Glaucoma in Iran and Contributions of Studies in Iran to the Understanding of the Etiology of Glaucoma

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Abstract

Epidemiologic and genetic/molecular research on glaucoma in Iran started within the past decade. A population-based study on the epidemiology of glaucoma in Yazd, a city in central Iran, revealed that 4.4% of studied individuals were affected with glaucoma: 1.6% with high tension primary open angle glaucoma (POAG), 1.6% with normal tension POAG, and 0.4% each with primary angle closure glaucoma (PACG) and pseudoexfoliation glaucoma (PEXG), and other types of secondary glaucoma. Two notable observations were the relatively high frequency of normal tension glaucoma cases (1.6%) and the large fraction of glaucoma affected individuals (nearly 90%) who were unaware of their condition. The first and most subsequent genetic studies on glaucoma in Iran were focused on primary congenital glaucoma (PCG) showing that cytochrome CYP1B1 is the cause of PCG in the majority of Iranian patients, many different CYP1B1 mutations are present among Iranian patients but only four mutations constitute the vast majority, and the origins of most mutations in the Iranians are identical by descent (IBD) with the same mutations in other populations. Furthermore, most of the PCG patients are from the northern and northwestern provinces of Iran. A statistically significant male predominance of PCG was observed only among patients without CYP1B1 mutations. Clinical investigations on family members of PCG patients revealed that CYP1B1 mutations exhibit variable expressivity, but almost complete penetrance. A great number of individuals harboring CYP1B1 mutations become affected with juvenile onset POAG. Screening of JOAG patients showed that an approximately equal fraction of the patients harbor CYP1B1 and (myocilin) MYOC mutations; MYOC is a well-known adult onset glaucoma causing gene. Presence of CYP1B1 mutations in JOAG patients suggests that in some cases, the two conditions may share a common etiology. Further genetic analysis of Iranian PCG patients led to identification of Latent-transforming growth factor beta-binding protein 2 (LTBP2) as a causative gene for both PCG and several diseases which are often accompanied by glaucomatous presentations, such as Weill-Marchesani syndrome 3 (WMS3). The findings on LTBP2 have contributed to recognize the importance of the extracellular matrix in pathways leading to glaucoma.

Keywords: Epidemiology; Extracellular Matrix; Genetics; Glaucoma; Iran

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INTRODUCTION

Glaucoma is a heterogeneous group of optic neuropathies with common structural and functional manifestations. Optic nerve head cupping or degeneration of the optic nerve result in a characteristic glaucomatous appearance and a specific pattern of visual field loss.[1,2] Glaucoma ultimately leads to blindness if left untreated and is considered the second leading cause of blindness worldwide.[3] It is estimated that over 60 million people...
It is well established that PACG is more common in oriental populations of the Far East Asia than in Caucasian and African residents.\cite{16,21,22} In fact, it has been reported that PACG is responsible for most bilateral glaucoma-induced blindness in Singapore, China, and India.\cite{22-28} Nevertheless, population-based surveys showing that PACG is more prevalent than POAG have been published only from Mongolia and Myanmar.\cite{6,7}

Secondary glaucomas are often associated with additional clinical presentations. IOP increases in all cases of secondary glaucoma. Pseudoxefoliation (PEX) syndrome is a prevalent disorder which and commonly accompanied by glaucoma.\cite{27} Aggregates in the form of what is known as PEX material mainly deposit in the anterior segment of the eye in affected individuals. Some other forms of secondary glaucoma include neovascular glaucoma caused by the abnormal formation of new blood vessels in the eye, pigmentary glaucoma occurring while the pigment granules of the iris enter the aqueous humor, uveitic glaucoma caused by swelling and inflammation of the uvea, and traumatic glaucoma due to injury to the eye.\cite{28,31} Advanced cataract or diabetes as well as use of certain drugs such as steroids may also lead to glaucoma.

In the present review, two aspects of glaucoma will be analyzed with reference to Iran. First, we will present the epidemiology of the disease in this Middle East country. Then, genetic findings accumulated by studies on Iranian patients and some of their implications will be discussed.

**EPIDEMIOLOGY OF GLAUCOMA IN IRAN**

Epidemiological data on PCG in Iran is meager. It is well known that the incidence of PCG is higher in populations with high rates of consanguineous marriage. Whereas its incidence in Western countries is estimated at 1:10,000,\cite{11} this rate in various inbred populations for which data is available, such as India\cite{32} and Saudi Arabia,\cite{12} ranges from 1:1,200-1:3,300.\cite{12-14,32} Although comparable figures from Iran are not available, patient recruitment information accrued during a genetic study confirmed that a significant proportion of affected individuals are the offspring of consanguineous parents. Out of 104
unrelated patients recruited from hospitals that are national reference centers and patients from throughout the country are referred to, 48 subjects (46%) were born to consanguineous parents. Additionally, it was evident that the majority of Iranian patients originate from the north and particularly, northwest of Iran [Figure 1].

