Stargardt Disease Panel

Stargardt disease also known as: Stargardt-Like Macular Disease, Other Macular Dystrophies, and Cone Dystrophies

Panel Gene List: ABCA4, ELOVL4 and PRPH2 (RDS)

Clinical Features:
Stargardt disease (STGD) / Fundus flavimaculatus (FFM) is the most common autosomal recessive macular dystrophy with an estimated prevalence of 1 in 10,000 individuals. STGD manifests in the first or second decade of life with decreased central vision, progressive bilateral atrophy of the retinal pigment epithelium, and the appearance of orange-yellow flecks distributed in the posterior pole, sometimes extending beyond the vascular arcade. A milder form of the same disorder, fundus flavimaculatus, has a later age at onset, slower progression, and more-widespread distribution of the flecks.

Autosomal dominant Stargardt-like macular dystrophy is clinically very similar to Stargardt disease. It is a highly penetrant retinal disorder, with typical onset in childhood characterized by progressive loss of central vision followed by a rapid progression to legal blindness. This disorder is characterized by atrophic macular lesions with sharp borders associated with or without yellow fundus flecks. The lesion becomes more advanced over the course of a few years with increased atrophy of the retinal pigment epithelium that resembles the lesions seen in patients with autosomal recessive Stargardt disease. Temporal atrophy of the optic nerve head is present in almost all patients. Age of onset does vary greatly within and between families.

Macular dystrophies constitute a group of disorders characterized by deposits of yellow orange or grey pigment, predominantly in the macular area that can resemble the flecks seen in Stargardt disease. Five main categories of pattern dystrophies are discriminated on the basis of the pattern of pigment distribution: adult-onset foveomacular vitelliform dystrophy (AFVD), butterfly-shaped pigment dystrophy, reticular dystrophy of the pigment epithelium, multifocal pattern dystrophy simulating fundus flavimaculatus. In general, these disorders are relatively benign, manifesting usually in midlife with mild-to-moderate disturbance of central vision. However vision loss may occur in up to 50% of the affected individuals after the age of 70.

Age-related macular Degeneration (AMD) is the leading cause of severe central visual impairment among the elderly and is associated both with environmental factors, such as smoking, and genetic factors. While few studies suggested that sequence variants in ABCA4 are associated with AMD, several other reports could not replicate these results and disputed the findings. Therefore, AMD is currently not a recommended indication for ABCA4 testing.
Cone-rod dystrophy (CORD) has an estimated prevalence of 1 in 40,000 individuals. Most patients experience visual loss, impaired color vision, and a central scotoma early in life. During the initial stage of disease, the fundus may be normal or show fine macular lesions and pallor of the optic disc. In the later stages, the fundus shows pigmentary deposits resembling bone spicules, frequently in the macular area. Cone-rod dystrophy is characterized by more severe cone degeneration, which in the electroretinogram (ERG), is distinguished by more distinctive reduction of the photopic cone b-wave amplitude than the scotopic (rod b-wave) amplitude, compared to rod degeneration.

**Inheritance Pattern/Genetics:**
Autosomal dominant or autosomal recessive

**Test Methods:**
The coding regions and splice junctions of the 3 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:** ATP-binding cassette, subfamily A, member 4
It is estimated that the carrier frequency of ABCA4 variants in the general population is 5-10 in 100. Sequencing of all 50 exons of ABCA4 in patients with Stargardt disease is expected to identify a pathogenic variant on 66-80% of disease alleles. It is also estimated that ABCA4 variants account for arCORD in 24–75% of patients. It is also estimated that ABCA4 variants account for arCORD in 24–75% of patients.

**ELOVL4:** Elongation of very long chain fatty acids-like 4
Variants in the ELOVL4 gene have been identified in all individuals diagnosed with autosomal dominant Stargardt-like macular dystrophy who were reported in the literature.

**RDS:** Peripherin 2, mouse, homolog of RDS variants account for 7-23% of families with adMD, although reduced penetrance has been observed in about 10% of cases with adMD. It is also thought that RDS variants likely account for a small number of cone and cone–rod dystrophy cases.
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<td>ABCA4</td>
<td>ATP-binding cassette, subfamily A, member 4</td>
<td>AR</td>
<td>Stargardt disease 1; cone-rod dystrophy 3; fundus flavimaculatus; retinal dystrophy, early-onset severe; retinitis pigmentosa 19; macular degeneration, age-related,2</td>
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<tr>
<td>ELOVL4</td>
<td>Elongation of very long chain fatty acids-like 4</td>
<td>AD</td>
<td>Stargardt disease 3; ichthyosis, spastic quadriplegia and mental retardation</td>
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<tr>
<td>RDS (PRPH2)</td>
<td>Peripherin 2, mouse, homolog of</td>
<td>AD, incomplete penetrance</td>
<td>Macular dystrophy, patterned,1; macular dystrophy, vitelliform, 3; choroidal dystrophy, central areolar 2; leber congenital amaurosis 18; retinitis pigmentosa 7, and digenic; retinitis punctate albescens</td>
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References: