

Costello Syndrome via *HRAS* Gene Sequencing

Brief Description: Costello Syndrome is a multiple congenital anomaly syndrome that overlaps phenotypically with Noonan and Cardio-Facio-Cutaneous (CFC) Syndromes. Symptoms include short stature, curly hair, thick and loose skin of the hands and feet, papillomata around the nose and mouth, mental retardation, cardiomyopathy, and benign tumors.

Genetics: Aoki et al. (*Nature Genetics*, 37:1038-1040, 2005) found heterozygous, *de novo* mutations in the *HRAS* gene in 12 of 13 Costello Syndrome patients. The mutations were all located in either codon 12 or 13 of exon 2. In a second publication, Gripp, et al., (*Am.J.Med.Genet. E* Pub 2005.) demonstrated *de novo* exon 2 mutations in 33 of 40 Costello Syndrome patients with the mutations again located in either codon 12 or 13. More recently, Kerr et al. (*J. Med. Genet. E* pub 1/2006) documented a potential causative mutation in codon 117 (K117R) (exon 4 by GeneWindow nomenclature). To date, no other causative mutations have been reported elsewhere in the *HRAS* gene.

Description of This Particular Test: The coding region for the primary *HRAS* mRNA is contained within four exons (exons 2, 3, 4 and 6; GeneWindow nomenclature). Clinical testing for causative *HRAS* mutations is performed at PreventionGenetics as one test with two tiers. Tier 1 involves sequencing of *HRAS* exon 2. If a likely causative mutation is found here, the test stops and is billed as described below. If Tier 1 is negative, testing continues with sequencing of *HRAS* exons 3, 4 and 6. Our testing involves the complete sequencing of genomic DNA containing the coding regions of these exons plus additional non-coding, flanking DNA.

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

Sensitivity of Test: Based on current literature, 82-92% of patients with well defined Costello Syndrome will have a causative mutation in the *HRAS* gene. Tier 1 testing (*HRAS* exon 2) should detect over 90% of these mutations.

Turn Around Time: Maximum of 40 days, although many tests are completed in less than 2 weeks.

Specimen Requirements: See page 4 of the Requisition Form

Tier 1: Sequence analysis of the *HRAS* gene exon 2 **\$190.00**
 If a causative mutation is found in *HRAS* exon 2, testing stops and you will not be charged for the second half of testing. If negative then:
Tier 2: Sequence analysis of *HRAS* gene exons 3, 4, 6 for an additional **\$260.00** **(total of \$450.00)**

Ascertainment	83890	\$30
DNA Isolation	83891	\$40
Amplification x 4	83898	\$80
Mutation Ident by Sequencing, Single Seg x 4	83904	\$120
Separation	83894	\$60
Interpretation and Report	83912	\$120

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