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 coartation 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 is extracted from the submitted specimen. The DNA is enriched for the complete coding regions and splice junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data is analyzed to identify sequence variants. Alternative methods are used to analyze or confirm regions with inadequate sequence. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants are not routinely reported but are available upon request. Available evidence for variant classification may change over time and the reported variant(s) may be re-classified according to the AMP/ACMG guidelines for variant classification (Richards et al. 2015), which may lead to re-issuing a revised report.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.
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.*

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Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample 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*.[9]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.[8] All of these *RAF1* variants were located in exons 7, 14 and 17, which are included in our comprehensive prenatal Noonan syndrome panel.

REFERENCES:

1. Achiron, et al (2000) Noonan Syndrome: A cryptic condition in early gestation. Am J Med Genet 92:159-165;
2. Adekunle, et al (1999) Increased first trimester nuchal translucency: pregnancy and infant outcomes after routine screening for Down's syndrome in an unselected antenatal population. Br J Radiol 72:457-60;
3. Benacerraf, et al (1989) The prenatal sonographic features of Noonan syndrome. J Ultrasound Med 8:59-63.; Ferguson et al. (2006) PTPN11 gene analysis in fetuses with abnormal ultrasound findings: The GeneDx experience. Poster presentation at the Cardiofaciocutaneous Syndrome & Noonan Syndrome International Symposium, Nov 17-19, 2006, Potomac, MD;
4. Hiippala, et al (2001) Fetal nuchal translucency and normal chromosomes: a long-term follow-up study. Ultrasound Obstet Gynecol 18:18-22;
5.Reynders, et al (1997) First trimester isolated fetal nuchal lucency: Significance and outcome. J Ultrasound Med 16:101-105; Souka,et al (2001) Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester.Ultrasound Obstet Gynecol 18:9-17;
6.Tartaglia, et al (2001) Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. NatGenet 29:465-8;
7.Trauffer, et al (1994) The natural history of euploid pregnancies with first-trimester cystic hygromas. Am J Obstet Gynecol 170:1279-84.
8.Pandit B et al. (2007) Nat Genet 39:1007-1012.
9.Lee et al. (2009) Clin Genet. 75(2):190-4.