore cyclodiode laser was performed.

Histopathology of both eyes (Figure 3) revealed similar changes to the left eye of Case 1, with peripheral disrupted segments of an abnormally thick Bowman's-like layer associated with abnormal cellularity, and corneal epithelial keratinization. There were regions of anterior condensed stroma with loss of lamellar architecture and myxoid deposits in the posterior lamellae with relatively normal architecture at the mid-level (Figure 3 A, Supplemental Figure S1). Segments of Descemet's layer were observed in both peripheral and central cornea, with reduced endothelial cell numbers (Figure 3 A, E). There were no histopathological changes to indicate Descemet's membrane rupture *in vivo* (Haab striae). The right eye additionally showed superficial chronic lymphocytic keratitis (Figure 3 F).

Genetic testing via Next Generation Sequencing (NGS) of 54 genes related to anterior segment dysgenesis revealed homozygosity for a *CYP1B1* missense variant (c.1333T>A, p.Phe445Ile) interpreted as pathogenic (ACMG criteria PM5, PM1, PP3, PP5, PM2). This variant is absent from the gnomAD population database but has been reported in the medical literature in a homozygous state in a patient with PCG.[16] The pedigree was significant for consanguinity, explaining the observed homozygosity. A full list of genes analyzed appears in Supplemental Data.

Case 3

A 3-year-old girl was referred for bilateral congenital glaucoma and right CCO. At birth, she was noted to have complete opacification of both corneas. Ophthalmic surgical history included bilateral trabeculectomy and Ahmed tube implantation, with satisfactory IOP control. Her parents reported that whilst the left cornea cleared, the opacification of the right eye did not improve. For this reason, selective endothelial removal was attempted in the right eye, again without improvement of the CCO.

At examination at UMPC Children's Hospital, she presented with right avascular corneal opacity with a crescent of clear cornea infero-temporally, ICA and irido-lenticular adhesions (Figure 1 B); the HFU highlighted that the tube was in an unusual position touching the

lens, which showed a mild anterior lens opacification at that site. The left cornea was clear with one linear Haab Striae. Visual acuity was counting fingers and 20/250 in the right and left eye, respectively. A topical treatment to control IOP was started bilaterally. Parents' eye examination was unremarkable except for father' mild iris hypoplasia.

She was treated with right peripheral iridectomy. Histopathology (Figure 4) showed iris stroma with iris pigment epithelium and focal areas of iris sphincter muscle. Much of the stroma was replaced by dense fibrosis, confirmed by Masson trichrome stain. The material did not stain for PAS or Congo red.

Genetic testing via NGS of 71 genes related to anterior segment dysgenesis revealed two *CYP1B1* pathogenic variants, specifically c.1064_1076del (p.Arg355Hisfs*69) and c.868dup (p.Arg290Profs*37). *CYP1B1* c.1064_1076del (p.Arg355Hisfs*69) was interpreted as pathogenic for the reasons previously described in Case 1. *CYP1B1* c.868dup (p.Arg290Profs*37) was interpreted as pathogenic (ACMG criteria PVS1, PP5, PM2) as it has been previously detected in a homozygous or compound heterozygous state in individuals with glaucoma.[7,9,11,17–20] Due to the genomic distance of the variants, the NGS testing method was unable to determine whether the variants are *in cis* or *in trans*. Segregation studies were declined by the parents and therefore not performed. A full list of genes analyzed appears in Supplemental Data.

Discussion

Autosomal recessive pathogenic variants of *CYP1B1* are the main known cause of primary congenital glaucoma (PCG), being responsible for up to 85% of cases depending on the population studied.[1,21,22] Rarely, biallelic variants of *CYP1B1* have been reported in association with corneal opacities unrelated to the elevated IOP. [2–4] Vincent et al described 3 patients with PA, underlying the possible role of *CYP1B1* in anterior segment developmental anomalies beyond PCG, since one of their patients showed CCO without glaucoma. The authors described an ocular phenotype characterized by CCO with ICA and irido-lenticular adhesions.[4] Edward et al found *CYP1B1* variants in 6 out of 11 patients with PA, without finding neither phenotypic nor histopathologic differences between the subjects with and without *CYP1B1* involvement.[2]

