Review Article

Anterior segment dysgenesis: Insights into the genetics and pathogenesis

Sushmita Kaushik, Suneeta Dubey[1], Sandeep Choudhary, Ria Ratna[1], Surinder S Pandav, Arif O Khan[2,3]

Childhood glaucoma is a treatable cause of blindness, provided it is recognized, diagnosed, and treated in time. WHO has estimated that it is responsible for Blind Years second only to cataracts. The fundamental pathophysiology of all childhood glaucoma is impaired outflow through the trabecular meshwork. Anterior segment Dysgeneses (ASD) are a group of non-acquired ocular anomalies associated with glaucoma, characterized by developmental abnormalities of the tissues of the anterior segment. The cause is multifactorial, and many genes are involved in the development of the anterior segment. Over the last decade, molecular and developmental genetic research has transformed our understanding of the molecular basis of ASD and the developmental mechanisms underlying these conditions. Identifying the genetic changes underlying ASD has gradually led to the recognition that some of these conditions may be parts of a disease spectrum. The characterization of genes responsible for glaucoma is the critical first step toward developing diagnostic and screening tests, which could identify individuals at risk for disease before irreversible optic nerve damage occurs. It is also crucial for genetic counseling and risk stratification of later pregnancies. It also aids pre-natal testing by various methods allowing for effective genetic counseling. This review will summarize the known genetic variants associated with phenotypes of ASD and the possible significance and utility of genetic testing in the clinic.

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Anterior segment dysgeneses (ASDs) are a group of nonacquired ocular anomalies characterized by developmental abnormalities of the anterior segment, often associated with glaucoma. The cause is multifactorial, and many genes are involved in the development of the anterior segment of the eye. The abnormalities characterizing ASDs are complex and affect multiple structures, which have made their clinical classification and description difficult. When associated with glaucoma, ASD presents with the secondary effects of raised intraocular pressure (IOP) in a young child. The consequences of the impact upon the cornea and anterior segment result in the requirement of additional interventions apart from lowering the IOP to ensure an optimum visual outcome. Many of the disorders also involve systemic abnormalities in addition to the arrested development of the anterior segment of the eye. Therefore, the treating team often requires inputs from subspecialties such as pediatricians, pediatric anesthesiologists, neonatologists, and geneticists.

Earlier Classifications

Earlier descriptions of ASD have loosely described terms like developmental glaucoma, mesodermal dysgenesis, and nonspecific congenital glaucoma. The early recognition of pediatric glaucoma began with the term buphthalmos, or ox-eyed, which characterized the expansion of the elastic infantile eye in response to raised IOP.[1] A more complex anatomic classification was given by Hoskins, which divided buphthalmos into trabecular meshwork, iris, and/or cornea.[2] The Shaffer–Weiss classification introduced the terms isolated congenital (infantile) glaucoma, glaucoma associated with congenital anomalies, and acquired glaucoma.[3] Walton proposed a detailed description of most disorders known to cause childhood glaucoma.[4]

The modern classification by Childhood Glaucoma Research Network

Unlike the adult definition of glaucoma, which focuses on the optic nerve and visual field defects, characterizing glaucoma in children is more difficult because the optic nerve can be difficult to evaluate correctly in the presence of corneal opacity. Recognizing this difficulty, the Childhood Glaucoma Research Network (CGRN) was formed, which comprised clinicians and scientists to manage children with glaucoma.

The CGRN proposed the definition of childhood glaucoma be based upon IOP-related damage to the eye rather than solely on optic nerve criteria, and has provided a new classification system of pediatric glaucoma, which is presented in Table 1.[5] In this classification system, all ASDs are clubbed under secondary glaucoma with nonacquired ocular anomalies.

This review will focus on the nonacquired childhood glaucoma resulting from developmental disorders of the anterior

Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, [1]Dr. Shroffs Charity Eye Hospital, Daryaganj, New Delhi, India, [2]Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE, [3]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA

Correspondence to: Dr. Sushmita Kaushik, Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: sushmita_kaushik@yahoo.com

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Table 1: Classification of Childhood Glaucoma (CGRN)*

Primary childhood glaucoma
IA. Primary Congenital Glaucoma (PCG)
1. Isolated angle anomalies (+/- mild congenital iris anomalies)
2. Meets glaucoma definition (usually with ocular enlargement)
3. Subcategories based on age of onset
a. Neonatal or newborn onset (0-1 month)
b. Infantile onset (>1-24 months)
c. Juvenile onset or late-recognized (>2 years)
4. Spontaneously arrested cases with normal IOP but typical signs may be classified as PCG
IB. Juvenile Open Angle Glaucoma (JOAG)
1. No ocular enlargement
2. No congenital ocular anomalies or syndromes
3. Open angle (normal appearance)
4. Meets glaucoma definition
Secondary childhood glaucoma
A: Glaucoma Associated with Non-Acquired Ocular Anomalies
Includes conditions of predominantly ocular anomalies present at birth which may or may not be associated with systemic signs and meets glaucoma definition
Includes:
Axenfeld Rieger spectrum (syndrome if systemic associations)
Peters anomaly spectrum (Syndrome if systemic associations)
Ectropion uveae; Congenital iris hypoplasia
Aniridia
Persistent fetal vasculature/PFV (if glaucoma present before cataract surgery)
Oculodermal melanocytosis (nevus of Ota)
Posterior polymorphous dystrophy
Microphthalmos
Ectopia lentis
Ectopia lentis et pupillae
Megalocornea with zonular weakness
B: Glaucoma Associated with Non-Acquired Systemic Disease or Syndrome
Includes conditions predominantly of systemic disease present at birth which may be associated with ocular signs and meets the definition of glaucoma
C. Glaucoma Associated with Acquired Condition
D. Glaucoma Following Congenital Cataract Surgery
Meets glaucoma definition after cataract surgery performed
Excludes acquired cataract or cataract in the setting of a syndrome with a known glaucoma relationship, such as Lowe syndrome, congenital rubella syndrome, aniridia.

*Adapted from Beck A, Chang TC, Freedman S. Section 1: Definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, editors. World Glaucoma Association Consensus Series-9: Childhood Glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2013. pp. 3–10.

segment. The clinical diagnosis of the various conditions, emphasizing phenotype recognition, pathophysiology, underlying genetic mechanisms that may be responsible, and a brief overview of the management will be discussed.

Pathogenesis of ASD

Primary congenital glaucoma (PCG) is the commonest cause of developmental glaucoma. Indian data from Andhra Pradesh reported a prevalence of 1:3300 births.[6] According to the Human Genome Organization (HUGO) Nomenclature Committee, loci for congenital glaucoma are designated by GLC3. GLC3A at chromosome locus 2p21 has been linked to a specific gene, *CYP1B1*,[7] and is the most significant known enzyme of the human cytochrome p450 pathway.[8] Recent studies have suggested that pathogenic variants in the gene myocilin are associated with hereditary primary open-angle glaucoma and juvenile open-angle glaucoma (JOAG) and in the gene L*TBP2* (latent transforming growth factor-β binding protein 2) may be minor contributors to PCG also.[9-12]

Primary Congenital Glaucoma

PCG is a potentially blinding disease. If not managed in time, it may result in a lifetime of blindness. A primary developmental anomaly at the anterior chamber angle impedes aqueous humor out of the eye. The resultant raised IOP symptoms include ocular enlargement (buphthalmos) and corneal haze, photophobia, and epiphora. Persistently increased IOP causes more severe damage to the optic nerve head and inevitable, irreversible blindness [Fig. 1]. PCG classically presents with a triad of photophobia, epiphora, and blepharospasm [Fig. 2]. Many children in India present with corneal edema initially [Fig. 3], without buphthalmos or classical signs.

The incidence of PCG varies from 1 in 1250 births in Slovakian Roms to 1:10,000 in Scandinavian regions.[13] In India, the incidence has been reported to be 1:3300 live births.[6] The variable incidence in various ethnic groups may be due to a genetic basis for the disease.

Inheritance

The possible genetic basis of PCG was recognized in 1836 when it was noted to occur endemically in the Jewish population in Algiers.[14] There is elegant documentation of a Swedish family[15] in which seven brothers were affected by congenital glaucoma and the parents and sisters were normal. Waardenburg[16] established that recessive inheritance is indicated by (1) a high frequency of parental consanguinity; (2) the presence of the disease in about 25% of sibs of probands; (3) the presence of the disease in all children of a marriage between two affected persons; and (4) the occurrence of glaucoma in collaterals of both parents in some families.

Genetic variants

According to the HUGO Nomenclature Committee,[7] congenital glaucoma loci are designated by GLC3, and letters are added to distinguish specific loci in order of their discovery. Three genetic loci have been linked to PCG: GLC3A at chromosome locus 2p21, GLC3B at chromosome locus 1p36, and GLC3C at chromosome locus 14q24.3. Only the GLC3A locus has been linked to *CYP1B1,* the most significant known enzyme of the human cytochrome p450 pathway.

CYP1B1 and PCG

Stoilov *et al*.[17] reported that the cytochrome P4501B1 gene (*CYP1B1*; OMIM 601771) located within the *GLC3A* locus is mutated in PCG patients. Significant allelic heterogeneity has been identified in *CYP1B1* pathogenic variants segregating with the disease phenotype.[18,19] Approximately 147 pathogenic variants, including missense, nonsense, regulatory, and insertions or deletions in *CYP1B1,* have been reported in various racial groups.[20] In ethnically mixed populations, pathogenic variants have been found in 20%–30% of patients with PCG, whereas in consanguineous populations, the reported prevalence is as much as 85%.[21] In a North Indian cohort, Kaushik *et al*.[22] found a higher proportion of *CYP1B1* variants in neonatal-onset compared to infantile-onset PCG.

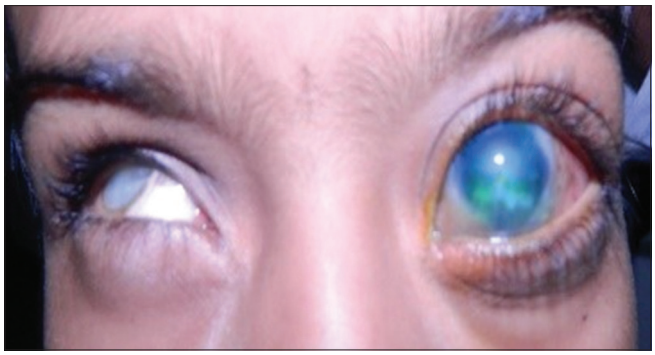

Figure 1: Clinical photograph of a child with neglected primary congenital glaucoma

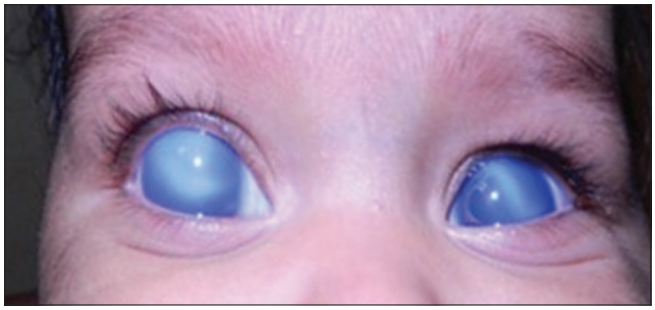

Figure 3: Clinical photograph of a patient with primary congenital glaucoma showing severe corneal haze

Structural anomalies

PCG (gene symbol, *GLC3*), by definition, is characterized by a developmental anomaly in the trabecular meshwork and anterior chamber angle, with no other ocular or systemic abnormalities. The exact structural changes in the angle are not evident. Electron microscopy has not verified the early suggestion of an imperforate membrane covering the trabecular meshwork. Histopathologic studies have shown that the iris insertion overlaps the posterior portion of the trabecular meshwork.[23] Tawara and Inomata[24] reported the juxtacanalicular area to be markedly thickened in trabeculectomy specimens from the eyes of patients with PCG. They observed that the outflow channels consisted of many layers of spindle-shaped cells with the surrounding extracellular matrix. These developmental anomalies of the anterior chamber angle prevent drainage of aqueous humor, resulting in elevated IOP.

