

Review

Not peer-reviewed version

Genetic Basis of Non-Syndromic Childhood Glaucoma Associated with Anterior Segment Dysgenesis

[Nicola Cronbach](#) , [Cécile Méjécase](#) , [Mariya Moosajee](#) *

Posted Date: 21 July 2025

doi: 10.20944/preprints2025071647.v1

Keywords: childhood glaucoma; anterior segment dysgenesis; gene editing; nonsense suppression; aniridia



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Review

Genetic Basis of Non-Syndromic Childhood Glaucoma Associated with Anterior Segment Dysgenesis

Nicola Cronbach ¹, Cécile Méjécase ^{1,2} and Mariya Moosajee ^{1,3,*}

¹ UCL Institute of Ophthalmology, EC1V 9EL, London, UK

² Ocular Genomics and Therapeutics, The Francis Crick Institute, NW1 1AT, London, UK

³ Moorfields Eye Hospital NHS Foundation Trust, EC1V 9EL, London, UK

* Correspondence: m.moosajee@ucl.ac.uk

Abstract

Twenty causative genes have been reported that cause non-syndromic childhood glaucoma associated with anterior segment dysgenesis. *FOXC1*, *PAX6* and *PITX2* are the most well-known, but cases linked to *SLC4A11*, *PITX3* and *SOX11* have also been reported. As genetic testing becomes increasingly widespread and rates of molecular diagnosis rise, the extent of phenotypic overlap between the different genetic causes of non-syndromic glaucoma associated with anterior segment dysgenesis is becoming more evident. Taking aniridia as an example, whilst *PAX6* mutations remain the predominant cause, variants in *CYP1B1*, *FOXC1*, *PXDN* and *SOX11* have also been reported in patients with childhood glaucoma and aniridia. Developments in molecular-based therapies for retinal and corneal disease are advancing rapidly, and pre-clinical studies of gene-based treatments for glaucoma and aniridia are showing promising results. Use of adeno-associated viral vectors for gene delivery is most common, with improvements in intraocular pressure and retinal ganglion cell survival in Tg-MYOC^{Y437H} mouse models of glaucoma, and successful correction of a germline *PAX6*^{G194X} nonsense variant in mice using CRISPR/Cas9 gene editing. This review will explore the actions and interactions of the genetic causes of non-syndromic glaucoma associated with anterior segment dysgenesis and discuss current developments in molecular therapies for these patients.

Keywords: childhood glaucoma; anterior segment dysgenesis; gene editing; nonsense suppression; aniridia

1. Introduction

Ocular development commences at gestational day 21 with induction of the eye field in the anterior neural plate prior to lateral evagination of the optic vesicles through the cephalic mesenchyme [1,2]. At gestational day 27, the optic vesicle contacts the surface ectoderm and signalling through bone morphogenetic protein (BMP) and retinoic acid first from the optic vesicle and then the lens placode stimulates invagination of both structures to form the optic cup and lens vesicle, which are present by day 37 (Figure 1a) [1]. By day 47, differentiation of the optic cup into primitive neural retina and retinal pigment epithelium (RPE) has commenced, and neural crest cells from the periocular mesenchyme begin to migrate into the developing anterior segment under the control of *PAX6* (Figure 1b) [3]. *PITX2* and *FOXC1*, expressed by the presumptive cornea, and *PITX3* and *FOXE3*, expressed by the developing lens, have roles in regulating differentiation of the periocular mesenchyme into corneal keratocytes and endothelium, and detachment of the lens vesicle from the cornea, respectively (Figure 1c) [2]. From gestational week 15, *PAX6*, *BMP4* and *OTX1* stimulate elongation of the peripheral tips of the optic cup, which express *CYP1B1* and *MEIS2*, along the anterior lens surface to form the epithelium of the ciliary body and iris (Figure 1d) [2,4–6]. Concurrently, a second wave of migration of the periocular mesenchyme into the anterior segment

occurs, expressing *PITX2*, *FOXC1* and *FOXC2*, which will form the ciliary body and iris stroma [2,3,5]. Trabecular meshwork development occurs from gestational week 20 with elongation, flattening and separation of mesenchymal cells in the iridocorneal angle to form lamellae, accompanied by vascular development in the adjacent sclera which becomes Schlemm's canal (Figure 1e) [2,7].

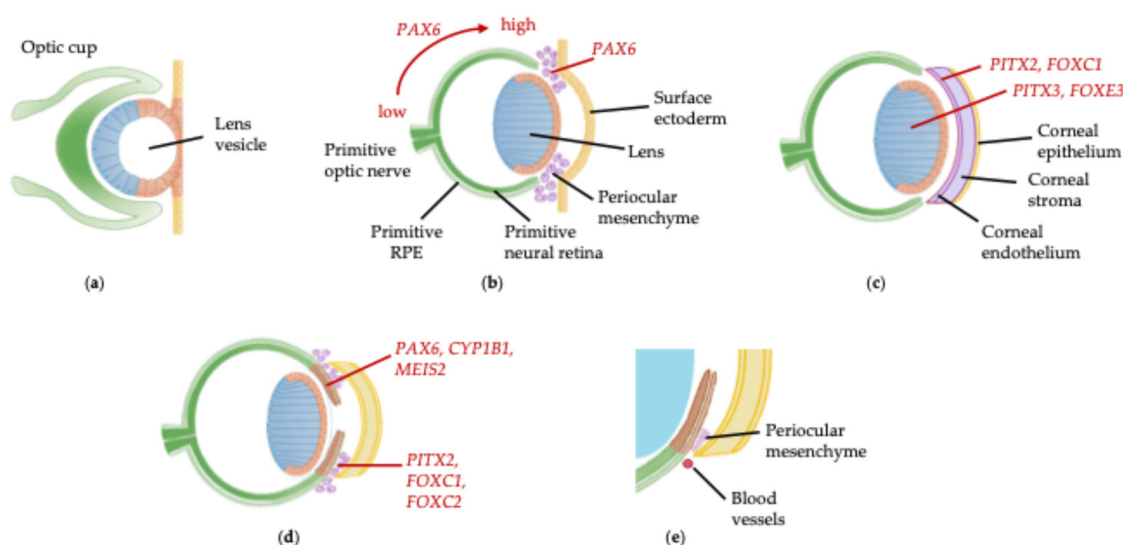


Figure 1. Anterior segment embryological development: (a) At day 37 of gestation a double layered optic cup and lens vesicle can be seen; (b) At 47 days the optic cup has formed primitive neural retina and retinal pigment epithelium with the optic stalk forming primitive optic nerve. Optic cup patterning is dependent on the *PAX6* expression gradient, from high expression at the peripheral optic cup tips down to low expression centrally. Cells of the central lens placode migrate to the posterior lens vesicle and elongate to form primary lens fibre cells, and the first wave of neural crest cells from the periocular mesenchyme migrates between the lens and surface ectoderm; (c) At 57 days the primitive corneal epithelium is formed from the surface ectoderm, the corneal stroma and endothelium are formed from neural crest cells of the periocular mesenchyme, there is separation of the lens stalk and formation of the anterior chamber; (d) By 15 weeks elongation of optic cup tips along the anterior lens surface to form the iris and ciliary body epithelium occurs, and there is a second wave of periocular mesenchyme migration into the anterior chamber to form the iris and ciliary body stroma; (e) At 20 weeks there is an accumulation of periocular mesenchyme in the iridocorneal angle which subsequently elongates and forms lamellae to become the trabecular meshwork, and vessels form in the adjacent sclera which will become Schlemm's canal. Gene expression marked in red. RPE, retinal pigment epithelium.

Glaucoma is an overarching term for optic neuropathies resulting from retinal ganglion cell loss, which are typified by optic disc cupping and associated visual field defects. Childhood glaucoma, affecting individuals under 18 years of age, accounts for 5% of paediatric blindness worldwide [8]. In addition to optic nerve changes and visual field defects, features of childhood glaucoma include corneal enlargement and Haab striae, increased axial length and intraocular pressure >21mmHg; two or more features are required for diagnosis [9]. Childhood glaucoma is classified according to the underlying cause, and whether this is primary or secondary to another ocular or systemic condition [9]. Primary congenital glaucoma (Figure 2a) develops before 4 years of age and may be further divided into neonatal (0-1 month), infantile (>1-24 months) and late (>24 months) onset disease. It is a primary goniodysgenesis and presents with an immature appearance of the iridocorneal angle (Figure 2b) [9,10]. Juvenile open angle glaucoma presents after 4 years of age and with normal angle appearances. Secondary causes of childhood glaucoma include onset following cataract surgery, glaucoma associated with non-acquired ocular or systemic anomalies, and glaucoma associated with acquired conditions such as trauma and uveitis.

Anterior segment dysgenesis (ASD) is a broad term that incorporates developmental anomalies involving structures in the anterior segment of the eye [11–13]. These may affect a single structure,

such as microcornea, or involve multiple structures, such as the iridocorneal and keratolenticular adhesions seen in Peters anomaly (Figure 2c). Between 30-75% of patients with ASD develop glaucoma depending on the subtype of dysgenesis [14,15], and young patients with either glaucoma or ASD should be thoroughly examined for features of each condition [13,15–17]. Many of the anterior segment dysgeneses have variable phenotypes with considerable overlap; for example, Axenfeld-Rieger anomaly (Figure 2d-e) may include corectopia, polycoria and iris hypoplasia in association with posterior embryotoxon, and like Peters anomaly, may also feature iridocorneal adhesions [15]. Patients with congenital aniridia (Figure 2f-h) present with underdevelopment of the iris of variable severity and foveal hypoplasia, although some will also have lenticular opacities and optic nerve hypoplasia from birth, many will develop glaucoma and aniridia-associated keratopathy by adulthood [14,18].

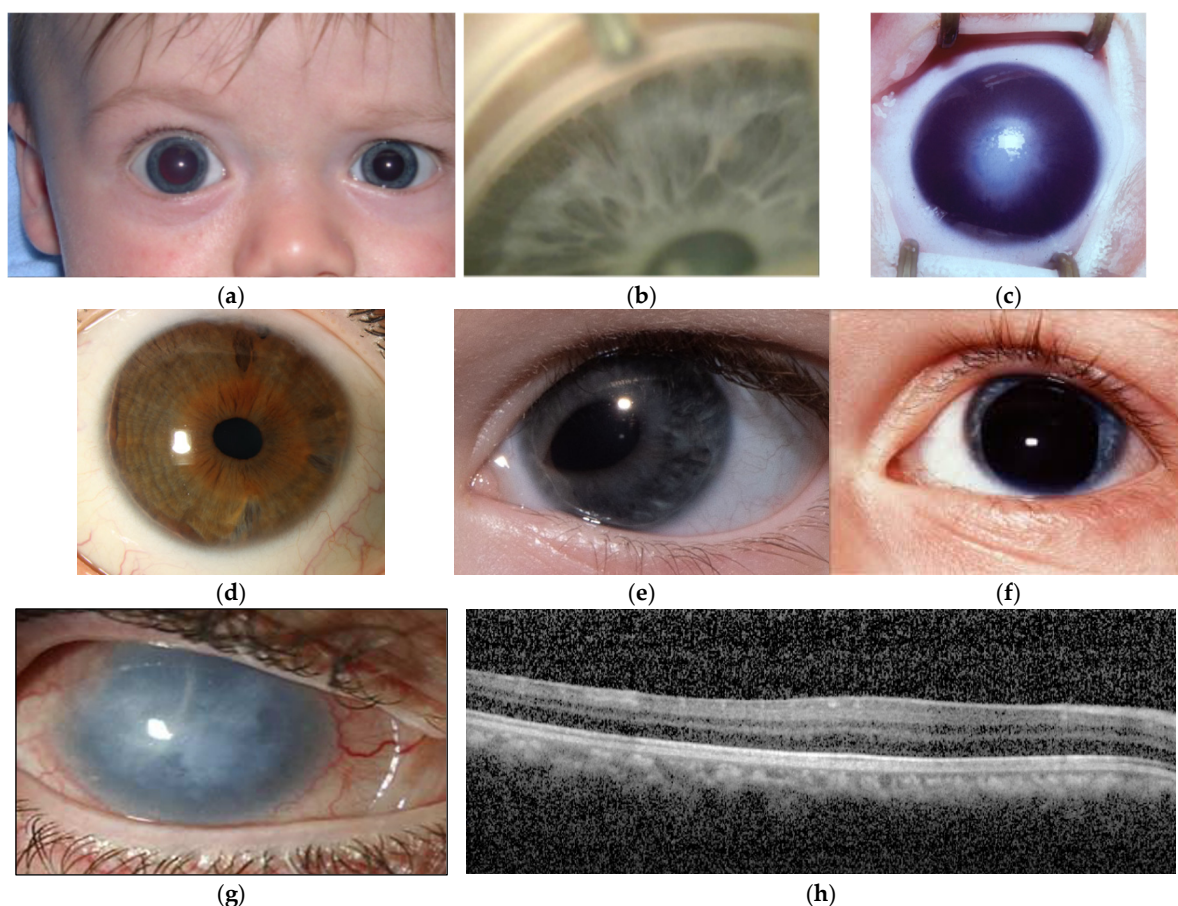


Figure 2. Clinical features of childhood glaucoma and anterior segment dysgenesis: (a) Right buphthalmos due to unilateral primary congenital glaucoma (PCG); (b) Immature scalloped appearance of iridocorneal angle in PCG; (c) Central corneal opacity in Peters anomaly; (d-e) Axenfeld-Rieger anomaly: (d) iris hypoplasia and posterior embryotoxon (white arrowhead); (e) Corectopia; (f-h) Congenital aniridia: (f) iris hypoplasia; (g) foveal hypoplasia; (h) aniridia-associated keratopathy.

