Literature Review:

Role of crystallin proteins, connexins proteins, major intrinsic proteins, cytoskeletal proteins in congenital cataract has been extensively reviewed (Santana and Waiswol, 2011). The major work on childhood blindness due to cataract involves finding mutations in the crystallin genes. Similarly it has been reported that CRYBA4, a novel human cataract gene, is also involved in microphthalmia and the authors identified a c.242T-->C (Leu69Pro) sequence change in exon 4 in one of the patients in a large Indian family, which is predicted to disrupt the beta-sheet structure in CRYBA4. This is the first report linking mutations in CRYBA4 to cataractogenesis and microphthalmia (Billingsley et al., 2006). Two mutations have been shown to be associated with familial cataract in crystallin genes (Burdon et al, 2004). Further identification of the disease causing crystallin mutations has been reported in paediatric cataract families from south eastern Australia. Although mutations in the five crystallin genes screened in this study account for 38% of paediatric cataract mutations in the literature, only two causative mutations were detected in 38 pedigrees, suggesting that crystallin mutations are a relatively rare cause of the cataract phenotype in this population (Burdon et al, 2004).

Identification of a new locus for an autosomal dominant anterior polar cataract on the short arm of chromosome 17 has been reported. Genetic linkage analysis with microsatellite markers in a four-generation pedigree was performed. The study provides the first genetic mapping of an autosomal dominant anterior polar cataract in blindness (Berry et al., 1996). The linkage of a locus for autosomal dominant posterior polar cataract (CPP) to the distal short arm of chromosome 1 has also been reported wherein molecular genetic linkage analysis using microsatellite markers in a three-generation pedigree was performed. This study provided the first evidence for genetic heterogeneity of autosomal dominant posterior polar cataract (Ionides et al. 1997).

Quaternary stability of the alphaA R116C mutant protein and its effect on chaperone-like activity, subunit exchange, and membrane association has been well studied. The results indicate that the complex polydisperity, the reduction of subunit exchange, and increased membrane binding capacity are all potential factors in the pathogenesis of alphaA R116C associated congenital cataracts (Cobb and Petrash, 2000).

Role of alpha-crystallin as a molecular chaperone explaining how it prevents the aggregation of other lens crystallin and proteins that have become unfolded by trapping the protein in a high mol wt. complex has been well documented (Derham et al. 1999).
Gene responsible for autosomal congenital cerulean cataract in a four generation Moroccan family has been mapped for the mutations. The mutation resulted in a proline to threonine substitution at amino acid 23 on the protein resulting in alteration of protein folding or decrease the thermodynamics stability or solubility of the protein (Nandrot et al. 2012). The association of a chain termination mutation in the human beta crystallin gene CRYBB2 with Cerulean cataract has earlier been reported (Litt et al., 1997). Kramer et al in 1996 have reported a second gene for cerulean cataracts that was mapped to the b crystallin region on chromosome 22 (Kramer et al 1996).

A Nonsense mutation in the CRYBB2 gene causing autosomal dominant progressive polymorphic congenital coronary cataracts in a large Chinese family has been identified. The study proved that CRYBB2 to a pathogenic gene for congenital cataract (Li et al. 2008).

A splice site mutation in CRYBA1/A3 causing autosomal dominant posterior polar cataract in a Chinese pedigree has been reported (Gu et. al., 2010). The same mutation in this gene had previously been reported to be associated with other phenotype cataracts. This study is the first report relating a mutation of CRYBA1/A3 to posterior polar cataract.

Identification of mutations in a Chinese family with congenital cataract and microcornea has been reported due to a novel missense mutation in CRYBA4 expanding the mutation spectrum of CRYBA4 useful in the study of molecular pathogenesis of cataract and microcornea (Zhou G, et. al., 2010).

Philly mouse, a mouse strain with an inherited cataract, with an abnormal bB2-crystallin was studied by Chambers and Russell in 1991. They first reported a mutation resulting into deletion of 4 amino acids to be the cause of the abnormal bB2-crystallin (Chambers and Russell 1991). The importance of mouse as mouse model system has been well enumerated with emphasis on the underlying genetic basis causing cataract. A broad variety of hereditary congenital cataract is discussed at molecular level (Graw, 2009). A guinea-pig hereditary cataract containing a splice-site deletion in a crystallin gene has been reported (Rodriguez et. al 1992). Heat-shock transcription factor 4 (HSF4) mutations associated with autosomal dominant lamellar cataract and Marner cataract in mice has been reported. The authors indicated the importance of HSF4 to lens development wherein the study showed that the disruption of Hsf4 gene leads to cataracts via three pathways, 1) down-regulation of γ-crystallin, particularly γS-crystallin; 2) decreased lens beaded filament expression; and 3) loss of posttranslational modification of αA-crystallin (Xiaohe et al 2009).
Characterization of a novel mutation in the CRYBB2 gene associated with autosomal dominant congenital posterior subcapsular cataract in a Chinese family has been reported (Ke et al., 2011). The authors studied an underlying genetic defect in four generations of a Chinese family affected with bilateral congenital posterior subcapsular cataracts. The study identifies a novel CRYBB2 gene mutation (c.5C to T), resulting in the amino substitution p.A2V (Alanine to valine) in the family. Further it has been shown that Autosomal dominant congenital nuclear cataracts caused by a CRYAA gene mutation. This study identifies a mutation in the CRYAA gene causing autosomal dominant nuclear cataracts. The results provide evidence that CRYAA is a pathogenic gene for congenital cataracts (Li et al., 2010).

Impact and importance of nutrition and diet to diseases in particular the eye diseases such as cataract and visual dysfunction has recently been documented (Lisa and Hammond, 2010).

