

Costello Syndrome: *HRAS* Gene Sequencing

Test Code: SHRAS

Turnaround time: 4 weeks

CPT Codes: 81404 x1

Condition Description

Costello syndrome is characterized by developmental delay, intellectual disability, diffuse hypotonia, failure to thrive in infancy (due to severe postnatal feeding difficulties), short stature, coarse facial features (full lips, large mouth); curly or sparse, fine hair; loose, soft skin, and tight Achilles tendons. Cardiac features includes cardiac hypertrophy, congenital heart defect, and arrhythmias. Individuals with Costello syndrome have an approximately 15% lifetime risk for malignant tumors. The solid tumors rhabdomyosarcoma and neuroblastoma occur most frequently in young children. Adolescents and young adults are at risk for transitional cell carcinoma of the bladder.

The *HRAS* gene is the only gene (11p15.5) currently known to be associated with Costello syndrome. In patients with a clinical diagnosis of Costello syndrome, 80-90% of mutations in the *HRAS* gene can be identified. Mutations in the *HRAS* gene are inherited in an autosomal dominant manner; however most individuals with Costello syndrome has a de novo mutation. Please note that the *HRAS* gene is part of the Ras/MAKP pathway and other syndromes should be considered as alternative diagnoses if an *HRAS* mutation is not identified.

For patients with suspected Costello syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

References:

- GeneReviews
- [OMIM #218040](#): Costello syndrome
- [OMIM #190020](#): *HRAS* gene

Genes

[HRAS](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Costello syndrome.
- Carrier testing in adults with a family history of Costello syndrome.

Methodology

PCR amplification of 4 exons contained in the *HRAS* 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, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: 80-90%. 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

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.

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.

Related Tests

- Deletion/duplication analysis of the *HRAS* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Please note that the *HRAS* gene is part of the Ras/MAKP pathway and other syndromes should be considered as alternative diagnoses if an *HRAS* mutation is not identified.
- 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.