MOLECULAR DETERMINANTS OF LENS DISORDERS

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بسم الله الرحمن الرحيم

Our Lord! Let not our hearts deviate from the truth after You have guided us, and bestow upon us mercy from Your grace. Verily You are the Giver of bounties without measure.

(Quran 3:8)

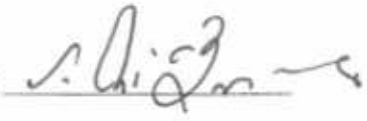
DEDICATED TO

My parents, my husband and specially to my little prince Rayyan

CERTIFICATE

It is certified that the research work described in this thesis is the original work of the author **Namerah Ahmad Sabir** and has been carried out under our direct supervision. We have personally gone through all the data reported in the manuscript and certify their correctness/authenticity. It is further certified that the material included in this thesis have not been used in part or full in a manuscript already submitted or in the process of submission in partial/complete fulfillment of the award of any other degree from any other institution. It is also certified that the thesis has been prepared under our supervision according to the prescribed format and we endorse its evaluation for the award of Ph.D. degree through the official procedures of the University.

In accordance with the rules of the Centre, data books # **604, M-81**and **M-129** are declared as unexpendable document that will be kept in the registry of the Centre for a minimum of three years from the date of the thesis defense examination.

Signature of the Supervisor: 

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SUMMARY

The last decade witnessed rapid progress in studies of the genetics of congenital disorders of the lens. This present study is designed to investigate the molecular and genetic basis of hereditary disorders of lens in Pakistani population. Among the disorders of the lens, cataract remains the most frequent disorders resulting in visual impairment and is responsible for approximately 48% of world blindness.

Here, in this dissertation, 39 consanguineous Pakistani families having a history of congenital disorders of the lens and an autosomal recessive pattern of inheritance have been reported. These families were identified through schools for blind children and ophthalmic clinics all over of Pakistan. Upon enrollment, a complete clinical history of the each family was obtained from family clinicians. All participating family members underwent a thorough clinical and a physical examination and denoted 8-10 cc blood samples that were used to extract genomic DNA. These genomic DNAs were initially subjected to exclusion analyses to check for reported loci for autosomal recessive congenital cataract. The families that were found associated with any of the known loci were excluded, whereas the rest of the unlinked families were interrogated in genome-wide scans to identify novel linkages and genes.

Genome wide linkage analysis was performed on 18 families and these efforts led to the identification of two novel non-syndromic autosomal recessive congenital cataract loci on chromosome 3q and chromosome 8p, respectively in two large families. On the 3p locus, a maximum two-point LOD score of 4.0 with marker D3S3609 was obtained for family PKCC144. Similarly maximum two-point LOD score of 3.17 with markers D8S550 was obtained for family PKCC146. Both these regions have not been associated with autosomal recessive congenital cataracts in any previous study.

Additionally, family PKCC139 manifested characteristics of Peter's anomaly, a rare form of anterior segment dysgenesis in which unusual cleavage of the anterior chamber occurs, which may involve the central or entire cornea. Genome wide scan was performed on family PKCC139 to determine the causative region segregating with the disease phenotype, which identified a region of significant linkage on chromosome 1p with two-point LOD score of

4.12 with marker D1S197. Additional markers were typed to refine the critical interval and defining the proximal and distal boundaries. This new reported region overlaps with the previous published region of congenital cataract but dissimilar clinical characteristics differentiate it as peters anomaly.

In short, this study reports the identification of two new loci for congenital cataracts on chromosomes 3q and 8p and one novel locus for syndromic cataract (peters anomaly) on chromosome 1p.

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May Allah bestow His blessings to all my family members and friends and may they live long, enjoy healthy lives forever and brighten the path of my life with their never-ending guidance and love.

Namerah Ahmad Sabir