**BEST1-related Disorders: BEST1 Gene Sequencing**

**Test Code:** SBEST  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81406 x1

### Condition Description

Pathogenic variants in the *BEST1* gene (11q12), also known as *VMD2*, have been associated with several ocular phenotypes. The *BEST1* gene encodes the bestrophin-1 protein, which is expressed in the retinal pigment epithelium and has also been detected in the kidney, brain, spinal cord, and testis. The most common *BEST1*-related disorder is best vitelliform macular dystrophy (BVMD). Pathogenic variants in the *BEST1* gene cause several clinically distinct disorders.

**Best Vitelliform Macular Dystrophy (BVMD)**
BVMD is a slowly progressive macular dystrophy that is inherited in an autosomal dominant manner. Onset is typically in childhood. Individuals with BVMD present with decreased central visual acuity and metamorphopsia. They retain normal dark adaptation and peripheral vision. Inter- and intrafamilial variability is seen regarding severity of vision loss and age of onset. The abnormalities observed in BVMD are restricted to the macula.

**Autosomal Dominant Vitreoretinochoroidopathy (ADVIRC)**
ADVIRC is characterized by a peripheral circumferential retinal band of pigmentary alterations, fibrillary vitreous condensations, punctate white pre or intraretinal deposits, and midperipheral and peripapillary chorioretinal atrophy. Most individuals with ADVIRC retain a fairly good visual acuity throughout life. Additional features include congenital or early-onset cataracts, microcornea, hypermetropic, and shallow anterior chamber.

**Autosomal Recessive Bestrophinopathy (ARB)**
Two pathogenic variants in *BEST1* cause the clinically distinct autosomal recessive ARB, which is characterized by central visual loss and hyperopia. The age of onset ranges from 4 to 40 years of age with the average being in the 20s.

Other rare clinical presentations associated with pathogenic variants in *BEST1* have also been described.

### References:

- GeneReviews
- OMIM #607852: BEST1 gene

### Genes

**BEST1**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of a *BEST1*-related disorder.
- Carrier testing in adults with a family history of a *BEST1*-related disorder.

### Methodology

PCR amplification of 9 exons contained in the *BEST1* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence deoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: BVMD Positive Family History – 96%; Negative Family History – 50-70%; ADVIRC and ARB - unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

### Specimen Requirements

Submit only 1 of the following specimen types

**Type:** DNA, Isolated

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Specimen Requirements:
- Microtainer
- 8µg
Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
- Orangene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions
Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests
- Deletion/duplication analysis of the BEST1 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Several comprehensive next generation sequencing Eye Disorder Panels are available.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.

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