Clinical Features

Elevated IOP in children younger than 3 years of age (infantile glaucoma) causes enlargement of the globe, primarily at the corneoscleral junction, due to its more elastic nature in this period. The endothelium of the cornea and Descemet's membrane are stretched. They often result in a linear rupture of the Descemet's membrane (Haab's striae) [Fig. 4]. If this rupture occurs acutely, it causes a rapid influx of aqueous into the stroma and epithelium, resulting in sudden corneal edema, termed acute hydrops [Fig. 5].[25]

Secondary Nonacquired Childhood Glaucoma

Congenital glaucoma is responsible for 4.2%–7% of childhood blindness in India.[26,27] The CGRN has classified developmental

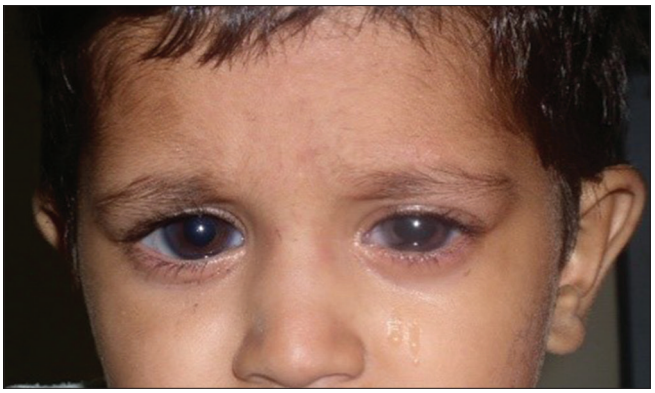

Figure 2: Clinical photograph of a child with primary congenital glaucoma showing blepharospasm and tearing

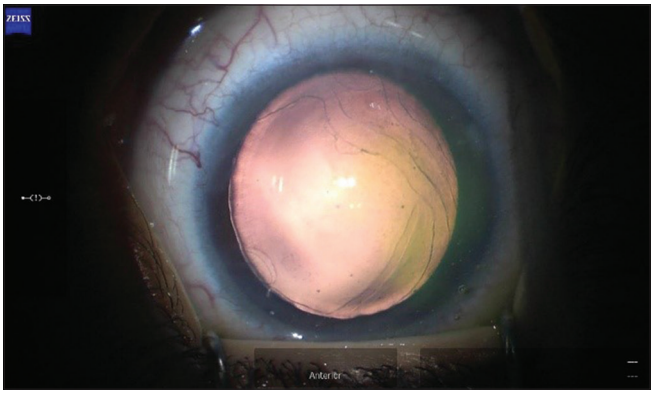

Figure 4: Operating microscope photograph of the eye showing presence of Haab's striae

disorders involving more than just the trabecular meshwork as secondary nonacquired glaucoma [Table 1]. They are usually associated with iris and/or corneal abnormalities and sometimes developmental lens abnormalities. The nonacquired glaucomas could be due to nonacquired ocular anomalies or nonacquired systemic abnormalities.

This section of the review will look at the nonacquired anomalies associated with glaucoma.

Nonacquired ocular anomalies

Nonacquired ocular anomalies are conditions meeting the definition of childhood glaucoma associated with ocular anomalies in addition to trabecular dysgenesis. Table 1 lists the conditions which fulfill this definition. We shall describe the common conditions usually encountered in the clinic.

Aniridia

The most well-known anterior segment abnormality affecting the iris is aniridia or absence of the iris. Aniridia is a panocular disorder affecting the cornea, anterior chamber, iris, lens, retina, macula, and optic nerve.[28] There is complete or incomplete iris absence or sometimes other iris abnormalities, including ectropion uveae (presence of iris pigment epithelium on the anterior surface of the iris) [Fig. 6].

Four phenotypes of aniridia have been identified based on associated ocular and systemic anomalies:[29]

1. aniridia with predominant iris changes and normal visual acuity;

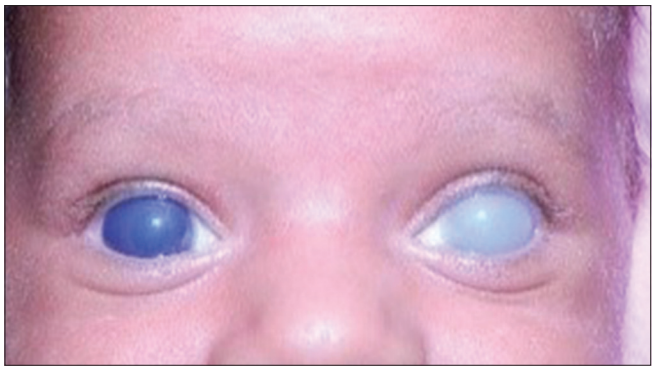

Figure 5: Child with congenital glaucoma presenting as acute hydrops left eye

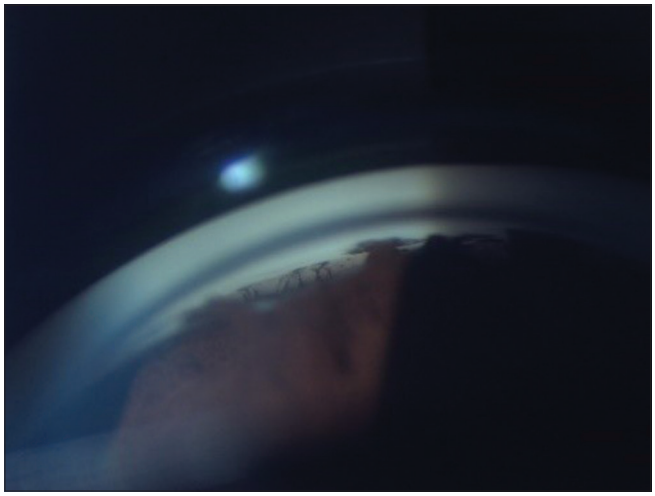

Figure 7: Gonioscopy image of a patient with Axenfeld and Rieger anomalies showing bridging synechiae

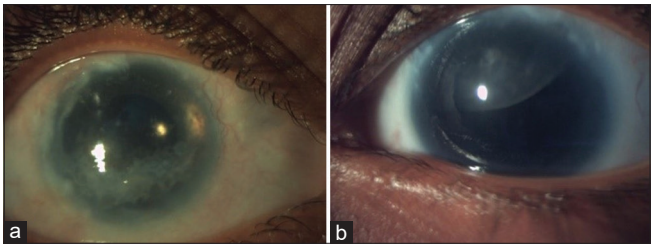

Figure 6: (a) Child with aniridia showing grade 2 keratopathy and subluxated cataract in Right eye (RE) being successfully managed with lensectomy with aniridic Intra-ocular lens (IOL) and non-valved glaucoma drainage implant (Aurolab aqueous drainage implant). (b) Left eye of the patient showing subluxated cataractous lens

Figure 8: Clinical photograph of a patient with Axenfeld and Rieger anomalies showing facial and dental anomalies

2. aniridia associated with foveal hypoplasia, nystagmus, corneal pannus, glaucoma, and reduced vision;
3. aniridia associated with Wilms' tumor (the aniridia–Wilms' tumor syndrome) or other genitourinary anomalies; and
4. aniridia associated with mental retardation.

The reported incidence of glaucoma later in childhood is 6%–75%.[29] Eyes with aniridia usually develop glaucoma in late childhood or early adulthood due to progressive anatomical changes in the drainage angle.[30]

Grant and Walton[31] found that progressive change in the angle structures may occur during the first two decades of life in patients who will develop glaucoma. These changes include attachment of the rudimentary iris to an anterior position, thereby covering the filtration area of the trabecular meshwork. Most of the filtration area is covered by the iris remnant in patients who develop glaucoma.

Axenfeld and Rieger anomalies

Axenfeld–Rieger Syndrome (ARS) is a rare genetic disease associated with ocular ASD and a high prevalence of early-onset glaucoma. First described in 1883, the variability of ARS presentation led to it initially being categorized as multiple distinct pathologies (Axenfeld anomaly, Rieger anomaly, Rieger Syndrome) (AXENFELD 1920; RIEGER 1935).[32] Due to dysregulation of aqueous humor flow through an abnormal angle, approximately 50% of patients with ASD develop glaucoma.[32,33] It may become manifest during infancy, although it more commonly appears in childhood or young adulthood. Congenital glaucoma has also been reported with ARS in conjunction with corneal edema or buphthalmos.[34,35]

Ocular defects in ARS are typically bilateral. Axenfeld anomaly is characterized by posterior embryotoxon (Schwalbe's line is visible by external examination) and peripheral iris attachments to Schwalbe's line and the cornea, obstructing or distorting angle structures, causing glaucoma. Peripheral anterior synechiae (bridging of tissue between the iris and anterior angle) is the most common feature [Fig. 7].[36,37] Posterior embryotoxon may occur in 15% of the normal population itself. Still, the additional feature of peripheral iris attachments indicates the presence of Axenfeld anomaly. The cornea is otherwise customary in the typical case of ARS, though occasionally patients may have a variable size or shape of the cornea.

Rieger anomaly has additional iris abnormalities, including corectopia (ectopic pupils), loss of iris stroma, and polycoria (multiple pupils). There is considerable overlap in the clinical features of Axenfeld and Rieger anomalies, and they are usually referred to together as the Axenfeld–Rieger anomaly (ARA).[38,39]

ARA associated with systemic abnormalities is termed ARS. The systemic anomalies most commonly associated with ARS are developmental defects of the teeth and facial bones [Fig. 8]. The dental abnormalities include a reduction in crown size (microdontia), a decreased but evenly spaced number of teeth (hypodontia), and a focal absence of teeth (oligodontia or anodontia).[40]

Facial anomalies include maxillary hypoplasia with flattening of the mid-face, a receding upper lip, and a prominent lower lip, especially in association with dental hypoplasia. Hypertelorism, telecanthus, and a broad flat nose have also been described.[41] The spectrum of ARS includes redundant periumbilical skin, oculocutaneous albinism, heart defects, middle ear deafness, mental deficiency, hypospadias, and a variety of neurologic and dermatologic disorders.[42,43]

Peters anomaly

Von Hippel reported a case of buphthalmos with bilateral corneal opacities and adhesions from these defects to the iris in 1897. Peters described similar patients in 1906. The hallmark of Peters anomaly (PA) is central corneal abnormality – a defect in the Descemet membrane and corneal endothelium with thinning and opacification of the corresponding area of the corneal stroma [Fig. 9]. It is characterized by iridocorneal and/or lenticulocorneal adhesions, central corneal opacity, and defects in the posterior corneal endothelium.[44]

Table 2: Glaucoma associated with non-acquired systemic disease or syndrome.

Conditions with predominantly known syndromes, systemic anomalies or systemic disease present at birth that might be associated with ocular signs
Chromosomal disorders such as Trisomy 21 (Down syndrome)
Marfan syndrome
Weill-Marchesani syndrome
Stickler syndrome
Metabolic disorders
Homocystinuria
Lowe syndrome
Mucopolysaccharidoses
Phacomatoses
Neurofibromatosis (NF-1, NF-2)
Sturge-Weber syndrome
Rubinstein-Taybi
Congenital rubella

*Adapted from Beck A, Chang TC, Freedman S. Section 1: Definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, editors. World Glaucoma Association Consensus Series-9: Childhood Glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2013. pp. 3-10.

Nearly half of the patients with PA will develop glaucoma, which is frequently present at birth. Some patients demonstrate changes in trabecular meshwork histopathologically along with peripheral anterior synechiae or a shallow or flat anterior chamber, which may play a role in the development of glaucoma.

The disorder has been subdivided into three groups, each of which may have more than one pathogenic mechanism.[44, he45] They are as follows:

- not associated with keratolenticular contact or cataract,
- associated with keratolenticular contact or cataract, and
- associated with ARS.

