Human iPSC-derived RPE and retinal organoids reveal impaired alternative splicing of genes involved in pre-mRNA splicing in PRPF31 autosomal dominant retinitis pigmentosa

Majlinda Lako; Adriana Buskin; Lili Zhu; Valeria Chichagova; Basudha Basu; Sina Mozaffari-Jovin; David Dolan; Alastair Droop; Joseph Collin; Gerrit Hilgen; Lyle Armstrong; Evelyne Sernagor; Reinhard Luehrmann; Sushma-Nagaraja Grellscheid; Colin Johnson

+ Author Affiliations & Notes

Abstract

Purpose : Retinitis pigmentosa (RP) is one of the most common forms of hereditary, progressive sight loss, affecting more than 1 million people worldwide. Autosomal dominant inheritance accounts for about 40% of RP, with an estimated 38% of these caused by mutations in six pre-mRNA processing factors (PRPFs). PRPFs are ubiquitously expressed, but mutations only cause retinal-specific degeneration, raising the question of why retinal cells are more susceptible to splicing deficiencies.

Methods : In this study, we used fibroblasts from four patients with two different *PRPF31* mutations (c.1115_1125del11 and c.522_527del6&IVS6+1to+10del) to derive induced pluripotent stem cells (iPSCs). Patient-specific iPSC and age-matched controls were differentiated into RPE and three dimensional retinal organoids in order to elucidate disease mechanisms and to identify cell-type and patient-specific target genes affected by *PRPF31* mutations.

Results : Our data show that *PRPF31* mutations result in impaired alternative splicing of genes encoding pre-mRNA splicing proteins in retinal cells, but not fibroblasts and iPSCs, providing mechanistic insights into retinal-specific phenotypes of PRPFs. These result in defective cilia, progressive degeneration, cell stress and impaired function in retinal pigmented epithelium (RPE) and photoreceptors.

Conclusions : Our data provide, for the first time, a mechanistic understanding of retinal-specific phenotypes in *PRPF31*-mutated RP patients. Our studies highlight the advantages of iPSC-based disease modelling for identifying the affected retinal cell types and target genes, and for testing potential targeted therapies.

This is an abstract that was submitted for the 2018 ARVO Annual Meeting, held in Honolulu, Hawaii, April 29 - May 3, 2018.