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LTBP2 variants in childhood glaucoma: Phenotypic expansion and clinical experience

Anshuman Verma,[1] Arif O. Khan,[2,3] Venkatesh Pochaboina,[1] Sirisha Senthil[4]

(The first and last authors contributed equally to this study.)

[1]Institute of Rare Eye Diseases and Ocular Genetics, LV Prasad Eye Institute, Hyderabad, India; [2]Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; [3]Department of Ophthalmology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; [4]VST Center for Glaucoma Care, L V Prasad Eye Institute, Hyderabad, India

Purpose: This study describes a distinct spectrum of latent transforming growth factor-β-binding protein 2 (*LTBP2*)–related ocular phenotypes in pediatric glaucoma with supporting genetic evidence and highlights our clinical experiences in its management.

Methods: A total of 189 children with childhood glaucoma underwent whole-exome sequencing–based genetic testing. Of these, 24 children displayed *LTBP2*-related phenotypes, among whom 18 cases who tested positive for *LTBP2* variants were included in the study. The identified variants were confirmed through Sanger sequencing whenever possible and analyzed using in silico tools. The clinical presentation, genetic variants, and management of these 18 cases were thoroughly reviewed and presented.

Results: All 36 eyes of the 18 children with biallelic *LTBP2* variants exhibited megalocornea without Descemet break, iridodonesis, and ectopia lentis. Pupillary changes were noted in all eyes, with persistent pupillary membrane in 78% (28/36) and ectropion uveae in 19% (7/36) eyes. Secondary glaucoma was observed in 72% (26/36) eyes, requiring surgery in 13 of these. Retinal pathology was noted in 47% (17/36) eyes. Lensectomy was performed in 94% (34/36) eyes with a mean age of 4.09 ± 3.5 years. Logistic regression analysis suggested that older age at lensectomy increased the risk of secondary glaucoma (hazard ratio, 1.69; [95% Confidence Interval: 1.00, 2.86], $p < 0.05$). The identified *LTBP2* variants included five stop-gain variations, six frameshift variations, and one substitution variation, with five being novel and seven classified as rare variants.

Conclusions: The study expands the classic *LTBP2*-related phenotype spectrum in an Indian pediatric glaucoma cohort, highlighting additional features such as persistent pupillary membrane, ectropion uveae, and associated retinal pathology. These ocular manifestations were predominantly linked to nonsense *LTBP2* variants. From a management standpoint, early lensectomy can help prevent secondary glaucoma, while timely identification and treatment of peripheral retinal pathology can reduce the risk of sight-threatening complications.

Latent transforming growth factor-β-binding protein 2 (*LTBP2*) plays a key role in the structural integrity of the extracellular matrix and its interactions with microfibril-containing elastic tissues [1]. *LTBP2*-related ocular dysgenesis is a rare autosomal recessive condition characterized by megalocornea, zonular weakness, and a predisposition to secondary lens-related glaucoma. The phenotypic spectrum associated with *LTBP2* variants is wide, and its ocular manifestations can be confused with those seen in primary congenital glaucoma (PCG) [2]. The diagnosis of PCG is clinical, with typical features including corneal enlargement, corneal edema or haze, Descemet membrane breaks (Haab striae), optic nerve cupping, ocular enlargement (buphthalmos), myopia, and astigmatism. The most common identifiable cause for PCG is biallelic mutations in cytochrome P4501B1 (*CYP1B1*) [3].

In 2009, *LTBP2* was suggested as a second gene that can be associated with PCG [4]. However, later, it became evident that biallelic *LTBP2* variants more commonly result in a PCG-mimicking phenotype: primary megalocornea with zonular weakness and secondary lens-related glaucoma [2]. Recognizing the classic *LTBP2*-related phenotype and differentiating it from PCG is crucial, as management strategies differ; *LTBP2*-related cases require lensectomy, while PCG typically necessitates angle surgery. In this study, we report our experience and observations for the largest genetically confirmed cohort of the classical *LTBP2*-related phenotype reported to date. We also describe additional phenotypic features, novel *LTBP2* variants, and management recommendations based on our clinical experiences.

Correspondence to: Sirisha Senthil, L.V Prasad Eye Institute, Kallam Anji Reddy campus, L V Prasad Marg, Road No: 2, Banjara Hills, Hyderabad, India-500034; Phone: +91 40 6810 2619; email: sirishasenthil@lvpei.org

METHODS

Patient recruitment, consent, and data collection: The patients were recruited from April 2020 to December 2023 at the L V Prasad Eye Institute, Hyderabad, India. The study had received approval from the institutional ethics committee, and explicit informed consent was obtained from the legal guardians. The study strictly adhered to the ethical guidelines outlined in the Code of Ethics of the World Medical Association, as per the Declaration of Helsinki.

A total of 189 children diagnosed with childhood glaucoma were subjected to whole-exome sequencing (WES)–based genetic testing. This group included children with typical or atypical features of PCG, secondary developmental glaucoma, or syndromic glaucoma. Among these, children with PCG (identified with the *CYP1B1* variant), syndromic ectopia lentis (Marfan syndrome, homocystinuria, etc.), secondary glaucoma due to posterior segment pathology, and isolated congenital megalocornea and keratoglobus, all negative for *LTBP2* variants, were excluded from the study. Phenotypically, 24 children exhibited classic *LTBP2*-associated features, including primary megalocornea without Haab striae and zonular weakness. Among these, two children had characteristic features, but no pathogenic variants were detected. Another child with similar features tested positive for a growth hormone receptor (*GH-R*) gene variant, indicative of Laron dwarfism. Additionally, three children with microspherophakia and ectopia lentis, along with suspected megalocornea, tested positive for C3 and PZP-like alpha-2-macroglobulin domain containing 8 (*CPAMD8*), cystathionine β-synthase (*CBS*), and fibrillin 1 (*FBN1*) genes, respectively. Following the exclusion of these six cases, 18 children with *LTBP2*-related ocular phenotypes and positive for biallelic *LTBP2* variants were included in the study. Consequently, the relative frequency of apparent biallelic *LTBP2* variants among the pediatric glaucoma cohort that underwent genetic testing was 9.5% (18 of 189), and among those exhibiting characteristic *LTBP2*-related features, the prevalence was 75% (18 of 24).

All the included 18 patients underwent a detailed ophthalmic examination in the clinic physically or under anesthesia. Anterior segment evaluation included horizontal corneal diameter (HCD), corneal clarity, iris or lens details, refraction, and measurement of intraocular pressure (IOP) with a Perkins and Goldmann applanation tonometer. Posterior segment evaluation involved examining the optic disc and assessing the retina with a 78D lens or 20D lens and indirect ophthalmoscopy. Patients also underwent ocular biometry, and anterior and posterior segment imaging was performed whenever possible. They were evaluated for their clinical presentation, treatment, and outcomes until the last follow-up in December 2023.

Genetic counseling and testing: Patients and their families received pretest and posttest counseling from a certified genetic counselor at the institute, providing education regarding the genetic nature of the condition, its inheritance pattern, and limitations of genetic testing. A multigenerational pedigree was drawn for all 14 families except one (family 11), who was unavailable for genetic counselling.