Kelberman et al previously reported 3 patients with glaucoma and corneal opacification that persisted despite early intervention and IOP control, suggesting that diffuse avascular limbus-to-limbus corneal opacity with no evidence of Haab's striae and unique corneal histopathologic findings can occur in patients with *CYP1B1* variants, albeit rarely. The outcomes of PK in these patients are good, whilst the IOP control may be difficult and can affect graft survival.[5] Clinical features of this phenotype named "*CYP1B1* cytopathy" included corneal diameter not exceeding 12 mm, diffuse corneal clouding without neovascularization and absence of ICA or kerato-lenticular adhesion (KLA). In particular, there were no signs of DM rupture related to Haab striae nor DM thickening as in corneal endothelial dystrophy (CHED). These histopathological features are important in the diagnosis of exclusion process since both two aforementioned conditions can present with total avascular corneal clouding and elevated IOP. Other authors reported a case with

phenotype and histopathology consistent with *CYP1B1* cytopathy. Since the outcomes of PK were poor in this report, they proposed that different pathogenic variants of *CYP1B1* may have a distinct prognostic value.[6] Edward et al also suggested that modifiers of the ocular phenotype can either mitigate or worsen the effects of *CYP1B1* variants, thus explaining the co-occurrence of PCG, PA, and a normal ocular phenotype in relatives with homozygous *CYP1B1* variants.[2]

In our case series, whilst the first patient fulfilled the diagnostic criteria for *CYP1B1* cytopathy as previously defined,[5] patients 2 and 3 showed a certain grade of phenotypic variability. First, they both presented increased corneal diameter. A horizontal corneal diameter greater than 13 mm has been reported as a risk factor for the development of Haab striae.[23] Despite this, in patient 2 (who presented the greater corneal diameters in our series), Haab Striae were absent clinically and pathologically, thus excluding the diagnosis of CCO secondary to uncontrolled raised IOP due to congenital glaucoma. The same patient presented with aniridia and was initially suspected as having Axenfeld-Rieger syndrome. Even though *CYP1B1* can be associated with Rieger's anomaly,[24] histopathological images were more consistent with *CYP1B1* cytopathy. Of note, ASDA, including aniridia, are also associated with *CYP1B1* pathogenic variants, both in the literature and in our clinical experience.[24,25]

Haab striae exhibit tight coiling or thickening from healing over the ends that indicate tissue reaction as evidence that they formed in a living eye.[26] In patient 1, there was clearly a normal DM on one profile that stretches across most of the length of the specimen, with artifactual separation from posterior cornea. In the other eye, segments of DM were present at the periphery and in the mid-periphery; they were uniform in thickness with no coiling or deposition to suggest healing reactions. In patient 2, a thin DM was observed in segments separated by short gaps across the entire posterior surface. Higher magnification examination of the gap areas suggests that a deeper cut into the block would have shown a more continuous DM. Again, there was no evidence of healing reaction to support multiple ruptures in vivo.

Finally, patient 3 presented with unilateral CCO due to ICA, analogous to the one previously reported by Vincent et al (PA type 1).[4]

In the first report of 2011, all *CYP1B1* cytopathy cases correlated with truncating variants with a presumed loss of protein function. In our series, patients 1 and 3 also had loss-of-function nonsense and frameshift variants, likely resulting in protein truncation or nonsense-mediated decay.[7] Of note, the c.1064_1076del (p.Arg355Hisfs*69) frameshift variant was identified in both cases and prior functional studies have demonstrated that this variant results in an absence of CYP1B1 enzymatic activity.[27] While a homozygous missense variant was detected in patient 2, prior *in vitro* functional data of another variant affecting the same residue (c.1334C>G, p.Phe445Cys) supports a significant reduction in CYP1B1 activity and suggests that this residue is functionally important.[28] The variants found in our patients have been previously reported in association with primary congenital glaucoma and several anterior segment abnormalities, such as corneal opacities and Rieger anomaly.[11,24]

It appears that there is not yet to be a specific phenotype-genotype correlation for *CYP1B1* cytopathy.[3,11,12]

Histopathologic findings in our patients were similar to the first report.[5] Neither Edward nor Biénzobas specified Bowman's appearance in the periphery of the cornea, so it's not possible to know if a thick Bowman-like layer was also present in their specimens. They reported a central absence of Bowman's layer and DM, with a concave appearance of the posterior corneal surface, which suggested the initial definition of "internal ulcer" by Von Hippel in 1897.[29] While our cases confirm central absence of Bowman's layer, DM was thin and sometimes discontinuous, but was present centrally in 3 of the 4 eyes we examined. Given the loss or reduction in corneal endothelial cells observed histologically in patients 1 and 2, preoperative assessments of corneal thickness would have been helpful. Unfortunately, no pachymetry data was available for these patients and the Integrated Operative OCT instrumentation used did not include a measuring reticle.

