Cardiovascular Diseases Genetic Testing Program

RASopathy/Noonan Spectrum Panel

RASopathies, including Noonan spectrum disorders are genetically heterogeneous conditions which overlap with a spectrum of other disorders, including cardio-facio-cutaneous (CFC) syndrome, LEOPARD syndrome, and Costello syndrome. Clinical features of RASopathies/Noonan spectrum disorders include short stature, cardiovascular disease (pulmonary valve stenosis and hypertrophic cardiomyopathy), characteristic facies, and developmental delay. Findings in the hematologic, skeletal, and cutaneous systems can also be associated with the spectrum of disorders. All of the RASopathy/Noonan spectrum disorders demonstrate autosomal dominant inheritance.

Noonan syndrome
Noonan syndrome is characterized by short stature, cardiovascular disease, and a varying degree of developmental delay. Common findings in Noonan syndrome include broad/webbed neck, chest wall abnormalities, cryptorchidism, characteristic facies, coagulation problems, ocular abnormalities, and lymphatic dysplasias. The diagnosis of Noonan syndrome can be made through clinical assessment. Mutations in *PTPN11* account for approximately 50% of cases of Noonan syndrome; however mutations in *SOS1*, *RAF1*, *KRAS*, *NRAS*, *RIT1*, and *SHOC2* have also been reported.

Cardio-Facio-Cutaneous (CFC) syndrome
CFC syndrome is characterized by cardiac, ectodermal abnormalities, and characteristic facies. Cardiac findings can include pulmonary valve stenosis or other valve dysplasias, septal defects, hypertrophic cardiomyopathy, and rhythm disturbances. Other common features include sparse, curly or slow-growing hair and skin abnormities such as atopic dermatitis and hyperkeratosis with ichthyosis-like lesions. Mild to severe intellectual disability is seen in the majority of individuals with CFC syndrome. Mutations in *BRAF* account for approximately 75% of cases of CFC syndrome; however mutations in *MAP2K1*, *MAP2K2*, and *KRAS* have also been reported.

LEOPARD syndrome (Noonan Syndrome with Multiple Lentigines)
LEOPARD syndrome is an acronym for the cardinal features (**L**entigines, **E**CG conduction abnormalities, **O**cular hypertelorism, **P**ulmonic stenosis, **A**bnormal genitalia, **R**etardation of growth, and sensorineural **D**eafness). Mutations in *PTPN11* (mainly exons 7, 12, and 13) have been detected in the majority of cases of LEOPARD syndrome; however mutations in *RAF1* have also been reported.

Costello syndrome
Costello syndrome is characterized by failure to thrive due to postnatal feeding difficulties, short stature, developmental delay, skeletal anomalies, typical craniofacial features, cardiac abnormalities, and an increased risk for malignant tumors. Cardiac findings can include pulmonary valve stenosis, septal defects, hypertrophic cardiomyopathy, or rhythm disturbances. Coarse facial features can be seen, as well as, curly or sparse hair, and hypertonia. Specific sequence variants in the *HRAS* gene are associated with Costello syndrome.

Other RASopathies include Neurofibromatosis type 1 (*NF1*), Leginus syndrome (*SPRED1*), Capillary Malformations-Arteriovenous Malformation (*RASA1*), and Noonan Syndrome-Like Disorder with Loosen Anagen Hair (*SHOC2*).

Indication
The RASopathy/Noonan spectrum panel is indicated for individuals with clinical suspicion for a RASopathy/Noonan spectrum disorder.

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

Methodology:

Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

Validation testing indicates an analytic sensitivity of greater than 99.8% and an analytic specificity of 100%.

Based on the literatures, the clinical validity is determined to be:

- 71%-88% for Noonan syndrome
- Greater than 95% for LEOPARD syndrome
- Greater than 99% for CFC syndrome
- 80-90% for Costello syndrome

References:

Allanson JE, Roberts AE. (Updated [August 4, 2011]). Noonan syndrome. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [7/27/2015].

Gelb BD, Tartaglia M. (Updated [May 14, 2015]). Noonan syndrome with multiple lentigines. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [7/27/2015].

Gripp KW, Lin AE. (Updated [January 12, 2012]). Costello syndrome. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [7/27/2015].

Rauen KA. (Updated [September 6, 2012]). Cardiofaciocutaneous syndrome. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.genetests.org. Accessed [7/27/2015].

CPT Codes:

Panel: 81442
Known Mutation Testing: 81403 or 81479, *PTEN* 81322

Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 513-636-4474

Turnaround Time:

Full Mutation Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

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Gene	RASopathy/Noonan Spectrum Panel	Prenatal RASopathy/Noonan Spectrum Panel	Prenatal Noonan Spectrum Reflex Panel	Panel CPT Code	Full gene sequencing CPT Code	Known mutation sequencing CPT Code
BRAF	x	x		81442	81406	81403
A2ML1	x		x		81479	81479
CBL	x		x		81479	81479
HRAS	x	x			81404	81403
KRAS	x	x			81405	81403
LZTR1	x	x			81479	81479
MAP2K1	x	x			81406	81403
MAP2K2	x	x			81406	81403
NF1	x		x		81408	81403
NF2	x		x		81406	81403
NRAS	x	x			81479	81479
PTEN	x		x		81321	81322
PTPN11	x	x			81407	81403
RAF1	x	x			81407	81403
RASA1	x		x		81479	81479
RASA2	x		x		81479	81479
RIT1	x	x			81479	81479
RRAS	x		x		81479	81479
SHOC2	x		x		81405	81403
SOS1	x	x			81406	81403
SOS2	x	x			81479	81479
SPRED1	x		x		81405	81403
TBCK	x		x		81479	81479
TSC1	x		x		81479	81479
TSC2	x		x		81479	81479