Genetic Testing of the *JAG1* Gene for Alagille Syndrome

Disorder also known as: AGS; Alagille-Watson Syndrome; Cholestasis with peripheral pulmonary stenosis; Arteriohepatic dysplasia; Syndromatic hepatic ductular hypoplasia

Clinical Features:
Alagille syndrome is one of the major forms of chronic liver disease in children. The disease generally presents with jaundice in the neonatal period. The cholestasis is due to absence or paucity of intrahepatic bile ducts, which may not necessarily be demonstrable on histologic exam in the newborn period. The most common cardiac manifestation is peripheral and branch pulmonic stenosis (2/3 of patients), with tetralogy of Fallot occurring in 7-16% of patients. Other associated findings include posterior embryotoxon and retinal pigmentary changes of the eye, vertebral anomalies ("butterfly" vertebrae), absent deep tendon reflexes, and characteristic facial features (broad forehead, deep-set eyes, pointed chin, elongated nose with bulbous tip), giving the face an inverted triangular shape. Published diagnostic criteria are defined by the presence of three out of five characteristic findings of the liver, heart, eye, skeleton, and face, or two of these features if the patient has a positive family history.[1] As there is wide variation in clinical presentation, even within families, the diagnosis of AGS should be considered in any infant with cholestasis. Liver failure requiring transplantation and hepatocellular cancer are complications leading to severe morbidity and mortality.
The twenty-year survival in patients with AGS is estimated at 75-80%.

Inheritance Pattern/Genetics:
Alagille syndrome is caused by pathogenic variants in the JAG1 gene and is inherited in an autosomal dominant manner. An estimated 50-70% of individuals with Alagille syndrome due to abnormalities in JAG1 are due to de novo variants.

Test Methods:
Bi-directional sequence analysis of the JAG1 gene is performed using genomic DNA extracted from the submitted specimen. Testing is offered in two tiers, as evidence suggests a higher frequency of variants occur in certain exons. Tier 1 includes sequence analysis of exons 1-6, 9, 12, 16, 17, 20, 23 and 24, and targeted array CGH analysis with exon-level resolution (ExonArrayDx) to evaluate for a deletion or duplication of one or more exons of this gene and is expected to identify 77% of JAG1 variants. Tier 2 analysis encompasses sequencing the remaining exons of the JAG1 gene (7, 8, 10, 11, 13-15, 18, 19, 21, 22, 25 and 26). Comprehensive JAG1 testing including sequence analysis of the entire gene plus deletion/duplication testing of the JAG1 gene (tiers 1 and 2) is also available. Reportable

variants are confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

Test Sensitivity:
Germline variants in JAG1 have been found in 94% of patients with Alagille syndrome who meet the published diagnostic criteria. Approximately 88% of Alagille patients have small intragenic DNA variants and approximately 6% of Alagille syndrome is due to large deletions involving the JAG1 gene. The two different methods used by GeneDx (sequencing and deletion/duplication testing by ExonArrayDx) are expected to identify >99% of variants/deletions in the JAG1 gene, if one exists.

Of intragenic variants identified by JAG1 gene sequence analysis, one study showed the following variant types: 25% nonsense, 14% missense, and 39% splice site variants. Small deletion and insertion variants also are common.[2]

References:

1. Kamath, BM. et al., Consequences of *JAG1* mutations. *J Med Genet.* 40: 891-895, 2003.
2. Warthen, DM. et al., Jagged1 (*JAG1*) Mutations in Alagille Syndrome: Increasing the Mutation Detection Rate. *Hum Mutat*.27: 436-443, 2006.