

Mutations in a novel BTB-Kelch protein, KLHL7, cause autosomal dominant retinitis pigmentosa

Retinitis pigmentosa (RP [MIM#268000]) is a major cause of inherited irreversible vision loss worldwide. RP constitutes a clinically and genetically heterogeneous group of progressive neurodegenerative diseases, resulting in the death of rod and cone photoreceptors. We have identified a novel RP gene KLHL7 through linkage analysis, mapping to chromosome 7p15, in a six-generation Scandinavian family with autosomal dominant RP (adRP).

Mutation screening of over 500 retinopathy patients has revealed three different missense mutations (c.449G>A, c.458C>T and c.457G>A) in 6 independent families. KLHL7 is widely expressed, including in rod photoreceptors, and encodes a protein of BTB-Kelch family that is implicated in ubiquitination through Cullin E3 ligases. Notably, all putative disease-causing KLHL7 mutations (p.S150N, p.A153V, and p.A153T) are within a conserved BACK domain; homology modeling suggests that mutant amino acid side-chains can potentially fill the cleft between two helices thereby affecting the ubiquitination complexes. Mutations in an identical region of another BTB-Kelch protein, gigaxonin, are also associated with a neurodegenerative disease, giant axonal neuropathy. These studies highlight the importance of ubiquitin-proteasome protein degradation pathway in maintaining neuronal health and in disease.

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