The clinical entity collectively known as glaucoma is a very specific optic neuropathy that affects individuals with various degrees of ocular complications and even with greater degrees of genetic heterogeneity.\[^{[1,2]}\] Although the very first genetic contribution to this group of eye disorders was described over 50 years ago,\[^{[3]}\] it took another 30 years before the first molecular studies of this condition were undertaken.\[^{[4,5]}\] The significant challenge in understanding the basic underlying genes, proteins, biochemical and molecular pathways that are involved in this group of disorders is due to many difficulties in accurate clinical diagnosis, classification, primary vs. secondary disease, as well as various degrees of both clinical and genetic heterogeneity.\[^{[6,7]}\] Furthermore, lack of suitable large families, extreme ages of onset, racial ethnicity and many other limiting factors compound our ability to find the majority of defective genes and proteins for this ocular condition.

It is against this background that finding or even relating certain mutations in one or more genes and their possible contributions to a specific form of glaucoma would be a significant addition to our understanding of the molecular basis of this condition. One such study is the current paper by Safari et al\[^{[8]}\] in which they studied the possible role of the \textit{LTBP2} gene in the etiology of primary angle closure glaucoma (PACG) as well as a single case with both PACG and pseudoexfoliation glaucoma (PXFG). Although the \textit{LTBP2} gene was originally reported to be the cause of primary congenital glaucoma (PCG) in certain Pakistani\[^{[9]}\] and Iranian\[^{[10]}\] families, subsequent studies by other investigators failed to confirm this observation in a group of American\[^{[11,12]}\] Turkish,\[^{[12]}\] English,\[^{[12]}\] Indian\[^{[13]}\] and Saudi Arabian\[^{[14]}\] PCG subjects. It is likely that the congenital glaucoma nature of patients reported in the earlier studies\[^{[9,10]}\] were in fact of a secondary nature, as those patients had a series of other ocular and non-ocular complications. Moreover, many other \textit{LTBP2} mutations have now been reported in megalocornea,\[^{[15]}\] spherophakia,\[^{[15]}\] microspherophakia,\[^{[15,16]}\] ectopia lentis\[^{[17]}\] and Weill-Marchesani syndrome.\[^{[18]}\] Interestingly, often these disorders are reported with secondary forms of glaucoma. Also, it has recently been reported that other \textit{LTBP2} sequence variations may contribute to the etiology of primary open angle glaucoma (POAG) and PXFG.\[^{[19]}\]

In the current paper by Safari et al\[^{[8]}\] the authors investigated the possibility of \textit{LTBP2} involvement in a group of PACG subjects. They sequenced a total of 54 PACG subjects for this gene and identified a number of interesting sequence variations. After careful scrutiny of the observed DNA variations, they concluded that 2 of the original 24 sequence changes may contribute to the disease status of one subject with PACG and another with both PACG and PXFG (Q1417R and G1660W, respectively). This is the first systematic investigation of \textit{LTBP2} gene mutations in a group of PACG subjects.

Although this is a very interesting report, one has to note that the same two mutations of Q1417R and G1660W are also identified in the South Asian subjects, though no specific clinical manifestation has been reported for these individuals. For Q1417R (rs137854863), the ExAC Browser\[^{[20]}\] reports 6 out of 16,506 South Asians and one out of 66,148 Europeans to have the same mutation. For G1660W (rs147223742), the comparable frequencies are 64 out of 16,512 South Asians and 1 out of 902 subjects from other unspecified populations. It is very interesting that these two mutations are reported primarily in South Asian populations with a known high frequency of PACG, as compared to other regions. Therefore, it is likely that the two mutations reported by Sarafi et al\[^{[8]}\] are possibly involved in the PACG phenotype. However, ultimate proof for such observation can only be demonstrated by proper functional studies of these two mutations.

It is equally likely that \textit{LTBP2} mutations will be reported for many other ocular and non-ocular conditions. Experience from exome sequencing data on over 60,000 individuals\[^{[20]}\] now clearly shows that many such individual mutations are present in other clinical entities and in other ethnically related individuals. Furthermore, as during exome or whole-genome sequencing over 25,000 genes are being simultaneously sequenced, for any given subject, hundreds of individual unique and previously unreported DNA variations are often observed. Therefore, the task of relating each of these uniquely observed DNA variations to a
specific clinical phenotype of an individual remains a significant challenge. Different uniquely-identified gene mutations are logically expected to have an ending clinical expression on a given phenotype. However, many of such clinical entities may have not even been discovered as yet or at least not identified in the person that has been sequenced. Therefore, presence of a single mutation in one or more affected subject is no longer indicative of its being specific and disease causing; the biological significance of such specific mutations and their individual causative nature may have to be shown first. This is even more relevant when a specific mutation is being reported for the first time in a new clinical entity. However, if a significant number of individuals show one or more mutations in the same gene and for the same new phenotype, then the likelihood for involvement of that gene in the etiology of that condition becomes increasingly higher.

Over the last 25 years a variety of glaucoma families and sporadic cases have been investigated by various molecular genetics techniques but only a handful of causative genes and a number of other specific gene associations have been identified.\textsuperscript{[21]} The first two identified glaucoma genes, i.e. MYOC\textsuperscript{[22]} and CYP1B1,\textsuperscript{[23]} have been extensively studied in juvenile-onset and congenital cases around the world and well-proven to be involved in a significant proportion of subjects.\textsuperscript{[21]} Moreover, these two genes have also been reported not only in glaucoma, but also in a number of other ocular disorders.\textsuperscript{[24‑27]} This is indicative of the fact that mutations in one specific gene may be responsible for various subtypes of a common clinical entity or completely different unrelated disorders. The study by Safari et al\textsuperscript{[8]} was an investigative approach to the same common goal.

Although a number of gene mutations have been identified for other glaucoma subtypes (POAG, NTG, PACG, PXFG)\textsuperscript{[20]} and similarly, a group of other common polymorphic DNA markers have been shown to be associated with a specific glaucoma subtype,\textsuperscript{[21]} none of these as yet has been identified as a single gene or an association that would be responsible for the majority of a primary form of a given glaucoma subtype. This in turn confirms the fact that a very large number of genes (perhaps several hundred) may be involved in the etiology of various forms of glaucoma and more specifically for different forms of POAG and other types of secondary glaucoma.

Given our limited success in understanding the molecular and biochemical pathways that lead to primary forms of various glaucoma subtypes, any specific contribution that may shed light on such challenging studies will be a welcome addition toward this common goal. Given the anticipated large number of genes that are expected to be involved in various forms of glaucoma, it may be many more years of extensive molecular investigation before we can have a better understanding of this devastating clinical phenotype that lead to blindness in many people around the world.

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