

BRAF-related Disorders: BRAF Gene Sequencing

Test Code: SBRAF

Turnaround time: 4 weeks

CPT Codes: 81406 x1

Condition Description

Germline mutations in the *BRAF* gene have been reported to be associated with cardiofaciocutaneous (CFC) syndrome. Somatic mutations in *BRAF* have also been reported at a high frequency in numerous cancers.

CFC Syndrome

Cardiofaciocutaneous (CFC) syndrome is characterized by features in three primary systems: cardiac, craniofacial, and ectodermal; however, other systems may be involved as well. Cardiac abnormalities can include pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, and rhythm disturbances. Individuals with CFC syndrome have a distinctive craniofacial appearance. Ectodermal features include skin findings, such as xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophorogenes, eczema, pigmented moles, palmoplantar hyperkeratosis; hair findings such as sparse, curly, fine or thick, woolly, or brittle hair, and possible absent eyelashes and eyebrows; and the nails may be dystrophic or fast growing. Cognitive delay (ranging from mild to severe) is seen in all affected individuals. Neoplasias have been reported in some individuals with CFC.

There are four genes known to be associated with CFC. Mutations in the *BRAF* gene account for ~75% of cases, *MAP2K1* and *MAP2K2* account for ~25% of cases, and *KRAS* accounts for <2% of cases. CFC syndrome is inherited in an autosomal dominant manner; however, most cases of CFC syndrome arise *de novo*.

[Click here](#) for the GeneTests summary on CFC syndrome.

Cancer

Somatic mutations in *BRAF* have been reported at a high frequency in numerous cancers including melanoma, thyroid, colorectal, and ovarian. One mutation, p.V600E, which results in increased kinase activity, accounts for more than 90% of *BRAF* mutations identified in human cancer. The presence of the p.V600E *BRAF* mutation in microsatellite instability high (MSI-H) colorectal cancers provides evidence that the cancer is sporadic and not caused by Lynch syndrome.

Testing for the p.V600E *BRAF* mutation can be ordered by marking "Other test" and then test code KM next to it on the test requisition. Do this by writing "p.V600E BRAF, KM."

Please note that this test is for the *BRAF* (7q35) gene only.

References:

- Bettstetter, M. *et al.* Distinction of hereditary nonpolyposis colorectal cancer and sporadic microsatellite-unstable colorectal cancer through quantification of *MLH1* methylation by real-time PCR. *Clin Cancer Res.* 2007; 13:3221-3228.
- Domingo, E. *et al.* *BRAF* screening as a low-cost effective strategy for simplifying HNPCC genetic testing. *J Med Genet.* 2004; 41:664-668.

Genes

[BRAF](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of a CFC syndrome

Methodology

PCR amplification of 18 exons of the *BRAF* 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 dideoxy 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, other regulatory elements, or the remaining 11 exons, and does not detect large deletions.

Detection

Clinical Sensitivity: *BRAF* mutations have been implicated in 75-80% of cases of CFC syndrome. Mutations in the promoter region and some mutations in the introns and other regulatory elements 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 biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Oragene™ 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.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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.

Related Tests

- Deletion/duplication analysis is available if sequencing is negative.
- Sequence and deletion/duplication analysis of the *KRAS*, *SOS1*, *RAF1*, *MAP2K1*, *MAP2K2* and *PTPN11* genes 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 to couples who have had a previously affected child with an identified mutation. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.