Noonan Syndrome and Related Disorders: Sequencing Panel

Condition Description

The Ras/mitogen activated protein kinase (MAPK) pathway is involved in the control of the cell cycle and differentiation. Because of this critical role, a disruption in the pathway results in congenital developmental conditions. A class of human genetic syndromes, called the rasopathies, are caused by germline mutations in the genes in this pathway. The rasopathies, while distinct syndromes, share some overlapping features such as craniofacial dysmorphology, varying degrees of neurocognitive impairments, cutaneous, ocular, and musculoskeletal abnormalities, and cardiac malformations. Some syndromes have an increased risk of cancer.

Noonan Syndrome

Noonan syndrome (NS) is an autosomal dominant disorder characterized by congenital heart defects, short stature, developmental delay, distinctive craniofacial features that change with age, broad or webbed neck, unusual chest shape, apparently low-set nipples and cryptorchidism. About one third of individuals with NS have mild intellectual disability. Individuals with NS have an increased risk for cancer.

There are seven genes known to cause NS; PTPN11, SOS1, RAF1, KRAS, NRAS, BRAF, and MAP2K1. Approximately 50% of NS cases are caused by mutations in the PTPN11 gene, 10%-13% by the SOS1 gene, 3-17% by the RAF1 gene, and fewer than 5% by the KRAS. Fewer than 1% of cases are caused by mutations in the NRAS, BRAF, and MAP2K1 genes.

LEOPARD Syndrome

LEOPARD syndrome (LS) is an autosomal dominant disorder characterized by features that make up the acronym LEOPARD. They are lentigens, EKG abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth, and sensorinerral deafness. Like NS, up to one third of individuals with LS have mild intellectual disability.

Three genes are known to cause LS; PTPN11, RAF1, and BRAF. Approximately 90% of LS cases are caused by mutations in the PTPN11 gene. Fewer than 5% of LS cases are caused by mutations in the RAF1 or the BRAF gene.

Cardiofaciocutaneous Syndrome

Cardiofaciocutaneous (CFC) syndrome is an autosomal dominant disorder 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 hyperkeratoses; 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; BRAF, MAP2K1, MAP2K2, and KRAS. 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.

Costello Syndrome

Costello syndrome is an autosomal dominant disorder 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 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 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.

Noonan-Like Syndrome with Loose Anagen Hair

Noonan-like syndrome with loose anagen hair (NS/LAH) is an autosomal dominant disorder characterized by facial features similar to Noonan syndrome, reduced growth, intellectual disability, distinctive hyperactive behavior, and hair anomalies. The hair is typically sparse, thin, easily pluckable, and slow growing. Additional features include hairless skin that is darkly pigmented, eczema or ichthyosis, sparse eyebrows, thin or dystrophic nails, hypernasal or hoarse voice, and cardiac anomalies.

The SHOC2 gene in the only gene known to be associated with NS/LAH.

References:
- GeneReviews

Genes

BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1

Indications
Confirmation of a clinical diagnosis of Noonan syndrome or a related disorder.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Noonan syndrome - 70-88%, Leopard syndrome – 95%, CFC - unknown, Costello syndrome – 80-90%, NS/LAH - unknown. 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: 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: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:

In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Single gene sequencing and deletion/duplication analysis are available for the PTPN11, SOS1, RAF1, KRAS, HRAS, BRAF, MAP2K1, MAP2K2, SHOC2 and NRAS genes.
- A next generation sequencing panel is available for short stature.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.

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