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Review Article

Molecular Genetic Markers of Glaucoma

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Abstract

The term "glaucoma" encompasses a heterogeneous group of progressive optic neuropathies unified by a common pathogenetic mechanism: the degeneration of retinal ganglion cells, leading to optic nerve atrophy, progressive visual impairment, and ultimately blindness. Despite significant advances in pharmacotherapy and surgical treatment, glaucoma remains the leading cause of irreversible vision loss worldwide.

Key Words: glaucoma, primary open-angle glaucoma; optic nerve; molecular genetic markers; monogenic mutations; polygenic risk; microRNA; MYOC; CYP1B1; blindness; lens; vision; optic neuropathy; angiogenesis

Introduction

The term "glaucoma" encompasses a heterogeneous group of progressive optic neuropathies unified by a common pathogenetic mechanism: the degeneration of retinal ganglion cells, leading to optic nerve atrophy, progressive visual impairment, and ultimately blindness [2]. Despite significant advances in pharmacotherapy and surgical treatment, glaucoma remains the leading cause of irreversible vision loss worldwide [3]. Elevated intraocular pressure (IOP) is a key modifiable risk factor for optic nerve degeneration [6]. However, approximately one-third of patients present with normal-tension glaucoma (NTG), in which progressive retinal ganglion cell loss and characteristic optic disc changes occur despite IOP values not exceeding 21 mmHg [1].

A major clinical challenge is that early-stage glaucoma is largely asymptomatic, and current diagnostic methods often fail to detect pathological changes before pronounced structural and functional impairment has occurred [2-7]. Current research indicates that the genetic architecture of glaucoma is complex, particularly in adult-onset disease, and involves numerous genetic risk factors and/or environmental factors [8, 16].

Genetic Determinants of Glaucoma

The risk of developing glaucoma is largely determined by genetic factors. The heritability of primary open-angle glaucoma is estimated at 70%, making it one of the most heritable common complex diseases [9, 19].

The contemporary genetic architecture of glaucoma comprises two main classes of genetic determinants [10]. On the one hand, there are rare Mendelian variants with high penetrance that underlie monogenic forms of the disease [21-23]. On the other hand, numerous common variants with small individual effects act cumulatively to shape polygenic susceptibility to adult-onset open-angle glaucoma [12].

Monogenic (or Mendelian) forms of glaucoma are caused by rare genetic variants localized to a single gene and characterized by high penetrance [23]. Such mutations are typically rare in the population and exert a significant deleterious effect on the function of the corresponding protein, thereby increasing disease risk [14]. Genetic variants associated with Mendelian glaucoma are estimated to account for approximately 3–4% of adult glaucoma cases and are more frequently encountered in early-onset disease [15-20].

In contrast, adult-onset open-angle glaucoma is overwhelmingly polygenic in nature, determined by the cumulative effect of hundreds or thousands of common genetic variants, each individually conferring a small effect on disease risk [16]. These variants are generally frequent (minor allele frequency of 5% or higher in the population) [12].

Molecular Genetic Markers in Different Glaucoma Subtypes

Glaucoma is classified by etiology (primary vs. secondary), anterior chamber angle anatomy (open-angle vs. angle-closure), and age at onset (infantile–juvenile vs. adult) [4]. The various forms of primary glaucoma are divided into three main groups: open-angle (POAG), primary angle-closure, and congenital (hereditary) glaucoma [3].

Primary Open-Angle Glaucoma (POAG)

Primary open-angle glaucoma is the most common variant in the adult population and is characterized by the absence of secondary causes (inflammatory, traumatic) and a normal anatomical structure of the anterior chamber angle [2]. Among primary open-angle glaucomas, a subgroup of

patients with normal-tension glaucoma is distinguished [1]. Exfoliative glaucoma (EG) is of particular interest; it is characterized by the accumulation of pathological fibrillar material on the tissues of the anterior segment of the eye (lens, ciliary body, trabecular meshwork), which impairs aqueous humor outflow [5].

The best-studied gene associated with monogenic adult-onset open-angle glaucoma is MYOC (myocilin), located at the GLC1A locus (1q24.3-q25.2) [9]. The pathogenic effect of mutant myocilin is related to its misfolding into the correct tertiary structure [10]. Mutant protein forms form aggregates in the endoplasmic reticulum (Russell bodies) and cytoplasm (aggresomes), triggering a cascade of pathological reactions: mitochondrial membrane depolarization, reduced ATP production, increased generation of reactive oxygen species, and activation of apoptosis [11]. Furthermore, myocilin aggregates disrupt the trabecular meshwork structure, leading to obstruction of aqueous humor outflow pathways, development of ocular hypertension, and glaucoma [13]. The most common pathogenic variant, p. Gln368Ter, exhibits incomplete penetrance (approximately 60–70%) and a mean age of onset around 52 years [14]. Other mutations, such as p. Pro370Leu or p. Gly367Arg, can lead to disease onset in childhood or adolescence [15].