Next-generation sequencing–based genetic testing was performed in all probands. Briefly, WES with an approximately 30-Mb region was conducted using the Illumina (San Diego, CA) NovaSeq platform. The targeted regions covered approximately 99% of the reference consensus coding sequence (CCDS) with an average sequencing depth of 80× to 100× and over 90% of bases covered at a depth of 20× within the target region. Variant calling against the reference genome was performed using the Genomic Analysis Tool Kit. The identified variants underwent annotation and filtering using the Golden Helix VarSeq and Varsome analysis workflow, adhering to the American College of Medical Genetics and Genomics (ACMG) 2015 update guidelines for the classification of sequence variants [5]. All potential modes of inheritance were considered and identified variants were evaluated based on family history and clinical information to assess pathogenicity and causality. The variant nomenclature followed the Human Genome Variation Society (HGVS) standard, with the *LTBP2* reference sequence (NM_000428.3).

In silico analysis: An in silico analysis of identified *LTBP2* variants was performed using Mutation Taster (Berlin, Germany), Franklin by Genoox (Palo Alto, CA), and Ensembl Variant Effect Predictor (VEP; Cambridge, UK). Different parameters under these tools were examined to determine the pathogenicity of the identified variants.

Statistical analysis: The clinical parameters of the 18 patients were analyzed for their association with the development of glaucoma using logistic regression analysis. The data were analyzed for normality using the Shapiro-Wilk test. Descriptive statistics included mean and standard deviation for normally distributed variables and median and interquartile range for nonnormally distributed variables. Categorical data were described in proportions. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic and ocular parameters: A total of 18 children (11 females, 7 males), with a median presenting age of 4 years (range: 4 months to 14 years), from 14 families (13

consanguineous and 1 non-consanguineous), were included in the study based on the established inclusion and exclusion criteria. Complete clinical details for the cases in this cohort, including the number of patients and eyes with associated ocular features, are presented in Appendix 1. The selected cohort exhibited no major systemic or syndromic abnormalities beyond ocular features through the last follow-up. Figure 1 shows the representation of different ocular features (in percentages) in 36 eyes of the 18 patients in the study cohort. In all 36 eyes (100%) of 18 children, there was megalocornea (HCD >12 mm) without Descemet breaks, evident gross iridodonesis, and the presence of ectopia lentis (Figure 2, Figure 3, and Figure 4). The mean HCD was 13.37 ± 0.8 mm (range, 12.5-15 mm). A persistent pupillary membrane (PPM) (Figure 2A, B) was noted in 28 of 36 eyes (78%) and ectropion uveae (Figure 2C) in seven of 36 eyes (19%), and in one eye, the pupil could not be visualized due to a hazy cornea. Several of them had nondilating pupils. There was a posteriorly dislocated crystalline lens (Figure 2D) in 12 of 36 eyes (33.3%), an anteriorly dislocated lens (Figure 2E) in two of 36 eyes (5.5%), a subluxated lens (Figure 2F) in 17 of 36 eyes (47.2%), and a subluxated cataractous lens in one of 36 eyes (3%), and 4 of 36 eyes (11%) were aphakic and had lensectomy performed for subluxated lens elsewhere. The central corneal thickness was available in 14 children, and the mean central corneal thickness was 547 ± 103 microns (range, 402–709). The median axial length of 19 eyes was 24.33 (22.74, 25.17) mm. Ten eyes had a shallow anterior chamber (AC), 23 eyes had a deep AC, two eyes had an irregular AC depth, and one had emulsified silicone oil bubbles in AC after vitreoretinal surgery for retinal detachment (RD; Appendix 1). Secondary glaucoma was detected in 72% (26 of 36) eyes showing disc damage (Figure 3A), which was intervened through lensectomy or glaucoma drainage devices (Figure 3B, C); there was no glaucoma in nine eyes; and two eyes were phthisical and hence glaucoma could not be assessed. Retinal pathology was noted in 47% eyes (17 of 36), including RD in seven eyes, peripheral retinal degeneration in eight eyes, and suprachoroidal hemorrhage in two eyes (Figure 4A-C and Figure 2G). The median follow-up of these children was 0.94 years (0.76, 6.51).

Management and outcomes: Different surgical management strategies, including lensectomy, glaucoma surgeries, and retinal surgeries, were performed according to clinician judgment (Appendix 1).

Lensectomy: Thirty-four of 36 eyes underwent pars plana lensectomy (four of these eyes had lensectomy done for ectopia lentis elsewhere), and two eyes were phthisical (one spontaneous RD and one eye phthisical after a primary glaucoma surgery performed elsewhere). The mean age at lensectomy was 4.09 ± 3.5 years (youngest, four months; oldest, 14 years). The mean refractive error after lensectomy was 9.2 ± 3.1 D.

Glaucoma and glaucoma surgeries: Secondary glaucoma, noted in 26 of 36 eyes, had a mean IOP at presentation of 16.35 ± 10.2 mm Hg, and four eyes had an IOP less than 5 mm Hg (RD or phthisis). The mean cup-to-disc ratio was 0.51 ± 0.28, and nine eyes had >0.8 cup-to-disc ratio. Thirteen eyes with glaucoma required surgery during the follow-up period for IOP control, with a few needing more than one surgery with a mean of 1.46 ± 0.6 surgeries. Types of surgeries included six glaucoma drainage devices, three goniotomies, one combined trabeculectomy with trabeculotomy, one trabeculectomy with mitomycin C, one external trabeculotomy alone, and seven cyclophotocoagulations. At the final follow-up, 19 eyes were on topical antiglaucoma medications with a mean of 1.2 antiglaucoma medications, and the mean IOP was 15.8 ± 9.2 mm Hg.

Posterior segment findings and management: Seventeen eyes (47%) had coexisting retinal pathologies, with seven of 17 eyes developing RD following lensectomy or a glaucoma procedure. Two of the 17 eyes developed suprachoroidal hemorrhage after undergoing combined trabeculectomy with trabeculotomy, which was mistakenly performed elsewhere due to a misdiagnosis of PCG. One of the misdiagnosed eyes was resolved with conservative management, and vision improved to 1.5 logarithm of the minimum angle of resolution, while the other eye (that had RD as well) became phthisical. Five of 17 eyes with lattice, with or without retinal holes, underwent peripheral retinal barrage laser intraoperatively during pars plana lensectomy with complete or core vitrectomy (pars plana vitrectomy) and did not develop RD until the last follow-up. Three of 17 eyes had peripheral pigmentary chorioretinal atrophic changes and were not treated but were kept under observation. None of the eyes had triamcinolone-guided posterior vitreous detachment induction during vitrectomy. RD after lensectomy occurred one year later in two eyes and two years later in the other two eyes and one year later after glaucoma surgery. All were rhegmatogenous RD, and one had a giant retinal tear.

Genetic analysis:

Pedigree analysis—The pedigree analysis showed 93% (13 of 14) parental consanguinity in the cohort (Appendix 2). Additionally, none of the children or their parents gave a history of any significant other systemic illness.