The molecular pathways involved in anterior segment development are highly complex and there is much overlap between genes that cause childhood glaucoma and those that cause anterior segment dysgenesis [11–13]. Many of the factors that contribute to this process remain unknown, and current molecular diagnostic rates for childhood glaucoma and anterior segment dysgenesis are below 25% [12,19], indicating the need for further studies to investigate additional genes and biological pathways that influence anterior segment development. This review summarises the genes identified to date in patients with non-syndromic childhood glaucoma associated with anterior segment dysgenesis, and discusses their functions, biological relationships and potential avenues for future treatments.

2. Results

Twenty genes linked to childhood glaucoma associated with anterior segment dysgenesis were identified, of which twelve were also reported to cause isolated childhood glaucoma. Reported phenotypes of anterior segment dysgenesis covered the full spectrum of cornea, iris, lens and mixed anomalies (Table 1). *PAX6*, *FOXC1* and *PITX2* are expressed in multiple anterior segment tissues during ocular development; other genes, such as *CYP1B1*, have more limited expression (Figure 3).

Table 1. Genes reported to be linked to childhood glaucoma associated with anterior segment dysgenesis, and the phenotypes identified in each.

Gene	OMIM ID	Phenotype(s) of anterior segment dysgenesis associated with childhood glaucoma	Associated with isolated childhood glaucoma
<i>CYP1B1</i>	601771	Peters anomaly [20–23], Axenfeld-Rieger anomaly [24], aniridia [25], corneal dystrophy [12,26], unclassified ASD [27].	Yes
<i>FOXC1</i>	601090	Peters anomaly [13,28], Axenfeld-Rieger anomaly [15,23,29], aniridia [13], unclassified ASD [12,13].	Yes
<i>PAX6</i>	607108	Aniridia [16,29,30], Peters anomaly [28].	Yes
<i>LTBP2</i>	602091	Weill-Marchesani syndrome [23,31], congenital cataract [12], lenticular anomalies [16,32], unclassified ASD [16].	Yes
<i>ADAMTSL4</i>	610113	Ectopia lentis [33].	Yes
<i>CPAMD8</i>	608841	Lenticular anomalies [34,35], iris anomalies [35], unclassified ASD [16,36].	Yes
<i>PXDN</i>	605158	Peters anomaly [37], congenital cataract [38], aphakia [37], aniridia [39], sclerocornea [28,40].	Yes
<i>TEK</i>	600221	Sclerocornea [31].	Yes
<i>SLC4A11</i>	610206	Congenital hereditary endothelial dystrophy [16,27,41].	Yes
<i>ADAMTS18</i>	607512	Microcornea [42].	Yes
<i>PITX3</i>	602669	Microcornea [43,44], congenital cataract [44].	Yes
<i>PITX2</i>	601542	Peters anomaly [13,16], Axenfeld-Rieger anomaly [16,28], sclerocornea [28].	No
<i>FOXE3</i>	601094	Peters anomaly [45–47], iris anomalies [45,46], congenital cataract/aphakia [46,48], microphthalmia [46,49].	No
<i>COL4A1</i>	120130	Congenital cataract [13,50,51], Axenfeld-Rieger anomaly [51], iris anomalies [13,50].	No
<i>SOX11</i>	600898	Peters anomaly [52], aniridia [31,52].	No

<i>GJA8</i>	600897	Sclerocornea [23,28,31].	No
<i>KERA</i>	603288	Unclassified ASD [34].	No
<i>CDH2</i>	114020	Peters anomaly [53].	No
<i>KDM5C</i>	314690	Peters anomaly [54].	No
<i>TFAP2A</i>	107580	Peters anomaly [55].	No

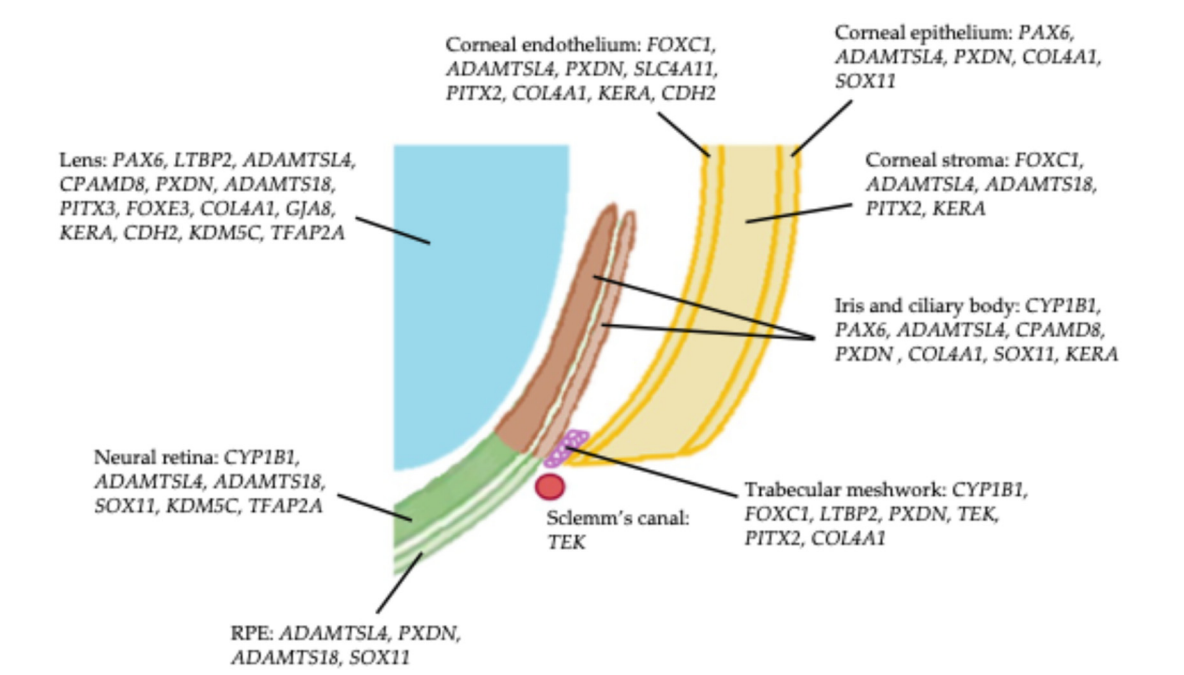


Figure 3. Ocular expression of genes causing non-syndromic childhood glaucoma and anterior segment dysgenesis.

2.1. *CYP1B1* (OMIM #601771)

CYP1B1 encodes a 543-amino acid enzyme which is part of the cytochrome P450 superfamily and is involved in retinol [56,57], melatonin [56] and 17 β -oestradiol metabolism [57,58]. It regulates myocilin production by limiting oestrogen-responsive activation of the *MYOC* promoter [58], and contributes to trabecular meshwork development through its modulation of periostin [59]. Pathogenic variants include missense, nonsense and frameshift mutations, and all have been identified throughout the gene [60]; the majority result in loss-of-function of metabolic activity [57,61,62], although some variants, such as c.1154C>A p.(Phe261Leu) and c.1776C>T p.(Arg469Trp) cause significantly increased retinol metabolism [57]. *CYP1B1* is the most commonly identified genetic cause of primary congenital glaucoma (PCG) [60,63], causing 15-35% of PCG in European studies [12,61], and up to 100% of PCG in some ethnic groups [64]. Many *CYP1B1* variants have also been associated with other anterior segment dysgeneses including aniridia [25], Axenfeld-Reiger anomaly [24] and Peters anomaly [20–22].

2.2. *FOXC1* (OMIM #601090)

FOXC1, part of the forkhead box family of transcription factors, is expressed in the periocular mesenchyme and is necessary for separation of the cornea and lens in the developing eye [2,5,65]. It acts in conjunction with *PITX2* to promote development of the corneal stroma and endothelium, iridocorneal angle and choroid, with co-expression of both transcription factors necessary for normal differentiation of these cellular populations [66]. In the trabecular meshwork, *FOXC1* activity is mediated by miR-204 and regulates *MEIS2* [67], a homeobox transcription factor which in turn is a direct regulator of *PAX6* [68]. *FOXC1* variants have been identified in patients with childhood

glaucoma associated with Axenfeld-Rieger anomaly [15,23,29], Peters anomaly [13,28] and aniridia [13]. In the context of Axenfeld-Rieger syndrome, *FOXC1* variants cause significantly more congenital glaucoma than do *PITX2* variants, which are more associated with juvenile- and adult-onset glaucoma [15]. Whole gene deletions account for approximately one third of anterior segment dysgenesis caused by *FOXC1* [12,15]. In a functional study, Medina-Trillo and colleagues showed that *FOXC1* variants can result in either significantly increased or decreased transcriptional activity compared with wild-type; hypermorphic variants including c.141C>G p.(Tyr47*) and c.316C>T p.(Gln106*) were associated with isolated dominant glaucoma, whilst hypomorphic variants including c.377T>G p.(Ile126Ser) were identified in patients with Axenfeld-Rieger anomaly [69].

2.3. *PAX6* (OMIM #607108)

Heterozygous pathogenic variants in *PAX6* are typically associated with autosomal dominant aniridia, or are part of the Wilms tumour-aniridia-genital anomalies-retardation (WAGR) syndrome if the whole gene is deleted along with *WT1* [11,18]. The *PAX6* transcription factor is known to have a role in ocular development from gestational day 22 in the differentiation of the eye field and optic vesicle, through to the development of the optic cup and lens vesicle at day 37, and then in corneal, iris, ciliary body and trabecular meshwork development from day 47 onwards [2,70,71]. It has both paired and homeobox DNA-binding domains, and interacts with numerous other genes during this process, including *SOX2*, *RAX*, *MEIS2* and *ALDH1A3* [5,68,70]. Close regulation of *PAX6* expression is required throughout embryogenesis to ensure normal development; under expression results in the aniridia spectrum of iris, foveal and optic nerve hypoplasia with associated glaucoma, cataracts and keratopathy, whilst overexpression causes microphthalmia, microcornea and ciliary body maldevelopment [72–74]. Whilst there are reports implicating *PAX6* in isolated juvenile open angle glaucoma and childhood glaucoma associated with Peters anomaly, childhood glaucoma caused by *PAX6* variants is very rarely diagnosed in patients without aniridia [28,75].

2.4. *LTBP2* (OMIM #602091) and *ADAMTSL4* (OMIM #610113)

Both *LTBP2* and *ADAMTSL4* contribute to cytoskeletal development through their interactions with fibrillin-1. *LTBP2* encodes a 1821-amino acid extracellular matrix protein which interacts with fibrillin-1-containing microfibrils [76,77] and is expressed in the cornea, trabecular meshwork and lens [77]. A causative gene for Weill-Marchesani syndrome [23,31,76], which presents with short stature, brachydactyly, microspherophakia, ectopia lentis and myopia, *LTBP2* has also been linked with congenital glaucoma associated with isolated microspherophakia [16], ectopia lentis [32] and congenital cataract [12]. The glycoprotein *ADAMTSL4* binds fibrillin-1 and facilitates microfibril assembly, and is expressed in many ocular tissues including the cornea, iris and ciliary body in the anterior segment, and the retinal ganglion cells, retinal pigment epithelium, choroid and sclera in the posterior segment [78]. It has been linked to congenital glaucoma with ectopia lentis [33].

