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

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

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 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 8 genes in the RAS/MAPK pathway: BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, and SOS1, as well as a part of exon 2 of SHOC2. 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.[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, RAF1, 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. Nat Genet 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.