## عنوان مقاله:

Functional and quantitative proteomic analyses of human iPSC-derived RPE and ۳D retinal organoids provide insights into the mechanism of retinitis pigmentosa type ۱۱ and its therapeutic strategies


## محل انتشار:

چهارمین کنگره بین المللی و شانزدهمین کنگره ملی ژنتیک (سال: 1399)

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## خلاصه مقاله:

Background and Aim: Retinitis pigmentosa (RP) is one of the most common forms of hereditary progressive retinal dystrophy with a prevalence of about ۱ in ۲۵۰۰ births leading to blindness. A large proportion of autosomal dominant forms of RP are caused by mutations in six pre-mRNA processing factors (PRPFs). PRPFs are ubiquitously expressed in human tissues, but RP mutations only cause retinal dysfunction, raising the question of why retinal cells are more susceptible to PRPF variations.Methods: We have generated induced pluripotent stem cells (iPSCs) from skin filbroblasts of patients with autosomal dominant RP type ۱۱ (RP۱۱) and unaffected controls, and differentiated these to retinal pigmented epithelial (RPE) cells and ۳D retinal organoids. Functional studies were performed to characterize the cellular phenotypes of RP patient RPE and ۳D organoids. Large-scale comparative RNA-seq analyses and quantitative mass spectrometry using TMT chemical labelling were performed to reveal the molecular pathways affected by RP۱۱ mutations.Results: Our data reveal that patient-specific RPE cells are the most affected cell line with multiple defective cellular and functional phenotypes. Photoreceptors also display impaired functional networks and progressive degenerative features. Pathway analysis of the alternatively spliced transcripts indicates that the genes most affected by misplicing are those involved in pre-mRNA splicing itself and that this is specific to patient retinal cells and not fibroblasts or iPSCs. Our proteomic data confirmed this and provided insights into molecular and cellular cascades significantly affected by RP۱۱mutations. CRISPR/Cas۹ mediated in situ gene editing corrected the RP۱۱ mutations and resulted in reversal of cellular and functional phenotypes in RPE and photoreceptors.Conclusion: Our data provide, for the first time, a mechanistic understanding of retinal-specific phenotypes in RP۱۱ patients. Furthermore, we provide proof of concept that CRISPR/Cas۹ mediated in situ correction is effective in future therapeutic strategies for this genetic disorder.

**کلمات کلیدی:**
retinitis pigmentosa; Proteomics; Transcriptomics; CRISPR/Cas۹-mediated gene editing; induced pluripotent stem cells