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Editorial Assistance: Dr Usha Raman, Mr Sam Balasundaram, Ms Sarika Jain Antony

Understanding the Genetics of Primary Glaucomas in the Indian Population

Balaiya M Sankarathi, Ph.D., and Subhabrata Chakrabarti, Ph.D.*

Kallam Anji Reddy Molecular Genetics Laboratory, L V Prasad Eye Institute, Hyderabad – 500034, India.

*Correspondence: subho@lvpei.org

Introduction

Glaucoma is a complex neurodegenerative disorder affecting 70 million people worldwide. It leads to progressive loss of vision due to the gradual death of retinal ganglion cells. Usually, it is a pain-free disorder associated with substantial visual damage before symptoms are detected. Hence an early diagnosis could to some extent prevent irreversible blindness.

It is estimated that glaucoma affects 15 million Indians and around 25 million are at risk of developing the disease. It manifests at different ages and presents a clinically and genetically heterogeneous picture. The prevalence increases over the age of 40 (it increases three times over the age of 60), which amounts to approximately 2.5 to 3 million rural Indians.

Several risk factors have been associated with the increased prevalence of glaucoma. It is 6-8 times more common among African-Americans and Hispanics than Caucasians and the susceptibility increases over the age of 60. Asians account for less than 10% of all clinical forms of glaucoma. A raised intraocular pressure (IOP), age, myopia, hypertension and diabetes are the clinical risk factors, while consanguinity, inbreeding and a positive family history are the genetic risk factors associated with glaucoma.

The underlying genetic mechanism in glaucoma has been widely explored in different ways. Studies conducted across different populations have indicated multifactorial etiology underlying

glaucoma pathogenesis. While there is evidence of age, gender and race being risk factors that predispose to primary glaucomas, genetic factors have also contributed to a significant risk in the disease etiology. Candidate genes that could alter some functions in the biochemical pathway leading to glaucoma have been identified through linkage analysis in large families and association studies on case-control cohorts. Being a complex disease the proportion of cases attributable to the candidate genes varies widely across multiple glaucoma phenotypes and populations.

Types of Glaucoma

There are three major forms of primary glaucoma. They constitute primary open angle (POAG), where the drainage canals of the eye get clogged over time leading to an increased intraocular pressure (IOP), and primary angle closure glaucoma (PACG), which is associated with anatomically narrow angles, where the outer edge of the iris branches over the drainage canals resulting in pupil enlargement. While these glaucomas have an onset in the post-juvenile period (usually from 5-65 years of age), primary congenital glaucoma (PCG) occurs at birth to early infancy (within 3 years) due to the developmental anomaly of the trabecular meshwork and anterior chamber.

In India, around 1.5 million people are blind due to glaucoma^{1,2} and the prevalence of POAG and PACG are almost the same in the general population. On the other hand, the prevalence of PCG is 1 in

3300 live births in the state of Andhra Pradesh,³ resulting in 2.4% of the prevailing blindness. Strikingly this is close to the Saudi Arabian and the Romano Gypsy population and can be attributed to the high consanguinity in the state.

Genetic Studies in Glaucoma

Gene mapping in large juvenile open angle glaucoma (JOAG) and adult-onset POAG families have led to the identification of 20 chromosomal loci on different chromosomes, of which 11 have been named, from *GLC1A* to *GLC1K*. But only three loci, namely, *GLC1A* (1q21-q31), *GLC1E* (10p15-p14) and *GLC1G* (5q22.1), have been identified to harbor the Myocilin (*MYOC*), Optineurin (*OPTN*) and *WDR36* genes, respectively. So far no genes have been implicated in PACG, while the Cytochrome P450 gene (*CYP1B1*) has been associated with PCG. The frequency of *MYOC* mutations range between 2-5% across populations and more than 70 different mutations have been observed indicating allelic heterogeneity. *CYP1B1* mutations account for varied proportions of cases worldwide (20-100%) and the frequency of mutations decreases from the Central Asian to South East Asian populations. Association studies have led to the identification of 15 other genes that may be potentially involved in the disease pathway.

Glaucoma Genetics in India

In India, the thrust of genetic studies in glaucoma has been on replicating the involvement of these candidate genes in

the disease pathogenesis. It was found that *MYOC* mutations were associated both with JOAG and adult-onset POAG and the Gln48His was the most prevalent mutant allele among these cases.⁴ This mutation was unique to Indian populations and was also observed in cases of primary congenital glaucoma indicating phenotypic heterogeneity. The *OPTN* gene, which was earlier, implicated in normal tension glaucoma, exhibited a putative mutation (Arg545Gln) in POAG. Some polymorphisms were also observed that were unlikely to be pathogenic.

