“Studies on Crystallin Protein Mutations in congenital cataract”

Introduction:

Cataracts are the most common cause of blindness worldwide. In simple terms it means opacity (cloudiness) in the lens of the eye. Lens is the portion behind the pupil responsible for focussing light so as to enable clear vision. Congenital or Inherited cataract is reported to be a clinically and genetically heterogeneous disease that most often shows autosomal dominant inheritance.

In cataract the crystallin lens, the part of eye responsible for clear vision loses its transparency and the refractive index of the lens differs significantly over distances. Changes in lens cell structure, changes in lens protein constituents, or both lead to the variation in the refractive index over these distances. The lens micro-architecture gets altered which may lead to loss of vision in cataract.

Cataracts can be divided into two types,

1. Developmental or Congenital cataract wherein genetic factors affect the normal development of the lens.
2. Degenerative cataract and senile which are associated with radiation or systemic diseases.

Worldwide it has been reported that cataracts are a significant cause of treatable blindness in infants accounting for 12 to 15% of visually impaired children in countries as diverse as Finland and India. An estimate of prevalence between 1 and 13 cases per 10,000 births has been reported in population based studies. Early childhood cataracts with a frequency of 30 cases in 100,000 births with further 10 cases being detected by the age of 15 years (mainly as dominant forms) has been reported in developed countries. These rates could be higher in developing countries because of rubella infections and consanguinity (for the recessive forms) (Krishnamurthy et al 2008); Most of the cases are reported to be of Congenital type meaning the normal development of lens is affected by genetic factors.

Congenital cataract has been reported as an important cause of visual impairment in children. Clinically featuring diverse etiologies meaning to be occurring either isolated or associated with other ocular diseases or as part of a multisystemic disorder.
Globally, an incidence of 1–6 per 10,000 live births has been reported. Cataract has been reported to be contributing to 15% childhood blindness in one of the southern states of India as per a population-based estimate. Approximately 50% of childhood cataracts have been reported to be genetic the majority being autosomal dominant. Phenotypes have been described mainly based on the physical appearance and the site of occurrence of the opacity. Clinical and genetic heterogeneity of congenital cataracts has been well reported (Sathiyavedu et al 2004).

Congenital cataracts have been classified according to morphologic type. Central cataracts include nuclear, lamellar, cortical, sutural, pulverulent, cerulean, and coralliform cataracts. Polar cataracts can either be anterior (anterior polar, anterior pyramidal, and anterior subcapsular) or posterior posterior subcapsular, posterior lenticonus, posterior fetal vascular (PFV). Congenital cataract has been reported to be one of the first autosomal diseases to be genetically mapped in humans (Krishnamurthy et al 2008).

Studies on congenital hereditary cataract have been implicated to a variety of lens membrane proteins, transcription factors, and major structural proteins of the lens cytosol, namely the soluble $\alpha$, $\beta$, and $\gamma$ crystallins. Study of the mutations in crystallins is interesting and convenient as it is possible to clone, express, and isolate the mutant proteins whose conformational and other properties can be compared with those of the normal (wild-type) molecules. Such a study would provide insights into the molecular phenotypic aspects of lens opacification and causes of cataract (Venu et al 2006).

The, $\beta$, and $\gamma$ crystallin genes express water soluble proteins that play a critical role in maintaining the clarity of lens.

Most inherited cataracts have been shown to be of autosomal dominant inheritance type with complete penetrance with highly variable expressivity.

**Crystallin genes**, encoding major structural proteins in the lens, are obvious candidate genes for cataracts. Five reports of mutations in mammalian crystallin genes associated with hereditary cataracts have been published. Chambers and Russell found an in-frame deletion of 12 nucleotides in the bB2-crystallin gene that was associated with inherited autosomal dominant cataract in the Philly mouse. Litt et al described a chain termination mutation in the human bB2-crystallin gene that was associated with autosomal dominant cerulean cataract. In the human autosomal dominant Coppock-like cataract, activation of a g-crystallin pseudogene by a cluster of sequence changes in the promoter region produces a 10-fold increase in the expression of mRNA encoding a truncated polypeptide. A splice site mutation in the g-
crystallin gene causes an autosomal dominant cataract in the guinea pig, and a single nucleotide deletion in the gE-crystallin gene of the Elo mouse mutant causes autosomal dominant cataract and microophthalmia.

Congenital cataracts are a common major abnormality of the eye that frequently cause blindness in infants. At least a third of all cases are familial, autosomal dominant congenital cataract (ADCC) is reported to be the most common familial form in the Western world. Twelve distinct loci in humans have been identified for 10 phenotypically distinct forms of ADCC (Litt et al 1997).

Pediatric cataract is the most common form of treatable childhood blindness and is both clinically and genetically heterogeneous. Autosomal dominant and recessive forms of cataract have been reported to be caused by mutations in 22 different genes so far. Of the cataract mutations reported to date, about half the mutations occur in crystallins, a quarter of the mutations in connexins, and the remainder is evenly divided between intrinsic membrane proteins, intermediate filament proteins, and transcription factors (Devi et al 2008).

**This study is aimed at identification of the spectrum and frequency of crystallin gene mutations in cataractous children in Maharashtrian population.**

Crystallins are the major cytoplasmic proteins of the lens and their stability and appropriate interactions are critical for lens transparency. Crystallin genes encode more than 95% of the water soluble structural proteins present in the vertebrate lens and their encoded proteins account for more than 30% of its mass. In 1894, Morner first separated bovine lens proteins into three soluble fractions and one insoluble fraction. The soluble fractions consisted of α-, β-, and γ-crystallins, which are found in all vertebrate lenses and are referred to as “ubiquitous crystallins.” In the mature human lens, α-crystallin makes up roughly 40%, β-crystallin 35%, and γ-crystallin 25% of the total crystallin protein. The β- and γ-crystallins form a super family as they share a common two domain structure composed of four extremely stable, torqued β-pleated sheets termed “Greek key” motifs. At least 13 functional crystallin genes have been identified in humans, and of these, 10 major crystallin genes have been associated with pediatric cataract.

**The aim of the present study is to investigate the presence of further novel genes or sequence elements involved in the pathogenesis of congenital cataract in Maharashtrian families. This could also lead to development of prognostic and diagnostic kits to monitor, treat and prevent the childhood cataract which also is an aim for the present study.**