Histopathologic analysis of the iris specimen of our patient 3 revealed abnormal findings. Since we did not analyze iris tissue from the remaining 2 patients, we can't conclude that these abnormalities were related to the disease; however, Doshi et al suggested that since CYP1B1 can be detected very early in the iris (57 days after conception), the enzyme may have a role in the development of the iris itself. In the same way, *CYP1B1* immunoreactivity can be found in fetal corneal epithelium and keratocytes, but not in adult's ones, thus suggesting a possible role of *CYP1B1* expression in the normal development of the anterior segment structures.[30] Interestingly, changes in anterior segment structures have also been described in CYP1B1 knockout mice, consisting primarily of focal iridocorneal synechiae.[31]

Although patients with PCG are often thought to have cloudy corneas only secondary to the raised IOP, the cases presented here indicate that *CYP1B1* pathogenic variants show a greater range of phenotypic variability than previously reported. In particular, there were abnormalities of corneal stromal architecture observed in Cases 1 and 2. In cases where glaucoma control has been achieved but corneal clouding remains, *CYP1B1* pathogenic variants should be suspected.

In conclusion, *CYP1B1* is associated with a range of anterior segment developmental anomalies, including CCO which have a variable phenotype: *CYP1B1* cytopathy and PA type 1 (due to ICA). Whether different pathogenic variants or external modifiers contribute to determine the phenotypic variability remains unclear and requires further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Lewis CJ, Hedberg-Buenz A, Deluca AP, et al. Primary congenital and developmental glaucomas. doi:10.1093/hmg/ddx205.
2. Edward DP, al Rajhi A, Lewis RA, et al. Molecular basis of Peters anomaly in Saudi Arabia. Ophthalmic Genet. 2004;25:257–270. doi:10.1080/13816810490902648. [PubMed: 15621878]