2.5. *CPAMD8* (OMIM #608841)

CPAMD8 is expressed in the human eye from gestational week 9 onwards [79]. From weeks 9 through 22 of gestation, *CPAMD8* expression increases in the lens and decreases in the retina, and strong expression is also observed in the iris and cornea at week 22 [79]. The pathways by which *CPAMD8* acts to contribute to ocular development remain undefined, but recent work by Escribano and colleagues in zebrafish suggests an interaction between *cpamd8* and *adamtsl4* [80], implicating a potential contribution of *CPAMD8* to development of fibrillar structures in the anterior segment. *CPAMD8* variants have been linked to anterior segment dysgenesis associated with both congenital and juvenile glaucoma [16,34–36], and were identified in 3.7% of patients diagnosed with PCG in a large Australasian cohort [16].

2.6. *COL4A1* (OMIM #120130) and *PXDN* (OMIM #605158)

Variants in *COL4A1* and *PXDN*, which are both basement membrane components, have been identified in patients with anterior segment dysgeneses associated with childhood glaucoma [13,28,37,38,50,51]. *COL4A1* encodes the alpha-1 subunit of type IV collagen, which is the main component of endothelial and epithelial basement membranes [81]. Peroxidase, the protein product of the *PXDN* gene, forms sulfilimine crosslinks between type IV collagen molecules, and is necessary for normal development of type IV collagen-, laminin- and fibronectin-based fibrillar networks in endothelial cells [82]. Type IV collagens are found throughout the developing eye, and by embryonic day 18.5 (E18.5) the alpha-1 isoform can be identified in all anterior segment tissues in mice [83].

2.7. *TEK* (OMIM #600221)

One of two receptor tyrosine kinases in the angiopoietin/TEK signalling pathway, autosomal dominant mutations in *TEK* have been identified in patients with primary congenital glaucoma [16] and congenital glaucoma associated with sclerocornea [31]. In mice, *TEK* is expressed in Schlemm's canal endothelial cells, and its ligand *Angpt1* is expressed in the trabecular meshwork [84,85]. Supporting the role of *TEK* in iridocorneal angle and Schlemm's canal development, studies of *Angpt1* knockout mice have revealed severe hypoplasia of both Schlemm's canal and the trabecular meshwork [85].

2.8. *SLC4A11* (OMIM #610206)

Pathogenic variants in *SLC4A11* are the most commonly identified genetic cause of congenital hereditary endothelial dystrophy (CHED) [86], which presents with early onset corneal oedema and, rarely, concomitant congenital glaucoma [16,27,41]. *SLC4A11* localises to the corneal endothelium, where it contributes to osmotic homeostasis of the cornea and thus to maintaining corneal transparency [86,87]. Homozygous missense variants cause approximately half of *SLC4A11*-related disease [86], and both families with congenital glaucoma whose variants have been reported had homozygous missense mutations [27,41].

2.9. *ADAMTS18* (OMIM #607512)

Part of the ADAMTS zinc-dependent metalloproteinase family, *ADAMTS18* is expressed in adnexal, anterior segment and retinal cells during murine ocular development, with expression persisting postnatally in the lens and lacrimal gland [88,89]. It is a key factor in branching morphogenesis of the embryonic lacrimal gland [88], but its role in other aspects of ocular development remains unclear. Pathogenic variants in *ADAMTS18* cause microcornea, myopic chorioretinal atrophy, and telecanthus (MMCAT) [90] and Knobloch syndrome (high myopia, vitreoretinal degeneration, retinal detachment, cataract and occipital encephalocoele) [91], but childhood glaucoma associated with microcornea has been reported in twins with compound heterozygous missense mutations of *ADAMTS18* identified through panel testing [42].

2.10. *PITX2* (OMIM #601542) and *PITX3* (OMIM #602669)

The bicoid-type homeodomain transcription factors *PITX2* and *PITX3* have a role in embryonic anterior segment and lens development [92,93]. As discussed above, *PITX2* interacts with *FOXC1* and in mice they are co-expressed in the periocular mesenchyme from E11.5 [66]. It is therefore unsurprising that the ocular phenotypes of *PITX2*-related disease are similar to those of *FOXC1* and include childhood glaucoma associated with Axenfeld-Rieger anomaly [16,28] and Peters anomaly [13,16]. *PITX3* is expressed in the lens placode at murine E10 and continues to be expressed in the lens throughout development, in addition to expression in the midbrain, tongue and other embryological craniofacial tissues [93]. Variants have been identified in patients with congenital glaucoma associated with microcornea and congenital cataract [43,44].

2.11. *FOXE3* (OMIM #601094)

FOXE3 variants are associated with a wide spectrum of anterior segment phenotypes and have been identified in patients with childhood glaucoma associated with Peters anomaly [45–47], congenital cataracts/aphakia [46,48] and microphthalmia [46,49]. The main role of the *FOXE3* transcription factor during embryogenesis is in the development of the lens, where it is expressed in mice from E12.5 onwards and directly regulates the autophagy-associated protein DNAJB1 [45]. Functional studies of *FOXE3* missense variants and small deletions isolated from patients with recessive disease showed significantly reduced transcriptional activity with homozygous or compound heterozygous variants, but no disease phenotype in their heterozygous parents, indicating that the presence of a single functional allele is sufficient for normal anterior segment development [48].

2.12. *SOX11* (OMIM #600898)

The *SOX11* SRY-Box transcription factor is a close homologue of *SOX2* [94], which is known to play a key role in ocular development from induction of the eye field at gestational day 21 onwards [70]. During *Xenopus* embryogenesis *sox11* is expressed in the optic vesicle, retina and anterior segment, and morpholino oligonucleotide (MO) knockdown of *sox11* results in decreased *pax6* expression in the eye field, loss of retinal lamination and a microphthalmic phenotype [95]. In *Sox11* knockout mice, *Pax6* expression is unaffected but *BMP7* expression is reduced, and the phenotype includes lenticular defects, Peters anomaly and anterior ocular coloboma [96]. *SOX11* variants have been reported in patients with congenital glaucoma associated with Peters anomaly and aniridia [31,52], although the gene is more commonly associated with intellectual developmental disorder with microcephaly with or without ocular malformations or hypogonadotropic hypogonadism (IDDMOH; Coffin Siris syndrome), of which congenital glaucoma can be a feature [23,52].

2.13. *GJA8* (OMIM #600897)

GJA8 encodes connexin 50 (Cx50), a gap junction protein of lens fibre cells which is necessary for maintaining lens transparency and cellular homeostasis [23,97]. Studies of the missense mutation c.217T>C p.(Ser73Pro) in transfected human lens epithelial cells have shown aggregation of the abnormal protein in the cytosol with loss of localisation to the plasma membrane, resulting in reduced function of gap junction channels and increased apoptosis [97]. Although *GJA8* variants are more commonly associated with congenital cataract [11], missense variants have also been identified in patients with congenital glaucoma associated with sclerocornea [23,28,31].

2.14. *KERA* (OMIM #603288)

KERA encodes keratocan, a keratan sulfate proteoglycan of the corneal stroma with a central role in maintaining collagen spacing and thus corneal transparency [98]. In adults, it is localised to stromal keratocytes [98]; during embryological development, studies of chicks by Conrad [99] and Gealy [100] have shown expression of *Kera* in the periocular mesenchyme from E4.5, with subsequent localisation to the anterior corneal stroma. Mutations in *KERA* are predominantly linked to cornea plana, in which there is flattening of the normal convex curvature of the cornea resulting in hyperopia [101], but one patient with anterior segment dysgenesis and congenital glaucoma associated with a homozygous nonsense *KERA* mutation has been reported [34].

2.15. *CDH2* (OMIM #114020), *KDM5C* (OMIM #314690) and *TFAP2A* (OMIM #107580)

CDH2, *KDM5C* and *TFAP2A* are involved in neural development, with roles including axonal pathfinding [102], neuronal differentiation [103] and neural crest migration [104], respectively. All are reported to be causative for congenital glaucoma associated with Peters anomaly [53–55]. *CDH2* encodes N-cadherin, which contributes to cell-cell adhesion in multiple tissues [53,102]. It is expressed in murine lens cells and the lens stalk at E10.75–11.0, and in lens and corneal endothelial

cells at E17.5 [53]. *Kdm5c* is strongly expressed throughout *Xenopus* neural and ocular development, particularly in the lens and retina, and MO knockdown studies have confirmed the essential role of this histone demethylase in this process [105]. In human eyes, expression of the transcription factor *TFAP2A* is seen in the anterior lens epithelium from gestational day 35 and in the equatorial lens epithelium, secondary lens fibres and neural retina by day 54 [106]. Whilst the detailed mechanism by which *TFAP2A* acts has not yet been elucidated, a study of embryological tooth development in mice showed dysregulation of *Pitx2* and *Sox2* in knockout models [107].

3. Management of Childhood Glaucoma and Anterior Segment Dysgenesis

Current treatment options for anterior segment dysgenesis and childhood glaucoma are predominantly surgical, although refractive, medical and supportive interventions, including genetic counselling and family planning, all contribute to the holistic management of these patients and their families [17,72,108]. For congenital glaucoma, angle surgeries (goniotomy and trabeculotomy) are first line; trabeculectomy with anti-fibrotic agents, glaucoma drainage devices and cyclodestructive procedures such as transscleral cyclophotocoagulation are used in refractory cases. Medical treatments (beta-blockers, carbonic anhydrase inhibitors and prostaglandin analogues) are used as adjuncts to surgery or as temporising measures while awaiting a procedure [108,109]. In patients with aniridia, cataract surgery and corneal and limbal grafts, alongside ocular lubricants, refraction and treatment of associated glaucoma have long been the mainstay of treatment [25,72]. Many patients with Peters anomaly require penetrating keratoplasty, although newer grafting techniques such as Descemet stripping automated endothelial keratoplasty (DSAEK) have been successfully employed in selected patients, and optical iridectomy may improve vision in patients with a smaller area of corneal opacity [17,110]. In all cases, refraction and amblyopia management should be provided as necessary, alongside educational and family support. Examination under anaesthetic should be considered for young children to enable detailed examination and identification of subtle signs of anterior segment dysgenesis or associated ocular conditions. Genetic testing is paramount to enable accurate genetic counselling, family planning advice and referral to other specialties in cases that may have an associated syndromic element. Furthermore, as the potential for molecular-based therapies is beginning to translate into practice with promising research including developments in gene editing and nonsense suppression drugs, genetic testing will allow patients access to targeted research.

4. Molecular Therapies Under Development

There are currently 41 FDA-approved cellular and gene therapies [111], of which only Luxturna (voretigene neparvovec-rzyl) targets an ocular condition, *RPE65*-related retinal dystrophy. Growing research into this field as a potential source of therapy for glaucoma and anterior segment disorders has focussed on animal and in vitro models, but in recent years this has begun translating into clinical trials [72,112]. Most of these studies have investigated treatments for corneal diseases and the various methods of gene delivery. Transduction of target cells with recombinant adenoviruses (rAds) and adeno-associated viruses (rAAVs) are the most common viral vectors [112–114], although retroviruses [115] and lentiviruses [116] have been used in some studies. Non-viral vectors include metal and magnetic nanoparticles, micelles and lipid nanoparticles [112,117–119], which may be delivered topically or by injection. Alternative methods that do not require a vector include corneal electroporation and iontophoresis [120,121]. In the anterior segment, research into gene-based therapies has focused predominantly on corneal and ocular surface disease, adult-onset glaucoma and aniridia [72,112,122,123], with no published trials of gene therapies for Peters anomaly or Axenfeld-Rieger syndrome. Here we summarise current research into cellular and gene-based therapies for glaucoma and aniridia.

4.1. Gene-Based Therapies for Glaucoma

Molecular-based therapies under development for glaucoma are predominantly targeted towards modification of the aqueous production/outflow pathways and minimising damage to retinal ganglion cells (RGCs) [122], as these are key factors in the development of multifactorial adult-onset glaucoma. Sulak and colleagues [123] identified 153 studies into gene-based therapies for glaucoma and noted that there were twice as many therapies targeting RGC neuroprotection compared with those targeting aqueous production and outflow. Strategies to modulate the molecular pathways involved in aqueous regulation are in development, with targets including myocilin (*MYOC*), aquaporin-1 (*AQP1*) and matrix metalloproteinases (MMPs).

Mutations in the *MYOC* gene, encoding the extracellular matrix protein myocilin, are the most commonly identified single gene cause of primary open angle glaucoma (POAG) and juvenile open angle glaucoma (JOAG), identified in 2-4% and 10-30% of cases, respectively [122]. Dominant gain-of-function mutations result in intracellular accumulation of the abnormal protein, resulting in increasing IOP and resultant glaucomatous damage to the retinal ganglion cells and optic nerve [114]. Mice with the *MYOC* p.(Tyr437His) variant (Tg-*MYOC*^{Y437H}) can be used as a model for POAG, developing these same pathogenic features, and may be employed for in vivo confirmation of therapeutic benefit [114,116].