Association studies in POAG on *p53* and *eNOS* gene polymorphism did not indicate any involvement with the disease phenotype. However these studies did not have sufficient power to exhibit a significant difference and were also not well characterized with respect to the phenotype.

Turning to primary congenital glaucoma (PCG), the candidate gene *CYP1B1* was implicated in ~50% of the cases. Although the mutation frequency was quite low compared to the Slovakian Gypsies and populations of Saudi Arabia, the frequency of the different types of mutations was highest in the Indian populations. Ten novel mutations were observed exhibiting varying degrees of severity and the Arg368His was the most frequent allele among the cases.³ It was also deciphered that there was a global clustering of these mutations across different PCG populations worldwide, which was strongly structured by their geographic and haplotype backgrounds.⁵ Interestingly, it was found that the *MYOC* gene was implicated in some of the PCG cases through the digenic involvement with *CYP1B1* or a yet unidentified locus.⁴ It

was also observed that *CYP1B1* was also involved in some POAG cases, but their causality is yet to be established.

It is important to mention that the Gln48His mutation has been involved across multiple glaucoma phenotypes (POAG and PCG), indicating an allelic condition of *MYOC*.⁴ The available data suggests that a mutation in *MYOC* (Gln48His) and *CYP1B1* (Arg368His) are unique to Indian populations and could be included in the molecular diagnosis of cases predisposed to PCG/POAG. Genotype-phenotype correlations in some studies have indicated variable phenotypic manifestation for a given mutation. Several lacunae exist with respect to the replication of polymorphism data as determinants of genetic risk factor across different ethnic groups in India, which could be attributed to variable diagnosis and other epidemiological issues. But the mutation data is quite uniform across various centres suggesting its applicability in prospective screening in cohorts and families harboring these *MYOC* and/or *CYP1B1* mutations.

Significance of Genetic Screening in Glaucoma

The different glaucoma genes identified so far contribute to only a small fraction of glaucoma. Animal models have not been quite successful as the trabecular meshwork tissue is present only in humans and higher order primates, thereby impeding the generation of an exact human disease phenotype. Hence, identifying the role of gene mutations in the death of retinal ganglion cells (RGC) and elevated intraocular pressure may provide valuable insights on the underlying molecular mechanisms leading to

glaucoma pathogenesis. While several interacting factors contribute to RGC death and raised IOP, their individual role also depends on the individuals' susceptibility to different environmental factors, life style and genotype.

With a relatively higher rate of consanguinity in most parts of India, the risk of developing glaucoma increases manifold compared to other populations. Thus, candidate gene screening would be helpful in identifying genetic risk factors that may predispose to glaucoma. In addition, the characterisation of these genes would provide further insights into the disease pathogenesis which would eventually aid better management of glaucoma. An extensive genotype-phenotype correlation would be helpful in assessing the disease prognosis over a period of time. Based on these data, genetic counseling can be provided to individuals at risk of developing glaucoma, particularly to those with a family history, to prevent further blindness. As surgical and medical intervention is the only choice of treatment available, understanding the genetic basis would help in devising molecular diagnostics for predictive testing and early intervention.

References and Further Reading

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Applying the recent clinical trials on primary open angle glaucoma: the developing world perspective

Thomas R, Kumar RS, Chandrasekhar G, Parikh R

Recent clinical trials have provided scientific guidelines for the treatment of ocular hypertension and primary open angle glaucoma. The developing world needs to apply these trials in a sensible and cost-effective manner. The number needed to treat (NNT) attempts to tailor treatment to the individual patient. The NNT for the average ocular hypertensive is 20. Those with intraocular pressure > or =26 mm Hg have an NNT of 6. Restricting treatment to those with lower central corneal thickness and or high cup disc ratios can further lower NNT and make treatment more cost effective. The NNT for the average patient with early POAG is 5. Targeting those at higher risk for progression, (bilateral POAG, higher IOP and or pseudo-exfoliation) can further reduce NNT. As far as the modality of treatment is concerned, provided quality can be ensured, collaborative initial glaucoma treatment study (CIGTS) could be interpreted to justify primary surgery in the developing world context. Population attributable risk percentage (PAR), a measure that reflects the public health importance of a disease was used to extrapolate results to the overall population. Ocular hypertension has an "effective" PAR of 8.5 per cent, a value not considered high enough to warrant public health intervention. POAG had an "effective" PAR of 16 per cent, perhaps high enough to be considered a public health problem and justify inclusion as a target disease in the VISION 2020 program. However the logistics and opportunity costs of diagnosis and treatment would probably prevent inclusion of POAG in public health budgets of most developing countries.

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