PRESENT WORK
Glaucoma (POAG) has been termed as the ‘Silent blinder’ because it is mostly asymptomatic (at least till the later stages of the disease). Many of the patients are unaware that they may be losing vision though their IOPs are normal. It is also a bilateral disease i.e., it can affect both the eyes. It can affect all age groups with the aged being at an increased risk of being affected. The loss of vision that results is irreversible. The life style of an individual is drastically affected due to the disease features such as loss of peripheral vision, depth perception and contrast sensitivity (Coleman, 1999).

The prevalence of glaucoma has been estimated to be high with POAG being the major type of glaucoma. Glaucoma is a preventable disease i.e., loss of vision can be prevented on early detection. The major difficulty then is the timely diagnosis of the disease (Stone et al., 1997). Identification of specific disease causing gene(s)/loci/mutations in gene(s) involved will make it possible to identify individuals at high risk of developing POAG (i.e., relatives of glaucoma probands) before loss of vision occurs and to direct them to therapy.

Mutation screening before the onset of the disease (POAG) will become an important clinical diagnostic tool (Richards et al., 1998). Identification of additional mutations in TIGR and/or other glaucoma gene(s) involved may help in the classification of glaucoma based on the underlying cause of the disease rather than on the age of onset. Alward et al. (1998a) have reported the prevalence of GLC1A associated glaucoma to be high.

Two reasons to study the gene for the presence of disease causing mutations are: a) to implicate the gene as a cause of a particular disease, b) to identify as many mutations as possible for the purpose of understanding the genotype-phenotype relationships, comparing mutation profiles in different populations or constructing practical genetic tests for clinical use (Fingert et al., 1999). This was the idea behind the present study i.e., to find out if the TIGR/MYOC gene was involved in sporadic
POAG cases on Indian origin and also to find out the mutations and to compare the genotype and phenotype relationship to that reported in other populations. This was done because of the fact that as far as our literature survey was carried out during the formulation of this work, there was no report of any such genetic analysis having been carried out in Indian populations.

Further, taking into account the simple exon-intron organization of the TIGR gene and the concentration of the pathogenic mutations in the 3rd exon, the search for mutations should be greatly simplified and this should facilitate the identification of at-risk individuals and directing them to effective treatment (Adam et al., 1997).

It has been observed that 27 of 30 mutations were present on exon III and of the remaining most of them were on the initial part of the exon I (two of three) (Fingert et al., 1999). The other important aspect of the initial part of exon I was the observation of the Arg46Stop mutation which resulted in truncated protein of just 45 amino acids and this was observed in the homozygous state and was associated with a severe phenotype in an Asian (Korean) patient (Yoon et al., 1999). Thus these two regions, being the most vulnerable part of the TIGR/MYOC gene for mutations were the regions of interest for the present work.

**Aim:**

The aim of the present study was to screen the 'Hot Spot' region of the TIGR/MYOC gene (namely exon III and the initial part of exon I [-36 to c. 212]) for mutations in randomly selected POAG patients from two populations: a) rural (Kanyakumari district) and b) urban (Chennai) populations of Tamil Nadu state of India. The selection of patients was random and not biased in any way. Further, the mutations and the mutation frequency were to be compared with that reported from other populations around the world.
Objectives:

- To create awareness amongst the patients (and family members) with regard to the disease entity called POAG. This was seen to be essential as most of the individuals were unaware of the important facts.

- To screen the region of interest of the TIGR/MYOC gene for mutations using PCR-SSCP methodology in 200 randomly selected patients and age and sex matched controls, so that the risk factor can be determined among these patients/families.

- To study the type(s) of mutation(s) present (if any) and to analyse the characteristics of the mutant sequences (DNA and amino acid sequences) and to enlighten its role in the causation of POAG.

- Comparison of the types of mutations and the mutation rate with that observed in other populations from all over the world, including the recent reports from Indian patients. Further, comparison of the mutations observed in the two populations involved in the present study.

- To establish the genotype-phenotype relationship to the best possible extent with the available clinical data and to compare it to the earlier reports.

- Follow-up studies especially counseling to the families of patients with a mutation in the TIGR/MYOC gene.

Identification of the genes and the mutations involved will also increase our understanding of the disease, leading to development of more effective treatment regimens (Alward, 2000). Vasconcellos et al. (2000) reported that, it is reasonable that the association of MYOC gene and POAG/JOAG may be used
as a screening test, allowing early treatment and possibly avoiding the disease related damage. Further, it may be possible to modify the gene in order to inhibit phenotypic changes induced by mutations. For this, the mutations of MYOC have to be characterized. Also the importance of the above mentioned Arg46Stop mutation is seen by the observation of the same homozygous mutation in normal individuals (Lam et al., 2000) thereby reiterating the presence of other mechanisms apart from haploinsufficiency to play a role in disease causation.

In India, most of the patients and their relatives are unaware of the detrimental effects of glaucoma, the fact that glaucoma is a hereditary disease and also that this disease can be prevented if diagnosed early. The situation in India was clearly stated in an epidemiological survey by Dandona et al. (2000), “..... the vast majority of the persons with glaucoma were undiagnosed in this population and a large proportion of those having definite POAG already had severe glaucomatous damage.....”. This was further elaborated in their later article as “The examination techniques required to detect glaucoma early are not practiced commonly in India, better training of eye care providers in India has to be initiated if blindness due to glaucoma has to be prevented” (Dandona et al., 2001). Further, the above said has been emphasised as: “the most effective way to diagnose it is when the primary care physician is aware of the risk factors and the need for a complete eye examination......” (Coleman and Brigatti, 2001).