3. Vincent A, Billingsley G, Priston M, et al. Phenotypic heterogeneity of CYP1B1: mutations in a patient with Peters' anomaly. J Med Genet. 2001;38(5):324–326. doi:10.1136/jmg.38.5.324 [PubMed: 11403040]
4. Vincent A, Billingsley G, Priston M, et al. Further support of the role of CYP1B1 in patients with Peters anomaly. Mol Vis. 2006;12:506–510. Published 2006 May 16. [PubMed: 16735991]
5. Kelberman D, Islam L, Jacques TS, et al. CYP1B1-Related Anterior Segment Developmental Anomalies: Novel Mutations for Infantile Glaucoma and Von Hippel's Ulcer Revisited. Ophthalmology. 2011;118:1865–1873. doi:10.1016/J.OPHTHA.2011.01.044. [PubMed: 21600657]
6. Oliva-Biénzobas V, Navas A, Astiazarán MC, et al. CYP1B1 Cytopathy: Uncommon Phenotype of a Homozygous CYP1B1 Deletion as Internal Corneal Ulcer of Von Hippel. Cornea. 2017;36:1256–1259. doi:10.1097/ICO.0000000000001263. [PubMed: 28644236]
7. Stoilov I, Akarsu AN, Sarfarazi M. Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. Hum Mol Genet. 1997;6:641–647. doi:10.1093/HMG/6.4.641. [PubMed: 9097971]
8. Stoilov IR, Costa VP, Vasconcellos JP, et al. Molecular genetics of primary congenital glaucoma in Brazil. Invest Ophthalmol Vis Sci. 2002;43(6):1820–1827. [PubMed: 12036985]
9. Campos-Mollo E, López-Garrido MP, Blanco-Marchite C, et al. CYP1B1 mutations in Spanish patients with primary congenital glaucoma: phenotypic and functional variability. Mol Vis. 2009;15:417–431. [PubMed: 19234632]
10. Lim SH, Tran-Viet KN, Yanovitch TL, et al. CYP1B1, MYOC, and LTBP2 mutations in primary congenital glaucoma patients in the United States. Am J Ophthalmol. 2013;155:508–517.e5. doi:10.1016/J.AJO.2012.09.012. [PubMed: 23218701]
11. Prokudin I, Simons C, Grigg JR, et al. Exome sequencing in developmental eye disease leads to identification of causal variants in GJA8, CRYGC, PAX6 and CYP1B1. Eur J Hum Genet. 2014;22:907–915. doi:10.1038/EJHG.2013.268. [PubMed: 24281366]
12. Ma A, Yousoof S, Grigg JR, et al. Revealing hidden genetic diagnoses in the ocular anterior segment disorders. Genet Med. 2020;22:1623–1632. doi:10.1038/S41436-020-0854-X. [PubMed: 32499604]
13. Lang E, Koller S, Bähr L, et al. Exome Sequencing in a Swiss Childhood Glaucoma Cohort Reveals CYP1B1 and FOXC1 Variants as Most Frequent Causes. Transl Vis Sci Technol. 2020;9:1–12. doi:10.1167/TVST.9.7.47.
14. García-Antón MT, Salazar JJ, De Hoz R, et al. Goniodysgenesis variability and activity of CYP1B1 genotypes in primary congenital glaucoma. PLoS One. 2017;12. doi:10.1371/JOURNAL.PONE.0176386.
15. Chavarria-Soley G, Michels-Rautenstrauss K, Pasutto F, et al. Primary congenital glaucoma and Rieger's anomaly: extended haplotypes reveal founder effects for eight distinct CYP1B1 mutations. Mol Vis. 2006;12:523–531. Published 2006 May 22. [PubMed: 16735994]
16. Sivadorai P, Cherninkova S, Bouwer S, et al. Genetic heterogeneity and minor CYP1B1 involvement in the molecular basis of primary congenital glaucoma in Gypsies. Clin Genet. 2008;74:82–87. doi:10.1111/J.1399-0004.2008.01024.X. [PubMed: 18537981]
17. Chitsazian F, Tusi BK, Elahi E, et al. CYP1B1 mutation profile of Iranian primary congenital glaucoma patients and associated haplotypes. J Mol Diagn. 2007;9:382–393. doi:10.2353/JMOLDX.2007.060157. [PubMed: 17591938]
18. Souzeau E, Hayes M, Zhou T, et al. Occurrence of CYP1B1 Mutations in Juvenile Open-Angle Glaucoma With Advanced Visual Field Loss. JAMA Ophthalmol. 2015;133:826–833. doi:10.1001/JAMAOPHTHALMOL.2015.0980. [PubMed: 25950505]
19. Micheal S, Ayub H, Zafar SN, et al. Identification of novel CYP1B1 gene mutations in patients with primary congenital and primary open-angle glaucoma. Clin Exp Ophthalmol. 2015;43:31–39. doi:10.1111/CEO.12369. [PubMed: 25091052]
20. Bagiyeva S, Marfany G, Gonzalez-Angulo O, Gonzalez-Duarte R. Mutational screening of CYP1B1 in Turkish PCG families and functional analyses of newly detected mutations. Mol Vis. 2007;13:1458–1468. Published 2007 Aug 27. [PubMed: 17893647]

21. Zahid T, Khan MU, Zulfiqar A, et al. Investigation of mutational spectrum in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma. Pak J Med Sci. 2023;39:409–416. doi:10.12669/PJMS.39.2.7081. [PubMed: 36950438]

22. Shah M, Bouhenni R, Benmerzouga I. Geographical Variability in CYP1B1 Mutations in Primary Congenital Glaucoma. J Clin Med. 2022;11:2048. doi:10.3390/JCM11072048/S1. [PubMed: 35407656]

23. Morin JD, Merin S, Sheppard RW. Primary congenital glaucoma--a survey. Can J Ophthalmol. 1974;9(1):17–28. [PubMed: 4544900]

24. Chavarria-Soley G, Michels-Rautenstrauss K, Caliebe A, et al. Novel CYP1B1 and known PAX6 mutations in anterior segment dysgenesis (ASD). J Glaucoma. 2006;15:499–504. doi:10.1097/01.IJG.0000243467.28590.6A. [PubMed: 17106362]

25. Alsaif HS, Khan AO, Patel N, et al. Congenital glaucoma and CYP1B1: an old story revisited. Hum Genet. 2019;138:1043–1049. doi:10.1007/s00439-018-1878-z. [PubMed: 29556725]

26. Fetal and Neonatal Eye Pathology. 2020. doi:10.1007/978-3-030-36079-5.

27. García-Antón MT, Salazar JJ, de Hoz R, et al. Goniodysgenesis variability and activity of CYP1B1 genotypes in primary congenital glaucoma. PLoS One. 2017;12. doi:10.1371/JOURNAL.PONE.0176386.