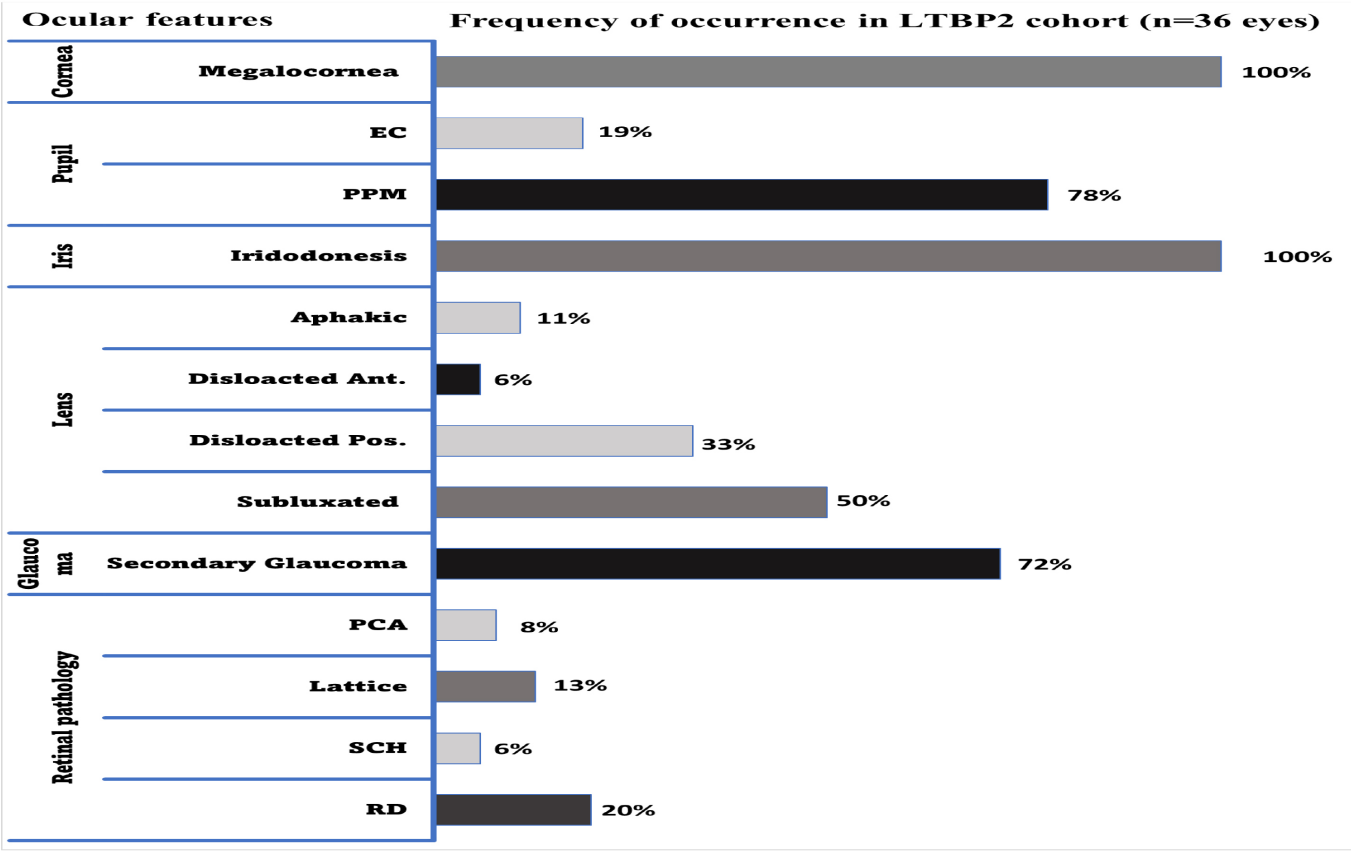

Figure 1. Frequency of ophthalmic features in the study cohort. The bar graph shows the occurrence of different clinical features (in percentage) in 36 eyes of 18 patients. These included ectropion uveae (EC), persistent pupillary membrane (PPM), anterior (ant) and posterior (pos.) dislocation of crystalline lens, subluxation of the lens, suprachoroidal haemorrhage (SCH), retinal detachment (RD) and peripheral chorioretinal atrophic changes (PCA).

Variant analysis—Using WES, genetic analysis successfully detected disease-related variants in the *LTBP2* gene as suspected across all 18 children from 14 families (Table 1). The identified *LTBP2* variants were subsequently confirmed through Sanger sequencing in the family (Appendix 3). These genetic alterations were observed in either a homozygous state in 16 cases or a compound heterozygous form in 2 cases.

In 14 families, 12 distinct *LTBP2* genetic variants were identified, including five stop-gain variations, six frameshift variations, and 1 substitution variation (Table 1 and Appendix 4). Variations p.Gln329Ter in exon 4 and p.Val586Glyfs*17 in exon 8 were recurrent in two unrelated families and therefore could be potentially hotspot *LTBP2* variants. The relatively higher frequency of these variants in a small cohort with prevalent consanguinity suggests they are likely founder variants. However, future reports of these frequent variants would provide clear insights.

No additional gene variants, including *CYP1B1* associated with PCG or any other genes involved in anterior segment dysgenesis, were identified except in two cases (P5 and P18) that reported additional heterozygote variants in genes myocilin (*MYOC*) and nuclear receptor subfamily 0 group B member 2 (*NR0B2*) genes, respectively (refer to Table 1 for details). The *MYOC* (NM_000261) gene is associated with glaucoma type 1A and primary open-angle glaucoma [6]. The identified *MYOC* heterozygous frameshift variant in P5 c.358delG (p.Glu120Serfs*4) was not observed in the 1000 Genomes Database but was seen in the ExAC database at a 0.00002 minor allele frequency. Phenotypically, P5 exhibited central corneal opacity (scar secondary to anteriorly dislocated lens) in the right eye (RE) with extensive staphyloma and secondary glaucoma and a typical *LTBP2* phenotype in the left eye. The RE had a posteriorly dislocated lens along with secondary glaucoma, which was managed medically (Appendix 5). The *NR0B2* (NM_021969.3) variant c.227delT (p.Phe76Serfs*30) in P18 has been reported to the

ClinVar database (submission accession SCV004113399) and is associated with early-onset obesity. Phenotypically, while there was no sign of obesity, P18 had a severe anterior segment *LTBP2* phenotype along with bilateral RD, with one eye having a giant retinal tear. P18 underwent surgery for RD with vitrectomy and silicone oil implantation, with its removal after a few months. P18, who developed uncontrolled intraocular pressure with emulsified silicone oil bubbles and advanced glaucoma, received sequential transscleral cyclophotocoagulation, which controlled the IOP, but ultimately lost vision in one eye due to recurrent vitreous hemorrhage and hyphema (Appendix 6).

Among the different protein structural domains of LTBP2 [7], most of the identified variants (6 of 12) were in the calcium-binding epidermal growth factor (EGF)–like domain of LTBP2 (Figure 5). Variants not reported in population genome databases, like the 1000 Genomes Database or the ExAC database, were given novel status, while other variants (with rs ID) had a minor allele frequency less than 0.01, signifying their rare status (Table 1). Among the 12 variants, 11 were classified as likely pathogenic, and one was a variant of unknown significance according to the ACMG criteria (Table 1). Extensive bioinformatic analyses using various in silico tools consistently categorized these variants as pathogenic, underscoring their significant detrimental effects on gene function (Table 2). Interestingly, most of these variants caused the generation of a premature stop codon due to nonsense or frameshift variations (details in Table 2).

Statistical analysis: For the risk of developing glaucoma, clinical parameters like type of ectopia lentis, HCD, age at lensectomy, presence of retinal pathology, and IOP at presentation were evaluated. In a logistic regression analysis, older age at lensectomy was associated with a greater risk of developing glaucoma (hazard ratio, 1.69; [95% CI: 1, 2.86]; $p < 0.05$). Other clinical parameters did not show any significant association.

