

Cardio-Facio-Cutaneous (CFC) Syndrome Testing via Sequencing of Selected *BRAF*, *KRAS*, *MEK1* and *MEK2* Gene Exons Sequential (Standard) Test – Test #110;

Brief Description: Cardio-Facio-Cutaneous (CFC) Syndrome is a rare disorder characterized by distinctive facial appearance, skin abnormalities, heart malformations and/or mental retardation. Dysmorphic features may include: macrocephaly with bitemporal constriction, a short, upturned nose with a low nasal bridge, and/or prominent external ears that are posteriorly angulated. Affected individuals may also have palpebral fissures, ocular hypertelorism, ptosis, esotropia, dry, brittle, curly scalp hair, and often lack eyebrows and eyelashes. For further information see <http://www.cfcsyndrome.org/> and Reynolds et al. Am J Med Genet 25:413-427, 1986.

Genetics: Rodriguez-Viciana et al. (Science 311:1287-1290, 2006) identified mutations in the MAPK pathway genes: *BRAF*, *MAP2K1* (*MEK1*) and *MAP2K2* (*MEK2*) as a cause of CFC. *BRAF* mutations were found in 78% of the 23 CFC patients studied and an additional 13% had mutations in *MEK1* or *MEK2*. More recently, researchers from Japan (Niihori et al. Nature Genet 38:294-296, 2006) confirmed the *BRAF*/CFC connection with *BRAF* mutations seen in 16 of 43 patients studied. They also demonstrated mutations in the *KRAS* gene in 3 other patients. Schubert et al. (Nature Genet 38:331-336, 2006) confirmed the *KRAS*/CFC link. All mutations reported to date have been *de novo*.

Description of This Particular Test: Clinical testing for CFC is performed at PreventionGenetics in two separate tests. Test 1 has two tiers: tier 1 involves initial sequencing of a panel of seven *BRAF* exons demonstrated to contain causative mutations (exons 6, 11-16). If a likely causative mutation is found here, the test stops; if not, the test continues with tier 2 sequencing of *MEK1* (exons 2 & 3), *MEK2* (exons 2 & 3) and *KRAS* (exons 2, 3, 4, 4a, and 4b) where additional causative mutations have been demonstrated. Test 2 involves sequencing of the remaining *BRAF* exons (1-5, 7-10, 17-18) where causative mutations have not yet been reported. This second test will only be performed if specifically requested.

Indications for Test: Candidates for this test are patients with symptoms consistent with a diagnosis of CFC. Symptoms of CFC patients overlap with those for Costello and Noonan Syndrome patients. CFC patients who test negative for the *BRAF*, *MEK1*, *MEK2* and *KRAS* genes may be candidates for *HRAS* (Costello) or *PTPN11* (Noonan) testing at PreventionGenetics. Conversely, Costello or Noonan Syndrome patients who test negative for *HRAS* or *PTPN11*, respectively, may be candidates for all or a portion of our CFC test.

Sensitivity of Test: Based on limited data reported in the literature, in a patient with clinically clear CFC, we estimate the sensitivity of this test to be between ~91% (Rodriguez-Viciana et al. 2006) and ~44% (Niihori et al. 2006).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Test 1: Sequence analysis of the <i>BRAF</i> gene exons 6, 11-16 (7 exons)	\$490
If a causative mutation is found in the <i>BRAF</i> exons, you will not be charged for the second half of testing. If negative then:	
Sequence analysis of <i>MEK1</i> and <i>MEK2</i> (exons 2, 3), and <i>KRAS</i> (exons 2, 3, 4, 4a, 4b)(9 exons) an additional	\$500
(for a total of	\$990)
Test 2: If test 1 is negative and ONLY IF SPECIFICALLY REQUESTED	
Sequence analysis of the remaining 11 <i>BRAF</i> gene exons	an additional \$790

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x16	83898	\$ 320	Sequencing x16	83904	\$ 470
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 90

Single exon sequencing for the presence of previously identified mutations in any of the *CFC* genes is also available for \$190.

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact for info: Dr. Khemissa Bejaoui, khemissa@preventiongenetics.com, www.preventiongenetics.com