28. Banerjee A, Chakraborty S, Chakraborty A, et al. Functional and Structural Analyses of CYP1B1 Variants Linked to Congenital and Adult-Onset Glaucoma to Investigate the Molecular Basis of These Diseases. PLoS One. 2016;11. doi:10.1371/JOURNAL.PONE.0156252.

29. v. Hippel E. Ueber Hydrophthalmus congenitus nebst Bemerkungen über die Verfärbung der Cornea durch Blutfarbstoff. Albrecht von Graefes Archiv für Ophthalmologie 1897 44:3. 1897;44:539–564. doi:10.1007/BF02017583.

30. Doshi M, Marcus C, Bejjani BA, et al. Immunolocalization of CYP1B1 in normal, human, fetal and adult eyes. Exp Eye Res. 2006;82:24–32. doi:10.1016/J.EXER.2005.04.016. [PubMed: 15979611]

31. Libby RT, Smith RS, Savinova OV., et al. Modification of ocular defects in mouse developmental glaucoma models by tyrosinase. Science. 2003;299:1578–1581. doi:10.1126/SCIENCE.1080095. [PubMed: 12624268]

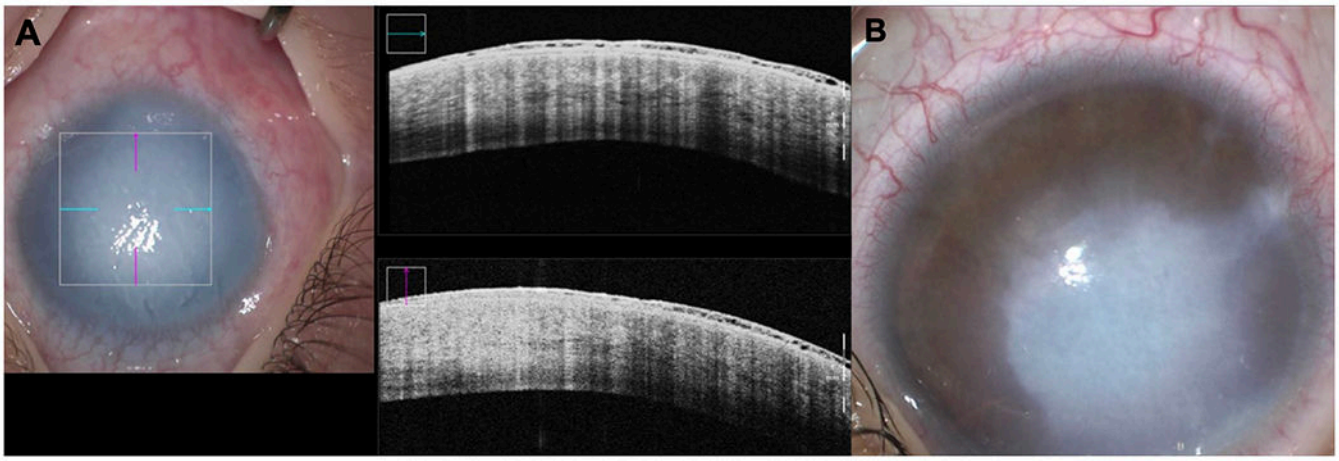

Figure 1.

Clinical appearance of *CYP1B1* cytopathy (A), with a limbus-to-limbus avascular corneal opacity. AS-OCT shows corneal thickening with subepithelial edema. Clinical appearance of the second phenotype related to *CYP1B1* biallelic pathogenic variants (B), with avascular CCO secondary to irido-corneal adhesions.