DISCUSSION

This study of 18 Indian children with *LTPB2*-related pediatric glaucoma is the largest genetically confirmed *LTBP2* group documented to date. Our findings expand the understanding of the *LTBP2* classic phenotype, characterized by congenital megalocornea with zonular weakness and lens-related

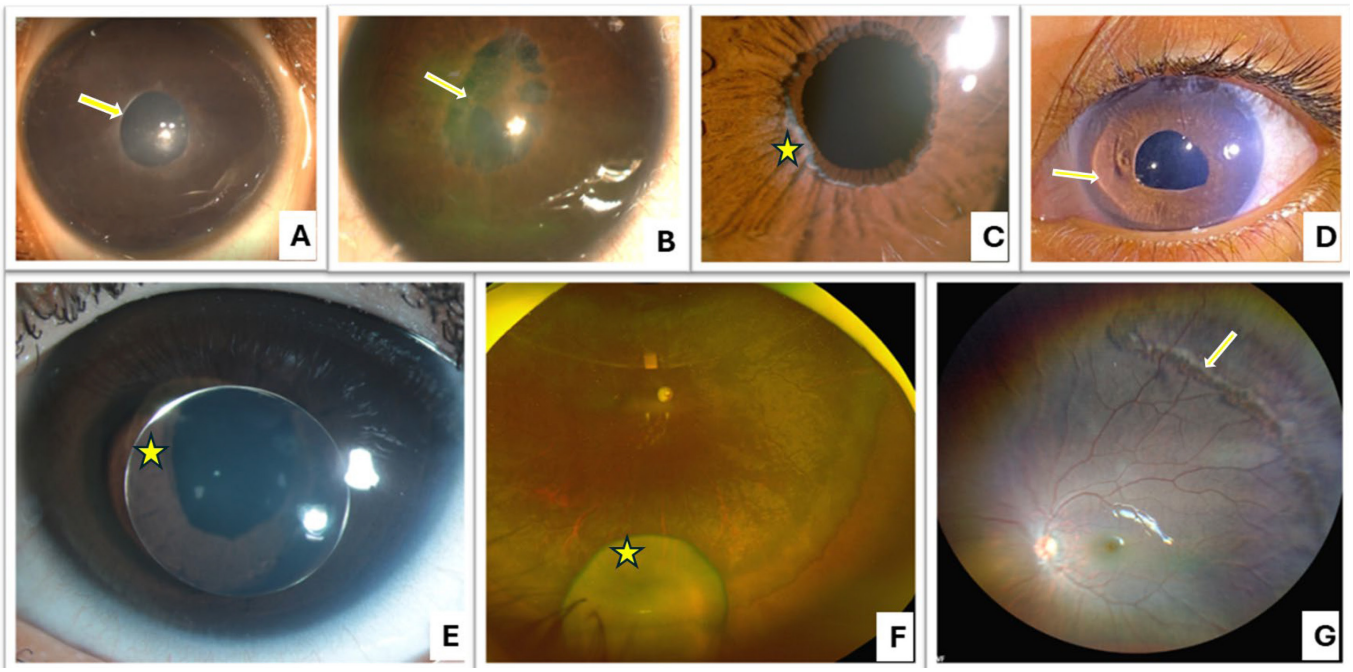

Figure 2. The spectrum of ocular features observed in the LTBP2 patient's cohort. **A**: Showing whitish pupillary border (possible persistent pupillary membrane (PPM) remnant, marked with arow), in right eye of case P1. **B**: Indicating PPM in the the left eye of case P1. **C**: Showing Ectropion Uveae (EC) in case P13 (note a small area of whitish membrane in the area where EC has not developed yet (marked with star). **D**: Showing anterior segment image with gross iridodonesis in an eye with posteriorly dislocated lens in case P17 (note the shadow of the iridodonesis marked with arrow). **E**: Showing an anteriorly dislocated microspherophakic lens in the LE of case P12 wandering between anterior and posterior chamber, (marked with star). **F**: Shows posteriorly dislocated lens in the RE of case P12, and **G**: Shows peripheral retinal lattice in case P2.

secondary glaucoma, to encompass additional features such as PPM, ectropion uveae, and peripheral RD. Making an initial diagnosis can be tricky in such a spectrum due to the presence of megalocornea and lens subluxation, which can mimic PCG and might lead to a consideration of glaucoma surgeries. However, certain signs, such as the absence of Descemet breaks (Haab striae) despite megalocornea, along with ectopia lentis, iridodonesis, and a whitish persistent pupillary margin, suggest a different clinical picture that needs to be recognized. Our cohort represents a different *LTBP2* clinical spectrum other than PCG that is reinforced by the absence of pathogenic variants in the *CYP1B1* gene, which is a common cause of PCG. We support our clinical findings with genetic evidence identifying novel *LTBP2* pathogenic variants, including stop-gain mutations (50%), frameshift mutations (45%), and substitutions (5%) in this cohort. The annotation and characterization of identified *LTBP2* variants using in silico tools further supported their pathogenicity. Furthermore, we provide practical recommendations for managing these patients based on our clinical insights.

LTBP2 is a member of the LTBP protein family, which is crucial for transforming growth factor β activation and regulation. Unlike other LTBP family members, LTBP2 operates independently of transforming growth factor B and is directly involved in stabilizing microfibril bundles and regulating elastic fiber assembly in the extracellular matrix (ECM) [8]. LTBP2 is widely expressed in tissues such as the liver, bone, trabecular meshwork, and ciliary processes [9]. Small interfering RNA–mediated knockdown of *LTBP2* in human trabecular meshwork cell cultures altered ECM gene regulation and induced apoptosis [10]. The role of *LTBP2* in ocular phenotypes is evident from animal studies as well. *LTBP2* knockout studies in animal models have shown weakened ciliary zonules and ectopia lentis [11]. Other phenotypes include altered skin features, fewer tail vertebrae, and longer

