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Retinal panel exome sequencing: A diagnostic tool to hereditary retinal disorders

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Purpose: To determine the molecular basis of the autosomal recessive retinal degeneration in a consanguineous South Indian family.

Methods: The proband and the available family members underwent a complete ophthalmic examination. Upon informed consent blood samples and case histories were documented. Genomic DNA sample of the proband was subjected to exome sequencing (selected panel of 105 genes involved in retinal degeneration). Variants were analyzed for co-segregation amongst family members using custom designed gene specific primers, direct sequencing and by RFLP. The mutation was subjected to *in silico* analysis (Polyphen2, Splice Port) to predict the effect of the mutation on structure and function of the transcript and its protein.

Results: The proband attended the clinic for difficulty in reading and writing. Fundus examination revealed a metallic or beaten bronze appearance, characterizing early stages of retinal degeneration. Retinal panel exome sequencing showed five novel variants in three different genes. Among which, a sequence variation viz., c.1250 T>A transversion in the candidate gene CDH23 encoding Cadherin 23 that alters amino acid at position 417 (p.I417N) was the only homozygous variant observed in the proband. This variant is located in the EC4 domain (extracellular domain) of the protein and was conserved across species. *In-silico* tools predicted this variant to be damaging. This substitution was in a heterozygous status in the unaffected family members (proband's parents and sibling) and absent in 100 healthy controls of the same ethnicity. Apart from this variant, we observed an insertion in intron 12, c.1290+236_1290+237insA. SplicePort tool predicts a splice site acceptor at this region. This intron variant might alter splicing, thereby acting as a modifier. However, this speculation needs to be functionally validated. Mutations in CDH23 are known to cause type I Usher syndrome and non-syndromic autosomal recessive deafness (DFNB12). Individuals with USH1D usually carry a truncated CDH23 protein, whereas DFNB12 carry missense mutation. Further clinical investigations showed that the proband is affected with Usher syndrome with atypical retinal degeneration.

Conclusions: Herein we report an atypical case of a novel CDH23 mutation with progressive retinal degeneration and hearing loss. We emphasize here that retinal exome panel sequencing aids in accurate diagnosis and prognostic genetic counseling for congenital eye disorders and in early management of the disorder.

Biography

K Dinesh Kumar is a Senior Research Fellow at Helmholtz Zentrum Munchen, Germany and working on molecular screening of animal models with eye disorders. He was a Research Scholar in Department of Genetics at University of Madras, Chennai. He has completed his MPhil at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala.

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