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An Insight into Genetics of Primary Congenital Glaucoma

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Abstract

Primary congenital glaucoma (PCG) is considered the most common type of pediatric glaucoma affecting children younger than four years. Its main pathology is in the trabecular meshwork & the angle of the anterior chamber (Isolated trabeculodysgenisis). The pattern of inheritance of PCG is not clear enough. Most of PCG cases are sporadic, however, up to 40% are familial. It has been determined that CYP1B1, particularly in inbred populations, is the primary cause of AR PCG. Nevertheless, there are known to be numerous heterozygous CYP1B1 patients as well as homozygous "carriers," which refutes the idea that PCG is simply an AR inheritance. Furthermore, JOAG, POAG, and PCG can result from CYP1B1 mutations; these forms of glaucoma have also been reported in single families. Furthermore, a significant number of individuals do not have a CYP1B1 mutation at all. These long-standing findings encouraged the hunt for potential genes and different pathways. It was investigated if there were any more distinct genes that caused the disease. Consequently, research was done on other genes such as LTBP2, MYOC, FOXC1, FOXC2, PITX2, TEK, and mtDNA. They all provide a useful explanation for certain PCG cases, but not all of them.

Keywords: Primary congenital glaucoma, Genetics.

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1. Introduction

Primary congenital glaucoma (PCG) is considered the most common type of pediatric glaucoma affecting children younger than four years. It accounts for about 25% of childhood glaucoma [1]. Its main pathology is located in the trabecular meshwork & the angle of the anterior chamber (Isolated trabeculodysgenisis) that results in obstruction of the aqueous outflow & elevated intraocular pressure [2]. PCG is typically presented clinically by enlarged globe (buphthalmos), enlarged opaque cornea with or without rupture of the Descemet's membrane (Haab's striae) in addition to scleral thinning, iris atrophy, deep anterior chamber and progressive glaucomatous optic atrophy if left untreated [3]. PCG is a rare congenital disease, its incidence is variable across countries and ethnic groups. The incidence of PCG is higher in the Middle East, where the rate of consanguineous marriages is higher. The presentation of PCG occurs at an earlier age among races with higher incidence compared to other races with lower incidence of consanguineous marriage [4]. The inheritance pattern of PCG is not well understood. The majority of PCG cases are sporadic, however, up to 40% are familial. The inheritance is proposed to be autosomal recessive (AR) by pedigree assessment, with a variable penetrance (40–100%). Other inheritance patterns, such as autosomal dominant and pseudodominant patterns have been recorded as well [5]. Genetic linkage analysis identified three PCG-associated chromosomal loci and recently a fourth locus was added (GLC3D) [6]. To describe these loci the term GLC, for glaucoma, is used. Suffix 3 refers to the infantile glaucoma type and letters A to D indicate the specific locus [7]. Only two have been linked to a specific corresponding gene.

2. Cytochrome P450 1B1

CYP1B1 gene in PCG is located on chromosome 2 and was identified in the GLC3A locus by Stoilov and coworkers [8]. There are significant racial differences in the occurrence of CYP1B1 mutations in PCG patients; in Caucasians, it ranges from 20% to nearly 100% [9]. It is known that the protein produced by this gene belongs to the cytochrome P450 family [10]. Although the precise underlying pathophysiology is yet unknown, numerous investigations have linked PCG to a malfunctioning metabolism of retinoid acid. The conclusion was that normal embryonic or early postnatal ocular development appears to be dependent on a certain CYP1B1 enzyme level, leading to trabeculodysgenesis [11]. Axonopathy of the retinal ganglion cells (RGCs) linked to CYP1B1 mutations has also been the subject of several recent investigations. RGC axonopathy was discovered to be caused by high IOP [12]. Consequently, CYP1B1 mutation may impair the RGCs' capacity to react to the stress brought on by elevated IOP.

Many aspects of mutations have been described: deletions, insertion, frame shift, missense and nonsense [10].

In addition, CYP1B1 mutations can also result in primary open-angle glaucoma (POAG) and juvenile open-angle glaucoma (JOAG), these homozygous "carriers" and ordinary heterozygous carriers may still be at danger of developing glaucoma in the future [10,12]. These late-onset glaucoma types are also seen in families where PCG is present, indicating a disease spectrum as opposed to distinct glaucoma entities. An identical twin who had a homozygous CYP1B1 mutation was the subject of a study; one twin had PCG and the other JOAG [13].