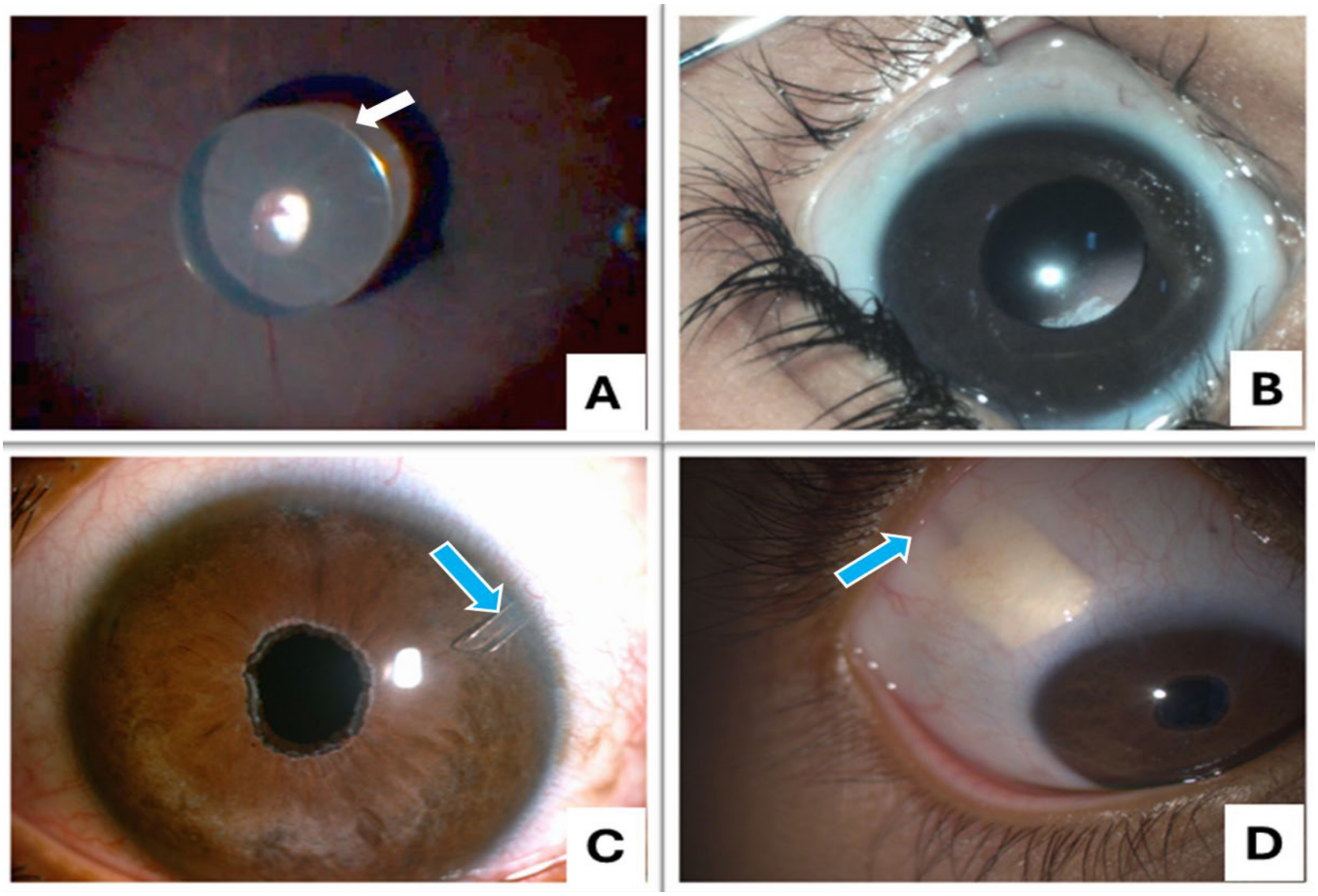

Figure 3. Clinical status of eyes with secondary glaucoma, initially treated with lensectomy followed by glaucoma surgery as needed in the study cohort. **A**: Advanced glaucomatous disc damage with posteriorly dislocated lens (marked by arrow) in case P3. **B**: Anterior segment picture of same eye of P3 after lensectomy. **C**, **D**: Anterior segment photograph of case P16 and case P7 respectively post glaucoma drainage device implantation for uncontrolled intraocular pressure, with well-positioned tube (arrow in **C**) and a diffuse bleb posteriorly (arrow in **D**).

bleeding times [12]. In a report, a homozygous duplication (insertion) c.5446dupC in *LTBP2* was found in affected family members with isolated microspherophakia [13]. Similarly, in three consanguineous families with secondary glaucoma linked to spherophakia or ectopia lentis, affected children in each family carried unique *LTBP2* variants: p.Ser338ProfsTer4 (c.1012delT), p.Gln1619Ter (c.4855C>T), and p.Cys1438Tyr (c.4313G>A), respectively [2]. In a previous study, genetic variants in *LTBP2* were identified in affected children from two families exhibiting distinct ocular phenotypes, including megalocornea, impaired vision, microspherophakia, ectopia lentis, and myopia, alongside Marfanoid features such as a high-arched palate and tall stature with an unusually large arm span over body height ratio [14]. Notably, there were no Marfan-like features or any other systemic features in our study cohort as of the last follow-up. Eight novel *LTBP2* variants were identified in the Chinese congenital ectopia lentis cohort, characterized by features of megalocornea, spherophakia, high myopia, and glaucoma [15]. The clinical spectrum of *LTBP2* involvement has also expanded to other diseases, including Weill-Marchesani syndrome and alveolar capillary dysplasia without misalignment of pulmonary veins [16,17]. *LTBP2* is also associated with low bone mineral density and may serve as a circulatory biomarker for pulmonary arterial hypertension and acute kidney injury [18,19]. Its overexpression in various cancers, such as nasopharyngeal cancer, esophageal cancer, melanoma, and cervical cancer, has shown prognostic significance [20]. Thus, the range of *LTBP2* clinical phenotypes is expanding in both ocular and nonocular forms.

The *LTBP2* variants identified in our cohort were novel or rare with low population frequency. Variants c.985C>T and c.1756dupG could be observed in probands from two unrelated families in a consanguineous population, suggesting they could be frequent causative founder variants. Most *LTBP2* pathogenic variants in our study were interpreted as likely pathogenic status according to ACMG guidelines, probably due to a lack of previous reports. One case (Cys1413Gly) was primarily classified as a variant of uncertain significance. However, the patient with this variant had a distinct *LTBP2* phenotype, and no other gene variants were found. This variant was absent from the 1000 Genomes Database and presented at a low frequency (0.000008) in the ExAC database. Multiple bioinformatics tools, including SIFT, PolyPhen, MutationTaster, and PROVEAN, predicted it to be deleterious.

LTBP2 has EGF-like repeats and four 8-cysteine motifs, similar to fibrillin 1 and fibrillin 2. Most genetic variants in our study were seen in the EGF domain (Figure 5). Interestingly, many of these identified variants were causing a premature stop codon with or without the frameshift of the LTBP2 protein. All of these protein truncation variants (premature termination codons [PTCs]) could activate the nonsense-mediated decay (NMD) pathway (Table 2).

NMD is a crucial quality control mechanism that eliminates fully or partially processed messenger RNA transcripts containing PTCs. The activation of NMD largely depends on the location of the PTC. According to the canonical rule, PTCs situated in the final exon or within 50 nucleotides upstream of the second to last exon generally evade NMD. In our cohort, none of the identified PTCs were located in