Gene editing approaches targeted to specific myocilin mutations are in development. Jain [114] used a CRISPR-Cas9 approach with an adenoviral Ad5 vector to introduce a truncating frameshift mutation into Tg-*MYOC*^{Y437H} mice. They demonstrated significant reduction of IOP into the normal range in both younger (age ≤1 month) and older (age ≥9 months) mice, with results sustained for at least 2 months post-injection. The group have subsequently shown positive results using the same CRISPR-Cas9 system with a lentiviral vector [116], with IOP reduction into the normal range in Tg-*MYOC*^{Y437H} mice maintained for at least 6 weeks post-injection. They additionally tested an AAV2 vector in vitro on human TM3 cells with Y437H or G364V *MYOC* mutations, but the reduction in accumulated myocilin was only 34% lower than untreated levels with the AAV2 vector compared with 62% reduction for the lentivirus. Another mechanism that has been proposed for reducing the pathogenicity of *MYOC* mutations is to use small interfering RNAs (siRNAs) to disrupt the expression of the gene. Preliminary results in TM5 cells demonstrated significant suppression of both wild type and mutant myocilin expression to 60% of control levels [124]. Whilst further work is needed, these approaches hold promise for potential gene-targeted therapies for *MYOC*-related glaucoma to become available in the future.

Another CRISPR-based approach employing a lentivirus vector carrying single guide RNA (sgRNA) to target the *TGFβ2* promoter has been developed by Mao's group [125]. Administration of the sgRNA lentivirus 2.5 weeks prior to induction of ocular hypertension prevented IOP increases, maintaining an IOP level below 20mmHg for at least 8 weeks post-injection, compared with an increase to over 30mmHg in controls. Aquaporin 1 (*AQP1*) has also been targeted with sgRNA. This transmembrane water channel is present in many tissues including the ciliary body, and deletion of *Aqp1* has been shown to significantly reduce IOP in mice [126]. Introduction of two *AQP1*-indel-inducing sgRNAs within a single AAV vector given by intravitreal injection has been shown to transduce the murine ciliary body and reduce IOP by 22% after 3 weeks, with neuroprotective effects sustained to at least 7 weeks post-injection [127]. There was also effective transfection of ex vivo human ciliary body epithelial cells. *AQP1* has therefore been proposed as a potential therapeutic target for glaucoma.

MMP activity is known to be reduced in glaucoma, and one of the key actions of the prostaglandin analogue drops used to treat open angle glaucoma is to increase MMP expression in the ciliary body [128]. Using an AAV9 vector to transduce corneal endothelial cells, O'Callaghan [129] introduced tetracycline-inducible murine MMP3 into Tg-*MYOC*^{Y437H} and dexamethasone-induced ocular hypertensive mice. In both groups, IOP 2 weeks after doxycycline induction was significantly reduced in the treated mice compared with controls. They also demonstrated significant increases in MMP3 expression and aqueous outflow in non-human primates in vivo, and increased aqueous

outflow in human donor anterior segments in vitro using this approach [129]. Similar effects have been achieved using intracameral I κ B α -silencing siRNA to transfect the anterior segment of nonhuman primates, with upregulation of MMP2 and MMP9 and resultant 49% reduction in IOP [130]. A lesser IOP reduction has been achieved through the use of the microRNA miR-21-5p, which is predicted to have downstream effects including activation of MMP9. Whilst preliminary results show potential, the maximal IOP reduction following administration was 17.8% [131], lower than the 20-35% achieved by current topical treatments [132].

Approaches to disrupt β 2-adrenoceptors have also shown promise. Loma [132] topically administered siRNAs designed to silence β 2-adrenoceptors to rabbits and compared the effects to commercially available topical dorzolamide, latanoprost and timolol. The siRNAs significantly reduced IOP by $30 \pm 5\%$ compared to controls, with effects detectable 24hrs after instillation and sustained for 5 days. The level of IOP reduction was comparable to that achieved by all commercial agents, but with a longer onset and offset time. A commercial compound, bamosiran, has recently completed its phase II trial. This RNA interference approach designed to prevent β 2-adrenoceptor production showed non-inferiority to timolol in patients with a baseline IOP ≥ 25 mmHg, but not across all patient groups [133]. However, the positive results achieved overall by these diverse approaches to molecular modulation of aqueous regulation lay a strong foundation for molecular therapies to become available for patients within the near future.

4.2. Gene-Based Therapies for Aniridia

A novel approach to treatment of aniridia is nonsense suppression therapy, using drugs that impair recognition of premature termination codons (PTCs) during translation to allow the production of a full-length protein [134]. In aniridia patients in whom a genetic cause is identified, dominant pathogenic *PAX6* mutations are responsible for approximately 90% of cases [14]; of these, nonsense and frameshift mutations resulting in a PTC comprise 70% of pathogenic and likely pathogenic *PAX6* variants [135], so a treatment that targets these mutations has the potential to benefit a large proportion of these patients. Promising results using nonsense suppression therapies, which work on in-frame nonsense mutations, have been reported in vitro [136] and in the *Sey* mouse model [137,138]. *Sey* mice with a heterozygous *PAX6* p.(Gly194X) nonsense mutation treated with topical nonsense suppression drugs from postnatal day 14-60 developed partial phenotypic rescue, including reversal of corneal, lens and retinal abnormalities [137,138]. However, these benefits have not yet been translated into positive results in clinical trials, with the Study of Ataluren in Participants With Nonsense Mutation Aniridia (STAR) unfortunately failing to meet its primary endpoints [139].

Gene editing is under investigation as another potential avenue of treatment for aniridia. Work in *Sey* mice has shown successful germline correction of the *PAX6* p.(Gly194X) mutation in vivo by microinjection of the targeted CRISPR/Cas9 complex into murine zygotes at day 0.5 post-coitus, with inheritance of the corrected gene by the offspring of these transgenic mice [140]. The progeny had normal eye development and normal *PAX6* levels in neural tissue at embryonic day 18.5, when microphthalmic changes are observed in *Sey* mice [140]. Further work has demonstrated the potential use of AAV vectors for delivery of gene therapy in aniridia, with results suggesting that the AAV9 capsid is able to safely transduce corneal and retinal cells of *Sey* mice [113].

Work to expand the therapeutic options for management of aniridia-associated keratopathy has shown that duloxetine and ritanserin, both anti-serotonin drugs which inhibit the MEK/ERK signalling pathway, can enhance endogenous *PAX6* expression in haploinsufficient corneal limbal epithelial stem cells [141–143]. A regulatory microRNA, miR-204-5p, has also been reported that upregulates *PAX6* in *PAX6*-knockdown corneal limbal stem cells and mature differentiated corneal epithelial cells in vitro; there was no significant change in *PAX6* expression in primary human limbal epithelial cells, human limbal stem cells or in the corneas of *Pax6*^(*Sey*/+) mice transfected with miR-204-5p [144]. Further work is needed to determine the effects of these modulating factors in other ocular cell types, but they provide another potential avenue for therapeutic development. However, any strategies to increase *PAX6* expression during embryogenesis need to ensure that induced levels

remain carefully modulated. Both under- and overexpression of *PAX6* can lead to ocular developmental anomalies as discussed earlier [73,74], therefore ensuring corrected *PAX6* expression levels are as close as possible to the normal embryological state is essential when correcting pathogenic variants. To address this, Simpson's team [145] have designed *PAX6* MiniPromoters and reported their robust and specific expression within the *PAX6*-positive RGC, amacrine, horizontal and Müller glial cells, with significantly better regulation of *PAX6* expression than achieved by the ubiquitous smCBA promoter.

4. Methods

A combination of strategies was used to identify genes that cause non-syndromic childhood glaucoma associated with anterior segment dysgenesis. A list was compiled of all green and amber genes in the NHS Genomics Medicine Service's "Structural Eye Disease" panel (v4.1) and all genes and conditions associated with the term "glaucoma" in Online Mendelian Inheritance in Man (OMIM) [146]. Each gene identified was then searched on PubMed for reports and studies confirming its association with childhood glaucoma and any anterior segment developmental anomaly. Any additional genes identified through these publications which met the criteria were also reviewed. Genes identified in patients with syndromic ASD, or in whom glaucoma was identified subsequently to cataract surgery, were excluded.

5. Conclusions

As the accessibility of genetic testing for ocular diseases has increased, so too has the number of genes identified that are linked to childhood glaucoma associated with anterior segment dysgenesis, although molecular diagnostic rates for these conditions remain low. To date, twenty genes have been associated with this subset of ocular developmental disorders, with many more involved in the pathogenesis of primary congenital glaucoma and anterior segment dysgenesis without glaucoma [11]. The pathways governing anterior segment development are complex and mutations in different genes can cause very similar clinical features. Furthermore, there is significant variation in the phenotype resulting from mutations within individual genes. Improvements in individualised patient prognostication and management will benefit from anatomical-based reporting of clinical features and gene-based diagnosis, both for identifying the most appropriate therapies and allowing detailed genotype-phenotype correlation studies of these rare conditions in the future. Additionally, it is a step towards the change in approach to treatment required in this advent of gene therapy. As the development of these targeted treatments begins to translate into clinically available management options, knowing a patient's underlying genetic diagnosis will be key to ensuring they receive appropriate treatment.

Author Contributions: Conceptualization, N.C. and M.M.; methodology, N.C.; writing—original draft preparation, N.C.; writing—review and editing, C.M. and M.M.; visualization, N.C.; supervision, M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Moorfields Eye Charity, the Wellcome Trust (205174/Z/16/Z), the National Institute for Health and Care Research (NIHR), Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust, and UCL Institute of Ophthalmology.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ASD	Anterior segment dysgenesis
BMP	Bone morphogenetic protein
CHED	Congenital hereditary endothelial dystrophy
CRISPR/Cas9	Clustered regularly interspaced palindromic repeats/CRISPR-associated protein 9
DSAEK	Descemet stripping automated endothelial keratoplasty
ECM	Extracellular matrix
FDA	US Food and Drug Administration
IOP	Intraocular pressure
JOAG	Juvenile open angle glaucoma
MEK/ERK	Mitogen-activated protein kinase-ERK kinase/extracellular signal related kinase
MMCAT	Microcornea, myopic chorioretinal atrophy and telecanthus
MMP	Matrix metalloproteinase
MO	Morpholino oligonucleotide
OMIM	Online Mendelian Inheritance in Man
PCG	Primary congenital glaucoma
POAG	Primary open angle glaucoma
PTC	Premature termination codon
rAAV	Recombinant adeno-associated virus
rAd	Recombinant adenovirus
sgRNA	Single guide RNA
siRNA	Small interfering RNA
RGC	Retinal ganglion cell
RPE	Retinal pigment epithelium
STAR	Study of Ataluren in Participants With Nonsense Mutation Aniridia

References

1. Shaham, O.; Menuchin, Y.; Farhy, C.; Ashery-Padan, R. Pax6: A Multi-Level Regulator of Ocular Development. *Prog. Retin. Eye Res.* **2012**, *31*, 351–376, doi:10.1016/j.preteyeres.2012.04.002.

2. Cvekl, A.; Tamm, E.R. Anterior Eye Development and Ocular Mesenchyme: New Insights from Mouse Models and Human Diseases. *BioEssays News Rev. Mol. Cell. Dev. Biol.* **2004**, *26*, 374, doi:10.1002/bies.20009.

3. Takamiya, M.; Stegmaier, J.; Kobitski, A.Y.; Schott, B.; Weger, B.D.; Margariti, D.; Cereceda Delgado, A.R.; Gourain, V.; Scherr, T.; Yang, L.; et al. Pax6 Organizes the Anterior Eye Segment by Guiding Two Distinct Neural Crest Waves. *PLoS Genet.* **2020**, *16*, e1008774, doi:10.1371/journal.pgen.1008774.

4. Stoilov, I.; Rezaie, T.; Jansson, I.; Schenkman, J.B.; Sarfarazi, M. Expression of Cytochrome P4501b1 (Cyp1b1) during Early Murine Development. *Mol. Vis.* **2004**, *10*, 629–636.

5. Davis-Silberman, N.; Ashery-Padan, R. Iris Development in Vertebrates; Genetic and Molecular Considerations. *Brain Res.* **2008**, *1192*, 17–28, doi:10.1016/j.brainres.2007.03.043.

