Review Article

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

Fatemeh Suri[1], MS; Shahin Yazdani[2,3], MD; Elahe Elahi[1,4], PhD

[1]*Department of Cell and Molecular Biology, School of Biology, College of Science, University of Tehran, Tehran, Iran*
[2]*Ocular Tissue Engineering Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[3]*Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Department of Biotechnology, College of Science, University of Tehran, Tehran, Iran*

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 P450 1B1 (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

J Ophthalmic Vis Res 2015; 10 (1): 68-76.

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

Correspondence to:
Elahe Elahi, PhD. School of Biology, College of Science, University of Tehran, Enghelab Ave, Tehran, Iran.
E-mail: elaheelahi@ut.ac.ir

Received: 16-02-2014 Accepted: 17-03-2014

Access this article online

Quick Response Code:

Website: www.jovr.org

DOI: 10.4103/2008-322X.156120

worldwide are presently affected and that 12 million are blind because of glaucoma.[4,5] According to surveys in various populations on subjects aged over 40 years, the prevalence of glaucoma ranges from o. 5% to 7.0%.[6-10] Details of the pathogenic pathways affecting glaucoma are not well understood, although significant advances have been made. It is sub-classified based on the etiology as primary and secondary. In the secondary forms in which the cause of glaucoma is "known", the glaucoma phenotype is often a condition that commonly presents along with other manifestations of a syndrome. Primary forms of glaucoma are classified on the basis of the anatomy of the anterior chamber drainage angle and age of onset into three main subgroups: Primary congenital glaucoma (PCG, OMIM 231300), primary open angle glaucoma (POAG, OMIM 137760) and primary angle closure glaucoma (PACG).[1] The implication of "primary" is that the etiology is unknown.

PCG, the most severe form of the disease, is characterized by an anatomical defect (trabeculodysgenesis) in the trabecular meshwork (TM) and age of onset in the neonatal or infantile period, generally before the age of 3 years.[11] It is most prevalent in populations with high rates of consanguineous marriages.[12-14] The developmental anomaly of the anterior chamber in PCG manifests by increased intraocular pressure (IOP), corneal edema, excessive tearing, photophobia, enlargement of the globe (buphthalmos), corneal opacity and optic nerve damage.

POAG is the most common form in Western populations and possibly other populations.[8,15-18] It is associated with variable severity and phenotypic expressivity.[19,20] Gonioscopy on POAG affected individuals reveals that the angle between the iris root and the posterior TM remains open just as in unaffected individuals; therefore it does not presumably induce a mechanistic barrier to the flow of aqueous humor. Most POAG patients exhibit high IOP, thought to be due to TM anomalies which hinder the flow of aqueous flow; these patients are classified as high tension POAG cases. IOP in some other POAG patients is within the statistically normal range, and these are classified as normal tension glaucoma (NTG) patients. Conversely, a diagnosis of ocular hypertension is made for subjects with consistently raised IOP without associated optic nerve damage. In addition to IOP, POAG patients are classified on the basis of age at the onset of symptoms. POAG usually involves individuals aged over 40 years (adult-onset POAG). In some patients, symptoms first appear between early childhood and the age of 40 years and these are sometimes distinguished as being affected with juvenile open angle glaucoma (JOAG).[19] Clinical features of the juvenile form are generally more severe.[20]

PACG is characterized by detecting a closed anterior chamber angle on gonioscopy which occurs due to contact between the peripheral iris and the posterior TM. The closure obstructs outflow of the aqueous humor from the eye. Contact between the iris and the TM may gradually damage TM function until it fails to keep pace with aqueous production, resulting in increased IOP. In cases referred to as "acute" primary angle closure, a rapid and sudden increase in pressure causes symptoms including severe pain, redness in the eyes, appearance of halos around bright lights and blurred vision. Primary angle closure suspect (PACS) and primary angle closure (PAC) refer to conditions wherein there are indications of angle closure, in the absence of glaucomatous optic neuropathy. It is well established that PACG is more common in oriental populations of the Far East Asia than in Caucasian and African residents.[16,21,22] In fact, it has been reported that PACG is responsible for most bilateral glaucoma-induced blindness in Singapore, China, and India.[23-26] Nevertheless, population based surveys showing that PACG is more prevalent than POAG have been published only from Mongolia and Myanmar.[6,7]

Secondary glaucomas are often associated with additional clinical presentations. IOP increases in all cases of secondary glaucoma. Pseudoexfoliation (PEX) syndrome is a prevalent disorder which and commonly accompanied by glaucoma.[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 occuring 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.[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,[11] this rate in various inbred populations for which data is available, such as India[32] and Saudi Arabia,[12] ranges from 1:1,200-1:3,300.[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.[8] 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.[2] 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.