The major population-based survey on the prevalence of glaucoma in Iran included 1990 individuals aged 40-80 years from Yazd, a central province of Iran. The design of the survey including recruitment of participants and diagnosis criteria was commendable. Glaucoma was diagnosed using structural and functional features and according to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria. Eighty-seven individuals, constituting 4.4% (95% CI: 3.3-5.4%) of the cohort, were diagnosed with glaucoma of which 64 subjects (3.2%) were diagnosed as POAG. Patients with POAG were divided into two groups including high tension and normal tension glaucoma cases. Seven subjects (0.4%) were diagnosed with PACG, 8 (0.4%) as pseudoexfoliation glaucoma (PEXG), and 8 (0.4%) with other types of secondary glaucoma. The prevalence of glaucoma in male and female subjects was comparable. In addition to, 47 cases (2.4%) had ocular hypertension, 32 (1.6%) were diagnosed as PACS, and 16 (0.8%) with PAC. The authors reported that the prevalence of high tension POAG (1.7%) and PACG (0.4%) in Iran as compared to other similar studies in Asia, were higher and lower, respectively. However, it is to be noted that most other surveys were performed in the Far East, and no data from neighboring countries of the Middle East have been reported. Two notable observations were the relatively high frequency of NTG cases (1.5%) and the large number of glaucoma affected individuals (nearly 90%) who were unaware of their condition. It was considered that IOP-independent mechanisms may be of high significance in the etiology of glaucoma among Iranians, and mere focus on IOP for diagnosis may be inappropriate.

GENETICS OF GLAUCOMA IN IRAN

CYP1B1

At the beginning of genetic studies on glaucoma in Iran in 2005, three PCG loci had been identified by linkage analysis of affected pedigrees including GLC3A (OMIM 231300), GLC3B (OMIM 600975), and GLC3C (OMIM 613085). The only gene associated with GLC3A is CYP1B1 (OMIM 601771), identified through studying families of Turkish origin. Disease-causing mutations were recessive. The CYP1B1 gene on chromosome 2 has three exons, encodes cytochrome P4501B1 and is a member of the cytochrome P450 superfamily of genes. Although screening of CYP1B1 mutations in different populations are not strictly comparable because of differences in experimental design, the proportion of PCG patients whose disease is attributable to CYP1B1 mutations is generally high, yet variable among different populations. Consistent with its recessive mode of inheritance, the highest proportion is seen in populations with high rates of consanguineous marriages; the proportion approaches 100% in Slovakia Romas and Saudi Arabia. In contrast, CYP1B1 mutations are observed in approximately 20% of Japanese patients. Various populations differ regarding both the contribution to disease burden and variability in the spectrum of mutations. As of December 2013, 164 variations in CYP1B1 have been publicly reported of which 136 cases are considered to be PCG associated (Human Genome Mutation Database; http://www.hgmd.cf.ac.uk/ac/index.php). One or a few mutations constitute the majority of disease causing alleles in inbred populations, for instance, in Saudi Arabia, whereas there is notable diversity with no single mutation making a large contribution in French and Japanese individuals.

Screening for CYP1B1 mutations in 104 Iranian PCG patients was performed in 2005-2006. The four major outcomes of the study included, 1) CYP1B1 is the cause of PCG in the majority of Iranian patients, 2) many different CYP1B1 mutations are present among Iranian patients, 3) only four mutations constitute the vast majority of disease causing mutations in these patients, and 4) the origins of most mutations in the Iranians are identical by descent (IBD) with the same mutations in other populations, particularly in countries neighboring Iran. Furthermore, as already mentioned, the majority of patients are from the Northern and Northwestern
The contribution of consanguineous mutations, should mutations, and not in those with CYP1B1 mutations. This suggests that other genes or factors may be involved in manifestation of PCG phenotypes in a sex dependent condition.

