# A frequent variant in the Japanese population determines quasi-Mendelian inheritance of rare retinal ciliopathy

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Hereditary retinal degenerations (HRDs) are Mendelian diseases characterized by progressive blindness and caused by ultra-rare mutations. In a genomic screen of 331 unrelated Japanese patients, we identify a disruptive Alu insertion and a nonsense variant (p.Arg1933*) in the ciliary gene RP1, neither of which are rare alleles in Japan. p.Arg1933* is almost polymorphic (frequency = 0.6%, amongst 12,000 individuals), does not cause disease in homozygosis or heterozygosis, and yet is significantly enriched in HRD patients (frequency = 2.1%, i.e., a 3.5-fold enrichment; p-value = 9.2 Œ 10; -5; ). Familial co-segregation and association analyses show that p.Arg1933* can act as a Mendelian mutation in trans with the Alu insertion, but might also associate with disease in combination with two alleles in the EYS gene in a non-Mendelian pattern of heredity. Our results suggest that rare conditions such as HRDs can be paradoxically determined by relatively common variants, following a quasi-Mendelian model linking monogenic and complex inheritance.

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