6. Miesfeld, J.B.; Brown, N.L. Eye Organogenesis: A Hierarchical View of Ocular Development. *Curr. Top. Dev. Biol.* **2019**, *132*, 351–393, doi:10.1016/bs.ctdb.2018.12.008.

7. Mizokami, K.; Sugiura, T.; San Juan, R.G. The Development of Human Trabecular Meshwork. *Med. Electron Microsc.* **1994**, *27*, 275–281, doi:10.1007/BF02349674.

8. Marchini, G.; Toscani, M.; Chemello, F. Pediatric Glaucoma: Current Perspectives. *Pediatr. Health Med. Ther.* **2014**, *5*, 15–27, doi:10.2147/PHMT.S44709.

9. Thau, A.; Lloyd, M.; Freedman, S.; Beck, A.; Grajewski, A.; Levin, A.V. New Classification System for Pediatric Glaucoma: Implications for Clinical Care and a Research Registry. *Curr. Opin. Ophthalmol.* **2018**, *29*, 385–394, doi:10.1097/ICU.0000000000000516.

10. Ko, F.; Papadopoulos, M.; Khaw, P.T. Primary Congenital Glaucoma. *Prog. Brain Res.* **2015**, *221*, 177–189, doi:10.1016/bs.pbr.2015.06.005.

11. Reis, L.M.; Seese, S.; Costakos, D.; Semina, E.V. Congenital Anterior Segment Ocular Disorders: Genotype-Phenotype Correlations and Emerging Novel Mechanisms. *Prog. Retin. Eye Res.* **2024**, 101288, doi:10.1016/j.preteyeres.2024.101288.

12. Patel, A.; Hayward, J.D.; Tailor, V.; Nyanhete, R.; Ahlfors, H.; Gabriel, C.; Jannini, T.B.; Abbou-Rayyah, Y.; Henderson, R.; Nischal, K.K.; et al. The Oculome Panel Test: Next-Generation Sequencing to Diagnose a

- Diverse Range of Genetic Developmental Eye Disorders. *Ophthalmology* **2019**, *126*, 888–907, doi:10.1016/j.ophtha.2018.12.050.
13. Reis, L.M.; Semina, E.V. Genetics of Anterior Segment Dysgenesis Disorders. *Curr. Opin. Ophthalmol.* **2011**, *22*, 314–324, doi:10.1097/ICU.0b013e328349412b.
 14. Hingorani, M.; Hanson, I.; van Heyningen, V. Aniridia. *Eur. J. Hum. Genet.* **2012**, *20*, 1011–1017, doi:10.1038/ejhg.2012.100.
 15. Reis, L.M.; Maheshwari, M.; Capasso, J.; Atilla, H.; Dudakova, L.; Thompson, S.; Zitano, L.; Lay-Son, G.; Lowry, R.B.; Black, J.; et al. Axenfeld-Rieger Syndrome: More than Meets the Eye. *J. Med. Genet.* **2023**, *60*, 368–379, doi:10.1136/jmg-2022-108646.
 16. Knight, L.S.W.; Ruddle, J.B.; Taranath, D.A.; Goldberg, I.; Smith, J.E.H.; Gole, G.; Chiang, M.Y.; Willett, F.; D'Mellow, G.; Breen, J.; et al. Childhood and Early Onset Glaucoma Classification and Genetic Profile in a Large Australasian Disease Registry. *Ophthalmology* **2021**, *128*, 1549–1560, doi:10.1016/j.ophtha.2021.04.016.
 17. Wowra, B.; Dobrowolski, D.; Parekh, M.; Wylegała, E. General Treatment and Ophthalmic Management of Peters' Anomaly. *J. Clin. Med.* **2024**, *13*, 532, doi:10.3390/jcm13020532.
 18. Moosajee, M.; Hingorani, M.; Moore, A.T. PAX6-Related Aniridia. In *GeneReviews®*; Adam, M.P., Feldman, J., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Amemiya, A., Eds.; University of Washington, Seattle: Seattle (WA), 1993.
 19. Jackson, D.; Malka, S.; Harding, P.; Palma, J.; Dunbar, H.; Moosajee, M. Molecular Diagnostic Challenges for Non-retinal Developmental Eye Disorders in the United Kingdom. *Am. J. Med. Genet. C Semin. Med. Genet.* **2020**, *184*, 578–589, doi:10.1002/ajmg.c.31837.
 20. Home - OMIM Available online: <https://omim.org/> (accessed on 1 October 2024).
 21. Vincent, A.; Billingsley, G.; Priston, M.; Glaser, T.; Oliver, E.; Walter, M.; Ritch, R.; Levin, A.; Heon, E. Further Support of the Role of CYP1B1 in Patients with Peters Anomaly. *Mol. Vis.* **2006**, *12*, 506–510.
 22. Edward, D.; Rajhi, A.A.; Lewis, R.A.; Curry, S.; Wang, Z.; Bejjani, B. Molecular Basis of Peters Anomaly in Saudi Arabia. *Ophthalmic Genet.* **2004**, *25*, 257–270, doi:10.1080/13816810490902648.
 23. Churchill, A.J.; Yeung, A. A Compound Heterozygous Change Found in Peters' Anomaly. *Mol. Vis.* **2005**, *11*, 66–70.
 24. Stingl, J.V.; Diederich, S.; Diel, H.; Schuster, A.K.; Wagner, F.M.; Chronopoulos, P.; Aghayeva, F.; Grehn, F.; Winter, J.; Schweiger, S.; et al. First Results from the Prospective German Registry for Childhood Glaucoma: Phenotype-Genotype Association. *J. Clin. Med.* **2021**, *11*, 16, doi:10.3390/jcm11010016.
 25. Tanwar, M.; Dada, T.; Dada, R. Axenfeld-Rieger Syndrome Associated with Congenital Glaucoma and Cytochrome P4501B1 Gene Mutations. *Case Rep. Med.* **2010**, *2010*, 212656, doi:10.1155/2010/212656.
 26. Samant, M.; Chauhan, B.K.; Lathrop, K.L.; Nischal, K.K. Congenital Aniridia: Etiology, Manifestations and Management. *Expert Rev. Ophthalmol.* **2016**, *11*, 135–144, doi:10.1586/17469899.2016.1152182.
 27. Franco, E.; Gagrani, M.; Scanga, H.L.; Areaux, R.G.; Chu, C.T.; Nischal, K.K. Variable Phenotype of Congenital Corneal Opacities in Biallelic CYP1B1 Pathogenic Variants. *Cornea* **2024**, *43*, 195–200, doi:10.1097/ICO.0000000000003395.
 28. Al-Saei, O.; Malka, S.; Owen, N.; Aliyev, E.; Vempalli, F.R.; Ocieczek, P.; Al-Khathlan, B.; Genomics England Research Consortium; Fakhro, K.; Moosajee, M. Increasing the Diagnostic Yield of Childhood Glaucoma Cases Recruited into the 100,000 Genomes Project. *BMC Genomics* **2024**, *25*, 484, doi:10.1186/s12864-024-10353-8.
 29. Ma, A.; Yousoof, S.; Grigg, J.R.; Flaherty, M.; Minoche, A.E.; Cowley, M.J.; Nash, B.M.; Ho, G.; Gayagay, T.; Lai, T.; et al. Revealing Hidden Genetic Diagnoses in the Ocular Anterior Segment Disorders. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **2020**, *22*, 1623–1632, doi:10.1038/s41436-020-0854-x.
 30. Thanikachalam, S.; Hodapp, E.; Chang, T.C.; Swols, D.M.; Cengiz, F.B.; Guo, S.; Zafeer, M.F.; Seyhan, S.; Bademci, G.; Scott, W.K.; et al. Spectrum of Genetic Variants Associated with Anterior Segment Dysgenesis in South Florida. *Genes* **2020**, *11*, 350, doi:10.3390/genes11040350.
 31. Collantes, E.R.A.; Delfin, M.S.; Fan, B.; Torregosa, J.M.R.; Siguan-Bell, C.; de Guzman Florcruz, N.V.; Martinez, J.M.D.; Masna-Hidalgo, B.J.; Guzman, V.P.T.; Anotado-Flores, J.F.; et al. EFEMP1 Rare Variants Cause Familial Juvenile-Onset Open Angle Glaucoma. *Hum. Mutat.* **2022**, *43*, 240–252, doi:10.1002/humu.24320.

32. Aghayeva, F.A.; Schuster, A.K.; Diel, H.; Chronopoulos, P.; Wagner, F.M.; Grehn, F.; Pirlich, N.; Schweiger, S.; Pfeiffer, N.; Hoffmann, E.M. Childhood Glaucoma Registry in Germany: Initial Database, Clinical Care and Research (Pilot Study). *BMC Res. Notes* **2022**, *15*, 32, doi:10.1186/s13104-022-05921-8.
33. Huang, L.; Xu, T.; Gan, J.; Mao, Y.; Zhao, L.; Jiao, X.; Fan, M.; Wang, T.; Zhang, D.; Xu, M.; et al. Zonule-Associated Gene Variants in Isolated Ectopia Lentis and Glaucoma. *J. Glaucoma* **2023**, *32*, e80–e89, doi:10.1097/IJG.0000000000002209.
34. Chen, Z.-X.; Jia, W.-N.; Sun, Y.; Chen, T.-H.; Zhao, Z.-N.; Lan, L.-N.; Liu, Y.; Song, L.-H.; Jiang, Y.-X. Biallelic ADAMTSL4 Variants in a Chinese Cohort of Congenital Ectopia Lentis: Implications for Genotype-Phenotype Relationships. *Hum. Mutat.* **2022**, *43*, 2141–2152, doi:10.1002/humu.24483.
35. Alsaif, H.S.; Khan, A.O.; Patel, N.; Alkuraya, H.; Hashem, M.; Abdulwahab, F.; Ibrahim, N.; Aldahmesh, M.A.; Alkuraya, F.S. Congenital Glaucoma and CYP1B1: An Old Story Revisited. *Hum. Genet.* **2019**, *138*, 1043–1049, doi:10.1007/s00439-018-1878-z.
36. Siggs, O.M.; Souzeau, E.; Taranath, D.A.; Dubowsky, A.; Chappell, A.; Zhou, T.; Javadiyan, S.; Nicholl, J.; Kearns, L.S.; Staffieri, S.E.; et al. Biallelic CPAMD8 Variants Are a Frequent Cause of Childhood and Juvenile Open-Angle Glaucoma. *Ophthalmology* **2020**, *127*, 758–766, doi:10.1016/j.ophtha.2019.12.024.
37. Bonet-Fernández, J.-M.; Aroca-Aguilar, J.-D.; Corton, M.; Ramírez, A.-I.; Alexandre-Moreno, S.; García-Antón, M.-T.; Salazar, J.-J.; Ferre-Fernández, J.-J.; Atienzar-Aroca, R.; Villaverde, C.; et al. CPAMD8 Loss-of-Function Underlies Non-Dominant Congenital Glaucoma with Variable Anterior Segment Dysgenesis and Abnormal Extracellular Matrix. *Hum. Genet.* **2020**, *139*, 1209–1231, doi:10.1007/s00439-020-02164-0.
38. Zhu, A.Y.; Costain, G.; Cytrynbaum, C.; Weksberg, R.; Cohn, R.D.; Ali, A. Novel Heterozygous Variants in PXDN Cause Different Anterior Segment Dysgenesis Phenotypes in Monozygotic Twins. *Ophthalmic Genet.* **2021**, *42*, 624–630, doi:10.1080/13816810.2021.1925929.
39. Khan, K.; Rudkin, A.; Parry, D.A.; Burdon, K.P.; McKibbin, M.; Logan, C.V.; Abdelhamed, Z.I.A.; Muecke, J.S.; Fernandez-Fuentes, N.; Laurie, K.J.; et al. Homozygous Mutations in PXDN Cause Congenital Cataract, Corneal Opacity, and Developmental Glaucoma. *Am. J. Hum. Genet.* **2011**, *89*, 464–473, doi:10.1016/j.ajhg.2011.08.005.
40. Zazo-Seco, C.; Plaisancié, J.; Bitoun, P.; Corton, M.; Artech, A.; Ayuso, C.; Schneider, A.; Zafeiropoulou, D.; Gilissen, C.; Roche, O.; et al. Novel PXDN Biallelic Variants in Patients with Microphthalmia and Anterior Segment Dysgenesis. *J. Hum. Genet.* **2020**, *65*, 487–491, doi:10.1038/s10038-020-0726-x.
41. Choi, A.; Lao, R.; Ling-Fung Tang, P.; Wan, E.; Mayer, W.; Bardakjian, T.; Shaw, G.M.; Kwok, P.-Y.; Schneider, A.; Slavotinek, A. Novel Mutations in PXDN Cause Microphthalmia and Anterior Segment Dysgenesis. *Eur. J. Hum. Genet. EJHG* **2015**, *23*, 337–341, doi:10.1038/ejhg.2014.119.
42. Yousaf, K.; Naz, S.; Mushtaq, A.; Wohler, E.; Sobreira, N.; Ho, B.-M.; Chen, L.-J.; Chu, W.-K.; Bashir, R. Exome Sequencing Reveals SLC4A11 Variant Underlying Congenital Hereditary Endothelial Dystrophy (CHED2) Misdiagnosed as Congenital Glaucoma. *Genes* **2023**, *14*, 310, doi:10.3390/genes14020310.
43. Liu, X.Y.; Tao, Y.F.; Mao, Y.K.; Chen, Z.J.; Wang, Y.; Hong, Y.F.; Fan, N. [A family with developmental glaucoma and microcornea due to novel ADAMTS18 gene mutations]. *Zhonghua Yan Ke Za Zhi Chin. J. Ophthalmol.* **2024**, *60*, 78–83, doi:10.3760/cma.j.cn112142-20231012-00134.
44. Zhou, L.; Xu, Z.; Wu, Q.; Wei, X. Unilateral Buphthalmos, Corneal Staphyloma and Corneal Fistula Caused by Pathogenic Variant in the PITX3 Gene: A Case Report. *BMC Ophthalmol.* **2022**, *22*, 385, doi:10.1186/s12886-022-02573-x.
45. Verdin, H.; Sorokina, E.A.; Meire, F.; Casteels, I.; de Ravel, T.; Semina, E.V.; De Baere, E. Novel and Recurrent PITX3 Mutations in Belgian Families with Autosomal Dominant Congenital Cataract and Anterior Segment Dysgenesis Have Similar Phenotypic and Functional Characteristics. *Orphanet J. Rare Dis.* **2014**, *9*, 26, doi:10.1186/1750-1172-9-26.
46. Khan, S.Y.; Vasanth, S.; Kabir, F.; Gottsch, J.D.; Khan, A.O.; Chaerkady, R.; Lee, M.-C.W.; Leitch, C.C.; Ma, Z.; Laux, J.; et al. FOXE3 Contributes to Peters Anomaly through Transcriptional Regulation of an Autophagy-Associated Protein Termed DNAJB1. *Nat. Commun.* **2016**, *7*, 10953, doi:10.1038/ncomms10953.
47. Plaisancié, J.; Ragge, N.K.; Dollfus, H.; Kaplan, J.; Lehalle, D.; Francannet, C.; Morin, G.; Colineaux, H.; Calvas, P.; Chassaing, N. FOXE3 Mutations: Genotype-Phenotype Correlations. *Clin. Genet.* **2018**, *93*, 837–845, doi:10.1111/cge.13177.