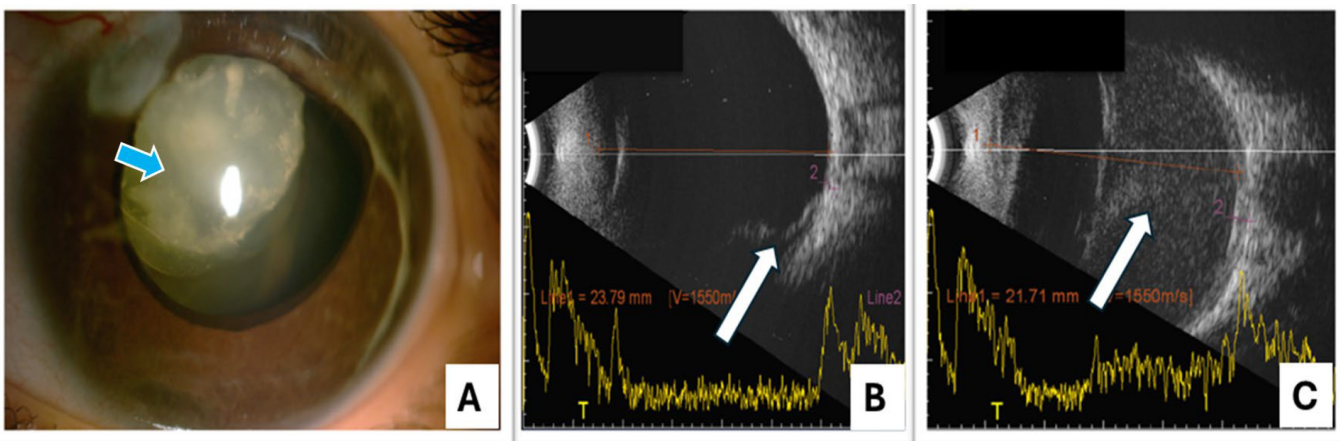

Figure 4. Ocular status of posterior segment complications in in patient associated with *LTBP2* variation. **A**: Anterior segment photograph showing a hypotonus eye with subluxated microspherophakic cataractous lens (marked by arrow) in an eye with retinal detachment in case P9. **B**: B-scan ultrasound showing retinal detachment (arrow marked) in an eye post lensectomy in case P8. **C**: Shows B -scan with suprachoroidal haemorrhage (arrow marked) following combined trabeculotomy with trabeculectomy done elsewhere in case P9.

Table 1. List of *LTBP2* variations identified in this study.

Family No.	Patient ID	Age	Sex	Consanguinity	LTBP2 nucleotide change	LTBP2 AA change	Variation type	Exon	Zygosity	ACMG	Variation status	Testing method	NGS coverage	Sanger validation	Other gene variation detected
F1	P1	0.4	M	Y	c.3499C>T	p.Gln1167Ter	stop gain	23	Homo	LP	Novel	WES	53X		No
F1	P2	2	F	Y	c.3499C>T	p.Gln1167Ter	stop gain	23	Homo	LP	Novel	Sanger		Y	
F2	P3	5	F	Y	c.3183C>A	p.Cys1061Ter	stop gain	21	Com Het	LP	Rare rs2087047140	WES	85X		No
				Y	c.328 C>T	p.Gln110Ter	stop gain	1	Com Het	LP	Rare rs1263916438	WES	135X		
F2	P4	1	F	Y	c.3183C>A	p.Cys1061Ter	stop gain	21	Com Het	LP	Rare rs2087047140	Sanger		Y	No
				Y	c.328C>T	p.Gln110Ter	stop gain	1	Com Het	LP	Rare rs1263916438	Sanger		Y	
F3	P5	7	F	Y	c.1921delA	p.Arg641Glyfs*100	frameshift	10	Homo	LP	Rare rs765897698	WES	48X		MYOC Het.c.358delG
F4	P6	2	M	Y	c.1756dupG	p.Val586Gfs*17	frameshift	8	Homo	LP	Novel	WES	95X		No
	P7	4	F	Y	c.1756dupG	p.Val586Gf*17	frameshift	8	Homo	LP	Novel			Y	No
F5	P8	2	F	Y	c.985C>T	p.Gln329Ter	stop gain	4	Homo	LP	Novel	WES	135X		No
	P9	7	F	Y	c.985C>T	p.Gln329Ter	stop gain	4	Homo	LP	Novel	WES	100X	Y	No
F6	P10	12	M	Y	c.4237T>G	p.Cys1413Gly	missense	29	Homo	VUS	Novel	WES	188X		No
F7	P11	3	F	Y	c.1201dupC	p.Gln401Profs*202	frameshift	6	Homo	LP	Novel	WES	84x	Y	No
F8	P12	6	F	No	c.3131C>G	p.Ser1044Ter	stop gain	20	Homo	LP	Rare rs1343693948	WES	61X	Y	No
F9	P13	1	M	Y	c.985C>T	p.Gln329Ter	stop gain	4	Homo	LP	Novel	WES	111X		No
F10	P14	4	F	Y	c.4171dupG	p.Ala1391Glyfs*8	frameshift	28	Homo	LP	Rare rs779044154	WES	100X	Y	No
F11	P15	10	F	Y	c.1756dupG	p.V586Glyfs*17	frameshift	8	Homo	LP	Novel	WES	31X	Y	No
F12	P16	4	M	Y	c.1756dupG	p.V586Glyfs*17	frameshift	8	Homo	LP	Novel	WES	106X	Y	No
F13	P17	5	M	Y	c.4545_4552delCG-GCTTCC	p.Gly1516Leufs*9	frameshift	31	Homo	LP	Rare rs144521879	WES	57X	Y	No
F14	P18	14	M	Y	c.2811delA	p.Val939Cysfs*71	frameshift	18	Homo	LP	Rare rs763673948	WES	42X		NR0B2 Het.c.227delT

Homo: Homozygous, Het: Heterozygous, Com Het: Compound heterozygous, LP: Likely pathogenic, VUS: Variant of unknown significance, ACMG: American college of medical genetics, Y: Yes, M-Male, F:Female. Note- Family 3 and 14 were identified with additional variants in unrelated genes.

terminal or preterminal exons, making them direct targets for NMD without escape. If a PTC escapes NMD, the resulting frameshifted, altered, or truncated proteins may retain partial function, exhibit dominant-negative effects, display gain of function, or have no significant impact. In contrast, robust NMD activation leads to the complete degradation of the messenger RNA, resulting in a total loss of the encoded protein and its associated function. While NMD can sometimes mitigate the effects of pathogenic mutations, most human PTC variants show that NMD typically exacerbates the detrimental consequences of truncating variants. Furthermore, studies show that activation of NMD may influence the expression of other normal genes as well [21]. In our cohort, where most PTC variants are predicted to be NMD targets, it suggests that the distinct and severe ocular manifestations associated with the *LTBP2* gene phenotype may be driven by NMD activation, leading to a complete loss of protein function. The phenotypic spectrum seen in our cohort in the context of *LTBP2* genotype needs to be understood for identifying the potential disease process and mechanism and genotype-phenotype correlations.

Lens dislocation: The primary pathology in these eyes is likely to be zonulopathy, which predisposes to luxation or dislocation of the lens. This weakening of the zonules has been closely linked to findings in *LTBP2* knockout mice, in which the structural organization of the zonules remains intact, but their tensile strength is compromised, leading to their degradation with movement and, consequently, reduced longevity [22]. The clinical manifestation of the displaced lens in our cohort could be seen as early as four months, signifying zonular breakage at an early stage. Therefore, we hypothesize the following: (1) absence of LTBP2 protein results in low-tensile strength zonules; (2) as the human eye undergoes saccades, it causes strain on the nasal and temporal zonules, which start breaking as early as two to three months of age; and (3) this results in ectopia lentis and subluxation.

