

BEST1 (VMD2) gene analysis in Bestrophinopathies

Disorder also known as: Best Vitelliform Macular Dystrophy (BVMD); Autosomal Recessive Bestrophinopathy (ARB); Autosomal Dominant Vitreoretinopathy; Autosomal Dominant Retinitis Pigmentosa (adRP); Adult-onset Foveomacular Vitelliform Dystrophy

Clinical Features:

Best Vitelliform Macular Dystrophy (BVMD): BVMD is characterized by the subretinal accumulation of yellowish material “egg yolk-like” unique lesion in the macular area. It is a slowly progressive evolving through distinct clinical stages characterized by the progression of the to this disorder. During the distinct clinical stages and transformations of the lesions, the patient’s central vision acuity and metamorphopsia continues to decrease while the peripheral vision and dark adaptation remain normal. The electrooculogram (EOG) is always abnormal and the full field electroretinogram (ERG) is normal. It is interesting to note that both the age of onset as well as the severity of vision loss demonstrates inter and intra-familial variability.^{1,5,6,9}

Autosomal Recessive Bestrophinopathy (ARB): Fundus eye exam shows dispersed punctate flecks, which are distinct from the extramacular vitelliform lesions. These patients also have an accumulation of fluid within and/or beneath the neurosensory retina in the macular region. These patients are hyperopic and may also have angle-closure glaucoma. Other typical features include a severe reduction in the EOG light rise and a reduced or delayed response for both cones and rods on full-field ERGs. These patients do not have vitelliform lesions.^{1,2}

Autosomal Dominant Vitreoretinopathy: This disorder is characterized by a peripheral retinal circumferential hyperpigmented band, vitreous fibrillar condensation, retinal neovascularization, and punctuate white opacities in the retina. A recent report of a three-generation pedigree noted ocular abnormalities including nanophthalmos, closed angle glaucoma, microcornea, and congenital cataract.^{1,10}

Autosomal Dominant Retinitis Pigmentosa (adRP): This disorder is characterized by a progressive degeneration of the retina that leads to severe visual impairment in the 5th to 6th decade of life. It usually manifests with decline and loss of night vision during adolescence, followed by loss of side 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, attenuated retinal vessels, abnormal, diminished, or absent ERG findings.

Adult-onset Foveomacular Vitelliform Dystrophy: Unlike BVMD, this disorder has a later age of onset, smaller lesion size, slower progression, and a slightly subnormal to normal EOG. The clinical presentation of this disorder is variable and may present as a pattern dystrophy or as BVMD, leading to misdiagnosis. The full-field ERG is also usually normal.^{1,5,8}

Inheritance Pattern/Genetics:

Best Vitelliform Macular Dystrophy (BVMD): Autosomal dominant with inter- and intra-familial variability

Autosomal Recessive Bestrophinopathy: Autosomal recessive

Vitreoretinopathy: Autosomal dominant

Retinitis Pigmentosa: Autosomal dominant

Adult-onset Foveomacular Vitelliform Dystrophy: Autosomal dominant with most cases appearing to be “sporadic”

Test Methods:

Using genomic DNA obtained from a blood sample in EDTA or buccal sample, bi-directional sequence of the coding exons of the BEST1 gene (exons 2-11) and their splice junctions is obtained and analyzed. Any variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. As pathogenic variants resulting in haploinsufficiency have been reported in the BEST1 gene, it is possible that deletions/duplications of one or more exons may play a role in this disorder. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of the BEST1 gene.

Test Sensitivity:

Best Vitelliform Macular Dystrophy: approximately 96% of patients with a family history of BVMD and 69% of patients with no family history were found to carry a pathogenic variant in the BEST1 gene.^{5,6,9}

Autosomal Recessive Bestrophinopathy: All affected individuals from the five reported ARB families, were either homozygous or compound heterozygous for loss-of-function variants in the BEST1 gene.²

Autosomal Dominant Vitreoretinopathy: Missense variants were identified in all affected families.¹⁰

Autosomal Dominant Retinitis Pigmentosa (adRP): (See adRP testing at GeneDx) 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 genes.⁴

Adult-onset Foveomacular Vitelliform Dystrophy: approximately 25-33% of patients with this disorder are heterozygous for a variant in the BEST1 gene.^{1,5,8}

References:

1. Boon et al., (2009) Progress in Retinal and Eye Research 28:187-205.
2. Burgess et al., (2008) Am J Hum Genet 82:19-31.
3. Burgess et al., (2009) J Med Genet 46:620-625.
4. Davidson et al., (2009) Am J Hum Genet 85:581-592.
5. Kramer et al., (2000) Eur J Hum Genet 8:286-292.
6. Kramer et al., (2003) Hum Mutat Mutation in Brief #660 Online.
7. Lafaut et al., (2001) Arch Clin Exp Ophthalmol 239:575-582.
8. Seddon et al., (2001) Ophthalmology 108:2060-2067.
9. White et al., (2000) Hum Mutat 15:301-308.
10. Yardley et al., (2004) Invest Ophthalmol Vis Sci 45:3683-3689.