48. Ormestad, M.; Blixt, A.; Churchill, A.; Martinsson, T.; Enerbäck, S.; Carlsson, P. Foxe3 Haploinsufficiency in Mice: A Model for Peters' Anomaly. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 1350–1357.
49. Islam, L.; Kelberman, D.; Williamson, L.; Lewis, N.; Glindzicz, M.B.; Nischal, K.K.; Sowden, J.C. Functional Analysis of FOXE3 Mutations Causing Dominant and Recessive Ocular Anterior Segment Disease. *Hum. Mutat.* **2015**, *36*, 296–300, doi:10.1002/humu.22741.
50. Rashid, M.; Qasim, M.; Ishaq, R.; Bukhari, S.A.; Sajid, Z.; Ashfaq, U.A.; Haque, A.; Ahmed, Z.M. Pathogenic Variants of AIPL1, MERTK, GUCY2D, and FOXE3 in Pakistani Families with Clinically Heterogeneous Eye Diseases. *PLoS ONE* **2020**, *15*, e0239748, doi:10.1371/journal.pone.0239748.
51. Sibon, I.; Coupry, I.; Menegon, P.; Bouchet, J.-P.; Gorry, P.; Burgelin, I.; Calvas, P.; Orignac, I.; Dousset, V.; Lacombe, D.; et al. COL4A1 Mutation in Axenfeld-Rieger Anomaly with Leukoencephalopathy and Stroke. *Ann. Neurol.* **2007**, *62*, 177–184, doi:10.1002/ana.21191.
52. Coupry, I.; Sibon, I.; Mortemousque, B.; Rouanet, F.; Mine, M.; Goizet, C. Ophthalmological Features Associated with COL4A1 Mutations. *Arch. Ophthalmol. Chic. Ill 1960* **2010**, *128*, 483–489, doi:10.1001/archophthalmol.2010.42.
53. Diel, H.; Ding, C.; Grehn, F.; Chronopoulos, P.; Bartsch, O.; Hoffmann, E.M. First Observation of Secondary Childhood Glaucoma in Coffin-Siris Syndrome: A Case Report and Literature Review. *BMC Ophthalmol.* **2021**, *21*, 28, doi:10.1186/s12886-020-01788-0.
54. Reis, L.M.; Houssin, N.S.; Zamora, C.; Abdul-Rahman, O.; Kalish, J.M.; Zackai, E.H.; Plageman, T.F.; Semina, E.V. Novel Variants in CDH2 Are Associated with a New Syndrome Including Peters Anomaly. *Clin. Genet.* **2020**, *97*, 502–508, doi:10.1111/cge.13660.
55. Reis, L.M.; Atila, H.; Kannu, P.; Schneider, A.; Thompson, S.; Bardakjian, T.; Semina, E.V. Distinct Roles of Histone Lysine Demethylases and Methyltransferases in Developmental Eye Disease. *Genes* **2023**, *14*, 216, doi:10.3390/genes14010216.
56. Weh, E.; Reis, L.M.; Happ, H.C.; Levin, A.V.; Wheeler, P.G.; David, K.L.; Carney, E.; Angle, B.; Hauser, N.; Semina, E.V. Whole Exome Sequence Analysis of Peters Anomaly. *Hum. Genet.* **2014**, *133*, 1497–1511, doi:10.1007/s00439-014-1481-x.
57. Pan, Y.; Iwata, T. Exploring the Genetic Landscape of Childhood Glaucoma. *Child. Basel Switz.* **2024**, *11*, 454, doi:10.3390/children11040454.
58. Banerjee, A.; Chakraborty, S.; Chakraborty, A.; Chakrabarti, S.; Ray, K. 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*, e0156252, doi:10.1371/journal.pone.0156252.
59. Mookherjee, S.; Acharya, M.; Banerjee, D.; Bhattacharjee, A.; Ray, K. Molecular Basis for Involvement of CYP1B1 in MYOC Upregulation and Its Potential Implication in Glaucoma Pathogenesis. *PLoS One* **2012**, *7*, e45077, doi:10.1371/journal.pone.0045077.
60. Zhao, Y.; Wang, S.; Sorenson, C.M.; Teixeira, L.; Dubielzig, R.R.; Peters, D.M.; Conway, S.J.; Jefcoate, C.R.; Sheibani, N. Cyp1b1 Mediates Periostin Regulation of Trabecular Meshwork Development by Suppression of Oxidative Stress. *Mol. Cell. Biol.* **2013**, *33*, 4225–4240, doi:10.1128/MCB.00856-13.
61. Kumar, A.; Han, Y.; Oatts, J.T. Genetic Changes and Testing Associated with Childhood Glaucoma: A Systematic Review. *PLOS ONE* **2024**, *19*, e0298883, doi:10.1371/journal.pone.0298883.
62. López-Garrido, M.-P.; Medina-Trillo, C.; Morales-Fernandez, L.; Garcia-Feijoo, J.; Martínez-de-la-Casa, J.-M.; García-Antón, M.; Escribano, J. Null CYP1B1 Genotypes in Primary Congenital and Nondominant Juvenile Glaucoma. *Ophthalmology* **2013**, *120*, 716–723, doi:10.1016/j.ophtha.2012.09.016.
63. Medina-Trillo, C.; Ferre-Fernández, J.-J.; Aroca-Aguilar, J.-D.; Bonet-Fernández, J.-M.; Escribano, J. Functional Characterization of Eight Rare Missense CYP1B1 Variants Involved in Congenital Glaucoma and Their Association with Null Genotypes. *Acta Ophthalmol. (Copenh.)* **2016**, *94*, e555–e560, doi:10.1111/aos.13017.
64. Khan, A.O. Genetics of Primary Glaucoma. *Curr. Opin. Ophthalmol.* **2011**, *22*, 347–355, doi:10.1097/ICU.0b013e32834922d2.
65. Plásilová, M.; Stoilov, I.; Sarfarazi, M.; Kádasi, L.; Feráková, E.; Ferák, V. Identification of a Single Ancestral CYP1B1 Mutation in Slovak Gypsies (Roms) Affected with Primary Congenital Glaucoma. *J. Med. Genet.* **1999**, *36*, 290–294.

66. Kidson, S.H.; Kume, T.; Deng, K.; Winfrey, V.; Hogan, B.L. The Forkhead/Winged-Helix Gene, Mf1, Is Necessary for the Normal Development of the Cornea and Formation of the Anterior Chamber in the Mouse Eye. *Dev. Biol.* **1999**, *211*, 306–322, doi:10.1006/dbio.1999.9314.
67. Berry, F.B.; Lines, M.A.; Oas, J.M.; Footz, T.; Underhill, D.A.; Gage, P.J.; Walter, M.A. Functional Interactions between FOXC1 and PITX2 Underlie the Sensitivity to FOXC1 Gene Dose in Axenfeld-Rieger Syndrome and Anterior Segment Dysgenesis. *Hum. Mol. Genet.* **2006**, *15*, 905–919, doi:10.1093/hmg/ddl008.
68. Paylakhi, S.H.; Moazzeni, H.; Yazdani, S.; Rassouli, P.; Arefian, E.; Jaber, E.; Arash, E.H.; Gilani, A.S.; Fan, J.-B.; April, C.; et al. FOXC1 in Human Trabecular Meshwork Cells Is Involved in Regulatory Pathway That Includes miR-204, MEIS2, and ITG β 1. *Exp. Eye Res.* **2013**, *111*, 112–121, doi:10.1016/j.exer.2013.03.009.
69. Zhang, X.; Friedman, A.; Heaney, S.; Purcell, P.; Maas, R.L. Meis Homeoproteins Directly Regulate Pax6 during Vertebrate Lens Morphogenesis. *Genes Dev.* **2002**, *16*, 2097, doi:10.1101/gad.1007602.
70. Medina-Trillo, C.; Sánchez-Sánchez, F.; Aroca-Aguilar, J.-D.; Ferre-Fernández, J.-J.; Morales, L.; Méndez-Hernández, C.-D.; Blanco-Kelly, F.; Ayuso, C.; García-Feijoo, J.; Escribano, J. Hypo- and Hypermorphic FOXC1 Mutations in Dominant Glaucoma: Transactivation and Phenotypic Variability. *PLoS ONE* **2015**, *10*, e0119272, doi:10.1371/journal.pone.0119272.
71. Harding, P.; Moosajee, M. The Molecular Basis of Human Anophthalmia and Microphthalmia. *J. Dev. Biol.* **2019**, *7*, 16, doi:10.3390/jdb7030016.
72. Adler, R.; Canto-Soler, M.V. Molecular Mechanisms of Optic Vesicle Development: Complexities, Ambiguities and Controversies. *Dev. Biol.* **2007**, *305*, 1, doi:10.1016/j.ydbio.2007.01.045.
73. Gour, A.; Tibrewal, S.; Garg, A.; Vohra, M.; Ratna, R.; Sangwan, V.S. New Horizons in Aniridia Management: Clinical Insights and Therapeutic Advances. *Taiwan J. Ophthalmol.* **2023**, *13*, 467, doi:10.4103/tjo.TJO-D-23-00140.
74. Schedl, A.; Ross, A.; Lee, M.; Engelkamp, D.; Rashbass, P.; Heyningen, V. van; Hastie, N.D. Influence of PAX6 Gene Dosage on Development: Overexpression Causes Severe Eye Abnormalities. *Cell* **1996**, *86*, 71–82, doi:10.1016/S0092-8674(00)80078-1.
75. Mort, R.L.; Bentley, A.J.; Martin, F.L.; Collinson, J.M.; Douvaras, P.; Hill, R.E.; Morley, S.D.; Fullwood, N.J.; West, J.D. Effects of Aberrant Pax6 Gene Dosage on Mouse Corneal Pathophysiology and Corneal Epithelial Homeostasis. *PLoS ONE* **2011**, *6*, e28895, doi:10.1371/journal.pone.0028895.
76. Gupta, V.; Somarajan, B.I.; Gupta, S.; Mahalingam, K.; Singh, A.; Sharma, A. A New Association of PAX6 Variation with Juvenile Onset Open Angle Glaucoma. *J. Hum. Genet.* **2023**, *68*, 355–358, doi:10.1038/s10038-022-01115-z.
77. Haji-Seyed-Javadi, R.; Jelodari-Mamaghani, S.; Paylakhi, S.H.; Yazdani, S.; Nilforushan, N.; Fan, J.-B.; Klotzle, B.; Mahmoudi, M.J.; Ebrahimian, M.J.; Chelich, N.; et al. LTBP2 Mutations Cause Weill-Marchesani and Weill-Marchesani-like Syndrome and Affect Disruptions in the Extracellular Matrix. *Hum. Mutat.* **2012**, *33*, 1182–1187, doi:10.1002/humu.22105.
78. Narooie-Nejad, M.; Paylakhi, S.H.; Shojaei, S.; Fazlali, Z.; Rezaei Kanavi, M.; Nilforushan, N.; Yazdani, S.; Babrzadeh, F.; Suri, F.; Ronaghi, M.; et al. Loss of Function Mutations in the Gene Encoding Latent Transforming Growth Factor Beta Binding Protein 2, LTBP2, Cause Primary Congenital Glaucoma. *Hum. Mol. Genet.* **2009**, *18*, 3969–3977, doi:10.1093/hmg/ddp338.
79. Gabriel, L.A.R.; Wang, L.W.; Bader, H.; Ho, J.C.; Majors, A.K.; Hollyfield, J.G.; Traboulsi, E.I.; Apte, S.S. ADAMTSL4, a Secreted Glycoprotein Widely Distributed in the Eye, Binds Fibrillin-1 Microfibrils and Accelerates Microfibril Biogenesis. *Invest. Ophthalmol. Vis. Sci.* **2012**, *53*, 461, doi:10.1167/iovs.10-5955.
80. Cheong, S.-S.; Hentschel, L.; Davidson, A.E.; Gerrelli, D.; Davie, R.; Rizzo, R.; Pontikos, N.; Plagnol, V.; Moore, A.T.; Sowden, J.C.; et al. Mutations in CPAMD8 Cause a Unique Form of Autosomal-Recessive Anterior Segment Dysgenesis. *Am. J. Hum. Genet.* **2016**, *99*, 1338, doi:10.1016/j.ajhg.2016.09.022.
81. Escribano, J.; Tevar, A.; Bonet-Fernandez, J.-M.; Atienzar-Aroca, R.; Aroca-Aguilar, J.-D. Functional Interaction between Zebrafish Adamtsl4 and Cpamd8 Matrix Metalloproteinase-Related Genes: Implications in Ocular Anterior Segment Development and Glaucoma. *Invest. Ophthalmol. Vis. Sci.* **2024**, *65*, OD6.
82. Abreu-Velez, A.M.; Howard, M.S. Collagen IV in Normal Skin and in Pathological Processes. *North Am. J. Med. Sci.* **2012**, *4*, 1, doi:10.4103/1947-2714.92892.