The combination of abnormalities in PA causes significant visual impairment due to interruption of the visual axis, often in combination with cataracts.[46]

Peters plus syndrome

Clinical features of Peters plus syndrome include PA with short stature, cleft lip/palate, brachydactyly, facial dysmorphism, and intellectual disability.[46] Rarely, patients can also have congenital cardiac defects (atrial and ventricular septal defects, aortic and pulmonary stenosis), structural brain abnormalities, hearing loss, and genitourinary abnormalities.

Congenital primary aphakia

Congenital primary aphakia (CPA) is a rare ASD resulting from aborted lens development during the fourth week of gestation due to failed lens placode induction from the surface ectoderm.[47,48] The presence of the lens is crucial for the development of other anterior segment structures. Abnormal lenticular development has been shown to have a detrimental effect on the formation of other anterior segment structures.[49] Disrupted lens development results in a variety of ocular disorders that include glaucoma, microcornea, microphthalmia, PA, and primary aphakia.[50]

CPA has often been labeled the nonspecific term "sclerocorneal."[5] The implication of accurate recognition of this entity lies in avoiding incisional surgery, which almost always results in phthisis bulbi.[51] Eyes with cloudy corneas and a silvery-blue hue should be suspected to have CPA [Fig. 10]. Ultrasound biomicroscopy (UBM) demonstrates absence of the lens and no precise details of the iris or angle visible.

Nonacquired systemic anomalies

Nonacquired systemic anomalies include conditions predominantly of systemic disease present at birth, which may be associated with ocular signs and meet glaucoma's definition. The CGRN has identified the conditions presented in Table 2 to qualify for nonacquired systemic anomalies.

Some of these conditions are described below:

1. **Sturge–Weber syndrome (encephalofacial angiomatosis, encephalotrigeminal angiomatosis)**

Table 3. Severity index for grading PCG phenotypes

Clinical parameters used for grading	Normal	Mild	Mod	Severe/V severe
Corneal diameter	Up to 10.5	>10.5-12	>12-13	>13
IOP#	Up to 16	>16-20	>20-30	>30
Cup-disc ratio	0.3-0.4	>.4-.6	>.6-.8	>.8
Last recorded BCVA*	20/20			<20/200:<20/400-NPL
Corneal clarity	No edema	Mild edema	Severe edema	Sev edema + Haab's striae

#Intraocular pressure, *Best corrected visual acuity.

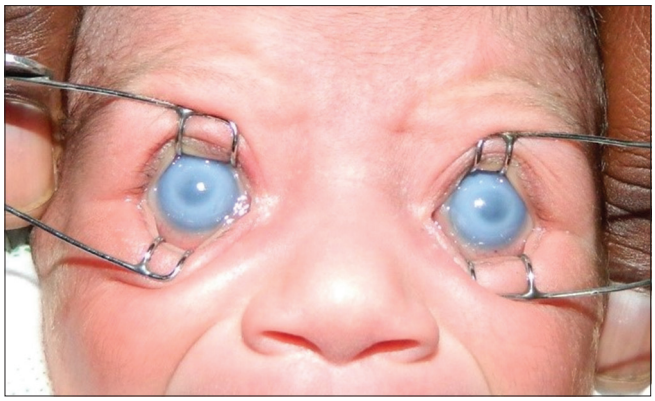

Figure 9: Peters anomaly in a newborn. Note the clear central area in the cloudy cornea

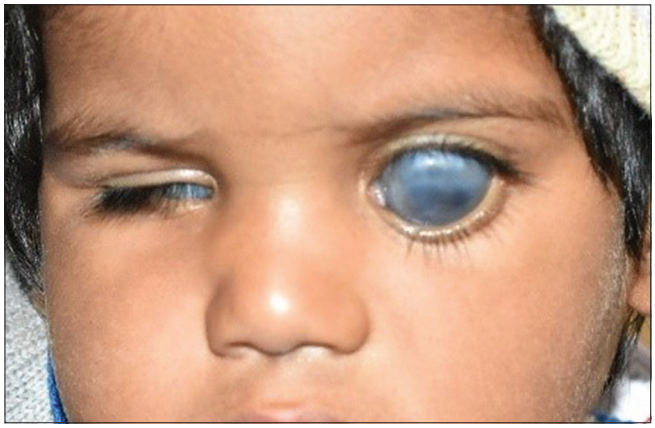

Figure 10: Clinical photograph of a child with congenital primary aphakia with glaucoma. Note the buphthalmos and silvery hue characteristic of the condition

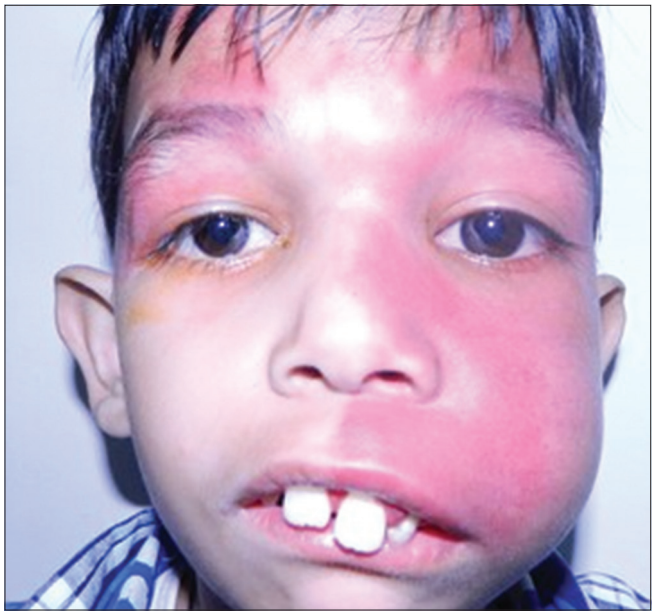

Figure 11: Clinical photograph of a child with Sturge–Weber syndrome showing left-sided port-wine stain and left facial hemihypertrophy

Sturge–Weber syndrome is characterized by a flat facial capillary malformation that follows the distribution of the fifth cranial nerve [Fig. 11]. Glaucoma is seen in nearly 50% of the patients and is more likely to appear in infancy than later.[52] Sturge–Weber glaucoma is present when the facial vascular malformation involves the lids or conjunctiva. If glaucoma occurs in infancy, the mechanism is an isolated trabeculodysgenesis type of angle anomaly with or without abnormalities in the canal of Schlemm and juxtacanalicular tissue. As the child ages, the elevated IOP is due to an elevation of episcleral venous pressure. Hypotony and choroidal detachments often complicate the postoperative course due to rapid expansion of the choroidal hemangioma with fluid effusion into the suprachoroidal and subretinal spaces.[53] Medical therapy involves perioperative oral propranolol[54] and antiglaucoma medications, and definitive therapy is usually surgery.