Iridodonesis: Microfibrils are an essential component of elastic fibers in body connective tissue, encoded by the *FBN1* (fibrillin) gene. Structurally, they are 0.5 to 1.0 microns and have a central core and peripheral surrounding ring cover. FBN1 and FBN2 are present in the inner and outer rings. The interactions between LTBP2 and the FBN1/2 protein

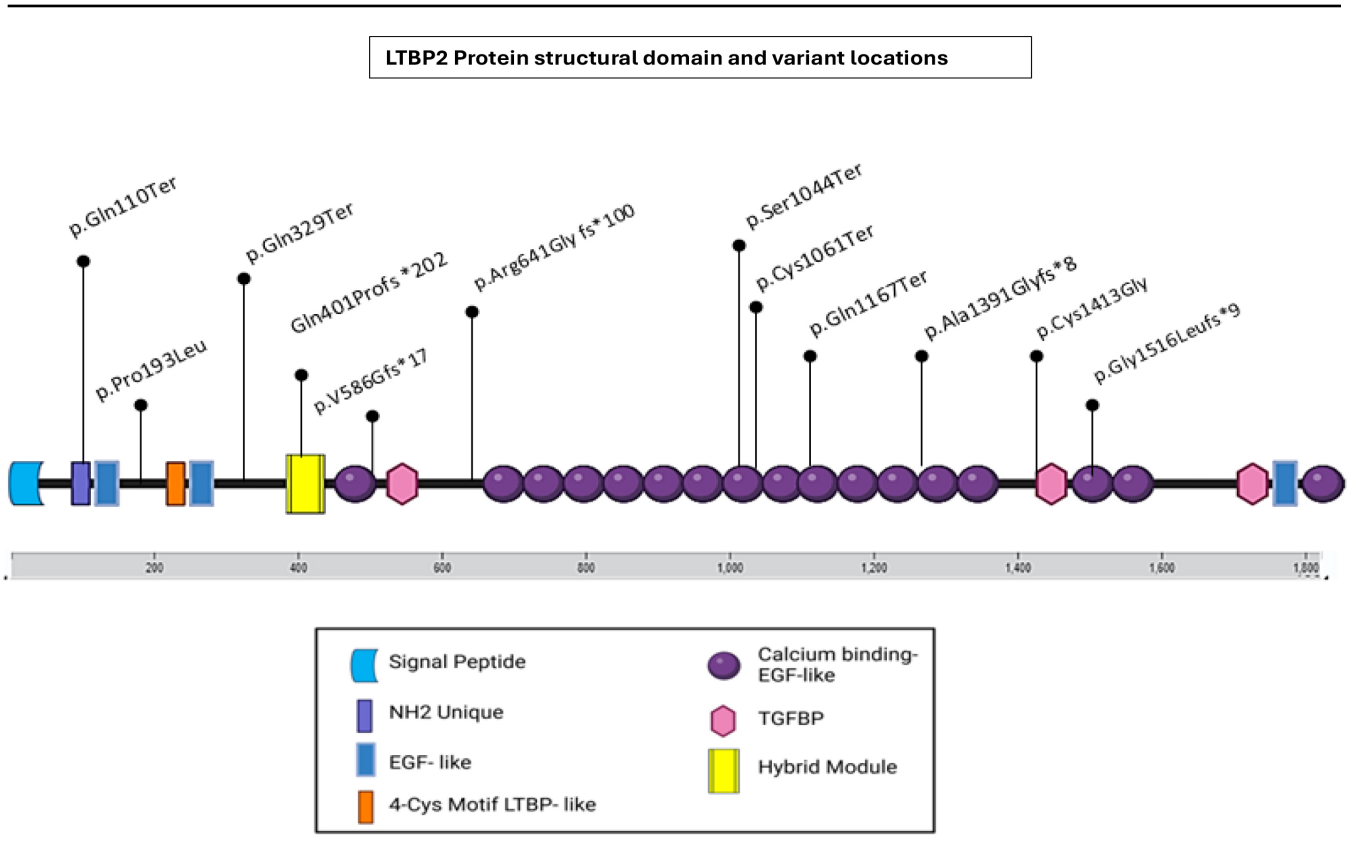

Figure 5. Distribution of identified LTBP2 genetic variants across LTPB2 protein domains. The 7 domains of LTBP2 protein are highlighted in this figure and variant domain-wise locations is specified. Notably, the calcium-binding epidermal growth factor–like domain contains the highest number of variants, accounting for six out of the twelve identified variants.

Table 2. In silico analysis of identified LTBP2 variants.

Variant No.	LTBP2 cDNA variant	LTBP2 protein variant	Variant chromosomal location	Variation impact	Franklin prediction	Mutation taster prediction	PhyloP	Phast Cons	Potential target for NMD (Y/N)	Potential effect on splicing (Y/N)	MutPred 2	CADD_phred Score
1	c.3499C>T	p.Gln1167Ter	14:74508857-74508857	STOPGAIN at 1167 aa	LP	Disease causing	2.241	1	Y	No	0.83405	41
2	c.3183C>A	p.Cys1061Ter	14:74509828-74509828	STOPGAIN at 1061 aa	LP	Disease causing	3.18	1	Y	Y	0.80611	36
3	c.328C>T	p.Gln110Ter	14:74611617-74611617	STOPGAIN at 110 aa	LP	Disease causing	0.237	0.982	Y	Y	0.64702	37
4	c.1921del	p.Arg641GlyfsTer101	14:74532491-74532492	FS at Arg causing PSC at 101 aa downstream	LP	Disease causing	2.643	1	Y	Y	0.683	NA
5	c.1756dupG	p.Val586GlyfsTer17	14:74549896-74549896	FS at Val-586 replaced by Gly causing PSC at 17 aa downstream	LP	Disease causing	3.067	0.418	Y	N	0.537	NA
6	c.985C>T	p.Gln329Ter	14:74555539-74555539	STOPGAIN at 329 aa	LP	Disease causing	0.538	0.305	Y	Y	0.78926	38
7	c.4237T>G	p.Cys1413Gly	14:74505115-74505115	Substitution of Cys with Gly at 1413 aa	VUS	Disease causing	5.65	1	N	N	0.51	26.3
8	c.1201dupC	p.Gln401ProfsTer202	14:74552385-74552385	FS at Gln-401 replaced by Pro causing PSC at 202 aa downstream	LP	Disease causing	2.59	1	Y	N	0.905	NA
9	c.3131C>G	p.Ser1044Ter	14:74510111-74510111	STOPGAIN at 1044 aa	LP	Disease causing	-0.458	0.119	Y	Y	0.80079	36
10	c.4171dupG	p.Ala1391GlyfsTer8	14:74506054-74506054	FS at Ala-1391replaced by Gly causing PSC at 8aa downstream	LP	Disease causing	0.693	0.283	Y	N	0.101	NA
11	c.4545_4552del	p.Gly1516LeufsTer9	14:74503955-74503963	FS at Gly 1516 replaced by Leu causing PSC at 9 aa downstream	LP	Disease causing	0.26	0.999	Y	N	0.956	NA
12	c.2811del	p.Val939CysfsTer71	14:74516918-74516919	FS at Val-939 replaced by Cys causing PSC at 71 aa downstream	LP	Disease causing	0.579	0.001	Y	Y	0.468	NA

PSC: premature stop codon, FS: Frameshift, LP: Likely Pathogenic, Y:Yes, N:No • PhyloP assigns scores between −14 and +6, with positive values indicating conservation and negative values indicating faster-than-expected evolution. • PhastCons assess nucleotide conservation among 46 different species with score range of (0–1) higher scores show higher conservation. • MutPred Indel analyses impact of insertions/deletions (indels) in human protein structure and functions. Scores range from 0 to 1, with higher scores indicating a greater chance of being pathogenic. • CADD Phred-like score based on whole genome CADD raw scores. The larger the score the more likely the SNP has damaging effect.

are required for the structural integrity and functionality of microfibrils [23]. In the absence of LTBP2 protein, these interactions may be compromised, which may further lead to the weakening of connective tissue in the ciliary zone. This, in turn, can further contribute to lens dislocation, secondary to which iridodonesis may be noted. Also, there could be a possibility of dilator muscle hypoplasia that results in iridodonesis and a small nondilating pupil.

