A clinical, genetic and molecular study on X-linked retinoschisis (XLRS)
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X-Linked Retinoschisis (XLRS) is a monogenic, vitreoretinal degenerative disorder that affects males and is currently incurable. Despite extensive research, the pathophysiology behind phenotype variability in XLRS still remains uncertain. Therefore, this study aimed to carry out a comprehensive investigation on the clinical, genetic and molecular basis of XLRS to gain insights on the disease pathogenesis.

Towards this, 29 patients were recruited based on opthalmic examination which demonstrated a broad spectrum of clinical presentation iterating phenotype heterogeneity. On genetic screening, 89% of the patients harboured mutations in the causative RS1 gene, wherein 7 were novel. The mutant constructs were genetically engineered and their secretion profiles were studied in COS7 cells. Regardless of the mutation type, most retinoschisin (RS1) mutants exhibited intracellular protein retention. Intriguingly, phenotype-genotype correlation analysis with reference to molecular findings demonstrated varying disease severity even among patients showing same secretion profile. To understand this heterogeneity, subcellular distribution and localization of mutants were investigated which indicated that a fraction of the non-secreted mutants might get localized to the plasma membrane of the cell. Thus, it is hypothesized that this fraction of mutant protein reaching the plasma membrane might perform varying degrees of cell adhesion function that could explain the differing clinical severity. Structural analysis by molecular modelling and dynamic simulation studies corroborated with the in vitro findings.
Furthermore, protein-protein interaction studies of RS1 in human retina identified putative binding partners associated with MAPK pathway, which strongly suggests the involvement of this pathway in the regulatory network of RS1. Besides, high-throughput mass spectrometric analysis of the surgically extracted intraschisis fluid revealed 3 canonical pathways viz., LXR/RXR activation, complement system and acute phase response that may get dysregulated during the course of the disease.

Our study has led to the novel finding that non-secreted mutant RS1 might get localized to the outer plasma membrane. And, the phenotype heterogeneity of XLRS is not merely dependent on the secretory profile of mutant, but, the precise localization and structural conformation of the mutant protein. Functional studies indicate that immune responses might play a key role in the pathogenesis of XLRS. Finally, the significance of genetic testing is well pronounced in this study as it can help in differential diagnosis and genetic counselling also benefitting the affected family in terms of prenatal diagnosis and carrier testing.