

GENETICS OF GLAUCOMA AND FUTURE RELEVANCE

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Introduction

- **Genetic factors are considered to play a key role in all major forms of glaucoma.**
- In recent years the curtain that has blocked our view of the genetic cause of glaucoma has begun to lift, ushering in a new era of hope in our understanding of the fundamental causes of glaucoma.

Introduction Contd.

- The recent advances of the human genome project have made genetic analysis of many human disorders possible. A genetic approach is especially productive when the quantity or accessibility of diseased tissues is limited. One aspect of the molecular approach that has been particularly important to glaucoma research is that only DNA from affected individuals and their relatives is required for analysis.

Introduction Contd.

- Genetic approaches investigate the disease process at the DNA level and do not require samples of diseased tissues or even knowledge about how the disease may affect particular tissues.
- Collecting sufficient quantities of trabecular meshwork to perform biochemical and cellular studies, however, has been difficult.

Introduction Contd.

- Specific gene defects can be identified using DNA purified from lymphocytes obtained from a routine blood sample. The study of genes responsible for glaucoma will identify the role of specific protein products in the development of the disease without requiring direct access to ocular tissue

Primary open-angle glaucoma (POAG)

- Although mutations in **several** genes, including myocilin, optineurin, and CYP1B1, have been reported to cause POAG, these genes account for less than 10% of cases worldwide.
- In the past few years, large scale genetic studies that have examined the blood samples of thousands of glaucoma patients have been instrumental in the discovery of more common genetic risk factors for POAG.

POAG Contd.

- For glaucoma, these genetic factors include changes in the DNA sequences (near or in the genes such as caveolin 1 and 2 (CAV1/CAV2), CDKN2B antisense RNA, TMCO1, SIX1/SIX6, and LRP12/ZFPM2 genes) or actual loss of DNA (TBK1 and GALC), and several different genes have been implicated. How these genes cause or influence the likelihood of developing POAG is of major interest.

POAG Contd.

It is therefore likely that the hereditary aspect of many of the remaining cases of POAG is due to the combined effects of several genes (polygenic) and that gene-environment interactions are important.

Quantitative endophenotype traits related to POAG pathogenesis such as IOP, vertical cup-to-disc ratio (VCDR), and CCT are highly heritable, likely to be influenced at least in part by genes, and are highly polymorphic.

POAG Contd.

- Recent advances in genomic technologies and genome-wide association studies (GWAS) have greatly accelerated the discovery and understanding of genes and genomic regions associated with POAG and influencing the quantitative endophenotype traits related to POAG pathogenesis.

Primary congenital glaucoma (PCG)

- Is the most common childhood glaucoma affecting children from birth to age 3 and is a major cause of blindness in this young population.
- Mutations in the CYP1B1 gene have been found to cause PCG in children worldwide and are the dominant genetic cause for glaucoma in children in the Middle East and central Europe.
- In the United States only 15% of children with PCG have a mutation in CYP1B1, so there are ongoing efforts to identify additional causes in these young patients.

Glaucoma in Older Children

- The genes implicated in these forms of glaucoma (Juvenile glaucomas) play a key role in the development of the eye, so when they malfunction they cause abnormalities in aqueous drainage system which leads to elevated IOP and glaucoma.
- The genes currently known to be associated with these forms of glaucoma include PITX2, PITX3, FOXC1, FOXE3, PAX6, LMX1B, and MAF.

Primary angle-closure glaucoma (PACG)

- is the second most common form of glaucoma and affects over 16 million people globally.
- Very recently a large scale genetics study identified genetic variants that are associated with this form of glaucoma.
- These variants are in or near PLEKHA7, PCMTD1/ST18, and COL11A1. How these genes contribute to this form of glaucoma is not clear.

Exfoliation glaucoma (XFG)

- Also called pseudoexfoliation glaucoma, affects millions and is the most common identifiable form of open-angle glaucoma in the world.
- XFG results from exfoliation syndrome, a common condition characterized by the deposit of white protein-like material that forms on the lens and within the fluid drainage system of the eye, as well as tissues throughout the body.
- Genetic variants of LOXL1 and CNTNAP2 genes have been associated

SUMMARY

- In summary, there has been a remarkable expansion of our understanding of the genetic underpinnings of the major forms of glaucoma. At the moment these advances in our knowledge are tantalizing since these genetic discoveries are not yet at the stage that they can be put to practical use. We still don't quite understand how these gene abnormalities actually cause glaucoma,

FUTURE PROMISE

- Based on the current and new genes identified in glaucoma, it may be possible to develop an algorithm of single nucleotide polymorphisms (SNPs) risk scores to assess the future risk of glaucoma in patients, which could be clinically useful.

- However, despite the tremendous progress, the genetic basis of the various forms of glaucoma is still not completely understood and further investigations are needed to identify novel genes and pathways contributing to glaucoma that may help define disease-specific targets and facilitate the development of diagnostic and therapeutic strategies

CONCLUSION

- As for the development of new therapeutic agents, the process will be lengthy and may take several years before effective therapeutic modalities for primary glaucomas are available. The whole process from discovering new genetic markers (SNPs) or genes to developing new therapeutic agents may take several steps and many years.

CONCLUSION

- Those steps are:
- (i) Discover those genes and/or SNPs associated the glaucomas, which is underway thanks to new emerging technologies in molecular genetics such as exome sequencing and genome-wide association studies (GWAS) technologies. This may take up to 10 years to complete;

CONCLUSION Contd.

- (ii) Establish the association of various SNPs and genes with primary glaucomas in various ethnicities, larger cohorts, and in multiple centers. This is important as initial discovery studies are conducted on specific ethnicities and in smaller cohorts

CONCLUSION Contd.

- ; (iii) Conduct functional studies in order to understand how those genes and/or SNPs contribute to primary glaucoma pathogenesis;
- (iv) Develop therapeutic agents based on our understanding of the function of the genes associated with the glaucomas. This step is the longest and expected to take at least 10-15 years.

CONCLUSION Contd.

- This should not hold us back or make us think less of genetic studies as those may prove to be the only way to improve our current understanding of the etiology of glaucoma and facilitate the development of diagnostic and therapeutic strategies.