83. Lee, S.-W.; Kim, H.-K.; Naidansuren, P.; Ham, K.A.; Choi, H.S.; Ahn, H.-Y.; Kim, M.; Kang, D.H.; Kang, S.W.; Joe, Y.A. Peroxidase Is Essential for Endothelial Cell Survival and Growth Signaling by Sulfhydryl-Dependent Crosslink-Dependent Matrix Assembly. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2020**, *34*, 10228–10241, doi:10.1096/fj.201902899R.
84. Bai, X.; Dilworth, D.J.; Weng, Y.-C.; Gould, D.B. Developmental Distribution of Collagen IV Isoforms and Relevance to Ocular Diseases. *Matrix Biol. J. Int. Soc. Matrix Biol.* **2009**, *28*, 194–201, doi:10.1016/j.matbio.2009.02.004.
85. Kizhatil, K.; Ryan, M.; Marchant, J.K.; Henrich, S.; John, S.W.M. Schlemm's Canal Is a Unique Vessel with a Combination of Blood Vascular and Lymphatic Phenotypes That Forms by a Novel Developmental Process. *PLoS Biol.* **2014**, *12*, e1001912, doi:10.1371/journal.pbio.1001912.
86. Thomson, B.R.; Souma, T.; Tompson, S.W.; Onay, T.; Kizhatil, K.; Siggs, O.M.; Feng, L.; Whisenhunt, K.N.; Yanovitch, T.L.; Kalaydjieva, L.; et al. Angiopoietin-1 Is Required for Schlemm's Canal Development in Mice and Humans. *J. Clin. Invest.* **2017**, *127*, 4421–4436, doi:10.1172/JCI95545.
87. Patel, S.P.; Parker, M.D. SLC4A11 and the Pathophysiology of Congenital Hereditary Endothelial Dystrophy. *BioMed Res. Int.* **2015**, *2015*, 475392, doi:10.1155/2015/475392.
88. Vilas, G.L.; Loganathan, S.K.; Liu, J.; Riau, A.K.; Young, J.D.; Mehta, J.S.; Vithana, E.N.; Casey, J.R. Transmembrane Water-Flux through SLC4A11: A Route Defective in Genetic Corneal Diseases. *Hum. Mol. Genet.* **2013**, *22*, 4579–4590, doi:10.1093/hmg/ddt307.
89. Wang, L.; Sun, M.; Zhang, Q.; Dang, S.; Zhang, W. ADAMTS18 Regulates Early Branching Morphogenesis of Lacrimal Gland and Has a Significant Association with the Risk of Dry Eye in Mice. *Exp. Eye Res.* **2022**, *218*, 109020, doi:10.1016/j.exer.2022.109020.
90. Ataca, D.; Caikovski, M.; Piersigilli, A.; Moulin, A.; Benarafa, C.; Earp, S.E.; Guri, Y.; Kostic, C.; Arsenijevic, Y.; Soininen, R.; et al. Adamts18 Deletion Results in Distinct Developmental Defects and Provides a Model for Congenital Disorders of Lens, Lung, and Female Reproductive Tract Development. *Biol. Open* **2016**, *5*, 1585–1594, doi:10.1242/bio.019711.
91. Aldahmesh, M.A.; Alshammari, M.J.; Khan, A.O.; Mohamed, J.Y.; Alhabib, F.A.; Alkuraya, F.S. The Syndrome of Microcornea, Myopic Chorioretinal Atrophy, and Telecanthus (MMCAT) Is Caused by Mutations in ADAMTS18. *Hum. Mutat.* **2013**, *34*, 1195–1199, doi:10.1002/humu.22374.
92. Aldahmesh, M.A.; Khan, A.O.; Mohamed, J.Y.; Alkuraya, H.; Ahmed, H.; Bobis, S.; Al-Mesfer, S.; Alkuraya, F.S. Identification of ADAMTS18 as a Gene Mutated in Knobloch Syndrome. *J. Med. Genet.* **2011**, *48*, 597–601, doi:10.1136/jmedgenet-2011-100306.
93. Cvekl, A.; Camerino, M.J. Generation of Lens Progenitor Cells and Lentoid Bodies from Pluripotent Stem Cells: Novel Tools for Human Lens Development and Ocular Disease Etiology. *Cells* **2022**, *11*, 3516, doi:10.3390/cells11213516.
94. Semina, E.V.; Ferrell, R.E.; Mintz-Hittner, H.A.; Bitoun, P.; Alward, W.L.M.; Reiter, R.S.; Funkhauser, C.; Daack-Hirsch, S.; Murray, J.C. A Novel Homeobox Gene PITX3 Is Mutated in Families with Autosomal-Dominant Cataracts and ASMD. *Nat. Genet.* **1998**, *19*, 167–170, doi:10.1038/527.
95. Dodonova, S.O.; Zhu, F.; Dienemann, C.; Taipale, J.; Cramer, P. Nucleosome-Bound SOX2 and SOX11 Structures Elucidate Pioneer Factor Function. *Nature* **2020**, *580*, 669–672, doi:10.1038/s41586-020-2195-y.
96. Cizelsky, W.; Hempel, A.; Metzger, M.; Tao, S.; Hollemann, T.; Kühl, M.; Kühl, S.J. Sox4 And Sox11 Function during Xenopus Laevis Eye Development. *PLOS ONE* **2013**, *8*, e69372, doi:10.1371/journal.pone.0069372.
97. Tamm, E.R.; Wurm, A.; Sock, E.; Fuchshofer, R.; Wegner, M. The High-Mobility-Group Transcription Factor Sox11 Plays an Important Role During Anterior Eye Segment Development. *Invest. Ophthalmol. Vis. Sci.* **2006**, *47*, 3874.
98. Li, L.; Fan, D.-B.; Zhao, Y.-T.; Li, Y.; Yang, Z.-B.; Zheng, G.-Y. GJA8 Missense Mutation Disrupts Hemichannels and Induces Cell Apoptosis in Human Lens Epithelial Cells. *Sci. Rep.* **2019**, *9*, 19157, doi:10.1038/s41598-019-55549-1.
99. Kao, W.W.-Y.; Liu, C.-Y. Roles of Lumican and Keratocan on Corneal Transparency. *Glycoconj. J.* **2002**, *19*, 275–285, doi:10.1023/A:1025396316169.
100. Conrad, A.H.; Conrad, G.W. The Keratocan Gene Is Expressed in Both Ocular and Non-Ocular Tissues during Early Chick Development. *Matrix Biol.* **2003**, *22*, 323–337, doi:10.1016/S0945-053X(03)00039-8.