The other issues delved into with respect to CYP1B1 mutations were their penetrance and expressivity. Incomplete penetrance of some CYP1B1 mutations was long before reported. The issue of penetrance of CYP1B1 disease-associated genotypes was queried by genetic and clinical analysis of family members of probands carrying four common disease-associated mutations in Iranian populations. The participants were members of 40 unrelated families with 56 PCG affected siblings and 178 apparently unaffected family members. Among the latter, 20 subjects from 12 families were observed to harbor two CYP1B1 mutations, suggesting an average penetrance of 73% for all the mutations, exactly the same penetrance rate as previously reported for the Saudi Arabian population. These 20 subjects ranged in age from 14 to 54 years. The novelty of the study in Iran was that the non-penetrant individuals underwent clinical examination. Ophthalmologic examination on 14 of the 20 apparently non-penetrant individuals showed that 8 subjects were affected with JOAG or POAG, and that 3 subjects were glaucoma suspects. One of the individuals with JOAG was the identical twin sibling of a proband affected with PCG. Considering only those who were definitively diagnosed with JOAG or POAG and not counting those who had features suggestive of these disorders, 57.1% of those examined who were non-penetrant regarding PCG were affected with glaucoma at the time of examination. If the glaucoma suspects were considered affected, more than 78% of those examined who were non-penetrant with respect to PCG were shown to be affected with glaucoma to varying degrees. Considering all subjects who received clinical examination (56 + 14), penetrance increased to over 90%. The figure may approach 100% because the 3 individuals shown to be asymptomatic were aged 30, 37, and 50 years at the time of examination on 14 out of the 20 apparently non-penetrant individuals.

PCG is reported to be more prevalent in male subjects than females. Steroid hormones may somehow be relevant to the expression of the CYP1B1 gene or to the function of the encoded protein. For instance, transcription of the gene is induced by the arylhydrocarbon receptor. Moreover, estradiol can act as a substrate for the CYP1B1 protein and mutation in the gene affects hydroxylation of this substrate. Sex ratio comparisons between patients with and without CYP1B1 mutations had been presented in only one report on Japanese patients. Consistent with data on PCG patients from other populations, the overall incidence of PCG in Iran seems to be higher among male subjects. However, it was found that male predominance was statistically significant only among patients without CYP1B1 mutations, and not in those with CYP1B1 mutations. This suggests that other genes or factors may be involved in manifestation of PCG phenotypes in a sex dependent condition.

The high variability observed in the CYP1B1 sequence is partly due to the fact that Iran, as a major gateway in human history, has encountered various races leading to a rich genetic legacy. Other genetic studies have supported this proposition. The mutations causing p.Gly61Glu constituted 22% of the CYP1B1 mutated alleles and this mutation along with those that caused p.Arg390His, p.Arg469Trp, and p.Arg368His constituted 22% of the mutations in Iranian patients. The frequency of these mutations prompted establishment of easy PCR assays for their detection. These assays are potentially useful for diagnostic purposes, premarital screenings and epidemiological surveys. Unfortunately, they have not as yet been put to good use for these ends. P.Gly61Glu and p.Arg469Trp are the most common CYP1B1 mutations in Saudi Arabia, and p.Arg368His is the most common in India. P.Arg390His has been mostly observed in Pakistan and India. Most mutations from the American continent and Western Europe were not observed in Iranian patients. Haplotype analysis based on intragenic polymorphisms suggested that most mutations observed in Iranians had a common origin with the respective mutation observed in other populations. In addition to glaucoma, a role for CYP1B1 has been implicated in cancer. Although cancer-associated alleles are associated with increased enzyme activity, glaucoma causing mutations generally disrupt this activity.

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The penetrance/expressivity study on CYP1B1 mutations described above suggests that some commonalities may exist in the etiologies of congenital and adult onset glaucoma. This was confirmed in two additional studies conducted on Iranian patients. In one of the studies, a microarray-based assay for detection of CYP1B1 mutations was set up. Both studies revealed that approximately 20% (9/44) of Iranian juvenile onset POAG patients harbored two mutated CYP1B1 alleles. Mutations in CYP1B1 in JOAG patients have also been reported in other studies. In addition to JOAG patients, mutated CYP1B1 alleles were observed in patients affected with the more common late onset form of POAG, but at a statistically significant lower frequency (2 out of 42 screened patients). The shared etiology between at least some forms of PCG and POAG suggested by the genetic studies is important, and needs to be considered in proposed molecular pathways leading to glaucoma. The molecular mechanism by which CYP1B1 contributes to glaucoma is unknown. Recent findings in this regard will be presented below.

