LABupdate

Noonan Syndrome and Related Conditions

Noonan syndrome (NS) is characterized by short stature, facial dysmorphisms, and congenital heart defects such as hypertrophic cardiomyopathy, pulmonary valve stenosis, and other structural defects (for example, atrial or ventricular septal defects or tetralogy of Fallot).[1,2] Additional manifestations of Noonan syndrome include coagulation defects, a short or webbed neck and an unusual chest shape, cryptorchidism in males, hearing loss, ocular abnormalities, lymphatic dysplasias, developmental delay, and mild intellectual disability.[1,2] Noonan syndrome is estimated to affect between 1 in 1000 and 1 in 2500 individuals.[1,2]

NS shows clinical overlap with a number of other, rarer syndromes, including LEOPARD (lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome, Costello syndrome (CS), and cardiofaciocutaneous syndrome (CFC).[1,2] Depending on the actual syndrome present, certain clinical features may be more severe. In addition, each syndrome is associated with specific manifestations or risks, such as bleeding diathesis or increased risk of certain hematological malignancies in the case of NS[1,2], increased risk of certain solid tumors in the case of CS[3], and increased risk of severe skin infections in the case of CFC.[4]

Noonan syndrome and related disorders can be caused by a mutation in one of several different genes. Clinical overlap of the various syndromes is explained by the fact that all of these genes code for components of the same intracellular signaling pathway, namely the RAS/MAPK signaling cascade.[1-6]

NS and related disorders are autosomal dominant conditions, with many cases of Noonan syndrome and the majority of cases of Costello syndrome and CFS being the result of *de novo* mutations.[1,3-5]

Genetic testing for Noonan syndrome and related disorders may[1,3-5]:

- Establish or confirm a clinical diagnosis of Noonan syndrome, LEOPARD syndrome, Costello syndrome, or cardiofaciocutaneous syndrome.
- Identify previously undiagnosed parents, siblings, and other relatives of patients with Noonan syndrome, LEOPARD syndrome, Costello syndrome, or cardiofaciocutaneous syndrome.
- Facilitate appropriate genetic counseling for family members.

Relevant Assays*

Test Name	Test No.
GeneSeq®: Cardio Noonan Syndrome and Related Conditions Profile	451441
GeneSeq®: Cardio Gene Specific Sequencing, NGS**	452053
Mutation-specific Sequencing, Whole Blood†	451382

* Visit the online Test Menu at www.LabCorp.com for more information, including a current list of included genes, test methodology, and specimen requirements. To request a sample shipping kit, please call 866-647-0735.
**Full Gene Sequencing for any gene(s) on any of the GeneSeq: Cardio panels
†Known mutation testing for any gene(s) on any of the GeneSeq: Cardio panels

References

1. Allanson JE. Noonan syndrome. GeneReviews Web site. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=noonan. Updated August 4, 2011. Accessed September 7, 2011.
2. Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. *Horm Res*. 2009;71:185-193.
3. Gripp KW, Lin AE. Costello syndrome. GeneReviews Web site. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=costello. Updated January 12, 2012. Accessed May 11, 2012.
4. Rauen KA. Cardiofaciocutaneous syndrome. GeneReviews Web site. Updated http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cfc. Updated March 3, 2016. Accessed June 21,2016.
5. Gelb BD, Tartaglia M. LEOPARD syndrome. GeneReviews Web site. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=leopard. Updated November 16, 2012. Accessed September 7, 2011.
6. Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr Opin Genet Dev*. 2009;19:230-236.

LabCorp