

Autosomal Dominant Retinitis Pigmentosa (adRP) Panel

Panel Gene List: BEST1 (VMD2), CRX, IMPDH1, PRPF3, PRPF8, PRPF31, PRPH2 (RDS), RHO and RP1

Clinical Features:

Retinitis Pigmentosa (RP) is a group of disorders involving progressive degeneration of the retina that leads to severe visual impairment. The age of onset of visual symptoms is variable from early childhood to adulthood and is usually more severe if the disorder is inherited as an autosomal trait. The disorder usually manifests with decline and loss of night vision during adolescence, followed by loss of peripheral vision in young adulthood, and loss of central vision in later life due to the progressive loss of rod and cone photoreceptors. Common symptoms include night blindness and a decreasing visual field, leading to tunnel vision, legal blindness or, in many cases, complete blindness. Clinical hallmarks are an abnormal fundus with bone-spicule deposits and attenuated retinal vessels. The electroretinogram (ERG) findings in RP patients show reduced rod and cone response amplitudes, which is moderate in dominant inheritance and barely detectable in recessive and X-linked patients.

Inheritance Pattern/Genetics:

Autosomal dominant (with incomplete penetrance of some variants)

Test Methods:

The coding regions and splice junctions of the 9 genes of this panel are enriched using a proprietary targeted capture system developed by GeneDx. The targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequence is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 19 reads are achieved by NextGen sequencing.

Test Sensitivity:

BEST1 gene: Bestrophin 1

A recent study identified BEST1 variants in 5 out of 95 (2%) of adRP families that were negative for variants in the common adRP genes including the entire RHO, RDS genes and select regions of the ORP1, PAP1, PRPF31, IMPDH1 and PRPF8 genes⁶.

CRX gene: Cone-Rod Homeobox-Containing gene

Variants in the CRX gene contribute to less than 1% of adRP⁴. However, CRX variants are also implicated in adCRD, adLCA and rare cases of arLCA.

IMPDH1 gene: Inosine monophosphate dehydrogenase 1

Variants in *IMPDH1* account for approximately 2% of families with adRP^{1,4}, and de novo *IMPDH1* variants have also been found in patients with isolated Leber congenital amaurosis.

PRPF3 gene: pre-mRNA processing factor 3 homolog

Variants in *PRPF3* account for 1-4% of adRP.

PRPF8 gene: pre-mRNA processing factor 8 homolog

PRPF8 variants account for 2-3% of adRP⁴.

PRPF31 gene: pre-mRNA processing factor 31 homolog

Variants in *PRPF31* cause adRP in nearly 8% of patients. DNA sequencing would detect about 3-6% of adRP cases caused by *PRPF31*, although copy number variants not detectable by sequencing account for approximately 3% of *PRPF31* variants⁴.

PRPH2 (RDS) gene: peripherin 2

RDS variants account for 8–9% of cases with adRP although variants in *RDS* have also been associated with adMD.

RHO gene: Rhodopsin

Rhodopsin variants are the most common cause of adRP, and are found in approximately 26-28% of patients⁴. *RHO* variants can also cause autosomal recessive RP (arRP), congenital stationary night blindness (CSNB) and retinitis punctata albescens (RPA).

RP1 Gene: Oxygen-related photoreceptor protein 1

ss in the *RP1* gene are responsible for 5–10% of adRP cases in the American and British populations¹². Sequence analysis of a region in exon 4 that encodes amino acid residues 500-790 is expected to detect ~3.5% of adRP.

In a few Pakistani families only, *RP1* variants with autosomal recessive inheritance were observed. Most of these recessive *RP1* variants are located outside the regions that are tested for autosomal dominant RP¹².

Gene	Protein	Inheritance	Disease Associations
<i>BEST1</i> (<i>VMD2</i>)	Bestrophin 1	AD	Bestrophinopathy; Macular dystrophy, vitelliform, 2; Microcornea, rod-cone dystrophy, cataract, and posterior staphyloma; Vitreoretinopathology
<i>CRX</i>	Cone-Rod Homeobox-Containing gene	AD	Cone-rod retinal dystrophy-2; Leber congenital amaurosis 7
<i>IMPDH1</i>	Inosine monophosphate dehydrogenase 1	AD	Leber congenital amaurosis 11
<i>PRPF3</i>	pre-mRNA processing factor 3 homolog	AD	Retinitis pigmentosa 18
<i>PRPF8</i>	pre-mRNA processing factor 8 homolog	AD	Retinitis pigmentosa 13

<i>PRPF31</i>	pre-mRNA processing factor 31 homolog	AD	Retinitis pigmentosa 11
<i>PRPH2 (RDS)</i>	peripherin 2	AD	Retinitis pigmentosa 7; Retinitis punctuate albescens; Choroidal dystrophy, central areolar 2; Leber congenital amaurosis 18; Macular dystrophy, patterned, 1; Macular dystrophy, vitelliform, 3
<i>RHO</i>	Rhodopsin	AD	Retinitis pigmentosa 4, AD or AR; Retinitis punctuate albescens; Night blindness, congenital stationary, AD 1
<i>RP1</i>	Oxygen-related photoreceptor protein 1	AD	Retinitis pigmentosa 1

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