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Understanding the Genetics of Primary Glaucomas in the Indian Population

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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.

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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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VISION 2020-India Initiatives (June – October 2006)

VISION 2020: The Right to Sight-India had initiated very unique and strategic partnership activities during the months June-October 2006

A Step toward – XI Five Year Plan

A delegation comprising Dr G N Rao, President, IAPB, Mr Thulasiraj, President (India forum), Dr G V Rao, (ORBIS International) Treasurer and Dr S Badrinath, Member of VISION 2020-India met with Shri P Chidambaram, Union Finance Minister, Government of India on 10th August 2006 in New Delhi to lobby for financial support in the XI plan.

Dr G N Rao, Dr G V Rao, Country Director, ORBIS International and Mr P K M Swamy, Executive Director, VISION 2020-India met Dr Montek Singh Ahluwalia, Deputy Chairman of Planning Commission, Govt of India on 1st September 2006 in New Delhi. The team shared with Dr Ahluwalia and his team the growing Public-Private Partnership at national and international levels in vision care under the VISION 2020: The Right to Sight global initiative. They made a presentation on the next XI Five Year plan (2007-2012) and sought support for the plan under NPCB of MOHFW and if possible with additional resources.

State Plan Facilitation

VISION 2020: The Right to Sight-India was actively involved in facilitating the development of State Plans and providing necessary support in finding ways to streamline the working of the various state chapters.

Andhra Pradesh

To streamline the functioning of Andhra Pradesh Right to Sight Society (APRTS), Mr. PKM Swamy, Executive Director VISION 2020-India participated in the APRTS Executive Committee meeting on 16-17 June in Hyderabad. Dr I V Subbarao, Principal Secretary, Ministry of Health and Family Welfare, Government of Andhra Pradesh chaired the meeting. He promised to address the issues that are preventing APRTS from functioning well.

A state-level meeting of NGO partners was held on 29th June to discuss the importance of establishing Vision Centers and the need for more concerted effort by the NGOs in the movement against avoidable blindness.

The Andhra Pradesh NGO Eye Hospitals forum was formed on 26th July 2006 and had its first convention on 20 August 2006 at Hyderabad.

Kerala

Dr Viswas Mehta, IAS, Secretary Health, Government of Kerala convened a state-level meeting on 29th August 2006 in Trivandrum to discuss VISION 2020-state plan development and streamline the Grant-In-Aid to the NGO hospitals working in eye care. There were about 50 participants both from NGO and Government sectors in the meeting.

The interface helped bridge gaps in perceptions and sort out the differences between the government and the NGO sector in relation to the grant in aid. It also provided the opportunity to carry out a situation analysis of blindness and plan a future course of action in the form of a state plan and its implementation through the *Kerala Eye NGO Hospitals Forum*.

Maharashtra

Joint Director of Health Services (NPCB) Mumbai had called first ever meeting of the VISION 2020 state plan committee, to work on the draft VISION 2020 State plan on 27th September 2006 in Mumbai. Mr Swamy and other key members Col (Dr) Deshpande, Prof. Lahane and the team led by Dr Bagde, Joint Director NPCB state wing participated in the meeting and developed strategies for the development and launch of the plan.

Chhatisgarh

Chhatisgarh has begun its own state-level VISION 2020 initiatives. About 35 participants drawn from state apparatus, INGOs and NGOs met on 28 October to review the current situation and future strategies. The meeting was facilitated by the VISION 2020-India team consisting of Mr John Tressler, Secretary and Mr Swamy, Executive Director assisted by Mr Antony N J, area representative, Sight Savers International. It was decided to collect the basic inputs for planning from each district and present them at the next meeting. The Chhatisgarh VISION 2020 Plan and Implementation Committee (CVPIC) was formed apart from a core committee of five members.

Membership

Six members were co-opted into the VISION 2020-India during the period. These are Bollineni Eye Hospital & Research Centre, Nellore, Andhra Pradesh; Global Hospital Institute of Ophthalmology, Mount Abu, Rajasthan; Gomabai Netralaya, Neemuch, Madhya Pradesh; Sewa

Rural, Bharuch, Gujarat; Kalinga Eye Institute & Research Centre, Orissa; Bejan Singh Eye Hospital, Nagorcoil, Tamil Nadu and Little Flower Hospital, Angamally, Kerala.

Second Annual Conclave

The second Annual Conclave of VISION 2020-India was organised from 10th to 11th August 2006 in Pune with the support of H V Desai Eye Hospital during which the following events were organised:

- ◆ Member Service Workshop
- ◆ Induction of Ms. Hema Malini as Brand Ambassador
- ◆ 2nd Annual General Body Meet
- ◆ XI Board Meeting

Member Service Workshop

A Member Service workshop was organised on 10th August. The objective was to invite ideas from the members to design and develop a package of services to be offered to them and also to solicit opinions on what specific contribution they could make to the organisation. This exercise was done in groups and followed by presentations on expectations as well as contributions from the members.