101. Gealy, E.C.; Kerr, B.C.; Young, R.D.; Tudor, D.; Hayes, A.J.; Hughes, C.E.; Caterson, B.; Quantock, A.J.; Ralphs, J.R. Differential Expression of the Keratan Sulphate Proteoglycan, Keratocan, during Chick Corneal Embryogenesis. *Histochem. Cell Biol.* **2007**, *128*, 551–555, doi:10.1007/s00418-007-0332-4.
102. Pellegata, N.S.; Dieguez-Lucena, J.L.; Joensuu, T.; Lau, S.; Montgomery, K.T.; Krahe, R.; Kivelä, T.; Kucherlapati, R.; Forsius, H.; de la Chapelle, A. Mutations in KERA, Encoding Keratocan, Cause Cornea Plana. *Nat. Genet.* **2000**, *25*, 91–95, doi:10.1038/75664.
103. Accogli, A.; Calabretta, S.; St-Onge, J.; Boudrahem-Addour, N.; Dionne-Laporte, A.; Joset, P.; Azzarello-Burri, S.; Rauch, A.; Krier, J.; Fieg, E.; et al. De Novo Pathogenic Variants in N-Cadherin Cause a Syndromic Neurodevelopmental Disorder with Corpus Callosum, Axon, Cardiac, Ocular, and Genital Defects. *Am. J. Hum. Genet.* **2019**, *105*, 854, doi:10.1016/j.ajhg.2019.09.005.
104. Karwacki-Neisius, V.; Jang, A.; Cukuroglu, E.; Tai, A.; Jiao, A.; Predes, D.; Yoon, J.; Brookes, E.; Chen, J.; Iberg, A.; et al. WNT Signalling Control by KDM5C during Development Affects Cognition. *Nature* **2024**, *627*, 594–603, doi:10.1038/s41586-024-07067-y.
105. Schorle, H.; Meier, P.; Buchert, M.; Jaenisch, R.; Mitchell, P.J. Transcription Factor AP-2 Essential for Cranial Closure and Craniofacial Development. *Nature* **1996**, *381*, 235–238, doi:10.1038/381235a0.
106. Kim, Y.; Jeong, Y.; Kwon, K.; Ismail, T.; Lee, H.-K.; Kim, C.; Park, J.-W.; Kwon, O.-S.; Kang, B.-S.; Lee, D.-S.; et al. Physiological Effects of KDM5C on Neural Crest Migration and Eye Formation during Vertebrate Development. *Epigenetics Chromatin* **2018**, *11*, 72, doi:10.1186/s13072-018-0241-x.
107. Gestri, G.; Osborne, R.J.; Wyatt, A.W.; Gerrelli, D.; Gribble, S.; Stewart, H.; Fryer, A.; Bunyan, D.J.; Prescott, K.; Collin, J.R.O.; et al. Reduced TFAP2A Function Causes Variable Optic Fissure Closure and Retinal Defects and Sensitizes Eye Development to Mutations in Other Morphogenetic Regulators. *Hum. Genet.* **2009**, *126*, 791–803, doi:10.1007/s00439-009-0730-x.
108. Shao, F.; Phan, A.-V.; Yu, W.; Guo, Y.; Thompson, J.; Coppinger, C.; Venugopalan, S.R.; Amendt, B.A.; Van Otterloo, E.; Cao, H. Transcriptional Programs of Pitx2 and Tfap2a/Tfap2b Controlling Lineage Specification of Mandibular Epithelium during Tooth Initiation. *PLOS Genet.* **2024**, *20*, e1011364, doi:10.1371/journal.pgen.1011364.
109. Mandal, A.K.; Chakrabarti, D.; Gothwal, V.K. Approach to Primary Congenital Glaucoma: A Perspective. *Taiwan J. Ophthalmol.* **2023**, *13*, 451, doi:10.4103/tjo.TJO-D-23-00104.
110. Coviltir, V.; Marinescu, M.C.; Urse, B.M.; Burcel, M.G. Primary Congenital and Childhood Glaucoma—A Complex Clinical Picture and Surgical Management. *Diagnostics* **2025**, *15*, 308, doi:10.3390/diagnostics15030308.
111. Hashemi, H.; Ghaffari, R.; Mohebi, M. Posterior Lamellar Keratoplasty (DSAEK) in Peters Anomaly. *Cornea* **2012**, *31*, 1201–1205, doi:10.1097/ICO.0b013e31825697a4.
112. Research, C. for B.E. and Approved Cellular and Gene Therapy Products. *FDA* **2024**.
113. Amador, C.; Shah, R.; Ghiam, S.; Kramerov, A.A.; Ljubimov, A.V. Gene Therapy in the Anterior Eye Segment. *Curr. Gene Ther.* **2022**, *22*, 104–131, doi:10.2174/1566523221666210423084233.
114. Mirjalili Mohanna, S.Z.; Korecki, A.J.; Simpson, E.M. rAAV-PHP.B Escapes the Mouse Eye and Causes Lethality Whereas rAAV9 Can Transduce Aniridic Corneal Limbal Stem Cells without Lethality. *Gene Ther.* **2023**, *30*, 670–684, doi:10.1038/s41434-023-00400-6.
115. Jain, A.; Zode, G.; Kasetti, R.B.; Ran, F.A.; Yan, W.; Sharma, T.P.; Bugge, K.; Searby, C.C.; Fingert, J.H.; Zhang, F.; et al. CRISPR-Cas9–Based Treatment of Myocilin-Associated Glaucoma. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 11199–11204, doi:10.1073/pnas.1706193114.
116. Behrens, A.; Gordon, E.M.; Li, L.; Liu, P.X.; Chen, Z.; Peng, H.; La Bree, L.; Anderson, W.F.; Hall, F.L.; McDonnell, P.J. Retroviral Gene Therapy Vectors for Prevention of Excimer Laser-Induced Corneal Haze. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 968–977.
117. Patil, S.V.; Kaipa, B.R.; Ranshing, S.; Sundaresan, Y.; Millar, J.C.; Nagarajan, B.; Kiehlbauch, C.; Zhang, Q.; Jain, A.; Searby, C.C.; et al. Lentiviral Mediated Delivery of CRISPR/Cas9 Reduces Intraocular Pressure in a Mouse Model of Myocilin Glaucoma. *Sci. Rep.* **2024**, *14*, 6958, doi:10.1038/s41598-024-57286-6.
118. Tandon, A.; Sharma, A.; Rodier, J.T.; Klivanov, A.M.; Rieger, F.G.; Mohan, R.R. BMP7 Gene Transfer via Gold Nanoparticles into Stroma Inhibits Corneal Fibrosis In Vivo. *PLoS ONE* **2013**, *8*, e66434, doi:10.1371/journal.pone.0066434.

119. Tong, Y.-C.; Chang, S.-F.; Liu, C.-Y.; Kao, W.W.-Y.; Huang, C.H.; Liaw, J. Eye Drop Delivery of Nano-Polymeric Micelle Formulated Genes with Cornea-Specific Promoters. *J. Gene Med.* **2007**, *9*, 956–966, doi:10.1002/jgm.1093.
120. Yoon, K.C.; Bae, J.A.; Park, H.J.; Im, S.K.; Oh, H.J.; Lin, X.H.; Kim, M.Y.; Lee, J.H.; Lee, S.E.; Ahn, K.Y.; et al. Subconjunctival Gene Delivery of the Transcription Factor GA-Binding Protein Delays Corneal Neovascularization in a Mouse Model. *Gene Ther.* **2009**, *16*, 973–981, doi:10.1038/gt.2009.50.
121. Blair-Parks, K.; Weston, B.C.; Dean, D.A. High-Level Gene Transfer to the Cornea Using Electroporation. *J. Gene Med.* **2002**, *4*, 92–100.
122. Vinciguerra, P.; Romano, V.; Rosetta, P.; Legrottaglie, E.F.; Kubrak-Kisza, M.; Azzolini, C.; Vinciguerra, R. Iontophoresis-Assisted Corneal Collagen Cross-Linking with Epithelial Debridement: Preliminary Results. *BioMed Res. Int.* **2016**, *2016*, 3720517, doi:10.1155/2016/3720517.
123. Henderson, J.; O'Callaghan, J.; Campbell, M. Gene Therapy for Glaucoma: Targeting Key Mechanisms. *Vision Res.* **2024**, *225*, None, doi:10.1016/j.visres.2024.108502.
124. Sulak, R.; Liu, X.; Smedowski, A. The Concept of Gene Therapy for Glaucoma: The Dream That Has Not Come True Yet. *Neural Regen. Res.* **2023**, *19*, 92–99, doi:10.4103/1673-5374.375319.
125. O'Callaghan, J.; Delaney, C.; O'Connor, M.; van Batenburg-Sherwood, J.; Schicht, M.; Lütjen-Drecoll, E.; Hudson, N.; Ni Dhubhghaill, S.; Humphries, P.; Stanley, C.; et al. Matrix Metalloproteinase-3 (MMP-3)–Mediated Gene Therapy for Glaucoma. *Sci. Adv.* **9**, eadf6537, doi:10.1126/sciadv.adf6537.
126. Wu, J.; Bell, O.H.; Copland, D.A.; Young, A.; Pooley, J.R.; Maswood, R.; Evans, R.S.; Khaw, P.T.; Ali, R.R.; Dick, A.D.; et al. Gene Therapy for Glaucoma by Ciliary Body Aquaporin 1 Disruption Using CRISPR-Cas9. *Mol. Ther.* **2020**, *28*, 820, doi:10.1016/j.ymthe.2019.12.012.
127. Tan, C.; Song, M.; Stamer, W.D.; Qiao, Y.; Chen, X.; Sun, X.; Lei, Y.; Chen, J. miR-21-5p: A Viable Therapeutic Strategy for Regulating Intraocular Pressure. *Exp. Eye Res.* **2020**, *200*, 108197, doi:10.1016/j.exer.2020.108197.
128. Wójcik-Gryciuk, A.; Gajewska-Woźniak, O.; Kordecka, K.; Boguszewski, P.M.; Waleszczyk, W.; Skup, M. Neuroprotection of Retinal Ganglion Cells with AAV2-BDNF Pretreatment Restoring Normal TrkB Receptor Protein Levels in Glaucoma. *Int. J. Mol. Sci.* **2020**, *21*, 6262, doi:10.3390/ijms21176262.
129. Jiang, W.; Tang, L.; Zeng, J.; Chen, B. Adeno-Associated Virus Mediated SOD Gene Therapy Protects the Retinal Ganglion Cells from Chronic Intraocular Pressure Elevation Induced Injury via Attenuating Oxidative Stress and Improving Mitochondrial Dysfunction in a Rat Model. *Am. J. Transl. Res.* **2016**, *8*, 799–810.
130. Richardson, R.; Smart, M.; Tracey-White, D.; Webster, A.R.; Moosajee, M. Mechanism and Evidence of Nonsense Suppression Therapy for Genetic Eye Disorders. *Exp. Eye Res.* **2017**, *155*, 24–37, doi:10.1016/j.exer.2017.01.001.
131. “pax6” [GENE] - ClinVar - NCBI Available online: <https://www.ncbi.nlm.nih.gov/clinvar> (accessed on 27 January 2025).
132. Lima Cunha, D.; Sarkar, H.; Eintracht, J.; Harding, P.; Zhou, J.H.; Moosajee, M. Restoration of Functional PAX6 in Aniridia Patient iPSC-Derived Ocular Tissue Models Using Repurposed Nonsense Suppression Drugs. *Mol. Ther. Nucleic Acids* **2023**, *33*, 240–253, doi:10.1016/j.omtn.2023.06.016.
133. Gregory-Evans, C.Y.; Wang, X.; Wasan, K.M.; Zhao, J.; Metcalfe, A.L.; Gregory-Evans, K. Postnatal Manipulation of Pax6 Dosage Reverses Congenital Tissue Malformation Defects. *J. Clin. Invest.* **2014**, *124*, 111–116, doi:10.1172/JCI70462.
134. Wang, X.; Gregory-Evans, K.; Wasan, K.M.; Sivak, O.; Shan, X.; Gregory-Evans, C.Y. Efficacy of Postnatal In Vivo Nonsense Suppression Therapy in a Pax6 Mouse Model of Aniridia. *Mol. Ther. Nucleic Acids* **2017**, *7*, 417–428, doi:10.1016/j.omtn.2017.05.002.
135. PTC Therapeutics A Phase 2, Multicenter, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Ataluren (PTC124) for the Treatment of Nonsense Mutation Aniridia; clinicaltrials.gov, 2022;
136. Mirjalili Mohanna, S.Z.; Hickmott, J.W.; Lam, S.L.; Chiu, N.Y.; Lengyell, T.C.; Tam, B.M.; Moritz, O.L.; Simpson, E.M. Germline CRISPR/Cas9-Mediated Gene Editing Prevents Vision Loss in a Novel Mouse Model of Aniridia. *Mol. Ther. Methods Clin. Dev.* **2020**, *17*, 478–490, doi:10.1016/j.omtm.2020.03.002.
137. Korecki, A.J.; Cueva-Vargas, J.L.; Fornes, O.; Agostinone, J.; Farkas, R.A.; Hickmott, J.W.; Lam, S.L.; Mathelier, A.; Zhou, M.; Wasserman, W.W.; et al. Human MiniPromoters for Ocular-rAAV Expression in

- ON Bipolar, Cone, Corneal, Endothelial, Müller Glial, and PAX6 Cells. *Gene Ther.* **2021**, *28*, 351–372, doi:10.1038/s41434-021-00227-z.
138. Dorot, O.; Roux, L.N.; Zennaro, L.; Oved, K.; Bremond-Gignac, D.; Pichinuk, E.; Aberdam, D. The Antipsychotropic Drug Duloxetine Rescues PAX6 Haploinsufficiency of Mutant Limbal Stem Cells through Inhibition of the MEK/ERK Signaling Pathway. *Ocul. Surf.* **2022**, *23*, 140–142, doi:10.1016/j.jtos.2021.12.003.
 139. Oved, K.; Zennaro, L.; Dorot, O.; Zerbib, J.; Frank, E.; Roux, L.N.; Bremond-Gignac, D.; Pichinuk, E.; Aberdam, D. Ritanserin, a Potent Serotonin 2A Receptor Antagonist, Represses MEK/ERK Signalling Pathway to Restore PAX6 Production and Function in Aniridia-like Cellular Model. *Biochem. Biophys. Res. Commun.* **2021**, *582*, 100–104, doi:10.1016/j.bbrc.2021.10.036.
 140. Moustardas, P.; Abbasi, M.; Javidjam, D.; Asamoah, C.S.; Schweitzer-Chaput, A.; Cisternino, S.; Bremond-Gignac, D.; Aberdam, D.; Lagali, N. Duloxetine Enhances PAX6 Expression and Suppresses Innate Immune Responses in Murine LPS-Induced Corneal Inflammation. *Ocul. Surf.* **2024**, *34*, 225–234, doi:10.1016/j.jtos.2024.08.008.
 141. Abbasi, M.; Amini, M.; Moustardas, P.; Gutsmedl, Q.; Javidjam, D.; Suiwal, S.; Seitz, B.; Fries, F.N.; Dashti, A.; Rautavaara, Y.; et al. Effects of miR-204-5p Modulation on PAX6 Regulation and Corneal Inflammation. *Sci. Rep.* **2024**, *14*, 26436, doi:10.1038/s41598-024-76654-w.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.