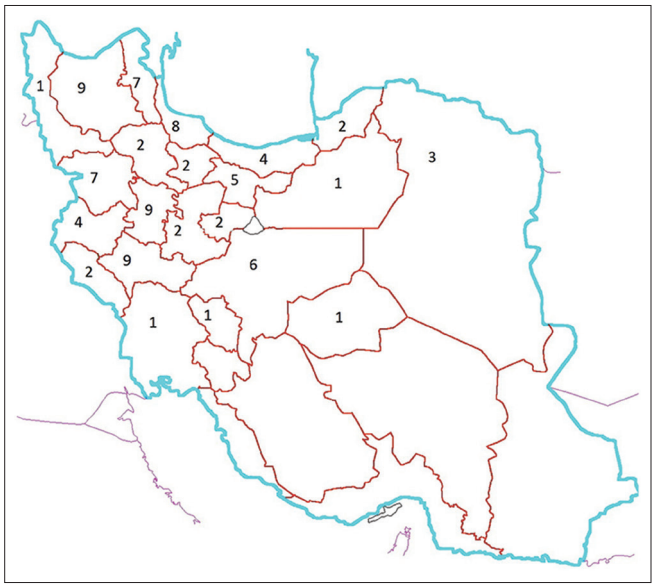

Figure 1. Geographic distribution of 88 Iranian PCG patients randomly recruited from national reference centers to which patients from throughout the country are referred. Origin of 16 individuals in the cohort of 104 patients was unknown.

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),[33] GLC3B (OMIM 600975),[34] and GLC3C (OMIM 613085).[35] The only gene associated with GLC3A is *CYP1B1* (OMIM 601771), identified through studying families of Turkish origin.[36] 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.[37] 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 Roma[14] and Saudi Arabia.[12] In contrast, *CYP1B1* mutations are observed in approximately 20% of Japanese patients.[38] 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.[38,39]

Screening for *CYP1B1* mutations in 104 Iranian PCG patients was performed in 2005-2006.[40] 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.[40] Furthermore, as already mentioned, the majority of patients are from the Northern and Northwestern

provinces of Iran suggesting that the expansion of *CYP1B1* mutations into the interior of the country has been limited.

CYP1B1 mutations were observed in nearly 70% of Iranian PCG patients. This high contribution of the gene to PCG prevalence in Iran is due to the combined effects of the high frequency of mutated *CYP1B1* alleles in the Iranian population and the high rate of consanguineous marriages.[40] The contribution of consanguineous marriages is evidenced by the fact that nearly 75% of familial cases harbored homozygous mutations. Screening 104 patients, nineteen disease-associated mutations and ten variations not associated with disease were observed of which ten and three were novel, respectively. At the time of the study in Iran when screenings in many populations had already been performed, only 70 *CYP1B1* variations had been reported; the number of known sequence variations significantly increased by thirteen novel mutations. 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.[41] 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 over 75% of *CYP1B1* mutations in Iranian patients. The frequency of these mutations prompted establishment of easy PCR assays for their detection.[40] 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.[42,43] 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.[44,45] Although cancer-associated alleles are associated with increased enzyme activity, glaucoma causing mutations generally disrupt this activity.[44-47]

PCG is reported to be more prevalent in male subjects than females.[48] 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.[49-52] Moreover, estradiol can act as a substrate for the CYP1B1 protein and mutation in the gene affects hydroxylation of this substrate.[53] Sex ratio comparisons between patients with and without *CYP1B1* mutations had been presented in only one report on Japanese patients.[48] 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.[54] 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.[55] Incomplete penetrance of some *CYP1B1* mutations was long before reported.[12,56-60] 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.[55] 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.[12] 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 out 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[8] and not counting those who had features suggestive of these disorders,[3] 57.1% of those examined who were non-penetrant[14] 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 and some of these individuals may develop signs at a later age.[55] These findings suggest that it may be more appropriate to emphasize that *CYP1B1* genotypes harboring two mutated alleles may exhibit variable expressivity rather than non-penetrance. The clinical implication of this observation is that seemingly unaffected relatives of patients with PCG, particularly those known to harbor *CYP1B1* mutations, should undergo regular ophthalmologic examination to allow early diagnosis.