2. **Phacomatosis pigmentovascularis**
   Phacomatosis pigmentovascularis (PPV) is characterized by the coexistence of vascular and pigmentary birthmarks.[55] Signs and symptoms may include port-wine birthmark, dermal melanocytosis, patches of hyperpigmentation [Fig. 12], and café au lait spots [Fig. 13].[56] About half of people with PPV have systemic involvement, such as neurologic, ocular, or muscular abnormalities.[57] Several subtypes of PPV have been identified, which are generally distinguished based on the specific type (s) of skin features present. Ocular melanosis (also called ocular melanocytosis) commonly occurs along with nevus of Ota and may affect one or both eyes. Complications of nevus of Ota include glaucoma and melanoma. Other eye conditions reported in PPV include iris hamartomas and iris nodules.[58]
3. **Neurofibromatosis**
   Neurofibromatosis 1 (NF1), also known as the von Recklinghausen's disease (birth incidence varies from 1 in 2500 to 1 in 4000–5000), is a rare dermatosis with an autosomal dominant inheritance, characterized by a myriad of symptoms and signs that mirror the involvement of skin, eye, peripheral nervous system, and skeletal system.[59] The National Institute of Health (NIH) Consensus Development Conference proposed the term NF1 and formulated the current diagnostic criteria in 1987.[60] NF1 is the form with the most characteristic ocular manifestations. Lisch nodules of the iris are among the well-known diagnostic criteria for the disease. Glaucoma and associated globe enlargement have been described in a significant proportion of patients with NF1 [Fig. 14]. Optic nerve glioma may cause strabismus and proptosis, and palpebral neurofibroma may reach a considerable size and occasionally show malignant transformation.[61] NF1 patients can present with or without orbital-facial involvement. In patients with orbito-facial involvement, glaucoma was present in 23% of patients.[62]
4. **Rubinstein–Taybi syndrome**
   Rubinstein–Taybi syndrome (RSTS) is a rare autosomal dominant genetic disorder, with a reported prevalence of 1:125,000 live births. The diagnosis of RSTS is essentially clinical, with typical characteristics such as beaked nose, broad thumbs, and hallux valgus. Ocular features reported commonly include lacrimal duct obstruction, corneal abnormalities, congenital glaucoma, congenital cataract, and coloboma of the iris and optic nerve head.[63] Congenital glaucoma is an infrequently reported condition in RSTS. A review of ocular findings in 614 patients with RSTS reported glaucoma in 32 cases and corneal opacities

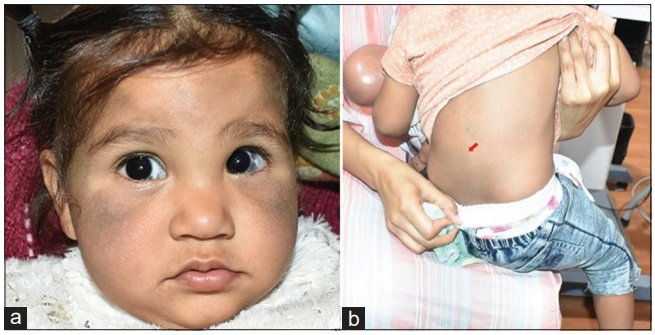

Figure 12: Clinical photographs of a child with phacomatosis pigmentovascularis showing facial hemangioma (a) and melanocytosis on the back (red arrow) (b)

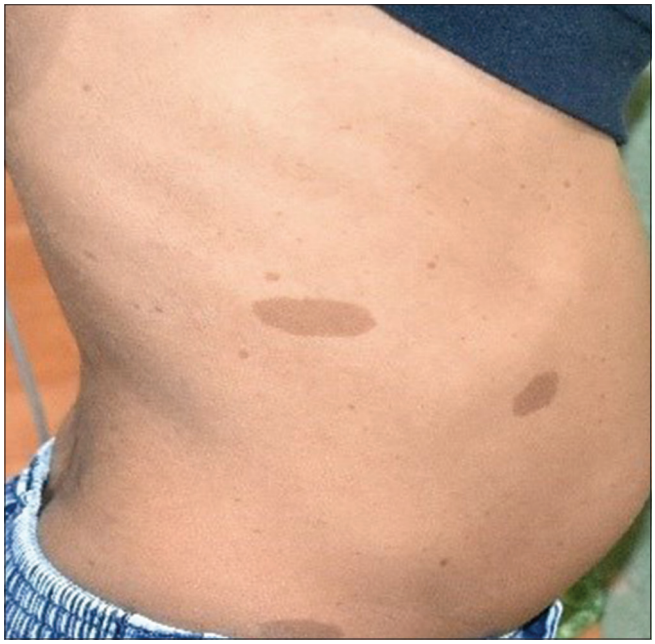

Figure 13: Clinical photograph showing café au lait spots on the torso

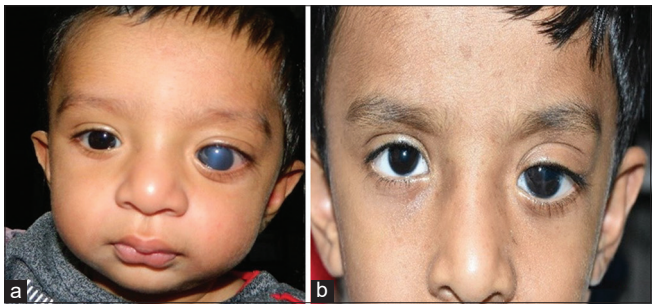

Figure 14: Clinical photographs of a patient with neurofibromatosis with glaucoma in the left eye (a) at the time of presentation during infancy and (b) 5 years after surgery

in 25 cases.[64] In a series of 24 patients with ocular features in RSTS, only one had bilateral congenital glaucoma.[65]