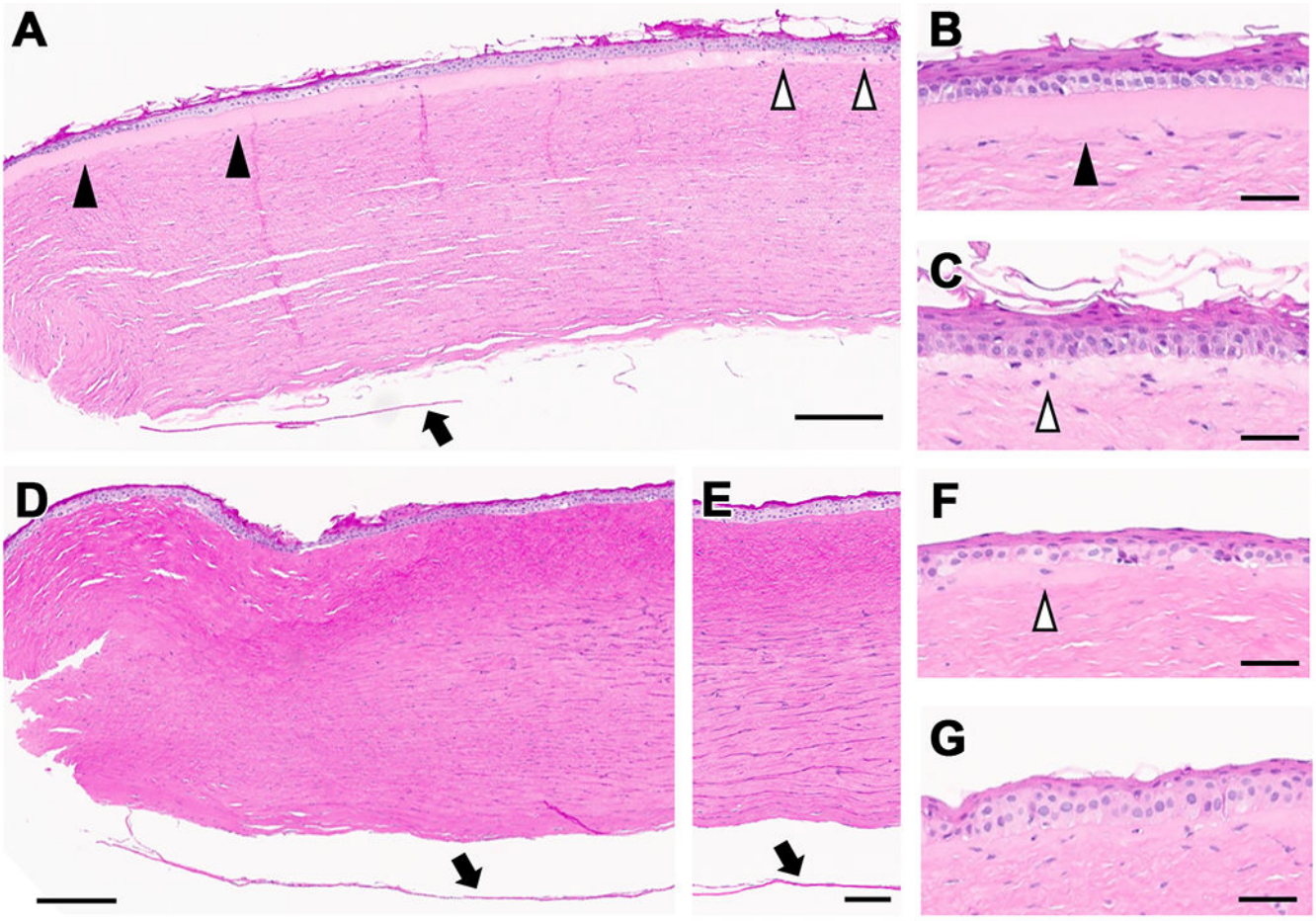

Figure 2.

The right cornea (A, PAS) exhibits severe hyperkeratosis and a markedly thickened Bowman's layer (closed arrowheads) that is most striking towards the periphery (B, H&E). In the central cornea (C, H&E), this layer becomes more attenuated with fragmentation/loss and appearance of nuclei within the Bowman's-like layer (open arrowheads). Descemet's membrane is present at the periphery (A, arrow). The left cornea (D, PAS) shows keratinization of the corneal epithelium and small subepithelial bullae. Descemet's layer is present peripherally (arrow) as well as centrally (E, arrow, PAS). The peripheral left cornea exhibits fragmented segments of a Bowman's-like layer containing nuclei (F, open arrowhead, H&E), similar to the central region of the right eye. Bowman's is mostly absent in the central region of the left eye (G, H&E). See also high resolution images in Supplemental Figure S1 for additional stromal changes. Scale bars: Panels A, D = 200 μm; Panels B-C, F-G = 50 μm; Panel E = 100 μm.