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.[61,62] In one of the studies, a microarray-based assay for detection of *CYP1B1* mutations was set up.[62] 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.[37,56,58,63,64] 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.[65] 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.[19,66-68] 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.[19,20,69,70] The encoded protein is bipartite, containing a myosin-like NH2-terminal domain and an olfactomedin homology COOH-terminal domain.[71] 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.[61] 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.[20,69,70] 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.[61] The contributions of the two genes appeared to be independent, as no patient carried mutations in both genes.[61] Digenic etiology for POAG has been suggested by some other investigators.[59,60,72-74]

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.[75] *MYOC* mutations have occasionally been reported in PCG patients from other populations.[76,77] *MYOC* was screened in twenty Iranian PCG patients known not harbor *CYP1B1* mutations[75] 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.[78] 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.[79] *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.[80] 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.[81-83] 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.[84-86] LTBP2 is expressed in elastic tissues and associates with fibrillin-1 containing microfibrils.[87] 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 LTBPs 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.[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.[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.[80,90-92] However, mutations in *LTBP2* in megalocornea[93,94] and microspherophakia[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).[96] Specifically, among the PCG patients who were originally identified as carriers of *LTBP2* mutations, EL were also reported in a number of subjects.[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.[96] Thus, *LTBP2* mutations seem to be involved in various forms of syndromic glaucomas.[96,97]

Finally, *LTBP2* was considered as a candidate causative gene for POAG and pseudoexfoliation syndrome (PEX; OMIM 177650).[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.[99,100] Investigations on the potential role of other ECM proteins with respect to glaucoma are warranted.[101] The most recent findings suggest that even *CYP1B1* mutations may affect disease status by their effects on the ECM.[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.[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.[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.

ACKNOWLEDGEMENTS

Financial support was provided by the Ophthalmic Research Center at Shahid Beheshti University of Medical Sciences and the Iranian National Science Foundation.

