5.0 Summary

- Pediatric cataract is the most common treatable form of childhood blindness and is heterogeneous both clinically and genetically. Understanding the genetic basis of childhood cataract may help us in the better understanding of the protein pathway involved in lens opacification may give a perspective of its age-related counterpart.

- This report describes the first simultaneous clinical and genetic characterization of families affected with congenital and childhood cataract in a large panel of samples of the same population, represented by 60 south Indian families.

- This study investigated the spectrum and frequencies of crystallin gene and connexin mutations 60 unrelated south Indian families affected with congenital / childhood cataract. Mutations were identified in 14 families, of the 13 different mutations found 8 were novel. The identified mutations co-segregated with the diseases phenotype and were found to absent in 100 - 200 normal control chromosomes analysed.

- Mutational analysis of CRYAA in the cohort revealed potential disease-causing missence variants in three families. Two of the amino acid substitutions, R12C and R21W have been reported previously to be pathogenic (Hansen et al, 2007) and a novel R54C substitution was identified. It is interesting to note that the three mutation lie outside the SHPs conserved domain and the affected members of these families had developed bilateral congenital nuclear cataract in association with microcornea, except for family affected with R21W where in the affected members also had microphthalmous. The prevalence of mutations in CRYAA causing inherited congenital cataract in this population is 5%.
Molecular analysis of the functional candidate gene CRYAB revealed a novel A171T mutation in one family (1.6%). The probands was the only available clinically confirmed affected member for the study diagnosed with lamellar cataract phenotype with no other ocular or systemic abnormality.

A previously reported CRYBA1 splice site mutation was identified in two families (3.3%) with an AD mode of inheritance. The mutation identified in this study is a G>A transition in the 5’ donor splice site (IV3+1 G>A), but unlike the previous reports, this is associated with a zonular lamellar cataract but displays a variability in expressivity of opacification and severity of the disease.

Analysis of CRYBB2 revealed Q155X mutation in a three generation family affected with posterior cortical cataract with pulverulent opacities (1.6%). This is the sixth report of this chain-termination mutation, the others being reported in an American, Morrocon, Swiss, Chinese and an Indian family. Perhaps this is the most common mutation in this crystallin gene.

Mutation screening of CRYGC, CRYGD and CRYGS revealed mutations in three families one in each of the genes (1.6% per gene). CRYGC revealed a R168W causing lamellar cataract. One novel non-sense mutation R140X was identified in CRYGD was found associated with congenital nuclear cataract. A unique missence mutation in CRYGS (S39C) affected a family with juvenile onset cataract with phenotypic variation in opacification between members and even between the eyes of the same person. This is the second report of a CRYGS mutation and the findings are similar to the previous report (Sun et al, 2005).
Two novel missense mutations were identified in GJA3 (3.3%). R76G mutation was identified in the family with a total cataract phenotype. Whereas the V28M mutation is the second report of a mutation in the first transmembrane domain of connexin 46, the cataract phenotype in the family varied in severity and the age of onset. The mutation was also identified in 2 unaffected individuals of the family and the intrafamilial variation of the disease suggests the possibility of a modifier gene(s) or the effects of environmental factors being involved.

Molecular analysis of GJA8 revealed two novel missense mutations V44E and R198Q, in the population screened. GJA8 mutations were observed in two of the 60 unrelated families with cataracts. Affected individuals in both of whose families also had microcornea and variable myopia. This is the first report of mutations in GJA8 to be associated with autosomal dominant cataract and microcornea. Mutations in GJA8 cause 3.3% of congenital cataracts in the population of India.

In this study no mutations were detected in CRYBA2, CRYBB1 and CRYBB3. It is noteworthy that all of the mutations identifies in crystallin gens in this study have been responsible for ADCC and no mutations have been identified in these genes to cause AR cataract.

The frequency of involvement of the 12 genes analysed (10 crystallin and 2 connexin) in the Indian families suggested that mutations in crystallin genes might account for as much as 16.6% and Connexins for 6.6% of inherited congenital or childhood cataracts in the Indian population. Causative mutations were not identified in over -76% of the families (n=46). Thus the pathogenesis of the majority of cataract families in India is not accounted for by mutations in the coding exons of the candidate genes tested.
This study aimed to investigate the molecular pathology of families affected with pediatric inherited cataract by performing a genome wide scan to map, identify and characterize the gene responsible for the disease condition. Among the 46 families with an unidentified genetic cause for the diseases, eight large families were chosen for linkage analysis with 382 microsatellite markers. Of these families identified 4 inherited autosomal dominant and 4 autosomal recessive cataract. Whole genome scan revealed linkage of two families, one to a known loci on chromosome 16 and another to a novel loci on chromosome 20.

Mutation screening of the known candidate gene HSF4 in chromosome 16 revealed a novel mutation (S39I). This is the first report of an autosomal recessive mutation identified in the DNA binding region of the HSF4 protein as the previously described five different missense mutations within the HSF4 DNA binding domain have been characterized with autosomal dominant cataracts (Bu et al, 2002 and Ke et al, 2006).

An autosomal recessive cataract in an Indian family mapped to a 5.43 Mb interval on chromosome 20q flanked by markers D20S852 and D20S912 and including the BFSP1 gene. Sequencing of BFSP1 shows deletion of exon 6 in all affected members of the family, demonstrating for the first time association of human cataracts with a mutation in the gene encoding Bfsp1.

This study is the first simultaneous and comprehensive clinical/molecular analysis of most of the currently known congenital cataract causing genes in a well characterized set of families. This will improve genetic counseling and shed further light on the molecular mechanisms underlying this disorder. Extensive linkage analysis will assist in the identification of molecular pathology of the other affected pediatric cataract families.