

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 families²¹. 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 70²⁵. 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^{1,2,7} several other reports could not replicate these results and disputed the findings^{4,6,7,11}. 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:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific

filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Capillary sequencing is used to perform targeted analysis for select deep intronic variants of ABCA4 previously reported in the literature in association with Stargardt disease (5196+1216C>A, 5196+1159G>A, 5196+1137G>A, 5196+1136C>A, 5196+1056A>G, 570+1798A>G, 1938-619A>G, 2160+584A>G, 3050+370C>T, 4540-2036C>A, 4539+2064C>T, 4539+2028C>T, 4539+2001G>A, 4539+1729G>T).²⁹⁻³²

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^{2,5,8,9,10}. It is also estimated that ABCA4 variants account for arCORD in 24–75% of patients^{2,3,13}. **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 literature²²⁻²⁴. **RDS:**Peripherin 2, mouse, homolog of RDS variants account for 7-23% of families with adMD²⁶⁻²⁷, 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.

Gene	Protein	Inheritance	Disease Associations
ABCA4A	ATP-binding cassette, subfamily A, member 4	AR	Stargardt disease 1; cone-rod dystrophy 3; fundus flavimaculatus; retinal dystrophy, early-onset severe; retinitis pigmentosa 19; macular degeneration, age-related, ²
ELOVL4	Elongation of very long chain fatty acids-like 4	AD	Stargardt disease 3; ichthyosis, spastic quadriplegia and mental retardation
RDS (PRPH2)	Peripherin 2, mouse, homolog of	AD, incomplete penetrance	Macular dystrophy, patterned, ¹ ; macular dystrophy, vitelliform, 3; choroidal dystrophy, central areolar 2; leber congenital amaurosis 18; retinitis pigmentosa 7, and digenic; retinitis punctata albescens

REFERENCES:

- Allikmets et al., (1997) Science 19;277(5333):1805-7(PMID: 9295268)
- Allikmets et al., (1998) Gene 215:111-122(PMID: 9666097)
- Cremers et al., (1998) Hum Molec Genet 7:355-362(PMID: 9466990)
- Stone et al., (1998) Nat Genet 20:328-329(PMID: 9843201)
- Lewis et al., (1999) Am J Hum Genet 64:422-434(PMID:9973280)
- De La Paz et al., (1999) Ophthalmology 106:1531-1536(PMID: 10442900)
- Allikmets et al., (2000) Am J Hum Genet 67:793-799(PMID: 10970771)
- Rivera et al., (2000) Am J Hum Genet 67:800-813(PMID: 10958763)

9. Shroyer et al., (2001) Hum Molec Genet 10:2671-2678(PMID: 11726554)
10. Yatsenko et al., (2001) Hum Genet 108(4):346-55(PMID: 11379881)
11. Guymer et al., (2001) Arch Ophthalmol 119(5):745-51(PMID: 11346402)
12. Jaakson et al., (2003) Hum Mutat 22:395-403(PMID: 14517951)
13. Klevering et al., (2004) Eur J Hum Genet 12(12):1024-32(PMID: 15494742)
14. Wiszniewski et al., (2005) Hum Mol Genet 14(19):2769-78(PMID: 16103129)
15. Rozet et al., (1998) Eur J Hum Genet 6(3):291-5(PMID: 9781034)
16. Maugeri et al., (1999) Am J Hum Genet 64:1024-1035(PMID: 10090887)
17. Klevering et al., (2005) Graefes Arch Clin Exp Ophthalmol 243(2):90-100(PMID: 15614537)
18. Valverde et al., (2006) Mol Vis 12:902-908(PMID: 16917483)
19. Valverde et al., (2007) Invest Ophthalmol Vis Sci 48:985-990(PMID: 17325136)
20. Aleman et al., (2007) Invest Ophthalmol Vis Sci 48(3):1319-29(PMID: 17325179)
21. Yatsenko et al., (2003) Hum Mutat 21(6):636-44(PMID: 12754711)
22. Zhang et al., (2001) Nat Genet 27:89-93(PMID: 11138005)
23. Bernstein et al., (2001) Invest Ophthalmol Vis Sci 42: 3331-3336(PMID: 11726641)
24. Maugeri et al., (2004) Invest Ophthalmol Vis Sci 45:4263-4267(PMID: 15557430)
25. Boon et al., (2007) Br J Ophthalmol 91:1504-11(PMID: 17504850)
26. Gamundi et al., (2007) Mol Vision 13:1031-1037(PMID: 17653047)
27. Boon et al., (2008) Prog Retin Eye Res 27:213-35(PMID: 18328765)
28. Dryja et al., (1997) Invest Ophthalmol Vis Sci 38:1972-82(PMID: 933126)
29. Braun et al. (2013) Human Molecular Genetics 22 (25):5136-45 (PMID: 23918662)
30. Zernant et al. (2014) Hum. Mol. Genet. 23 (25):6797-806 (PMID: 25082829)
31. Bauwens et al. (2015) Hum. Mutat. 36 (1):39-42 (PMID: 25346251)
32. Schulz et al. (2017) Invest. Ophthalmol. Vis. Sci. 58 (1):394-403 (PMID: 28118664)