REFERENCES

1. Ray K, Mukhopadhyay A, Acharya M. Recent advances in molecular genetics of glaucoma. *Mol Cell Biochem* 2003;253:223-231.
2. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002;86:238-242.
3. Thylefors B, Négrel AD. The global impact of glaucoma. *Bull World Health Organ* 1994;72:323-326.
4. Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol* 1996;80:389-393.
5. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;90:262-267.
6. Casson RJ, Newland HS, Muecke J, McGovern S, Abraham L, Shein WK, et al. Prevalence of glaucoma in rural Myanmar: The Meiktila Eye Study. *Br J Ophthalmol* 2007;91:710-714.
7. Foster PJ, Baasanhu J, Alsbirk PH, Munkhbayar D, Uranchimeg D, Johnson GJ. Glaucoma in Mongolia. A population-based survey in Hövsgöl province, northern Mongolia. *Arch Ophthalmol* 1996;114:1235-1241.
8. Pakravan M, Yazdani S, Javadi MA, Amini H, Behroozi Z, Ziaei H, et al. A population-based survey of the prevalence and types of glaucoma in central Iran: The Yazd eye study. *Ophthalmology* 2013;120:1977-1984.
9. Wang D, Huang W, Li Y, Zheng Y, Foster PJ, Congdon N, et al. Intraocular pressure, central corneal thickness, and glaucoma in Chinese adults: The liwan eye study. *Am J Ophthalmol* 2011;152:454-462.e1.
10. Wang YX, Xu L, Yang H, Jonas JB. Prevalence of glaucoma in North China: The Beijing Eye Study. *Am J Ophthalmol* 2010;150:917-924.
11. Sarfarazi M, Stoilov I, Schenkman JB. Genetics and biochemistry of primary congenital glaucoma. *Ophthalmol Clin North Am* 2003;16:543-554, vi.
12. Bejjani BA, Stockton DW, Lewis RA, Tomey KF, Dueker DK, Jabak M, et al. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. *Hum Mol Genet* 2000;9:367-374.
13. Levy J, Tessler Z, Tamir O, Lifshitz T. Primary congenital glaucoma. *Harefuah* 2004;143:876-880, 910.
14. Plásilová M, Stoilov I, Sarfarazi M, Kádasi L, Feráková E, Ferák V. Identification of a single ancestral CYP1B1 mutation in Slovak Gypsies (Roms) affected with primary congenital glaucoma. *J Med Genet* 1999;36:290-294.
15. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996;103:1661-1669.
16. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 1991;266:369-374.
17. Wensor MD, McCarty CA, Stanislavsky YL, Livingston PM, Taylor HR. The prevalence of glaucoma in the Melbourne Visual Impairment Project. *Ophthalmology* 1998;105:733-739.
18. Wolfs RC, Borger PH, Ramrattan RS, Klaver CC, Hulsman CA, Hofman A, et al. Changing views on open-angle glaucoma: Definitions and prevalences – The Rotterdam Study. *Invest Ophthalmol Vis Sci* 2000;41:3309-3321.
19. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, et al. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;275:668-670.
20. Wiggs JL, Lynch S, Ynagi G, Maselli M, Auguste J, Del Bono EA, et al. A genomewide scan identifies novel early-onset primary open-angle glaucoma loci on 9q22 and 20p12. *Am J Hum Genet* 2004;74:1314-1320.
21. Foster PJ, Johnson GJ. Glaucoma in China: How big is the problem? *Br J Ophthalmol* 2001;85:1277-1282.
22. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, et al. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 1992;99:1499-1504.
23. Dandona L, Dandona R, Mandal P, Srinivas M, John RK, McCarty CA, et al. Angle-closure glaucoma in an urban population in southern India. The Andhra Pradesh eye disease study. *Ophthalmology* 2000;107:1710-1716.
24. Foster PJ, Oen FT, Machin D, Ng TP, Devereux JG, Johnson GJ, et al. The prevalence of glaucoma in Chinese residents of Singapore: A cross-sectional population survey of the Tanjong Pagar district. *Arch Ophthalmol* 2000;118:1105-1111.
25. Jacob A, Thomas R, Koshi SP, Braganza A, Muliyil J. Prevalence of primary glaucoma in an urban south Indian population. *Indian J Ophthalmol* 1998;46:81-86.
26. Quigley HA, Congdon NG, Friedman DS. Glaucoma in China (and worldwide): Changes in established thinking will decrease preventable blindness. *Br J Ophthalmol* 2001;85:1271-1272.
27. Ritch R, Schlötzer-Schrehardt U. Exfoliation syndrome. *Surv Ophthalmol* 2001;45:265-315.
28. Farrar SM, Shields MB. Current concepts in pigmentary glaucoma. *Surv Ophthalmol* 1993;37:233-252.
29. Miller NR. Severe vision loss and neovascular glaucoma complicating superior ophthalmic vein approach to carotid-cavernous sinus fistula. *Am J Ophthalmol* 1998;125:883-884.
30. Panek WC, Holland GN, Lee DA, Christensen RE. Glaucoma in patients with uveitis. *Br J Ophthalmol* 1990;74:223-227.
31. Sihota R, Sood NN, Agarwal HC. Traumatic glaucoma. *Acta Ophthalmol Scand* 1995;73:252-254.
32. Dandona L, Williams JD, Williams BC, Rao GN. Population-based assessment of childhood blindness in southern India. *Arch Ophthalmol* 1998;116:545-546.
33. Sarfarazi M, Akarsu AN, Hossain A, Turacli ME, Aktan SG, Barsoum-Homsy M, et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (Buphthalmos) to 2p21 and evidence for genetic heterogeneity. *Genomics* 1995;30:171-177.
34. Akarsu AN, Turacli ME, Aktan SG, Barsoum-Homsy M, Chevrette L, Sayli BS, et al. A second locus (GLC3B) for primary congenital glaucoma (Buphthalmos) maps to the 1p36 region. *Hum Mol Genet* 1996;5:1199-1203.
35. Sarfarazi M, Stoilov I. The third genetic locus (GLC3C) for primary congenital glaucoma (PCG) maps to chromosome 14q24.3. *Am J Hum Genet* 2002;71:455.
36. Stoilov I, Akarsu AN, Sarfarazi M. Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. *Hum Mol Genet* 1997;6:641-647.
37. Nebert DW, Russell DW. Clinical importance of the cytochromes P450. *Lancet* 2002;360:1155-1162.
38. Mashima Y, Suzuki Y, Sergeev Y, Ohtake Y, Tanino T, Kimura I, et al. Novel cytochrome P4501B1 (CYP1B1) gene mutations in Japanese patients with primary congenital glaucoma. *Invest Ophthalmol Vis Sci* 2001;42:2211-2216.
39. Colomb E, Kaplan J, Garchon HJ. Novel cytochrome P450 1B1 (CYP1B1) mutations in patients with primary congenital glaucoma in France. *Hum Mutat* 2003;22:496.
40. Chitsazian F, Tusi BK, Elahi E, Saroei HA, Sanati MH, Yazdani S, et al. CYP1B1 mutation profile of Iranian primary congenital glaucoma patients and associated haplotypes. *J Mol Diagn* 2007;9:382-393.

41. Alavi A, Nafissi S, Rohani M, Zamani B, Sedighi B, Shamshiri H, et al. Genetic analysis and SOD1 mutation screening in Iranian amyotrophic lateral sclerosis patients. *Neurobiol Aging* 2013;34:1516.e1-8.
42. Sena DF, Finzi S, Rodgers K, Del Bono E, Haines JL, Wiggs JL. Founder mutations of CYP1B1 gene in patients with congenital glaucoma from the United States and Brazil. *J Med Genet* 2004;41:e6.
43. Stoilov I, Akarsu AN, Alozie I, Child A, Barsoum-Homsy M, Turacli ME, et al. Sequence analysis and homology modeling suggest that primary congenital glaucoma on 2p21 results from mutations disrupting either the hinge region or the conserved core structures of cytochrome P4501B1. *Am J Hum Genet* 1998;62:573-584.
44. Ko Y, Abel J, Harth V, Bröde P, Antony C, Donat S, et al. Association of CYP1B1 codon 432 mutant allele in head and neck squamous cell cancer is reflected by somatic mutations of p53 in tumor tissue. *Cancer Res* 2001;61:4398-4404.
45. Peter Guengerich F, Chun YJ, Kim D, Gillam EM, Shimada T. Cytochrome P450 1B1: A target for inhibition in anticarcinogenesis strategies. *Mutat Res* 2003;523-524:173-182.
46. Fritsche E, Brüning T, Jonkmanns C, Ko Y, Bolt HM, Abel J. Detection of cytochrome P450 1B1 Bfr I polymorphism: Genotype distribution in healthy German individuals and in patients with colorectal carcinoma. *Pharmacogenetics* 1999;9:405-408.
47. McGrath M, Hankinson SE, Arbeitman L, Colditz GA, Hunter DJ, De Vivo I. Cytochrome P450 1B1 and catechol-O-methyltransferase polymorphisms and endometrial cancer susceptibility. *Carcinogenesis* 2004;25:559-565.
48. Ohtake Y, Tanino T, Suzuki Y, Miyata H, Taomoto M, Azuma N, et al. Phenotype of cytochrome P4501B1 gene (CYP1B1) mutations in Japanese patients with primary congenital glaucoma. *Br J Ophthalmol* 2003;87:302-304.
49. Chang JT, Chang H, Chen PH, Lin SL, Lin P. Requirement of aryl hydrocarbon receptor overexpression for CYP1B1 up-regulation and cell growth in human lung adenocarcinomas. *Clin Cancer Res* 2007;13:38-45.
50. Trombino AF, Near RI, Matulka RA, Yang S, Hafer LJ, Toselli PA, et al. Expression of the aryl hydrocarbon receptor/transcription factor (AhR) and AhR-regulated CYP1 gene transcripts in a rat model of mammary tumorigenesis. *Breast Cancer Res Treat* 2000;63:117-131.
51. Villard PH, Sampol E, Elkaim JL, Puyoou F, Casanova D, Sérée E, et al. Increase of CYP1B1 transcription in human keratinocytes and HaCaT cells after UV-B exposure. *Toxicol Appl Pharmacol* 2002;178:137-143.
52. Yang X, Solomon S, Fraser LR, Trombino AF, Liu D, Sonenshein GE, et al. Constitutive regulation of CYP1B1 by the aryl hydrocarbon receptor (AhR) in pre-malignant and malignant mammary tissue. *J Cell Biochem* 2008;104:402-417.
53. Jansson I, Stoilov I, Sarfarazi M, Schenkman JB. Effect of two mutations of human CYP1B1, G61E and R469W, on stability and endogenous steroid substrate metabolism. *Pharmacogenetics* 2001;11:793-801.
54. Suri F, Chitsazian F, Khoramian-Tusi B, Amini H, Yazdani S, Nilforooshan N, et al. Sex bias in primary congenital glaucoma patients with and without CYP1B1 mutations. *J Ophthalmic Vis Res* 2009;4:75-78.
55. Suri F, Yazdani S, Narooie-Nejhad M, Zargar SJ, Paylakhi SH, Zeinali S, et al. Variable expressivity and high penetrance of CYP1B1 mutations associated with primary congenital glaucoma. *Ophthalmology* 2009;116:2101-2109.
56. Acharya M, Mookherjee S, Bhattacharjee A, Bandyopadhyay AK, Daulat Thakur SK, Bhaduri G, et al. Primary role of CYP1B1 in Indian juvenile-onset POAG patients. *Mol Vis* 2006;12:399-404.