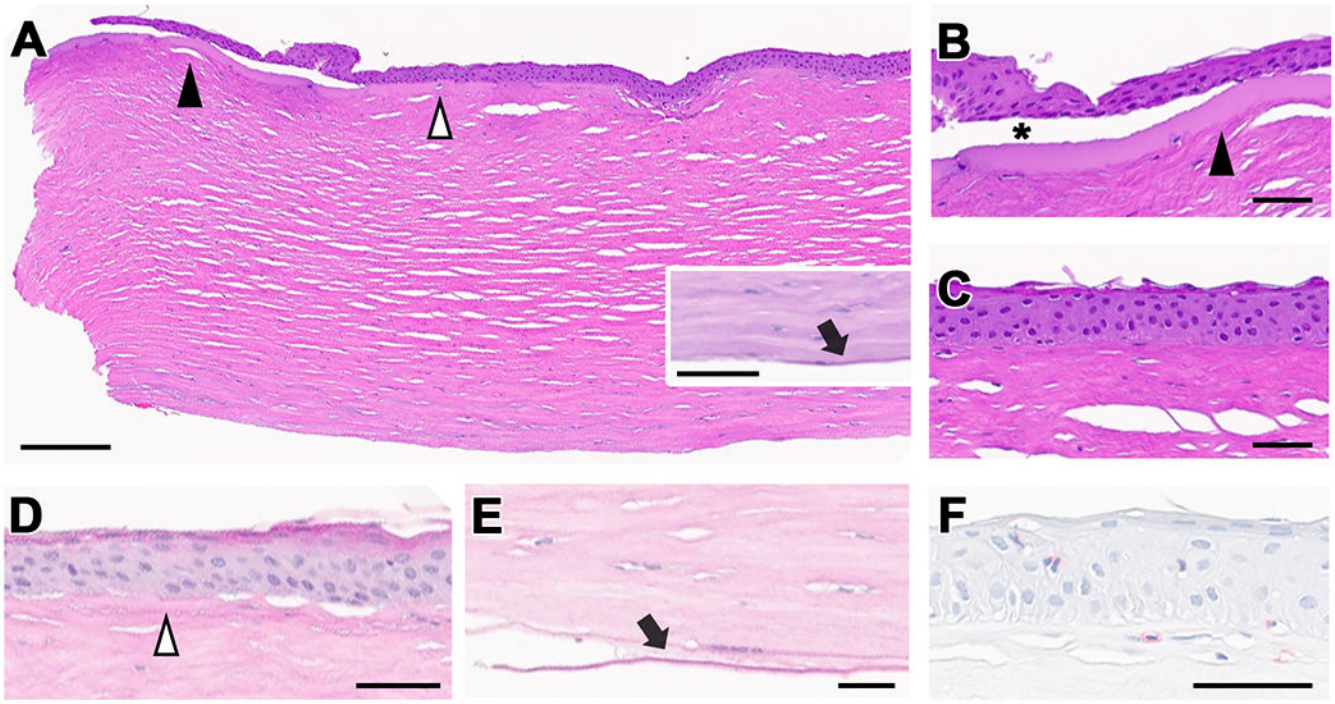

Figure 3.

Histopathological findings of patient 2. A thickened Bowman's-like layer (arrowhead) containing extra nuclei (open arrowhead) are observed on the left eye (A, H&E). PAS stain reveals thin, discontinuous segments of Descemet's membrane lacking endothelial cells spanning both peripheral and central cornea (A, inset, arrow). Higher magnification image of the peripheral cornea reveals mild keratinization of the corneal epithelium and subepithelial bullae (B, H&E, asterisk). Bowman's layer is absent in the central cornea (C, H&E). The right eye showed short discontinuous segments of a Bowman's-like layer that was not obviously thickened and extended into the central region (D, PAS, open arrowhead). A thin Descemet's membrane was present along most of the specimen, showing occasional breaks (E, PAS, arrow). Centrally, there was some intraepithelial and subepithelial lymphocytes (F, leucocyte common antigen, red AEC chromagen). See also high resolution images in Supplemental Figure S1 for additional stromal changes. Scale bars: Panel A = 200 μm, inset A = 100 μm; Panels B, C, D, E, F = 50 μm.

