

## Prenatal Testing for Noonan Syndrome in Fetuses with Abnormal Ultrasound Findings, including Cystic Hygroma

**Panel Gene List:** BRAF, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1

### Clinical Features:

Individuals with Noonan syndrome (NS) have dysmorphic facial features, such as hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Other features include short stature, pterygium colli, short, webbed neck, deafness, motor delay, and bleeding diathesis. Structural cardiac defects (A-V canal defects, pulmonic stenosis, and coarctation of the aorta) may be suspected prenatally; however, hypertrophic cardiomyopathy, secundum ASD and patent ductus arteriosus are usually identified after delivery. Most of the features of Noonan syndrome are not identified in the first or second trimester of pregnancy, although transient first trimester cystic hygroma has been associated with a clinical diagnosis of Noonan syndrome in 1-4% of cases with normal karyotype. In addition to Noonan syndrome, increased nuchal translucency has been seen in association with fetal chromosome abnormalities, fetal demise, heart defects, infection, and a number of other genetic conditions. Third trimester ultrasound findings of abnormal facies, lymphedema, macrosomia, cardiac defects, and the obstetric complication of polyhydramnios have been reported in Noonan syndrome.

### Genetics:

Noonan syndrome is a genetically heterogeneous, autosomal dominant disorder. Many cases are sporadic and are likely due to new variant.

### Test Methods:

Genomic DNA obtained from chorionic villi, cultured villi, or cultured amniocytes, captured by hybridization and PCR amplified (TruSeq Custom Amplicon). The amplicons were sequenced using a novel solid-state sequencing-by-synthesis process (MiSeq) that allows sequencing a large number of amplicons in parallel. The panel includes the complete coding regions and canonical splice junctions of 11 genes in the RAS/MAPK pathway: BRAF, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2 and SOS1. In addition, for each test we will perform genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination. ***Therefore, in all cases a maternal sample (either blood in EDTA or buccal swabs) should accompany the fetal sample.***

## Test Sensitivity:

In fetuses, transient first trimester cystic hygroma has been associated with a clinical diagnosis of Noonan syndrome in 1-4% of cases with normal karyotype. In a recent retrospective study of 134 fetuses with sonographic findings suggestive of Noonan syndrome, including data from GeneDx and Mount Sinai School of Medicine, 9% (12 fetuses) were found to have a heterozygous missense variant in PTPN11.<sup>9</sup> The prevalence of PTPN11 variants was higher in fetuses with cystic hygroma associated with additional abnormalities (24%), in particular with congenital heart defects (37%). The variant detection rate for BRAF, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, RAF1, RIT1, SHOC2, and SOS1 has not yet been established. However, a study of 14 patients positive for a RAF1 variant with postnatal diagnosed Noonan syndrome and available prenatal ultrasound data reports that 6 patients had fetal macrosomia, 5 had polyhydramnios, and 1 had increased nuchal translucency.<sup>8</sup> All of these RAF1 variants were located in exons 7, 14 and 17, which are included in our comprehensive prenatal Noonan syndrome panel.

## References:

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