REPORT

Nonsense Mutations in FAM161A Cause RP28-Associated Recessive Retinitis Pigmentosa

Thomas Langmann 1, 2, 3, 4, Silvio Alessandro Di Gioia 2, 9, Isabella Rau 2, 9, Heidi Stöhle 5, Nela S. Maksimovic 3, 11, Joseph C. Corbo 4, Agnes B. Renner 5, Eberhart Zrenner 5, Govindasamy Kumarananickavet 7, Marcus Karlstetter 3, Yvan Arsenijevic 6, Bernhard H.F. Weber 1, Andreas Gal 3, 10, 13, 15 and Carlo Rivolta 2, 10, 13, 15

1 Institute of Human Genetics, University of Regensburg, D-93053 Regensburg, Germany
2 Department of Medical Genetics, University of Lausanne, CH-1005 Lausanne, Switzerland
3 Institute of Human Genetics, University of Regensburg, D-93053 Regensburg, Germany
4 Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, MO 63110, USA
5 Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, D-20246 Hamburg, Germany
6 Centre for Ophthalmology, Institute for Ophthalmic Research, University of Tübingen, D-72076 Tübingen, Germany
7 Department of Genetics and Molecular Biology, Sankara Nethralaya, Chennai - 600 006, India
8 Unit of Gene Therapy and Stem Cell Biology, Jules-Gonin Eye Hospital, University of Lausanne, CH-1004 Lausanne, Switzerland
9 Permanent address: Institute of Human Genetics, School of Medicine, University of Belgrade, 11000 Belgrade, Serbia

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.