OPTN (optineurin) is a gene located at the GLC1E locus (10p15-14) and is associated with hyper-, hypo-, and normotensive forms of POAG [16]. Optineurin protects cells from oxidative damage and apoptosis by blocking cytochrome C release from mitochondria [18]. The OPTN gene is activated in response to prolonged IOP elevation and long-term dexamethasone treatment, suggesting its stress-inducible nature and a putative protective role in the trabecular meshwork [20]. Most OPTN mutations are inherited in an autosomal dominant manner, though recessive variants have also been described [9].

SIX1/SIX6 (locus 14q23) are homeobox genes involved in eye development and cell cycle regulation [22]. The polymorphism rs33912345 in SIX6 is associated with thinning of the retinal nerve fiber layer and optic disc size, confirming its significance in glaucoma pathogenesis [23].

METTL23 encodes a methyltransferase involved in epigenetic regulation [24]. Data on mutation frequency are limited; however, the gene is considered a rare cause of normal-tension glaucoma [1].

Among polygenic loci identified in genome-wide association studies, the most significant is CDKN2B-AS1 (9p21) – a long non-coding RNA that regulates the expression of the tumor suppressor genes CDKN2A and CDKN2B, which are involved in the cell cycle and aging [9]. Importantly, CDKN2B-AS1 is also associated with cardiovascular disease, potentially pointing to shared pathogenetic mechanisms linking glaucoma to systemic pathology [11].

Functionally diverse loci such as TMCO1 and CAV1/CAV2 influence POAG risk through regulation of aqueous humor outflow [13]. TMCO1 encodes a transmembrane protein involved in maintaining intracellular calcium homeostasis, suggesting its influence on the smooth muscle tone of the trabecular meshwork [15]. CAV1 and CAV2, encoding caveolin proteins, are expressed in the trabecular meshwork and participate in outflow regulation via NO-mediated mechanisms, as well as in cholesterol metabolism [9]. Thus, although each of these loci confers a small individual contribution, their combined effect creates a polygenic background that modulates the functional state of the eye's drainage system [16].

Increased optic disc area is considered a risk factor for POAG: larger discs are more susceptible to the damaging effects of elevated IOP, manifesting as increased excavation [14-19]. Variability in disc size and retinal nerve fiber layer thickness as phenotypic risk markers is associated with several genetic loci: ATOH7 (encoding Math5, essential for retinal ganglion cell development), SIX1/SIX6, and CDKN2B (cell cycle regulator) [23].

Primary Angle-Closure Glaucoma (PACG)

Primary angle-closure glaucoma is characterized by an anatomically narrow anterior chamber angle, leading to impaired aqueous humor outflow and elevated IOP [4]. PACG is a major cause of preventable blindness, affecting over 20 million people worldwide [3]. The disease is three times more likely to cause blindness than POAG and has a high prevalence in Asian populations [2].

Large-scale genome-wide association studies and meta-analyses have identified over 30 loci associated with PACG, with pronounced ethnic and phenotypic differences [7-11].

The identified PACG loci can be grouped according to their functional contribution to anatomical predisposition [13].

The first group comprises genes determining the biomechanical properties of the sclera and cornea, as well as the architecture of the anterior chamber angle [15]. PLEKHA7 is involved in cell adhesion and actin cytoskeleton organization, directly influencing the formation and stability of the anterior chamber angle, while COL11A1, encoding a subunit of type XI collagen, determines the elastic properties of the sclera and cornea, affecting the overall rigidity of the fibrous tunic of the eye [9].

The second group consists of genes affecting iris pigmentation and thickness — HERC2 and OCA2 [22]. The proposed mechanism for their involvement in PACG pathogenesis is that increased melanin content results in a darker and thicker iris, contributing to anatomical narrowing of the anterior chamber angle [23]. This explains the higher prevalence of PACG among populations with dark irises [4].

The third group includes genes determining axial length [24]. LAMA2, encoding a laminin subunit, is associated with hypermetropic refraction and reduced axial length [13]. An even more pronounced effect is conferred by mutations in MFRP – a key gene in nanophthalmos (congenital reduction in eye size), where shortening of the anteroposterior axis creates an extremely high risk of angle-closure glaucoma [15].

Congenital and Infantile–Juvenile Glaucoma

Childhood glaucoma is a heterogeneous group of diseases, subdivided into primary and secondary forms [17]. Primary childhood glaucoma is the most common subtype and includes primary congenital glaucoma (manifesting before age 3) and juvenile open-angle glaucoma (manifesting between ages 3 and 18) [19]. The rate of genetic diagnosis in childhood glaucoma reaches 38%, significantly higher than in adult forms [13, 24].

The genetic factors of PCG can be structured according to the embryological processes whose disruption underlies the disease [18].

The most frequent genetic cause of PCG in many populations is mutations in CYP1B1 (2p22.2), encoding a cytochrome P450 enzyme involved in retinoic acid and steroid metabolism [17]. Mutation frequency varies from 15 to 100% depending on the population, reaching a maximum in groups with high rates of consanguinity [19]. Patients with CYP1B1 mutations often have a more severe disease course with early onset (in the first months of life), high IOP, and a worse prognosis, requiring multiple surgical interventions [21]. The pathogenic mechanism involves disrupted embryonic development of the trabecular meshwork and anterior chamber angle [17].