Ms Hema Malini as Branch Ambassador

Ms Hema Malini was invited to be Brand Ambassador for VISION 2020-India. She attended the XI Board meeting and 2nd Annual General Body Meeting. About 45 delegates from 30 member organisations participated in the Annual Conclave.

Responding to the warm reception that she had from the members Ms Hema Malini declared that she would support the movement both as an actress and parliamentarian. She also interacted with children with visual impairment and inaugurated the VISION 2020-India Pavilion that showcased the Forum's achievements.



AGBM/Board Meeting

Second Annual General Body

The 2nd Annual General Body Meeting of VISION 2020: The Right to Sight-India was held on 11th August morning from 8:30 am to 12:00 noon in Pune. There were 45 delegates from 30 member organisations out of a total of 49 member organisations.

XI Board meeting

The Board met both on 10th and 11th August with the participation of 10 members out of 15. The highlights of the meeting were inclusion of Ms Hema Malini as the Brand Ambassador with a charter of activities, lobbying for support to XI Five Year Plan and review of the Annual progress and financial transactions relating to long range strategic plan.

National Workshop on "IT Applications in Eye Care"

The VISION 2020: The Right to Sight-India organised the first ever National workshop on "IT Applications in Eye Care" in partnership with our members Aravind Eye Care System, Madurai and Sankara Nethralaya, Chennai from 3rd to 5th August 2006 in Madurai.



Participants at the National Workshop

This workshop was designed for participants to gain knowledge about current trends and status of Information Technology and share experiences of various IT applications in eye care settings. It brought together the people from the IT field as well as eye hospitals that have been implementing and using IT in a big way. Resource persons from Aravind Eye Hospital, Madurai, Sankara Nethralaya, Chennai, Tata Consultancy Services, Bangalore, AxSys Health Care, Hyderabad were among those who participated. There were about 70 delegates from all over India and from Nepal and Bangladesh.

Giants come together

Sankara Nethralaya, Chennai, Aravind Eye Hospital, Madurai and L V Prasad Eye Institute, Hyderabad all major member organizations met on 28th August 2006 in Chennai for a preliminary discussion on how they could work together. A small step by the three hospitals had been initiated considering the benefit to India that could accrue if they work together and their collective wisdom could bring big rewards for ophthalmic care in India.

WSD Celebrations-2006

(a) Government efforts

Activities were organised by the National Program for Control of Blindness and the Ministry of Health and Family Welfare with two objectives: one, to promote national coverage through public awareness strategies and two, to invite the visible participation of Union Health Ministers and politicians. This year World Sight Day theme in India was "Diabetic Retinopathy".

A press conference was held on 9th evening to brief the media about World Sight Day as a partnership endeavour by the Government of India and VISION 2020-India.



Dr Kalam, Dr GN Rao, Lenor Balezze and Antonio Borges

The Government also published an advertisement on World Sight Day in all the leading daily newspapers across the country.

Member organisations around the country observed World Sight Day in a variety of ways, holding public awareness programmes, competitions for children, free eye screenings and exhibitions. A complete report of events may be accessed at www.v2020.org.

(b) VISION 2020-India's Team

Mr P K M Swamy, Executive Director, VISION 2020-India participated in the 3rd International Forum on Vision and

Development organized jointly by UNESCO and ESSILOR on the occasion of the World Sight Day at India Habitat Centre, New Delhi.

Mr Swamy also participated in the World Sight Day function at Venu Eye Institute and Research Centre, New Delhi. On this occasion a group of individuals with visual and hearing impairment were felicitated for their adventurous journey from Patiala to New Delhi on Tandem Cycle, sponsored by CBM.

Member Service

As part of member service Mr Swamy visited states like Kerala, Chhatisgarh, Maharashtra, Tamil Nadu and Andhra Pradesh during the period and interacted not only with our member organizations but also with other eye care institutions to understand what members need as growing organization. As part of this he visited hospitals under CBM, Lions and Sight Savers International. The CBM Partners' Meet was held in Tiruchirapalli, and the Lions Club International Foundation held the first Lions Sight First Conclave of NGO hospitals in the Eastern region in Kolkata.

Launching of the Antonio Champalimaud Science Award

The Antonio Champalimaud Science Award for supporting translational research that directly impacts vision and alleviation of blindness was launched on 9th October afternoon from Rastrapati Bhawan, New Delhi by His Excellency, Dr APJ Abdul Kalam, the President of India.

The Award money EURO 1.0 million (annually) will be awarded for Vision and related science research work. On the occasion Dr Kalam appreciated the benefactor *Antonio de Sommer Champalimaud* for his vision.



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