1 SCOPE OF THE STUDY

Cataract or opacification of all or part of the lens of the eye reduces the optical performance, most commonly manifested by decreased visual acuity, contrast sensitivity and glare. It is one of the most common and major eye abnormalities that often lead to blindness and the only treatment available under medicare is the surgical removal of the opacified lens.

Magnitude of the problem
Pediatric cataracts are common and represent one of the most treatable causes of life long visual impairment. The global estimate of 20 million children under the age of 16 suffer from cataract and 200,000 (15%) children severely visually impaired and blind with bilateral cataract (Johnson et al, 2003; Foster et al, 1997). This is relatively low compared to the 17 million (40%) adults who are blind owing to cataract (Dawson and Schwab 1981). However the burden of disability in terms of “blind-years” is huge because of the child’s life expectancy after developing the visual disability. This presents an enormous problem to developing countries in terms of human morbidity, economic loss and social burden.

In developed nations of Europe and northern America, national surveillance or cross sectional studies on congenital cataract suggest a prevalence of 1-4 cases per 10,000 children (Stoll et al, 1997; Abrahamsson et al, 1999). In southern India the prevalence is higher, at approximately 6.5 cases per 10,000 children and bilateral childhood cataract accounts for about 12% of all ocular disorders registered (Dandona et al, 1998). It occurs as a primary disorder or secondarily in association with multi system disorders. Childhood cataract is both clinically and genetically heterogeneous; about one half of all the bilateral congenital cataract case has a genetic basis. All three forms of Mendelian traits have been observed and the most frequently seen is autosomal dominant (AD) transmission
in non-consanguineous population (Francis et al, 2000). Autosomal recessive (AR) (Pras et al, 2002) and X-linked forms have also been reported (Francis et al, 2002).

**Need for genetic analysis**

- Understanding the genetic basis of childhood cataract may assist with cataract prevention strategies by providing a better understanding of the protein pathway involved in lens opacification.
- Thereby providing new insights to the pathogenesis of its more common age-related counterpart.
- Thus will provide a rational design in delaying the disease or possibly preventing it by development of anti-cataract drugs.
- It would help in identifying individuals at risk and will assist in providing them appropriate genetic counseling.
- It will aid in development of newer techniques that will allow rapid identification of the molecular pathology of the disease.

**Genetics of Congenital cataract**

To date at least 34 loci in human genome have been reported to be associated with various forms of congenital cataract and infantile cataract. Of the mapped loci mutations have been identified in 20 specific genes including those encoding crystallins [CRYAA (Litt et al, 1998), CRYAB (Berry et al, 2001), CRYBA1 (Kannabiran et al, 1998), CRYBA4 (Billingsley et al, 2006), CRYBB1 (Mackay et al, 2002), CRYBB2 (Litt et al, 1997), CRYBB3 (Riazuddin et al, 2005), CRYGC, CRYGD (Santhiya et al, 2002) and CRYGS (Sun et al, 2005)], a cytoskeletal protein [BFSP2 (Conley et al, 2000)], membrane proteins [GJA3 (Rees et al, 2000) GJA8 (Shiels et al, 1998), and MIP (Berry et al, 2000), LIM2 (Pras et al, 2002)] transcription factors [HSF4 (Bu et al, 2002), PITX3 (Semina et al, 1998) MAF (Vanita et al, 2006)] and glucosaminyl (N-acetyl) transferase 2 [GCNT2 (Pras et al, 2004)]
The manner by which mutations in the lens genes result in cataract is yet to be fully established. Dysfunction of any element essential for the maintenance of transparency to the visible light could result in opacity. A mutant protein for instance crystallin may lose its optical properties or fail to interact appropriately with its intercellular environment. The failure of cytoskeletal proteins, to facilitate crystallin packing may result in loss of homogeneity. Mutation in the transmembrane protein results in the disturbance of signal transduction and the homeostasis, accumulating abnormal precipitates or disrupting the cellular architecture. The transcription factor plays a critical in the timing and the location of gene expression. Mutation in these genes results in abnormal development of the lens and opacification.

This study aimed to investigate the molecular pathology of families affected with childhood cataract. The samples were ascertained from southern India which offers few critical advantages for the study. The higher incidence of cataract in this population facilitates recruitment of more number of families with a positive history of childhood cataract. There is a more common practice of consanguineous marriage in this population which provides an opportunity to study the genes associated with autosomal recessive cataracts.

**Specific Aims**

On the basis of the current studies, of the cataract mutations reported to date about half the mutations occurs in crystallins, a quarter of the mutations in connexins and the remainder are evenly divided between membrane intrinsic protein, intermediate filament protein and transcription factors. However it is still unclear that mutations in which of these genes contribute to a significant cause of childhood cataract.

1. **Thus in this study a systematic screening of mutations in the known candidate genes (crystallins and connexin) in a large panel of samples was**
performed to understand what proportion of cataract these genes are responsible for in our study population.

2. A genome wide scan was performed to map, identify and characterize gene in large families that do not have a mutation in the above candidate gene screening.

3. Finally an attempt was made to understand the genotype-phenotype correlation of the identified mutations of this highly clinically and genetically heterogeneous group of disease.