Another common cause of PCG is impaired formation of Schlemm's canal, which functions in aqueous humor outflow [21]. This mechanism is mediated by mutations in genes of the ANGPT1–TEK signaling pathway [17, 22]. TEK (TIE2) encodes a receptor tyrosine kinase, and ANGPT1 encodes its ligand [21]. Both genes are associated with autosomal dominant PCG and are found in approximately 5% of cases [19]. Disruption of this signaling

cascade leads to Schlemm's canal dysfunction and increased outflow resistance [25].

Genes whose mutations cause not only glaucoma but also systemic developmental abnormalities of the anterior segment, often within syndromic forms, are of particular clinical significance [17]. In contrast to CYP1B1 and ANGPT1–TEK, where pathology is limited to the drainage system, mutations in FOXC1 and LTBP2 affect a broader range of structures [19]. FOXC1 (6p25.3) encodes a transcription factor essential for the embryogenesis of the iris, cornea, and trabecular meshwork [21-25]. Its mutations are associated with anterior segment dysgenesis (Axenfeld–Rieger syndrome), where glaucoma is accompanied by iris hypoplasia, anterior chamber angle adhesions, and corneal anomalies [17]. LTBP2 (14q24.3) is involved in extracellular matrix organization [24]. Its autosomal recessive mutations lead to megalocornea, spherophakia with lens ectopia, and glaucoma arising against a background of lens pathology [19].

Less frequent but phenotypically significant genes include THBS1 (involved in cell adhesion and angiogenesis), as well as CEP164 and INPP5E — genes related to ciliary–centrosomal functions [18]. Recent studies using whole-exome sequencing have identified rare pathogenic variants in the latter two genes in patients with PCG, suggesting primary cilium dysfunction as a potential mechanism in PCG pathogenesis [21].

Exfoliative Glaucoma

Exfoliative glaucoma is the most common form of secondary open-angle glaucoma, characterized by the accumulation of pathological fibrillar material in the tissues of the anterior segment of the eye (lens, ciliary body, trabecular meshwork) [5]. EG shows marked geographic and ethnic variability, with the highest prevalence in Scandinavia, Russia, and some Mediterranean populations [3].

LOXL1 is the strongest genetic risk factor for EG [9, 14]. It is located on chromosome 15q24.1 and encodes an enzyme involved in the cross-linking of elastin and collagen in the extracellular matrix [13]. LOXL1 variants impair elastogenesis and predispose to the accumulation of abnormal exfoliative material [11]. Risk alleles of LOXL1 are found in the vast majority of EG patients; however, their population frequency is high and penetrance low, indicating the need for additional factors (age, sex, ultraviolet exposure) for disease manifestation [15].

Other genes associated with EG include CACNA1A (a calcium channel involved in neuronal signaling), POMP (a proteasomal subunit), TMEM136 (a transmembrane protein of unknown function), AGPAT1 (involved in phospholipid synthesis), RBMS3 (an RNA-binding protein involved in transcriptional regulation), and SEMA6A (a semaphorin involved in axonal guidance) [22].

The Role of MicroRNAs and Epigenetic Mechanisms

In recent years, microRNAs (miRNAs) have been actively investigated as potential biomarkers of glaucoma [18, 24]. According to data from systematic reviews and meta-analyses, several miRNAs (notably miR-143-3p and miR-182) are significantly associated with the disease [25]. The strongest correlations have been observed in aqueous humor; however, the invasiveness of sample collection limits the clinical application of this approach [3, 26]. Analysis of miRNAs in blood appears more promising for screening purposes [24].

Beyond their diagnostic potential, certain miRNAs are being explored as therapeutic targets [25]. For instance, miR-182 is involved in regulating retinal ganglion cell apoptosis through modulation of FOXO1 and PDCD4 expression [26].

Conclusion

Contemporary genomic studies have identified key genes involved in glaucoma pathogenesis [9]. The study of these genes reveals cellular and molecular pathways that may serve as targets for targeted gene therapy [8, 25]. Furthermore, the identification of novel mutations facilitates the development of predictive tests that can identify disease risk before irreversible changes develop [16]. Further research is required to fully understand the genetic architecture of glaucoma [12].

The integration of genetic testing into clinical practice has direct practical implications [26]. The main indications for molecular genetic diagnostics include: a family history of glaucoma (especially in early-onset forms), bilateral involvement, severe disease course, and suspicion of syndromic forms (co-occurrence with other congenital anomalies) [17]. In most clinical situations, the optimal approach is the use of targeted gene panels (e.g., MYOC, OPTN, CYP1B1, FOXC1, LTBP2, TEK, LOXL1), which effectively identifies monogenic forms of the disease [19]. However, result interpretation remains challenging: 15–20% of identified variants are classified as variants of uncertain significance (VUS), necessitating caution in report formulation and mandatory longitudinal follow-up [20]. It is important to emphasize that a negative genetic test result does not exclude a polygenic form of glaucoma and does not obviate the need for regular ophthalmological examinations [23].

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