3. Latent Transforming Growth Factor (TGF)-beta Binding Protein 2 (LTBP2)

Using familial haplotype analysis, latent transforming growth factor beta binding protein 2 (LTBP2) was found to be situated next to the GLC3C gene [6]. It was reported to have a twofold heterozygosity for LTBP2 and CYP1B1. In contrast to MYOC and CYP1B1, which have been suggested to have a common biochemical mechanism, the two genes may be involved in distinct processes of ocular development and glaucoma pathogenesis, even though not all double carriers exhibit evident clinical signs. The majority of patients of LTBP2 glaucoma do, in fact, have marfanoid characteristics [6]. It was recently hypothesized that rather than PCG, lens subluxation causes pupillary block in children, which results in a secondary glaucoma [14].

4. The myocilin gene (MYOC)

The myocilin gene (MYOC) was defined as a risk factor in primary open angle glaucoma. It was also related to juvenile onset of open angle glaucoma and PCG cases, by interaction with CYP1B1 by means of digenic process [15]. Many CYP1B1 negative PCG patients were discovered as carriers of heterozygous or homozygous MYOC mutations [12]. A PCG patient was reported to have both heterozygous CYP1B1 and MYOC mutations. This provided evidence in favor of MYOC's function as a modifier gene in PCG [16].

5. Forkhead BoxC1 gene (FOXC1), FOXC2, PITX2

The forkhead BoxC1 gene (FOXC1) is part of the winged helix/forkhead family of transcription factors. Anterior segment dysgenesis is considered the main result of the mutations in FOXC1 gene. Thus, it was presumed that FOXC1 mutations may be involved in PCG pathogenesis [17]. There is a strong relation between FOXC2 and FOXC1 as regarding the structure & function. The paired-like homeodomain transcription factor 2 (PITX2), is also involved in neural crest migration, as well [18]. There was a large cohort study that researched the involvement of FOXC2 and PITX2 genes in PCG disease. It revealed heterozygous FOXC2 variants, the presence of other genes was excluded. In addition, a small CYP1B1 positive PCG group was evaluated for presence of FOXC2 and PITX2 to evaluate the role of these genes. They concluded that PITX2 has a role as a modifier gene in PCG [18]. While FOXC1 and FOXC2 undoubtedly play a part, it's critical to distinguish between Axenfeld Rieger syndrome and actual PCG. As a result, assessing these genes is crucial to the diagnosis process; yet a thorough clinical examination of the eye is necessary to prevent the misinterpretation of Axenfeld Rieger and simple PCG.

6. Angiopoietin Receptor Tyrosine Endothelial Cell Kinase (TEK)

The tunica interna endothelial cell kinase (TEK) pathway was recently discovered as a crucial signaling mechanism for the establishment of Schlemm's canal and the trabecular meshwork (TM). Rare heterozygous TEK mutations were recognized in a PCG cohort study involved 189 families [19]. Since the detected mutations appear to be inherited vertically in two families and are heterozygous, AD inheritance may be presumed. Eight PCG families were found to have TEK mutations in a 2020 study; surprisingly, two of the families also had JOAG and POAG mutations. One family had PCG that was more severe. It has been found to reduce TEK expression, which may act as a disease modulator by preventing TM from developing.

7. mtDNA genome

The genome of the mitochondria (mtDNA), the identification of potentially harmful nucleotide alterations in the mtDNA provided a logical pathophysiological explanation [20]. Reduced synthesis of adenosine triphosphate (ATP) and increased creation of free radicals, which produces reactive oxygen species (ROS), are the results of mitochondrial dysfunction. Eventually, the oxidative stress in the TM and RGCs causes the iridocorneal angle to not develop and differentiate properly (because developing TM lack antioxidant enzymes) [20].

8. Other genes

Guanylate Cyclase activator 1C (GUCA1C) was detected in 3 patients presented with PCG. It is a calcium-binding protein that controls the TM and Schlemm's canal cell volume [21]. Rare mitochondrial dynamin like GTPase (OPA1) and WD repeat-containing protein 36 (WDR36) variations were discovered in a group of Chinese patients including PCG patients [22]. Additionally, same study also found neurotrophins 4 (NTF4) as a potential gene that causes PCG [23].

9. Conclusion

PCG is a multifactorial, possibly blinding condition that manifests in both familial and sporadic forms. Our goals were to present the various genes linked to the disease and pinpoint the precise inheritance pattern. Our review of the literature leads us to the conclusion that people with PCG have a more complicated underlying illness mechanism in addition to the straightforward inheritance linked to AR CYP1B1. It has been suggested that CYP1B1 and genes like LTBP2, TEK, MYOC, FOXC1, FOXC2, PITX2, and mitochondrial alterations are linked to the condition. There have also been reports of a few uncommon gene mutations. Considering the existence of many glaucoma forms and the established involvement of CYP1B1 and MYOC in late-onset glaucoma, it is reasonable to interpret primary congenital glaucoma, juvenile open angle glaucoma, and primary open angle glaucoma as a continuum.

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