Costello Syndrome: HRAS Gene Deletion/Duplication

**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 in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of Costello syndrome in whom sequence analysis was negative.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**
Specimen Requirements:
Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### 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

- Sequence analysis of the HRAS gene is available and is required before deletion/duplication analysis.
- 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.