57. Kumar A, Basavaraj MG, Gupta SK, Qamar I, Ali AM, Bajaj V, et al. Role of CYP1B1, MYOC, OPTN, and OPTC genes in adult-onset primary open-angle glaucoma: Predominance of CYP1B1 mutations in Indian patients. *Mol Vis* 2007;13:667-676.
58. López-Garrido MP, Sánchez-Sánchez F, López-Martínez F, Aroca-Aguilar JD, Blanco-Marchite C, Coca-Prados M, et al. Heterozygous CYP1B1 gene mutations in Spanish patients with primary open-angle glaucoma. *Mol Vis* 2006;12:748-755.
59. Melki R, Colomb E, Lefort N, Brézin AP, Garchon HJ. CYP1B1 mutations in French patients with early-onset primary open-angle glaucoma. *J Med Genet* 2004;41:647-651.
60. Vincent AL, Billingsley G, Buys Y, Levin AV, Priston M, Trope G, et al. Digenic inheritance of early-onset glaucoma: CYP1B1, a potential modifier gene. *Am J Hum Genet* 2002;70:448-460.
61. Bayat B, Yazdani S, Alavi A, Chiani M, Chitsazian F, Tusi BK, et al. Contributions of MYOC and CYP1B1 mutations to JOAG. *Mol Vis* 2008;14:508-517.
62. Suri F, Kalhor R, Zargar SJ, Nilforooshan N, Yazdani S, Nezari H, et al. Screening of common CYP1B1 mutations in Iranian POAG patients using a microarray-based PrASE protocol. *Mol Vis* 2008;14:2349-2356.
63. Chakrabarti S, Kaur K, Komatireddy S, Acharya M, Devi KR, Mukhopadhyay A, et al. Gln48His is the prevalent myocilin mutation in primary open angle and primary congenital glaucoma phenotypes in India. *Mol Vis* 2005;11:111-113.
64. Stoilov I, Jansson I, Sarfarazi M, Schenkman JB. Roles of cytochrome p450 in development. *Drug Metabol Drug Interact* 2001;18:33-55.
65. Fan BJ, Wang DY, Lam DS, Pang CP. Gene mapping for primary open angle glaucoma. *Clin Biochem* 2006;39:249-258.
66. Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, Liebmann J, et al. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. *Hum Mol Genet* 2005;14:725-733.
67. Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 2002;295:1077-1079.
68. Pasutto F, Matsumoto T, Mardin CY, Sticht H, Brandstätter JH, Michels-Rautenstrauss K, et al. Heterozygous NTF4 mutations impairing neurotrophin-4 signaling in patients with primary open-angle glaucoma. *Am J Hum Genet* 2009;85:447-456.
69. Alward WL, Fingert JH, Coote MA, Johnson AT, Lerner SF, Junqua D, et al. Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). *N Engl J Med* 1998;338:1022-1027.
70. Fingert JH, Héon E, Liebmann JM, Yamamoto T, Craig JE, Rait J, et al. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum Mol Genet* 1999;8:899-905.
71. Tamm ER. Myocilin and glaucoma: Facts and ideas. *Prog Retin Eye Res* 2002;21:395-428.
72. Baird PN, Foote SJ, Mackey DA, Craig J, Speed TP, Bureau A. Evidence for a novel glaucoma locus at chromosome 3p21-22. *Hum Genet* 2005;117:249-257.
73. Copin B, Brézin AP, Valtot F, Dascotte JC, Béchetoille A, Garchon HJ. Apolipoprotein E-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am J Hum Genet* 2002;70:1575-1581.
74. Craig JE, Baird PN, Healey DL, McNaught AI, McCartney PJ, Rait JL, et al. Evidence for genetic heterogeneity within eight glaucoma families, with the GLC1A Gln368STOP mutation being an important phenotypic modifier. *Ophthalmology* 2001;108:1607-1620.
75. Elahi E, Narooie-Nejhad M, Suri F, Yazdani S. Myocilin mutations are not a major cause of primary congenital glaucoma in Iranian patients. *J Ophthalmic Vis Res* 2010;5:101-104.
76. Kaur K, Reddy AB, Mukhopadhyay A, Mandal AK, Hasnain SE, Ray K, et al. Myocilin gene implicated in primary congenital glaucoma. *Clin Genet* 2005;67:335-340.

