MAYO CLINIC
Mayo Medical Laboratories

TEST ID: PMNSR

POSTMORTEM NOONAN AND RELATED PANEL

USEFUL FOR

- Providing a comprehensive postmortem genetic evaluation in the setting of sudden cardiac death and suspicion for Noonan syndrome or related disorders
- Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the *BRAF*, *CBL*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *SHOC2*, and *SOS1* genes.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel; see **KVAR1 / Known Variant Analysis-1 Variant**, **KVAR2 / Known Variant Analysis-2 Variants**, or **KVAR3 / Known Variant Analysis-3+ Variants**. Contact Mayo Medical Laboratories to confirm the appropriate test code for targeted testing if testing for a gene not included on this panel is needed.

CLINICAL INFORMATION

Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity whose characteristic features can include short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. In approximately 20% to 30% of cases, Noonan syndrome and related disorders are associated with hypertrophic cardiomyopathy, which may lead to sudden cardiac death. Postmortem diagnosis of Noonan syndrome or a related disorder may assist in confirmation of the cause of death, as well as risk assessment in living family members. Other heart defects associated with Noonan syndrome and related disorders include pulmonary valve stenosis (20–50%), atrial septal defects (6–10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults.

REFERENCE VALUES

An interpretive report will be provided.

ANALYTIC TIME

6 weeks

SPECIMEN REQUIRED

PREFERRED

Type
Tissue

Container/Tube
Tissue block

ACCEPTABLE

Type
Blood spot

Container/Tube
Whatman FTA Classic Card or Whatman Protein Saver 903 Card

Specimen Volume
3–5 blood spots

01/2018

The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: *PTPN11*, *RAF1*, *SOS1*, and *KRAS*. Heterozygous mutations in *NRAS*, *HRAS*, *BRAF*, *SHOC2*, *MAP2K1*, *MAP2K2*, and *CBL* have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a pathogenic variant in approximately 75% of affected individuals. NS can be sporadic and due to new (de novo) mutations; however, an affected parent can be recognized in 30% to 75% of families.

Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that *PTPN11* mutations are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with *RAF1* mutations, but rarely associated with *PTPN11*.

A number of related disorders exist that have phenotypic overlap with NS and are caused by mutations in the same group of genes. *PTPN11* and *RAF1* mutations have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Mutations in *BRAF*, *MAP2K1*, *MAP2K2*, and *KRAS* have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with mutations in *HRAS*. Variation in *SHOC2* has been associated with a distinctive phenotype involving features of Noonan syndrome and loose anagen hair.

INTERPRETATION

Evaluation and categorization of variants is performed using the most recent published ACMG recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.