Novel mechanism of inheritance detected

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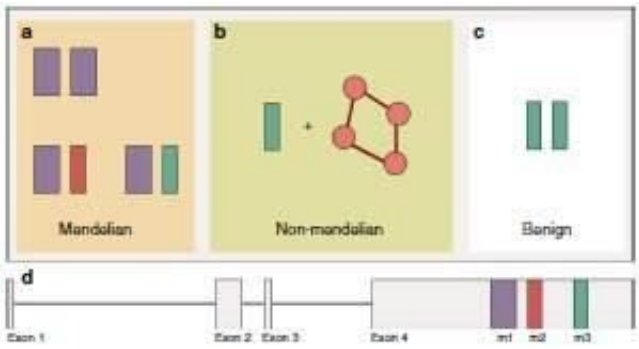

Credit: Institute of Molecular and Clinical Ophthalmology Basel (IOB)

Non-Mendelian, oligogenic inheritance could be an unrecognized and important element for occurrence of hereditary retinal degenerations (HRDs, comprising retinitis pigmentosa) which are caused by ultra-rare mutations and cause progressive blindness.

HRDs are almost invariantly inherited as a monogenic, Mendelian trait through the presence of at least one dominant or two recessive mutations in the same gene. To date, almost 300 genes and thousands of mutations have been identified as causing HRDs. The average contribution of any given HRD gene to the disease is typically very small. Most mutations are so rare that they are often detected only in one single patient's family worldwide.

Carlo Rivolta, Professor for Ophthalmic Genetics at the Medical Faculty of the University of Baseland Group Leader at the Institute of Molecular

and Clinical Ophthalmology Basel, Switzerland (IOB), led a research team which conducted a genomic screen of a few hundred unrelated Japanese patients. The study showed that two specific mutations in RP1, a gene encoding for a ciliary protein in photoreceptors,are responsible for a relatively large number of Mendelian HRD cases in Japan.

"Interestingly, none of these two changes is rare in this population at all, compared to the average frequencies of classical HRD mutations. This DNA change is almost polymorphic in East Asia, but does not cause disease either in heterozygous or homozygous carriers. However, in combination with rare mutations in at least another HRD gene it causes disease by inheritance mechanisms that transcend the Mendelian model. While they genetically behave like multigenic conditions, the combined mutations display a Mendelian pattern of inheritance," Rivolta explains.

Benefit for the patients

"A better understanding of the genetic causes of inherited eye diseases will contribute to the genetic profiling of patients we see in the Basel University Eye Clinic and Department of Ophthalmology. This will strengthen our efforts to establish personalized ophthalmological medicine in Basel," says Hendrik Scholl, director of IOB and Professor and Chairman, Department of Ophthalmology, University of Basel.

Creating computational tools for elucidating the genetic bases of vision loss is an important cornerstone for IOB. It will contribute to the development of an atlas of gene expression patterns in every cell type of the human eye, which is one of the research goals of IOB.

More information: Konstantinos Nikopoulos et al. A frequent variant in the Japanese population determines quasi-Mendelian inheritance of rare retinal ciliopathy, *Nature Communications* (2019). DOI: 10.1038/s41467-019-10746-4

Provided by Institute of Molecular and Clinical Ophthalmology Basel (IOB)