77. Zhuo YH, Wang M, Wei YT, Huang YL, Ge J. Analysis of MYOC gene mutation in a Chinese glaucoma family with primary open-angle glaucoma and primary congenital glaucoma. *Chin Med J (Engl)* 2006;119:1210-1214.
78. Narooie-Nejad M, Paylakhi SH, Shojaee S, Fazlali Z, Rezaei Kanavi M, Nilforushan N, et al. Loss of function mutations in the gene encoding latent transforming growth factor beta binding protein 2, LTBP2, cause primary congenital glaucoma. *Hum Mol Genet* 2009;18:3969-3977.
79. Ali M, McKibbin M, Booth A, Parry DA, Jain P, Riazuddin SA, et al. Null mutations in LTBP2 cause primary congenital glaucoma. *Am J Hum Genet* 2009;84:664-671.
80. Sharafieh R, Child AH, Khaw PT, Fleck B, Sarfarazi M. LTBP2 gene analysis in the GLC3C-linked family and 94 CYP1B1-negative cases with primary congenital glaucoma. *Ophthalmic Genet* 2013;34:14-20.
81. Hyytiäinen M, Penttinen C, Keski-Oja J. Latent TGF-beta binding proteins: Extracellular matrix association and roles in TGF-beta activation. *Crit Rev Clin Lab Sci* 2004;41:233-264.
82. Rifkin DB. Latent transforming growth factor-beta (TGF-beta) binding proteins: Orchestrators of TGF-beta availability. *J Biol Chem* 2005;280:7409-7412.
83. Sinha S, Heagerty AM, Shuttleworth CA, Kielty CM. Expression of latent TGF-beta binding proteins and association with TGF-beta 1 and fibrillin-1 following arterial injury. *Cardiovasc Res* 2002;53:971-983.
84. Hyytiäinen M, Keski-Oja J. Latent TGF-beta binding protein LTBP-2 decreases fibroblast adhesion to fibronectin. *J Cell Biol* 2003;163:1363-1374.
85. Sinha S, Nevett C, Shuttleworth CA, Kielty CM. Cellular and extracellular biology of the latent transforming growth factor-beta binding proteins. *Matrix Biol* 1998;17:529-545.
86. Vehviläinen P, Hyytiäinen M, Keski-Oja J. Latent transforming growth factor-beta-binding protein 2 is an adhesion protein for melanoma cells. *J Biol Chem* 2003;278:24705-24713.
87. Gibson MA, Hatzinikolas G, Davis EC, Baker E, Sutherland GR, Mecham RP. Bovine latent transforming growth factor beta 1-binding protein 2: Molecular cloning, identification of tissue isoforms, and immunolocalization to elastin-associated microfibrils. *Mol Cell Biol* 1995;15:6932-6942.
88. Saharinen J, Keski-Oja J. Specific sequence motif of 8-Cys repeats of TGF-beta binding proteins, LTBPs, creates a hydrophobic interaction surface for binding of small latent TGF-beta. *Mol Biol Cell* 2000;11:2691-2704.
89. Johnson M. What controls aqueous humour outflow resistance? *Exp Eye Res* 2006;82:545-557.
90. Abu-Amero KK, Osman EA, Mousa A, Wheeler J, Whigham B, Allingham RR, et al. Screening of CYP1B1 and LTBP2 genes in Saudi families with primary congenital glaucoma: Genotype-phenotype correlation. *Mol Vis* 2011;17:2911-2919.
91. Lim SH, Tran-Viet KN, Yanovitch TL, Freedman SF, Klemm T, Call W, et al. CYP1B1, MYOC, and LTBP2 mutations in primary congenital glaucoma patients in the United States. *Am J Ophthalmol* 2013;155:508-517.e5.
92. Mohanty K, Tanwar M, Dada R, Dada T. Screening of the LTBP2 gene in a north Indian population with primary congenital glaucoma. *Mol Vis* 2013;19:78-84.
93. Désir J, Sznajer Y, Depasse F, Roulez F, Schrooyen M, Meire F, et al. LTBP2 null mutations in an autosomal recessive ocular syndrome with megalocornea, spherophakia, and secondary glaucoma. *Eur J Hum Genet* 2010;18:761-767.
