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Abstract Topic: - Complex traits and polygenic disorders

Abstract Title: - Rare variants and oligogenic contribution in primary concomitant strabismus

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Aims: - Occurrence of familial primary concomitant strabismus (PCS) comprising both, esotropia (ET) and exotropia (XT), supports a genetic basis for relatively common condition but this is largely unexplored. Linkage studies have not identified any specific gene for PCS; however, a few loci have been identified. To identify genetic determinants of PCS, we performed whole exome sequencing (WES) in an informative north Indian family with primary concomitant XT.

Methods: - Complete ophthalmic evaluation was performed in five affected and three unaffected members of a three-generation family of north Indian ancestry with likely autosomal dominant (AD) form of the primary concomitant XT phenotype. Putative disease causal rare variants identified by WES data analysis considering AD inheritance, were independently checked for segregation in the family using linkage analysis.

Results: - Three rare heterozygous missense variants in putative disease causal genes segregating with the phenotype of primary concomitant XT were identified, which were confirmed by Sanger sequencing. Further, linkage analysis using microsatellite markers around the loci encompassing the variants, which yielded a LOD score of 1.5 at Ø 0.0, independently support their likely contribution to the phenotype.

Conclusions: - Rare exonic variants in three biologically relevant genes co-segregating with the disease phenotype suggest an oligogenic contribution to the etiology of PCS. This encourages replication studies in additional families/other ethnic populations as well as functional validation of the findings.

Keywords: - Three rare heterozygous missense variants in putative disease causal genes segregating with the phenotype of primary concomitant XT were identified, which were confirmed by Sanger sequencing. Further, linkage analysis using microsatellite markers around the loci encompassing the variants, which yielded a LOD score of 1.5 at Ø 0.0, independently support their likely contribution to the phenotype.