Persistent pupillary membrane and ectropion uveae: PPM is a common congenital ocular anomaly in neonates, arising from residual tissue of the anterior tunica vasculosa lentis, which nourishes the lens during the first six months of fetal embryonic development. During embryogenesis, the embryologic lens is supplied by the anterior tunica vasculosa lentis network of capillaries. These blood vessels follow the course of the zonules in the channels. They regress within one to two weeks in the postnatal period [24]. Due to the earlier occurrence of zonular loss or breakage attributed to *LTBP2* genetic alteration, the zonules break before the vessels regress and may retain the PPM. In the presence of PPM, with time, it can lead to ectropion uveae, as reflected in our *LTBP2* cohort. This may also contribute to the nondilating pupil.

Megalocornea: The HCD at birth is between 9 and 10.5 mm. HCD >11 mm at birth and diameter >13 mm at any age are considered abnormal and referred to as megalocornea [25]. The enlarged corneal diameter was seen in 100% of patients in our cohort without the presence of Haab striae, indicating the absence of a corneal stretch or Descemet break. Moreover, it is unusual to have secondary megalocornea from increased IOP without Descemet breaks when HCD is >13 mm. The fact that the enlarged HCD in our *LTBP2* cohort could not be due to elevated IOP is further supported by the evidence that *LTBP2* null mice did not have elevated IOP [22]. Genetic variation in the chordin-like 1 (*CHRDL1*) gene has been reported to lead to X-linked megalocornea, characterized by enlarged anterior eye segments, mosaic corneal degeneration, presenile cataract, and secondary glaucoma [26]. Megalocornea seen in our *LTBP2* cohort may be associated with deep AC, an enlarged ciliary ring, weak zonules, and a small pupil or iris atrophic patches. The weakened connective tissue and ECM component due to *LTBP2* alterations can affect the structural integrity of the anterior segment of the eye, including the cornea. This could lead to progressive enlargement of the cornea leading to megalocornea.

Secondary glaucoma: The secondary glaucoma seen in our cohort can be caused by pupillary block, angle closure due to intermittent pupillary block, or a dislocated lens. However, the possibility of an inherent angle abnormality cannot be ruled out. The glaucoma did not develop in eyes that underwent lensectomy earlier than 2 years of age in the cohort. This suggests early lensectomy in this cohort prevents secondary glaucoma. Angle surgeries might be helpful when glaucoma occurs in the context of dysgenetic angles. As evident in case P13, the child underwent goniotomy for uncontrolled IOP one year after lensectomy, with open angles and high iris insertion that resulted in well-controlled IOP and stable visual acuity (Appendix 7). However, in established glaucoma, glaucoma drainage devices or transscleral cyclophotocoagulation may be required. Preventing sudden hypotony in these large aphakic eyes is of utmost important when performing any glaucoma intervention.

Retinal detachment: An important clinical feature noted in our cohort in a significant proportion was peripheral retinal degeneration and RD. We hypothesize that abnormal and stretched peripheral retina associated with retinal thinning and lattice degeneration may predispose to RD. Thorough peripheral retinal examination and treating these lesions would help prevent RD in these eyes. As was also reported earlier, performing primary glaucoma surgery in these eyes results in sight-threatening retinal complications [4,12].

In conclusion, this study highlights our experience with the unique ophthalmic phenotypic spectrum related to *LTBP2*. Early and appropriate management of secondary glaucoma in these cases involves the removal of the crystalline lens rather than glaucoma surgery. Regular and thorough peripheral retinal examinations, along with prompt treatment, are essential to prevent sight-threatening retinal complications. Additionally, early genetic testing and counseling are beneficial for accurate differential diagnosis, facilitating appropriate management. Further research and similar case studies will enhance understanding and optimize management strategies for these groups of cases.

APPENDIX 1. SUPPLEMENTARY TABLE 1.

To access the data, click or select the words "Appendix 1." Detailed clinical characteristics of the of the study cohort. HCD: Horizontal corneal diameter. Pres.: Presentation. Preop: Pre-operation, IOP: Intraocular pressure, Postop: Post-operation, SE: spherical equivalent, BCVA: Best corrected visual acuity, AGM: Antiglaucoma medications, LFU: Last follow up, Pos: Posterior, Ant: Anterior, Cat: Cataract, s/p CTT: status post combined trabeculotomy with tabeculectomy PPL: pars plana lensectomy, PPV: pars plana vitrectomy, EW: Elsewhere, RD: Retinal detachment, Sx: Surgery, SCH: Suprachoroidal hemorrhage, ECP: Endoscopic Cyclophotocoagulation, TSCPC: Trans scleral cyclophotocoagulation, AADI: Aurolab aqueous drainage device, CPC: Cyclophotocoagulation, HM: hand Motions, PL: Perception of light,

PR: projection of rays, CFCF: Counting fingers close to face, FFL: Fixing following light, NA: Not applicable, (blank)- not available

APPENDIX 2. SUPPLEMENTARY FIGURE 1.

To access the data, click or select the words "Appendix 2." Pedigree of the available families (F1-F14) of the study cohort. Proband is marked with an arrow. The affected individual is marked with filled boxes. Note 13 families had consanguinity. Family 11 (F11) pedigree was unavailable.

APPENDIX 3. SUPPLEMENTARY FIGURE 2.

To access the data, click or select the words "Appendix 3." Sanger sequencing chromatogram of LTBP2 variants validated among affected cases (P1-P18) of families (F1-F14) with altered nucleotide region highlighted.

APPENDIX 4. SUPPLEMENTARY FIGURE 3.

To access the data, click or select the words "Appendix 4." Representation of different types of genetic variants identified in the study cohort including stopgain mutations (50%), frameshift mutations (45%), and substitutions (5%). Note 95% of variants (stop gained and frameshift) identified in this study caused premature termination of protein synthesis.

APPENDIX 5. SUPPLEMENTARY FIGURE 4.

To access the data, click or select the words "Appendix 5." Ocular features of P5. **A.** Right eye megalocornea, central corneal opacity due to anteriorly dislocated lens and corneal scarring (arrow), extensive staphyloma due to secondary glaucoma (star); **B.** Left eye megalocornea, aphakia, PPM and ectropion uveae; **C**. Montage fundus photo of left eye showing posteriorly dislocated lens (arrow pointing to the shadow of the lens).

APPENDIX 6. SUPPLEMENTARY FIGURE 5.

To access the data, click or select the words "Appendix 6." Ocular features of P18. **A.** Megalocornea, aphakia post lensectomy and retinal detachment surgery; **B.** Ultrasound B-scan showing emulsified silicone oil filled vitreous cavity (star) and deep cupping of optic nerve head (arrow); **C.** Total hyphema in the left eye 1 month following limited transscleral cyclophotocoagulation (TSCPC); **D.** B-scan of left eye post TSCPC showing vitreous hemorrhage (arrow).

APPENDIX 7. SUPPLEMENTARY FIGURE 6.

To access the data, click or select the words "Appendix 7." This figure illustrates high iris insertion and open angle (white arrow) in case P13. Additionally, ectropion uveae and a whitish pupillary margin are observed in the same eye (yellow arrow). The eye underwent goniotomy for intraocular pressure management following lensectomy, one year postoperatively.

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