EGL Genetics | Eurofins Clinical Diagnostics
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# *KRAS*-related Disorders: *KRAS* Gene Sequencing

**Test Code:** ZG
**Turnaround time:** 4 weeks
**CPT Codes:** 81405 x1

## Condition Description

Germline mutations in the *KRAS* gene have been reported to be associated with two distinct syndromes: Noonan syndrome and cardiofaciocutaneous (CFC) syndrome. These syndromes share a common pattern of congenital anomalies, including typical heart defects, overlapping craniofacial dysmorphisms, short stature, and a variable degree of mental retardation. *KRAS* is also one of the most activated oncogenes in human cancer.

**Noonan Syndrome**
Noonan syndrome (NS) is an autosomal dominant dysmorphology syndrome characterized by short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, ocular abnormalities, and deafness. Characteristic facies include hypertelorism, downward sloping palpebral apertures, epicanthal folds, ptosis, and low-set posteriorly rotated ears. Early feeding difficulties such as poor suck or gastrointestinal dysfunction are also common. Although birth length is usually normal, final adult height approaches the lower limit of normal. Up to one-third of affected individuals have mild mental retardation. *KRAS* mutations have been implicated in 5% or less of cases of Noonan syndrome.

Click here for the GeneTests summary on Noonan syndrome.

**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 oophorogenes, 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**
*KRAS* is said to be one of the most activated oncogenes, with 17 to 25% of all human tumors harboring an activating *KRAS* mutation. *KRAS* mutations described to date in patients with Noonan syndrome/CFC are distinct from those found in malignancies.

Based on the provisional clinical opinion released by the American Society of Clinical Oncology in January, 2009, it is recommended that all patients with colorectal cancer (CRC) have tumors tested for *KRAS* oncogene prior to therapy. It is estimated that the incidence of the *KRAS* mutations in CRC is approximately 35-45%. Detection of *KRAS* mutations in CRC is beneficial in identifying patients who will benefit from treatment which in turn will improve the clinical outcome and help in determining the best therapy strategy. If a *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.

For patients with suspected *KRAS*-related conditions, 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.

Please note that this test is for the *KRAS* (12p12.1) gene only.

**References**
(1) Allegra, C. et al. American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti?Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. 2009. J Clin Oncol 27:2091-2096.
(2) Zenker, M. et al. Expansion of the genotypic and phenotypic spectrum in patients with KRAS germline mutations. 2007. J Med Genet 44:131-135.

## Genes

KRAS

## Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of a *KRAS*-related condition
- Individuals at-risk for a *KRAS*-related condition due to family history
- Testing of colorectal cancer tissue for therapeutic decisions

## Methodology

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PCR amplification of 4 exons contained in the *KRAS* 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: *KRAS* mutations have been implicated in 5% or less of cases of Noonan syndrome. *KRAS* mutations have been implicated in 5% or less of cases of CFC syndrome. 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 biochemical phenotype.

Analytical Sensitivity: ~99%

## Specimen Requirements

***Submit only 1 of the following specimen types***

### 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.

### Type: Saliva

**Specimen Requirements:**
Oragene™ Saliva Collection Kit
Orangene™ 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.

## Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

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

- Sequencing and deletion/duplication analysis of the *PTPN11* gene for Noonan syndrome is also available.
- Sequencing and deletion/duplication analysis of the *BRAF* and *MAP2K2* genes for CFC syndrome are also available.
- Deletion/duplication analysis of the *KRAS* gene by CGH array is available for those individuals in whom sequence analysis is negative.

- 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 adults who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.