

Mapping the mechanisms of retinal degeneration caused by mutations in the co-chaperone AIPL1

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Mutations in the photoreceptor/pineal-expressed gene AIPL1 cause Leber congenital amaurosis (LCA), the most severe form of childhood inherited retinopathy. AIPL1 is a photoreceptor-specific co-chaperone that interacts with HSP90 via a C-terminal tetratricopeptide repeat (TPR) domain to facilitate the correct assembly and activity of retinal cGMP phosphodiesterase (PDE6). The AIPL1 N-terminal FKBP-like domain interacts directly with the isoprenyl moiety of the PDE6 catalytic subunits. We investigated the functional impact of novel LCA-associated AIPL1 variants. Our data reveal that the relative domain organization and integrity of AIPL1 is important for PDE6-mediated catalysis, with variants mapping to one domain also affecting the activity of the other independently folded domain. The functional assessment and confirmation of likely pathogenic AIPL1 variants is moreover important for the accurate diagnosis and effective triage of patients for AIPL1-targeted gene replacement therapy.