

NOONAN SYNDROME AND RASOPATHIES PANEL: INCLUDING CARDIOFACIOCUTANEOUS SYNDROME, COSTELLO SYNDROME AND LEOPARD SYNDROME

The Noonan syndrome and RASopathies panel includes testing for the following disorders: Noonan syndrome, Noonan-like syndrome, Cardio-facio-cutaneous (CFC) syndrome, Costello syndrome and LEOPARD syndrome. This genetically heterogeneous group of disorders is associated with a defect of the RAS/MAPK signalling pathway. The clinical phenotypes overlap and include the following hallmark features: facial dysmorphology, cardiac defects (such as pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, rhythm disturbances), short stature, deafness, motor and cognitive delay of varying degrees, predisposition to tumors (including including rhabdomyosarcoma, neuroblastoma, ALL and transitional cell carcinoma) and prenatal presentation of lymphedema.

GENETICS

The inheritance of Noonan syndrome, CFC syndrome, Costello syndrome and LEOPARD syndrome is autosomal dominant. Most individuals have the condition as a result of a *de novo* pathogenic variant in one of the genes listed below.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with Noonan syndrome, CFC syndrome, Costello syndrome and LEOPARD syndrome.
- The relatives of a proband with identified pathogenic variant(s) in one of the Noonan spectrum disorder genes.

PRENATAL TESTING

Most of the features of Noonan syndrome are not identified in the 1st or 2nd trimester of pregnancy, although 1st trimester cystic hygroma has been associated with a clinical diagnosis of Noonan syndrome in 1-4% of cases with normal karyotype.

Fetuses at increased risk due to a family history of Noonan syndrome, CFC syndrome, Costello syndrome and LEOPARD syndrome or an ultrasound finding of lymphedema and/or cystic hygroma are eligible for prenatal testing.

TEST METHODS

Complete sequencing of the coding region and flanking intron/exon boundaries of the genes listed in the table below. This is done via NGS of a targeted panel of genes associated with Noonan spectrum disorders. Please refer to our "A Guide to Next-Generation Sequencing" information sheet available on our website, for further details.

Deletion/duplication analysis is available for the *SPRED1* gene by MLPA.

Genes on the panel	Condition variants in gene are associated with
BRAF	Noonan syndrome and CFC syndrome
CBL	Noonan-like syndrome
HRAS	Costello syndrome
KRAS	Noonan syndrome and CFC syndrome
MAP2K1	CFC syndrome
MAP2K2	CFC syndrome
NRAS	Noonan syndrome
PTPN11	Noonan syndrome and LEOPARD syndrome
RAF1	Noonan syndrome and LEOPARD syndrome
RIT1	Noonan syndrome
SHOC2	Noonan-like syndrome
SOS1	Noonan syndrome
SOS2	Noonan syndrome
SPRED1	Legius syndrome
LZTR1	Noonan syndrome

For More Information

GeneReviews

- <http://www.ncbi.nlm.nih.gov/books/NBK1124> - <http://www.ncbi.nlm.nih.gov/books/NBK1507/>
- <http://www.ncbi.nlm.nih.gov/books/NBK1186/> - <http://www.ojrd.com/content/3/1/13>

SickKids Genomic Diagnostics Laboratory:
www.sickkids.ca/genome-diagnostics

To locate a genetics center near you:

Canadian Association of Genetic Counsellors (CAGC):
www.cagc-accg.ca

National Society of Genetic Counselors (NSGC):
www.nsgc.org/



1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of Noonan, CFC, Costello or LEOPARD syndrome.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.