**MYOC**

Several loci have been reported for POAG, (GLC1A to GLC1O; Human Gene Nomenclature; http://www.genenames.org), but the causative gene in only four have been identified. The four genes including MYOC (at GLC1A; OMIM 601652), OPTN (at GLC1E; OMIM 602432), WDR36 (at GLC1G; OMIM 609669) and NTF4 (at GLC1O; OMIM 613100) encode myocilin, optineurin, WD repeat containing protein 36 and Neurotrophin-4, respectively. The functions of these genes in the eye are not known. The genes together are estimated to account for disease status in less than 10% of POAG patients. MYOC was the first glaucoma-causing gene identified. Mutations in MYOC have been found in sporadic cases and in patients inheriting the disease in an autosomal dominant feature, most often in those with juvenile onset. The encoded protein is bipartite, containing a myosin-like NH2-terminal domain and an olfactomedin homology COOH-terminal domain. Most disease-associated mutations in MYOC affect the olfactomedin-like domain. Mutation screening of MYOC has been done in a small cohort of Iranian JOAG patients. A mutation in MYOC was assessed to be the cause of JOAG in 4 out of 23 (17.4%) probands screened. This figure falls within the range reported for other populations. All patients carried a single mutated allele, consistent with dominant inheritance. Notably, MYOC and CYP1B1 appeared to equally contribute to the disease status among the Iranians JOAG patients. The contributions of the two genes appeared to be independent, as no patient carried mutations in both genes. Digenic etiology for POAG has been suggested by some other investigators. Considering that CYP1B1 mutations were observed in JOAG patients and MYOC generally affects the young onset form of open angle glaucoma, the contribution of MYOC to PCG in Iranian patients was perceived. MYOC mutations have occasionally been reported in PCG patients from other populations. MYOC was screened in twenty Iranian PCG patients known not harbor CYP1B1 mutations and MYOC mutations were not observed in any of the subjects. It is possible that in a larger sample, a few subjects carrying disease causing MYOC mutations could be observed. But the results show that the contribution of MYOC to PCG status in Iran is small or nonexistent.

**LTBP2**

As mentioned earlier, by the beginning of the present millennium, three PCG loci including GLC3A, GLC3B and GLC3C, and one PCG gene, CYP1B1, had been identified. In 2009, Iranian PCG families that did not harbor CYP1B1 mutations were analyzed by linkage analysis with the objective of identifying novel PCG-causing genes. The analysis was performed using high density microarray chips. PCG-causing mutations in LTBP2 that encodes latent transforming growth factor beta binding protein 2 (LTBP2) were identified in two families. Simultaneously, mutations in the same gene were reported in other investigations. LTBP2 lies very close to GLC3C on chromosome 14q24.2-14q24.3, but is not strictly within the locus originally defined by microsatellite markers. As such, it was not clear whether LTBP2 is the PCG-associated gene within GLC3C or the gene within this locus remains unknown and LTBP2 defines a fourth locus for PCG. The authors who had discovered the GLC3C locus have reported the absence of mutations in LTBP2 in patients originally linked to that locus suggesting that LTBP2 defines a novel PCG locus. In the National Center for Biotechnology Information (NCBI) website (http://www.ncbi.nlm.nih.gov), LTBP2 is defined as the gene positioned within locus GLC3D (OMIM 613086). Based on structural properties, the encoded LTBP2 protein is a member of a superfamily of proteins composed of fibrillins and latent transforming growth factor beta binding proteins. Although the precise function of LTBP2 remains unknown, there is evidence for its roles in tissue repair processes, cell adhesion and functions related to those of microfibrils and elastin fibers. LTBP2 is expressed in elastic tissues and associates with fibrillin-1 containing microfibrils. In addition to structural roles, it may affect TGF-β activities. TGF-βs are potent multifunctional cytokines which modulate many biological processes including extracellular matrix (ECM) production and oxidative stress response. They exist as latent complexes at the site of fibrillin containing microfibrils, and the LTBP2s can bind TGF-β latent proteins and possibly affect their activity. Only LTBP2 among the LTBP proteins does not covalently interact...
with TGF-β; however, noncovalent interactions of LTBP2 with TGF-β have not been ruled out.\textsuperscript{[88]} It has been shown that LTBP2 is expressed in human eyes, specifically in the TM and ciliary processes that are thought to be relevant to the etiology of PCG. Contrary to other known genes causing PCG (CYP1B1) or POAG (MYOC, OPTN, WDR36 and NTF4), a plausible cellular and molecular basis for association between LTBP2 and the glaucoma phenotype can be easily considered. Being an extracellular matrix microfibril protein, mutations in the gene may affect defects in the ECM of the TM and decrease facility of aqueous fluid outflow resulting in increased IOP.\textsuperscript{[89]} This notwithstanding, the consequences of LTBP2 mutations for regulating TGF-β signaling may also be relevant to the etiology of glaucoma. These propositions are expanded upon below.