Genetic Anomalies of ASDs

Over the last decade, molecular and developmental genetic research has transformed our understanding of the molecular basis of ASDs and the developmental mechanisms underlying these conditions.[32,66-68] Identification of the genetic changes underlying ASDs has gradually led to recognizing that some of these conditions may be parts of a disease spectrum. The nonacquired conditions ARS, aniridia, and glaucoma associated with ASDs are primarily caused by pathogenic variants in paired box protein Pax-6 (*PAX6*), *PITX2*, *FOXC1*, *CYP1B1*, and *LTBP2*.[67,68]

PAX6

The most common genetic alteration associated with aniridia is alterations in the *PAX6* gene. *PAX6* is a homeobox gene expressed in the early developed eye structures and forebrain, gut, endocrine pancreas, and ventral spinal cord of the body.[69] It functions as a transcription factor with a critical role in neurogenesis and oculogenesis.[70] Defect in a single allele in the form of a point pathogenic variant or contiguous gene deletion could lead to classical aniridia phenotype, thus making it an autosomal dominant inheritance disorder with 50% recurrence risk for the next generation.[71] Another phenotype is aniridia associated with foveal hypoplasia, nystagmus, corneal pannus, glaucoma, and reduced vision. Such etiology could also be attributed to an alteration in the *PAX6* gene. Nearly 30% of individuals with apparently isolated aniridia are likely to develop syndromic features of Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) that occur due to a contiguous gene deletion in *PAX6*, along with the gene adjacent to it, called *WT1* gene.[72] *PAX6* pathogenic variants in some families have also led to aniridia with mental retardation. Its involvement in PA is poorly understood; however, it is postulated to have a multifactorial effect on the disease etiology with the interaction of other genes.[44]

LTBP2

LTBP2 is located on chromosome 14q24.3, associated with the loci GLC3C known to have a role in the pathogenesis of PCG. It is a member of the latent transforming growth factor (TGF)-beta binding protein family, with structural resemblance to fibrillins. *LTBP2* is the second gene implicated in the pathogenesis of PCG. It is more commonly associated with a phenotype that resembles PCG, and thus may not be related to true PCG.[73,74] The precise mechanism of how *LTBP2* pathogenic variants would raise IOP is unclear. Null pathogenic variants in *LTBP2* have been reported in patients diagnosed with PCG, and an ethnic bias in the Gypsy population has also been noted.[73] Both alleles of the gene need to be mutated to cause phenotypic changes in the anterior segment of the eye, thus making it an autosomal recessive-type trait.[75] Although biallelic *LTBP2* pathogenic variants have been implicated in PCG, they more commonly cause a complex anterior segment phenotype of primary megalocornea with zonular weakness and secondary lens-related glaucoma, which can be mistaken as PCG.[73]

TEK/ANGPT1

The angiopoietin receptor TEK (tunica interna endothelial cell kinase, also known as Tie2) receptor tyrosine kinase is expressed in the Schlemm's canal endothelium. Mouse model studies have shown that deletion of a single allele of *TEK* or both Angiopoetins (ANGPTs) could lead to elevated IOP and glaucoma.[76] Heterozygous variants in *TEK* are known to cause PCG, while other genes, *CYP1B1*, *LTBP2*, *FOXC1*, and *MYOC*, are normal.[17,77] On the other hand, research by Kabra *et al*.[78] also reveals an interaction between *TEK* and *CYP1B1* genes causing PCG pathogenesis. Heterozygous carriers of the *TEK* or *CYP1B1*

allele were asymptomatic, indicating a potentially overlapping function. Co-transfection experiments on HEK293 cells confirmed this interaction between wild-type TEK and CYP1B1 proteins, while disease-causing variant interactions caused perturbed protein production.

PITX2/FOXC1

The human *PITX2* and *FOXC1* genes encode transcription factors of the homeodomain and forkhead types, respectively.[79] The physical interaction between the two gene products is associated with ARS via intragenic pathogenic variants. Both the proteins are in a common pathway, as *PITX2A* acts as a negative regulator of *FOXC1* transactivity. Ultimately, the functional interaction between the two genes underlies the sensitivity to *FOXC1* gene dosage in ASD.[79] Other phenotypes associated with the biallelic pathogenic variants include PA and iridogoniodysgenesis. *PITX2* pathogenic variants are majorly associated with ring dermoid of the cornea, ARS with oligodontia, and redundant umbilicus tag. *FOXC1* pathogenic variants are responsible for PCG, aniridia, and ARS with hearing or cardiac defects.[80]

Gene Testing in the Clinic: Who, When, and How?

Who:

Clinical diagnosis and management of pediatric glaucoma are guided by phenotype, not genotype. However, although genetic testing is not needed to manage a child's glaucoma, it can be instrumental in specific clinical scenarios.

When:

A. Genetic counseling is desired and reasonable:
   Knowledge of the underlying gene pathogenic variant for familial pediatric glaucoma can empower certain families. It enables accurate genetic counseling, can reduce the risk of disease recurrence, and allows enrollment in potential gene-specific gene therapy trials. Also, knowledge of the mechanism of familial disease can mitigate feelings of helplessness and anxiety of family members, giving them peace of mind that they understand the specific diagnosis. However, at the same time, knowledge of the genetic cause can sometimes cause some family members who are carriers of the disease to have feelings of guilt and anxiety. Education and proper genetic counseling are important and decrease such potential feelings of guilt and anxiety.
   It needs to be stressed that genetic counseling is not necessarily appropriate for all families. Some families consider their disease their fate and do not desire molecular diagnosis or family risk assessments. In addition, when pediatric glaucoma is sporadic, genetic counseling is less likely to be precise as finding a causative pathogenic variant can be more challenging. A causative pathogenic variant is unlikely to be found in sporadic unilateral cases.
B. When the ocular phenotype suggests underlying actionable systemic disease or systemic associations associated with gene pathogenic variant:
   Certain phenotypes confer risk for an extraocular disease that is actionable. Genetic testing is indicated in these situations. The classic example is sporadic aniridia. This ocular phenotype is often from a new heterozygous *PAX6* deletion. If this deletion is large, the contiguous gene *WT1* may also have been deleted, which confers a significant risk for Wilms' tumor of the kidney before 5 years of age (WAGR syndrome). Glaucoma in *PAX6*-related aniridia is typically juvenile, but it can be infantile onset.
   Another important phenotype is ASD with glaucoma. ASD with glaucoma is a variable phenotype resulting from pathogenic variants in different genes, some of which confer risk for extraocular disease.[33] One example is *COL4A1*-related disease, in which ASD is associated with a risk for cerebral hemorrhage and potentially renal disease. Most cases of ASD with glaucoma are not associated with the actionable extraocular disease. However, it is optimal to have a molecular diagnosis for glaucoma associated with ASD when possible.
C. When the ocular phenotype is in the context of systemic disease:
   Although individually rare, there are many genetic multisystem syndromes associated with ASDs collectively. Any child with ASD and glaucoma in the setting of systemic disease should have an evaluation and genetic testing by a geneticist.[78] Some of these syndromes include actionable extraocular disease. Examples include Pierson syndrome and Peters plus syndrome.
   In addition, there are numerous known and novel chromosomal abnormalities that can underlie ASD in the context of multisystem disease. Uncovering the chromosomal abnormality in such cases might also indicate the need for parental screening for balanced translocations and change the recurrence risk for the family. It may point toward other issues the child may be at risk of and can further research the causes of ASD.
D. When the diagnosis of glaucoma is in question in an area of the world where pathogenic variants underlying childhood glaucoma are common:
   In general, the diagnosis of pediatric glaucoma is clinical and does not depend on genetic testing. However, in borderline cases in regions of the world where childhood glaucoma is often from pathogenic variants, genetic testing can be a useful supportive evidence for clinical suspicion of disease. For example, in the Arabian Gulf, biallelic *CYP1B1* mutations underlie most cases of newborn glaucoma (with or without visible ASD).[81,82] Making the diagnosis is typically straightforward; however, a child may have a borderline phenotype with it, making it unclear whether or not the phenotype is glaucoma. Genetic testing for *CYP1B1* pathogenic variants can be useful in such a situation. If positive for the biallelic pathogenic variant, it is supportive for the diagnosis. If negative, it is less helpful.[83]

How:

The goal of the ophthalmologist should be to make the most detailed and specific clinical diagnosis possible and offer appropriate management. Some ophthalmologists may feel competent in ordering genetic testing. However, they should only do so if they understand test limitations, interpret results, counsel patients, or work with a trained individual such as a medical geneticist or genetic counselor. In general, genetic testing should be as focused as possible, ordered based on the specific phenotype. While whole-exome sequencing is also possible, the considerable number of uncovered variants is challenging to interpret and a significant undertaking.

Taking a good family history and pedigree helps direct the correct suspected molecular diagnosis. If inherited, the inheritance pattern can suggest autosomal recessive (e.g., *CYP1B1*-related) or autosomal dominant

(e.g., *FOXC1*-related) disease. Autosomal dominant disease can show significant variable expressivity. It can thus be helpful to screen parents of an affected child for signs of ASD or glaucoma, even if the parents do not report themselves as affected.[84]

Genetic testing could be in the form of a gene panel that includes common genes associated with the phenotype (e.g., a panel for nonspecific ASD) or specific gene analysis for a particular phenotype (e.g., *LTBP2* analysis for primary megalocornea with zonular weakness and secondary lens-related glaucoma). It is essential to be aware that not all pathogenic variants are detectable by conventional sequencing. Gene deletions and duplications are possible (and are well documented to occur for *PITX2* and *FOXC1)* – detection of these abnormalities requires copy number variation analysis. Similarly, if a contiguous gene syndrome related to a new large deletion is suspected (e.g., WAGR syndrome), copy number variation analysis of the suspected gene region is required. When a child has ASD in the context of multiple other congenital abnormalities that do not match a known single-gene syndrome, a microarray analysis to assess for genomic copy number variation is often appropriate. It is helpful to have samples collected from the parents for confirmatory segregation analysis whenever the genetic analysis is done for a child.

Management

The management of congenital glaucoma starts with parental counseling, which should include a discussion of what is glaucoma, the need for surgery and possibility of multiple surgeries, the need for lifelong follow-up, and the combination of problems to be tackled (IOP, amblyopia management, refractive correction, possible keratoplasty).

Examination under anesthesia is the first step to gauge the severity of the disease and the extent of glaucomatous damage. The parameters to be evaluated include corneal edema, IOP, and cup–disk ratio. Panicker *et al*.[21] have graded glaucoma severity depending upon the clinical features as given in Table 3. The severity index comprises clinical characteristics at any age. A combination of characteristics is scored, and the severity is assessed.

Treatment

The treatment of developmental glaucoma is surgical.[85] Medical management is a temporizing measure until the child can be posted for general anesthesia. Briefly, the surgical options include goniotomy, trabeculotomy, and trabeculectomy with antifibrotic agents.[86] A trabeculotomy–trabeculectomy combined surgery has resulted in more favorable outcomes, and many surgeons prefer this approach. The surgical success has been reported to be varied. In refractory cases not responding to surgery, repeat surgery is needed. Shunts in the form of valved and non-valved implants have been reported to be successful after the failure of conventional surgery.

Conclusion

With the varied phenotype of congenital glaucoma and the overlapping features among various forms of anterior segment dysgeneses, it sometimes becomes challenging to reach an exact diagnosis by clinical evaluation and investigation alone. A screening test of the most common genes implicated in the diseases we encounter would be the first step in unraveling the mystery of diagnosing these problematic conditions. Because information from genetic testing allows the determination of the mode of inheritance, it can also be used to inform genetic counseling and risk assessment for family members. This would result in a more holistic and informed management of these complex diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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