

## Intronic variants of TGIF1 (variant-008) have a potential to associate with high myopia in ethnic kashmiri population

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Myopia is the most common eye disorder which remains a significant ocular health problem associated with increased risk of visual loss around the world (Fredrick, 2002). High myopia considered as more advanced type of myopia may lead to degenerative changes in the eye (degenerative myopia) leading to blindness and often afflicts, people earlier in life when they may still be active professionally (Jacobia *et al.*, 2005). The wide spectrum of myopia-associated disorders strongly argues for an etiologically heterogeneous nature of myopic refractive errors, where multiple factors with genetic and epigenetic effects contribute at different stages during development (Feldkammer and Schaeffel, 2003). The concept that environmental factors influence ocular development has been well established in epidemiological and experimental animal studies (Saw *et al.*, 2002). Despite recognized importance of visual experience in the development of myopia there is abundant evidence for genetic factors determining refractive development (Francois, 1961). First, higher myopia prevalence in developed Asian countries compared to the western world suggests a genetic susceptibility to myopia development. Further, myopic parents are more likely to give rise to offsprings with myopia than non-myopic parents (Goldschmidt, 1981). Linkage studies have mapped at least eight loci (MYP1, MYP2, MYP3, MYP4, MYP5, MYP11, MYP12 and MYP13) responsible for high myopia with Mendelian inheritance (Young, 2004). TGIF1 is expressed in sclera, retina, cornea, and optic nerve and competitively inhibits binding of the retinoic acid receptor to a retinoid-responsive promoter (Young *et al.*, 1998a).

It is possible that mutations in TGIF1 gene may alter its

function and hence the phase of eye development, thus making it a potential candidate gene to study high myopia. One study has disregarded TGIF1 as potential contributor to the disease (Scavello *et al.*, 2004) although it has been associated with high myopia wherein six single nucleotide polymorphisms (SNPs) appear to associate with the disease in a Chinese cohort (Lam *et al.*, 2003). However, association could not be replicated in a second Chinese case control study of high myopia individuals (Li *et al.*, 2003). Another study with Japanese subjects failed to identify association of this gene with high myopia (Hasumi *et al.*, 2006). This discrepancy has largely been attributed to ethnic variations in the genetics of this disease.

Kashmiri population being a pure ethnic group provides an ideal scenario to substantiate the contribution of TGIF1 (if any) in the development of high myopia. 52 high myopic and 18 normal controls of Kashmiri ethnicity were recruited for TGIF1 polymorphism studies. DNA was isolated from venous blood samples and amplified by polymerase chain reaction. PCR products were purified and screened for mutations by heteroduplex assay employing CSGE (conformation sensitive gel electrophoresis). Samples showing differential mobility on CSGE were sent out for commercial sequencing. Sequences were analysed using different softwares like Chromas pro and Cluatal X2. After analyzing the data, we observed three novel and adjacent intronic SNPs with potential to have a bearing on the etiology of the disease.

Mutational screening of TGIF1 (variant-008, Transcript ID-ENST00000552383) in 52 high myopia affected and 18