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REPORT

Nonsense Mutations in *FAM161A* Cause *RP28*-Associated Recessive Retinitis Pigmentosa

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Abstract

Retinitis pigmentosa (RP) is a degenerative disease of the retina leading to progressive loss of vision and, in many instances, to legal blindness at the end stage. The *RP28* locus was assigned in 1999 to the short arm of chromosome 2 by homozygosity mapping in a large Indian family segregating autosomal-recessive RP (arRP). Following a combined approach of chromatin immunoprecipitation and parallel sequencing of genomic DNA, we identified a gene, *FAM161A*, which was shown to carry a homozygous nonsense mutation (p.Arg229X) in patients from the original *RP28* pedigree. Another homozygous *FAM161A* stop mutation (p.Arg437X) was detected in three subjects from a cohort of 118 apparently unrelated German RP patients. Age at disease onset in these patients was in the second to third decade, with severe visual handicap in the fifth decade and legal blindness in the sixth to seventh decades. *FAM161A* is a phylogenetically conserved gene, expressed in the retina at relatively high levels and encoding a putative 76 kDa protein of unknown function. In the mouse retina, *Fam161a* mRNA is developmentally regulated and controlled by the transcription factor *Crx*, as demonstrated by chromatin immunoprecipitation and organotypic reporter assays on explanted retinas. *Fam161a* protein localizes to photoreceptor cells during development, and in adult animals it is present in the inner segment as well as the outer plexiform layer of the retina, the synaptic interface between photoreceptors and their efferent neurons. Taken together, our data indicate that null mutations in *FAM161A* are responsible for the *RP28*-associated arRP.

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