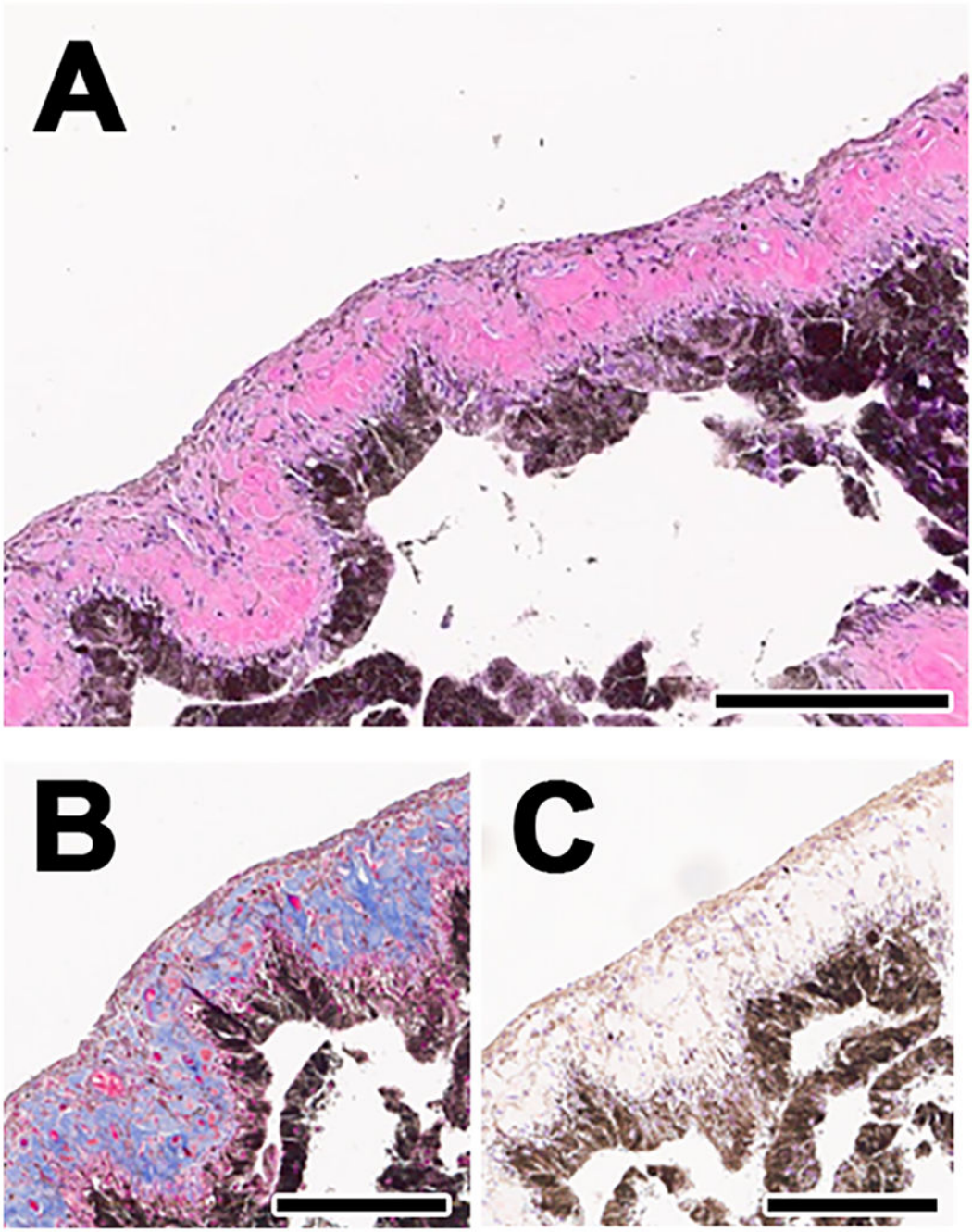

Figure 4.
Histopathological findings of patient 3. The iris showed dense eosinophilic tissue filling the stroma (A), which stained positive for collagen (B, Masson Trichrome, blue) and was negative for amyloid (C, Congo Red). Scale bars = 200 μm.

Table 1.

Clinical data of patients included in the study.

Patient (gender)	Age at presentation	Corneal diameter		Axial length	
		RE	LE	RE	LE
1, M	2 months	10	9.5	19.53	19.51
2, M	3 years	13.5	13	28.87	27.62
3, F	3 years	12	12.25	23.31	25.33