94. Khan AO, Aldahmesh MA, Alkuraya FS. Congenital megalocornea with zonular weakness and childhood lens-related secondary glaucoma-a distinct phenotype caused by recessive LTBP2 mutations. *Mol Vis* 2011;17:2570-2579.
95. Kumar A, Duvvari MR, Prabhakaran VC, Shetty JS, Murthy GJ, Blanton SH. A homozygous mutation in LTBP2 causes isolated microspherophakia. *Hum Genet* 2010;128:365-371.
96. Haji-Seyed-Javadi R, Jelodari-Mamaghani S, Paylakhi SH, Yazdani S, Nilforushan N, Fan JB, et al. LTBP2 mutations cause Weill-Marchesani and Weill-Marchesani-like syndrome and affect disruptions in the extracellular matrix. *Hum Mutat* 2012;33:1182-1187.
97. Azmanov DN, Dimitrova S, Florez L, Cherninkova S, Draganov D, Morar B, et al. LTBP2 and CYP1B1 mutations and associated ocular phenotypes in the Roma/Gypsy founder population. *Eur J Hum Genet* 2011;19:326-333.
98. Jelodari-Mamaghani S, Haji-Seyed-Javadi R, Suri F, Nilforushan N, Yazdani S, Kamyab K, et al. Contribution of the latent transforming growth factor-ß binding protein 2 gene to etiology of primary open angle glaucoma and pseudoexfoliation syndrome. *Mol Vis* 2013;19:333-347.
99. Baldwin AK, Simpson A, Steer R, Cain SA, Kielty CM. Elastic fibres in health and disease. *Expert Rev Mol Med* 2013;15:e8.
100. Sideek MA, Menz C, Parsi MK, Gibson MA. LTBP-2 competes with tropoelastin for binding to fibulin-5 and heparin, and is a negative modulator of elastinogenesis. *Matrix Biol* 2014;34:114-123.
101. Kuchtey J, Olson LM, Rinkoski T, Mackay EO, Iverson TM, Gelatt KN, et al. Mapping of the disease locus and identification of ADAMTS10 as a candidate gene in a canine model of primary open angle glaucoma. *PLoS Genet* 2011;7:e1001306.
102. Zhao Y, Wang S, Sorenson CM, Teixeira L, Dubielzig RR, Peters DM, et al. Cyp1b1 mediates periostin regulation of trabecular meshwork development by suppression of oxidative stress. *Mol Cell Biol* 2013;33:4225-4240.
103. Narooie-Nejad M, Chitsazian F, Khoramian Tusi B, Mousavi F, Houshmand M, Rohani MR, et al. Genotyping results of Iranian PCG families suggests one or more PCG locus other than GCL3A, GCL3B, and GCL3C exist. *Mol Vis* 2009;15:2155-2161.
104. Paylakhi SH, Fan JB, Mehrabian M, Sadeghizadeh M, Yazdani S, Katanforoush A, et al. Effect of PITX2 knockdown on transcriptome of primary human trabecular meshwork cell cultures. *Mol Vis* 2011;17:1209-1221.
105. Paylakhi SH, Moazzeni H, Yazdani S, Rassouli P, Arefian E, Jaberi E, et al. FOXC1 in human trabecular meshwork cells is involved in regulatory pathway that includes miR-204, MEIS2, and ITGß1. *Exp Eye Res* 2013;111:112-121.
106. Paylakhi SH, Yazdani S, April C, Fan JB, Moazzeni H, Ronaghi M, et al. Non-housekeeping genes expressed in human trabecular meshwork cell cultures. *Mol Vis* 2012;18:241-254.

How to cite this article: Suri F, Yazdani S, Elahi E. Glaucoma in Iran and contributions of studies in Iran to the understanding of the etiology of glaucoma. J Ophthalmic Vis Res 2015;10:68-76.

Source of Support: Financial support was provided by the Ophthalmic Research Center at Shahid Beheshti University of Medical Sciences and the Iranian National Science Foundation. **Conflict of Interest:** None declared.