An ADCC gene in family ADCC-2 has been studied and mapped to chromosome 21q22.3 near the alpha-crystallin gene CRYAA. By sequencing the coding regions of CRYAA, it was found that a missense mutation, R116C, is associated with ADCC in the family (Litt et al 1998). Autosomal dominant zonular cataract with sutural opacities localized to chromosome 17q11–12 has been reported (Padma et al., 1995). A new locus for dominant zonular pulverulent cataract has earlier been reported on chromosome 13 (Mackay et al. 1997).

Mutations leading to blindness due to cataract have been screened for four generations of the Chinese family. The authors in this study investigated a four generation Chinese family who are afflicted with anterior polar cataract. The study identifies a missense mutation (R116H) in the CRYAA gene that causes autosomal dominant congenital anterior polar cataract in the family. The study confirmed the high rate of independent mutations at this dinucleotide (Zhang et al., 2011).

It has been shown that Cell death is triggered by a novel mutation in the alphaA-crystallin gene which underlies autosomal dominant cataract linked to chromosome 21q. The authors in the study have identified a novel missense mutation in CRYAA that underlies an autosomal dominant form of ‘nuclear’ cataract segregating in a four-generation Caucasian family by linkage analysis (Mackay et al., 2003).

The spectrum and frequency of crystallin gene mutations in cataractous patients in an Indian population have been screened. Authors report the first simultaneous mutation analysis of 10 crystallin genes in the same population, represented by 60 south Indian families. The analysis allowed the identification of causative mutations in 10 of the families (three novel and six reported). This includes six missense mutations, two
nonsense mutations and one splice mutation (Devi et al., 2008). A novel fan shaped cataract-microcornea syndrome caused by mutation of CRYAA in an Indian family has been reported. The study involved molecular characterization of 10 members in four generations of the family affected with the disease (Vanita et al 2006).

Clinical variability of autosomal dominant cataract, microcornea and corneal opacity was reported earlier. A novel G414A transition in exon 3 of CRYAA that co-segregated with an autosomal dominant phenotype was identified in this study. The genotype-phenotype correlation of this mutation provided evidence that other factors, genetic and/or environmental, may influence the development of cataract as a result of this alteration (Richter et al 2008).

Factors related to cataract like embryology, morphology, types of cataract, etiology postoperative complications and pediatric surgery including the diverse spectrum of morphologies, etiologies and clinical presentations of congenital cataract has been previously reviewed (Krishnamurthy et al 2008).

Genetic etiology in Indian families having inherited or congenital cataract has been reviewed. The study identified three mutations being most likely causative for congenital or childhood cataracts in these families where in one affected the GJA3 gene encoding connexin 46 and the other two affecting CRYBB2 encoding β-crystallin (Sathiyavedu et al 2010). Another study involving nine Indian families having a history of congenital cataract identified a substitution W151C in exon 6 of CRYBB2 as the most likely causative mutation underlying the phenotype of central nuclear cataract in the affected members of the family. The study concluded that exon 6 of CRYBB2 gene appears to be a critical region susceptible for mutations leading to lens opacity (Sathiyavedu et al 2004).

A novel locus for cerulean cataract type 5 (CCA5) which is also known as blue dot cataract on chromosome 12q24 has been identified using genetic linkage and microsatellite markers in a five generation English family (Berry et al. 2011).

Mutation causing self-aggregation in crystallin leading to congenital cataract has been reported. The association of congenital lamellar cataract with R168W mutation in C-crystallin and that of a 5bp insertion with zonular pulverulent cataract was shown which lead to a conclusion that unfolding or structural destabilization is not always necessary for crystallin associated cataractogenesis (Venu et al 2006).

A novel mutation in the major intrinsic protein (MIP) associated with autosomal dominant congenital cataracts in a Chinese family has been reported. This was the first reported case of cataracts caused by a mutation in the second extracellular loop
domain of MIP (Wang et al 2010) One more novel mutation c.530 (A to G) in the MIP gene was reported to be associated with autosomal dominant congenital nuclear cataract in a Chinese family (Yang et al 2011). A novel T→G splice site mutation of CRYBA1/A3 associated with autosomal dominant nuclear cataracts in a Chinese family has been reported. The mutation caused aberrant splicing of the mature mRNA which caused the disease in the family. This report was the first to relate an IVS3+2 T→G mutation of CRYBA1/A3 to congenital cataracts (Yang et al 2012). A novel G→T splice site mutation of CRYBA1/A3 associated with autosomal dominant suture cataracts has been reported in a Chinese family, this was the first finding that related a G to T mutation of CRYA1/A3 to congenital Y-suture cataract (Zhenfei et al 2011).

A novel mutation in the connexin 46 (GJA3) gene associated with autosomal dominant pulverulent cataracts in a Chinese family has been reported. This study expanded the mutation spectrum of GJA3 in association with congenital cataract (Xuchen et al 2011). A novel nonsense mutation in CRYGC associated with autosomal dominant congenital nuclear cataract in a Chinese family has been reported. The study provides an evidence of relationship between genotype and the corresponding cataract phenotype (Yao et al 2008).

DNA-binding and transcriptional activities of human HSF4b that is a transcriptional activator of lens protein genes such as CRYAB, CRYGC, BFSP1 and BFSP2 which encode crystallins and beaded filament structural proteins in lens epithelial cells has been reported. Five missense mutations associated with congenital cataract inhibited DNA-binding of HSF4b thereby inhibiting its transcription activity ability. The relationship between HSF4 mutations, loss of lens protein, gene expression, and cataractogenesis has been well demonstrated (Yasuaki et al 2010).