Exploring the Basis of Sex Bias in Primary Congenital Glaucoma

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Glaucoma, an optic neuropathy characterized by progressive visual field loss, is the leading cause of irreversible blindness worldwide. The condition has a substantial heritable basis, as illustrated by the numerous loci and genes identified to date and the large proportion of patients with positive family history. When glaucoma manifests before the age of 40 years, it tends to be more aggressive, more resistant to medical therapy and associated with more visual impairment.[1,2] This category includes congenital/infantile glaucoma which is a genetically heterogeneous group by itself with the involvement of one gene (*CYP1B1*) and at least two other genetic loci.[3-6] The only known gene for primary congenital glaucoma (PCG), *CYP1B1*, encodes cytochrome P4501B1 that is involved in the metabolism of many compounds, including the 4-hydroxylation of 17β-estradiol.[7] It has been hypothesized that alterations in the metabolism of estrogens may be the basis for ocular abnormalities associated with defects in this gene.[8,9]

Male subjects account for approximately 65% of PCG cases.[10] As yet, no molecular cause for this observation has been identified. The *CYP1B1* gene that participates in the metabolism of 17β-estradiol is an attractive candidate to study the apparent sex bias observed in PCG. In this issue of JOVR, Suri et al[11] compare the phenotypic features of a relatively large number of Iranian PCG patients with and without *CYP1B1* mutations, with an emphasis on sex ratios. This study involves 66 patients with mutations in *CYP1B1* and is larger than the one previous Japanese study that did the same with 32 patients.[12] Despite the fact that steroids are relevant to *CYP1B1* gene expression and *CYP1B1* protein function, the authors did not observe sex related differences in incidence among patients harboring *CYP1B1* mutations, a finding consistent with the Japanese study. It is possible that a still larger cohort may be required to draw a definite conclusion, on the other hand a meta-analysis would be useful in such studies that deal with relatively rare diseases. As the authors quite rightly suggest, the higher male to female ratio among patients not harboring *CYP1B1* mutations could be due to another gene involved in the etiology of PCG in a sex dependent manner. Unlike late onset glaucoma, PCG seems to have a strong genetic basis and environmental factors are unlikely to have a strong influence on disease presentation. Therefore if one were to apply classic Mendelian inheritance to these observations, the higher incidence of PCG among male subjects in various populations could be attributed to a major X-linked gene that shows recessive inheritance pattern. The higher male to female ratio observed among Iranian patients without *CYP1B1* mutations suggests that this cohort of patients will be a good starting point to further explore and identify this possible X-linked gene. An important factor to bear in mind while carrying out genealogy in these families and probands is that inbreeding within families that actually segregate a recessive X-linked gene mutation will result in some affected females and the appearance of male to male transmission. In such instances these families may appear as classical autosomal recessive or even as pseudodominant pedigrees with incomplete penetrance.

Congenital glaucoma is generally inherited as an autosomal-recessive trait and is prevalent in countries where consanguinity is common.[3,4] Linkage analysis requires large pedigrees; in

fact the PCG locus on chromosome 2p21 (GLC3A) that harbors the *CYP1BI* gene was corroborated using homozygosity mapping with DNA pooling strategy in 3 large consanguineous Saudi PCG families.[4] Therefore patients and family pedigree resources available in countries such as Iran will be extremely valuable for the identification of recessive PCG genes, X-linked or otherwise. Identification of more PCG genes will help elucidate pathophysiologic mechanisms that are currently inadequately understood and may even provide new directions for glaucoma therapy. A more immediate benefit will be that it will enable screening of family members of PCG patients to identify potential gene carriers and facilitate genetic counseling. Increased awareness of the genetic basis of PCG and education may discourage consanguineous marriages and will hopefully decrease the incidence of this severe form of glaucoma.

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