

## Autosomal Recessive Retinitis Pigmentosa (arRP) Panel

**Autosomal Recessive Retinitis Pigmentosa also known as:** Sporadic Retinitis Pigmentosa

**Panel Gene List:** ABCA4, CERKL, CNGA1, CRB1, EYS, PDE6A, PDE6B, RPE65 and USH2A

### **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 recessive

### **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:**

ABCA4 gene: ATP-binding cassette, subfamily A, member 4

ABCA4 variants are responsible of 3%–5% of arRP<sup>3,8,32</sup>, 66-80% of Stargardt disease and 24%–75% of autosomal recessive cone rod dystrophy. Partial gene deletions have been reported in the ABCA4 gene in less than 1% of Stargardt patients.

CERKL gene: ceramide kinase-like

Variants in the CERKL gene have been identified in several extended families of various ethnicities who were diagnosed with autosomal recessive retinitis pigmentosa (arRP)<sup>36-41</sup>. Variants in this gene have also been reported in approximately 2% of autosomal recessive cone-rod dystrophy in patients who tested negative for ABCA4 variants<sup>42</sup>.

CNGA1 gene: cyclic nucleotide gated channel alpha 1

Variants in the CNGA1 gene have been reported in approximately 2%-4% of patients diagnosed with arRP<sup>33-35</sup>.

CRB1 gene: Crumbs homologue 1

Variants in the CRB1 gene have been reported in patients with a variety of autosomal recessive retinal dystrophies. In one study, 6 of 92 arRP families (6%) were found to have variants in CRB1<sup>5</sup>. In another study CRB1 variants were identified in 1% of families with Juvenile arRP and 22% of patients with isolated juvenile RP (2 out of 9)<sup>7</sup>. CRB1 variants have been found in 67%-83% of the patients with RP and preserved para-arteriolar retinal pigment epithelium<sup>13,15</sup> and in 29%-56% of RP patients who had developed Coats-like exudative vasculopathy, a relatively rare complication of RP characterized by vascular abnormalities, yellow extravascular lipid depositions, and severe cases retinal detachment<sup>14,15</sup>. In addition, variants in the CRB1 gene have been detected in 10%-13% of patients with Leber congenital amaurosis (LCA)<sup>14,21,19</sup>. Entire gene deletion of the CRB1 gene has been previously in a patient with LCA.

EYS gene: Eyes Shut Homolog

The EYS gene represents a significant cause of arRP, as 10%–25% of Spanish arRP families have been mapped to this locus, as well as several Chinese and Pakistani families<sup>1</sup>. Recently variants in the EYS gene have been reported to cause arRP. Two studies showed the presence of deletions of more than one exon in 2/6 families. In the remaining families frame shift or nonsense variants were identified<sup>2,9</sup>. In a recent study of 186 families Dutch RP families, using homozygosity mapping to select families linked to the EYS locus, variants in EYS have been identified in 7% of the families<sup>10</sup>.

PDE6A gene: Phosphodiesterase 6A, cGMP-specific, rod alpha subunit

Variants in PDE6A account for 3-4% of arRP patients and the variant spectrum includes missense, nonsense, splice site and frame-shift variants<sup>18,20</sup>.

PDE6B gene: Phosphodiesterase 6B, cGMP-specific, rod beta subunit<sup>23,11,30</sup>

Variants in the PDE6B accounts for 5-16% of arRP, but also can lead to autosomal dominant congenital stationary night blindness (CSNB). Variants in PDE6B include missense (52%), non-sense (23%), splice site (10%) and frame-shift (1%) variants. In one study of 19 arRP nuclear families, variants in PDE6B have been identified in 16% of the families (3 out of 19)<sup>12</sup>. In another study, 4 out of 88 unrelated arRP patients (~5%) were shown to carry variants that co-segregated with disease in their respective families<sup>22</sup>.

RPE65 gene: retinal pigment epithelium 65

RPE65 variants contribute to 8%-16% of LCA and 2% of arRP worldwide<sup>24,29</sup>.

USH2A gene: Usherin

Usherin variants are the most common cause of arRP, and are found in approximately in 10-12% of patients<sup>27,28</sup>. Among Usher syndrome type II patients, USH2A gene is the most frequent cause, accounting for 74%-90% of the USH2 cases<sup>25,31</sup>. The variant Cys759Phe in exon 13 has been reported to cause 4%-5% of cases of autosomal recessive retinitis pigmentosa without hearing loss<sup>26,5</sup>. In a study of 118 unrelated Scandinavian patients with Usher syndrome type II, variant analysis of the USH2A gene revealed that 2 patients carry homozygous large deletions including more than one exon<sup>6</sup>.

Gene	Protein	Inheritance	Disease Associations
<i>ABCA4</i>	ATP-binding cassette, subfamily A, member 4	AR	Retinitis pigmentosa 19; cone-rod dystrophy 3; fundus flavimuculatus; retinal dystrophy, early-onset severe; Stargardt disease 1; macular degeneration, age-related, 2
<i>CERKL</i> ( <i>RP26</i> )	ceramide kinase-like	AR	Retinitis pigmentosa 26
<i>CNGA1</i> ( <i>RP49</i> )	cyclic nucleotide gated channel alpha 1	AR	Retinitis pigmentosa 49
<i>CRB1</i> ( <i>LCA8</i> , <i>RP12</i> )	Crumbs homologue 1	AR	Retinitis pigmentosa 12; Leber congenital amaurosis 8; Pigmented paravenous chorioretinal atrophy
<i>EYS</i> ( <i>RP25</i> )	Eyes Shut Homolog	AR	Retinitis pigmentosa 25
<i>PDE6A</i>	Phosphodiesterase 6A, cGMP-specific, rod alpha subunit	AR	Retinitis pigmentosa 43
<i>PDE6B</i>	Phosphodiesterase 6B, cGMP-specific, rod beta subunit	AR	Retinitis pigmentosa 40; Congenital stationary night blindness, autosomal dominant 2
<i>RPE65</i>	retinal pigment epithelium 65	AR	Retinitis pigmentosa 20; Leber congenital amaurosis 2
<i>USH2A</i>	Usherin	AR	Usher syndrome, type 2A

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