Is Glaucoma a Genetic Disorder?

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Dear Friends

Season's Greetings!!

Glaucoma is a group of complex, clinically and genetically heterogeneous optic neuropathies, characterized by progressive and non-reversible changes in optic disc and retinal nerve fibre layer (RNFL). It is associated with visual field defect, wherein raised IOP is a major risk factor. Raised IOP is not necessarily responsible for optic nerve head damage, however other biological mechanisms are responsible for retinal ganglion cell apoptosis.

Glaucoma is the second most common cause of blindness worldwide[1]. Recently it has been reported that about 70 million people are affected by POAG. Studies suggest that by 2020 prevalence is estimated to increase to 76 million and 111.80 million by 2040 globally, because of increasing aging population[2]. Out of the total cases, 12 million are from Indian continent and by 2020 this is expected to be 16 million. In India, around 90% of glaucoma patients remain undiagnosed[3]. The risk and prevalence of glaucoma are known to vary widely, in different races/ ethnic groups and country, higher in blacks (4.7%) than white population (1.3%)[4]. High prevalence has been reported in Africans, followed by Asians and lowest in Europeans[5]. Rotterdaum study found that first degree relative of POAG patients have 10 times greater risk of glaucoma than general population[6].

Multiple molecular mechanisms are responsible for underlying pathogenesis of glaucoma e.g. altered morphology and function of TM tissue, loss of neurotrophic factors, oxidative stress related to neurodegeneration (RGC death) and Nitric oxide (NO) mediated glial cell apoptosis etc. Although the genetic basis of glaucoma is not fully known , however multiple chromosomal loci have been identified with linkage to glaucoma but mutation have been identified only in few genes; Myocilin (MYOC, GLC1A gene), Optineurin (OPTN, GLC1E gene), WD repeat domain 36 (WDR 36, GLC1G gene) and Neurotrophin -4 (NTF4, GLC1O). Mutation in above genes do not completely explain the disease pathogenesis due to variable penetrance and expressivity of the gene mutations. The disease- causing genes account for < 10% of POAG cases in general population. Hereditary aspects of remaining cases of POAG is due to combined effect of several genes (Polygenic) and gene-environmental interaction. Quantitative endophenotypic traits related to pathogenesis of POAG such as raised IOP, vertical cup-disc ratio (VCDR) and CCT are highly inheritable / influenced by genes and highly polymorphic[7].

The commonest candidate gene is MYOC gene, also called TIGR (trabecular meshwork-induced glucocorticoid receptor) is a glycoprotein, first demonstrated by Sheffiled et al on chromosome 1q21-q31(GLC1A). Approximately 10-33% of people with juvenile open-angle glaucoma and 2-5% of POAG have mutations in the *MYOC* gene. The *MYOC* gene is responsible for cytoskeleton organization and extracellular matrix (ECM) remodulation as it provides instructions for producing a protein called Myocilin. Myocilin is found in trabecular meshwork and the ciliary body that regulates the intraocular pressure. Mutations may alter the protein thus defective myocilin that is not incorporated into functional complexes may accumulate in the trabecular meshwork and ciliary body. The excess protein may prevent sufficient flow of fluid from the eye, resulting in increased intraocular pressure and causing signs and symptoms of early-onset glaucoma. Mutant MYOC may cause mitochondrial defects which may lead to apoptotic cell death of TM cell[8]. 20-40% of POAG patients have mutations in the *CYP1B1* gene. CYP1B1 gene has also been implicated in PCG and Juvenile onset glaucoma. The *CYP1B1* gene is responsible for cytochrome P450 protein production in the trabecular meshwork, ciliary body, and other structures

of the eye. The CYP1B1 protein may interact with myocilin and individuals with mutations in both the *MYOC* and*CYP1B1* genes may develop glaucoma at an earlier age and have more severe disease manifestation. *OPTN is* the gene in the GLC1E region (10p15-p14) that encodes the optineurin. Mutation in OPTN is strongly associated with normal tension glaucoma (NTG) and POAG. OPTN Overexpression protects TM cells from H_2O_2 - induced cell death. Recently, WDR36 gene, located on GLC1G locus (5q22.1) identified in POAG indirectly acts as a modifier gene[9]. Other gene NTF4 (Neuorotrophin factor 4) is located on chromosome 19q13.33 is translated as pro-neurotrophin [NTs]. The development, survival and differentiation of neurons depends on neurotrophin like growth factors. NTF4 mutation has been observed in POAG patients of European origin may leads to impaired neurotrophin release and RGC death.

Recent genome-wide association studies (GWAS) has been identified several single neucleotide polymorphisms (SNPs) at different loci including CAV1/ CAV2, TMCO1, CDKN2B-AS1, SIX1 / SIX6 and ATOH7 known to be associated with POAG and its related quantitative traits like IOP, VCDR, CCT etc., are helpful in better understanding of disease[10].

Despite of much progress in glaucoma study, genetic basis of glaucoma is still not completely understood and future investigations are needed to search novel genes and mechanisms contributing to glaucoma that may facilitate the development of diagnostic and therapeutic strategies.

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