Chapter 8

Genetic Causes of Glaucoma: An Overview of Current Knowledge and Future Directions

Cansu YÜKSEL ELGİN¹

¹ İstanbul University-Cerrahpaşa
Abstract

Glaucoma is a leading cause of irreversible blindness worldwide, characterized by progressive optic nerve damage and visual field loss. While elevated intraocular pressure (IOP) is a major risk factor for glaucoma, the disease has a complex etiology involving genetic and environmental factors. In recent years, significant progress has been made in identifying genetic variations associated with glaucoma, providing insights into the underlying mechanisms of disease pathogenesis. This review summarizes the current state of knowledge regarding the genetic causes of glaucoma, highlighting the major genes and pathways implicated in the disease. We also discuss the challenges and opportunities for further research in this field, including the development of personalized genetic testing and therapeutic strategies for glaucoma patients.
1- Introduction

Glaucoma is a heterogeneous group of optic neuropathies characterized by progressive loss of retinal ganglion cells (RGCs) and their axons, resulting in irreversible vision loss. The disease affects approximately 70 million people worldwide and is projected to increase in prevalence due to aging populations. (1) While elevated IOP is a major risk factor for glaucoma, up to 40% of patients have normal IOP levels, indicating the presence of other contributing factors, including genetic susceptibility. (1) In recent years, significant progress has been made in identifying genetic variations associated with glaucoma, providing insights into the underlying mechanisms of disease pathogenesis. This short review aims to provide an overview of the current state of knowledge regarding the genetic causes of glaucoma, highlighting the major genes and pathways implicated in the disease.

2- Genetic Causes of Glaucoma

2.1. Mendelian Inheritance Patterns

Glaucoma can be inherited in a variety of ways, including autosomal dominant, autosomal recessive, and X-linked modes of inheritance. (2) Several genes have been identified as causative or contributing factors in Mendelian forms of glaucoma. For example, mutations in MYOC, which encodes for myocilin, a protein involved in regulating aqueous humor outflow, have been associated with juvenile- and adult-onset open-angle glaucoma. (2, 3) Mutations in CYP1B1, which encodes for a cytochrome P450 enzyme, have been implicated in primary congenital glaucoma. (3, 4) Mutations in OPTN, which encodes for optineurin, a protein involved in autophagy and vesicle trafficking, have been associated with normal-tension glaucoma and some forms of primary open-angle glaucoma. (4, 5)

2.2 Genome-Wide Association Studies

In addition to Mendelian forms of glaucoma, genome-wide association studies (GWAS) have identified multiple common genetic variants associated with increased risk of glaucoma. For example, a common variant in the CDKN2B-AS1 locus, which regulates the expression of CDKN2B and CDKN2B-AS1, has been associated with primary open-angle glaucoma and normal-tension glaucoma. Other GWAS-identified genes include TMCO1, CAV1/CAV2, SIX1/SIX6, and AFAP1. (6, 7)
2.3 Gene-Environment Interactions

While genetic factors can contribute to glaucoma risk, they can also interact with environmental factors, such as IOP and aging, to influence disease onset and progression. For example, the risk of glaucoma associated with MYOC mutations is greater in individuals with higher IOP. Other gene-environment interactions have been identified, including between CYP1B1 mutations and consanguineous marriage. (7, 8, 9, 10)

Challenges and Opportunities

Despite significant progress in identifying genetic causes of glaucoma, several challenges remain. For example, many glaucoma patients do not have a known genetic cause, and the functional effects of many genetic variants remain unclear. Additionally, genetic testing for glaucoma is not yet widely available, and there is a lack of consensus regarding which genes should be tested and in which populations. Finally, while identifying genetic variants associated with glaucoma is a critical first step, understanding the underlying biological mechanisms and developing targeted therapies requires further research. However, there are also opportunities for further advances in this field. With the increasing availability of genetic testing and the development of more efficient and accurate sequencing technologies, it is now possible to identify rare genetic variants associated with glaucoma in large cohorts. This could lead to the discovery of novel genes and pathways involved in disease pathogenesis. Additionally, the use of genetic data in conjunction with other clinical and demographic factors could facilitate the development of personalized risk prediction models and tailored treatment strategies for glaucoma patients.

Conclusion

In conclusion, significant progress has been made in identifying genetic causes of glaucoma, providing insights into the underlying mechanisms of disease pathogenesis. While challenges remain, there are also opportunities for further advances in this field, including the development of personalized genetic testing and targeted therapies for glaucoma patients. Continued research in this area is critical for improving our understanding of glaucoma and ultimately preventing or treating this debilitating disease.

Several key areas of research have the potential to advance our understanding of the genetic causes of glaucoma. First, functional studies of known genetic variants can help elucidate the underlying biological mechanisms of disease pathogenesis. For example, studies using animal models or cellular systems can help identify the specific cell types or molecular pathways affected by these
variants. Second, genome-wide association studies (GWAS) can help identify common genetic variants associated with glaucoma risk. While most known genetic variants have been identified through targeted sequencing of candidate genes, GWAS have the potential to identify novel genes and pathways not previously implicated in disease pathogenesis. However, large sample sizes and careful control for population structure are needed to achieve sufficient statistical power. Third, studies of rare genetic variants can provide insights into the genetic architecture of glaucoma. Rare variants are often more penetrant than common variants, and identifying these variants can help identify novel genes and pathways involved in disease pathogenesis. Additionally, studies of families with multiple affected individuals can help identify rare genetic variants that segregate with disease. Finally, studies of gene-environment interactions can help elucidate the complex interplay between genetic and environmental factors in glaucoma pathogenesis. For example, identifying genetic variants that modify the effects of environmental risk factors (such as elevated intraocular pressure) could lead to the development of more personalized risk prediction models and targeted therapies. In summary, significant progress has been made in identifying genetic causes of glaucoma, but challenges remain in understanding the functional effects of genetic variants and developing targeted therapies. Advances in functional studies, GWAS, rare variant analysis, and gene-environment interactions have the potential to further our understanding of glaucoma and improve patient outcomes.
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References