LTBP2 mutations have not been identified in PCG patients in several subsequent studies.\textsuperscript{[90‑92]} However, mutations in LTBP2 in megalocornea\textsuperscript{[93,94]} and microspherophakia\textsuperscript{[95]} patients were reported shortly after the association of the gene with PCG was published. Glaucoma often accompanies these conditions. Various factors prompted considering LTBP2 in the etiology of isolated ectopia lentis (EL) and associated conditions such as Weill-Marchesani syndrome (WMS) and Marfan syndrome (MFS).\textsuperscript{[96]} Specifically, among the PCG patients who were originally identified as carriers of LTBP2 mutations, EL were also reported in a number of subjects.\textsuperscript{[78,79]} Furthermore, WMS and MFS are both often accompanied by either EL or glaucoma or both. Thirty unrelated Iranian patients affected by these diseases were screened and a disease causing recessive mutation was observed in a WMS proband (WMS3; OMIM 614819). Absence of mutations in other known WMS-causing genes and homozygosity mapping confirmed the role of the mutation. Light, fluorescent, and electron microscopy evidenced disruptions of the microfibrillar network in the ECM of the WMS proband’s skin. In conjunction with recent findings regarding other ECM proteins, the presented results strongly support the contention that anomalies in WMS patients are due to disruptions in the ECM and LTBP2 mutations can promote these disruptions. A heterozygous variation observed in a MFS patient possibly contributed to MFS-related phenotypes including ocular manifestations, mitral valve prolapse, and pectus excavatum.\textsuperscript{[96]} Thus, LTBP2 mutations seem to be involved in various forms of syndromic glaucomas.\textsuperscript{[95,97]}

Finally, LTBP2 was considered as a candidate causative gene for POAG and pseudoxfoliation syndrome (PEX; OMIM 177650).\textsuperscript{[98]} CYP1B1 can cause POAG suggesting that this PCG gene may also be the cause of POAG in some patients. As LTBP2 is among the proteins on PEX material in PEX patients who often develop secondary glaucoma, mutation screening of LTBP2 is justified in these patients. The results of the screenings suggested that some LTBP2 sequence variations can contribute to the etiology of POAG and PEX glaucoma syndrome. Microscopic studies again implicated that the mutations affect the ECM. The sum of functional studies on LTBP2 mutations emphasizes the potentially important role of the ECM in various forms of glaucoma.\textsuperscript{[99,100]} Investigations on the potential role of other ECM proteins with respect to glaucoma are warranted.\textsuperscript{[101]} The most recent findings suggest that even CYP1B1 mutations may affect disease status by their effects on the ECM.\textsuperscript{[102]} Disruptions in the ECM may have direct structural consequences or affect TGF-β related pathways.

Linkage analysis in Iranian PCG families have shown that in addition to the four known loci including GLC3A, GLC3B, GLC3C, and GLC3D, at least one other unknown PCG locus is expected to exist.\textsuperscript{[103]} Finally, as glaucoma is essentially a complex disorder, and as known glaucoma-causing genes are the reason for disease status in a minority of affected individuals, the value of non-genetic approaches aimed at realizing its etiology have not been overlooked in investigations performed in Iran. Specifically, studies on the role of transcription factors such as PITX2 and FOXC1 and miRNAs are being pursued.\textsuperscript{[104‑106]}

**SUMMARY**

Expanded epidemiologic studies on glaucoma in Iran seem necessary and with respect to PCG, the Northern and Northwestern provinces of Iran should be targeted. Combined clinical and genetic studies should be performed. Genetic studies are facilitated by the fact that a few mutations in CYP1B1 constitute the majority of CYP1B1 mutations which can be easily screened. CYP1B1 is the major PCG causing gene among Iranians and also contributes to the etiology of POAG, particularly the early onset form of the disease. This has implications on the shared etiology of PCG and POAG. It has also been shown that the penetrance of CYP1B1 mutations is very high, though their expressivity is variable. Considering public health objectives, it is recommended that unaffected relatives of patients with PCG, particularly those known to harbor CYP1B1 mutations, should undergo regular ophthalmologic examination to allow early diagnosis. LTBP2 was discovered as a causative gene for both PCG and several diseases often accompanied by glaucoma such as WMS3. This finding has limited public health value, as the fraction of patients harboring mutations in this gene is small. However, the finding on LTBP2 has contributed to recognize the importance of the extracellular matrix in pathways leading to glaucoma. It is hoped that the findings will ultimately benefit glaucoma patients and those at risk of developing the disease.
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