NAGS Gene Analysis in N-Acetylglutamate Synthase (NAGS) Deficiency

Clinical Features:
N-acetylglutamate synthase (NAGS) deficiency is an inborn error of the urea cycle. Onset may occur from the neonatal period to adulthood. The presentation ranges from early neonatal hyperammonemia with failure to feed, inability to maintain body temperature and drowsiness, to late onset hyperammonemia that may result in chronic gastrointestinal, neurological or psychiatric signs, sometimes triggered by infections or other stress. These symptoms can lead to coma and death in the most severe cases. Approximately half of reported cases have presented in the neonatal period. NAGS deficiency is clinically and biochemically indistinguishable from carbamylphosphate synthetase I (CPSI) deficiency. General treatments for NAGS deficiency are protein restriction, hypercaloric infusion and arginine supplementation, if needed. Hyperammonemia in NAGS deficiency may be be effectively treated with N-carbamylglutamate.

Genetics:
Autosomal recessive. NAGS deficiency is caused by pathogenic variants in the NAGS gene that encodes the liver N-acetylglutamate synthase (NAGS) enzyme that catalyzes the formation of N-acetylglutamate (NAG) from glutamate and acetyl coenzyme A. NAG is an essential cofactor for the carbamylphosphate synthetase 1 (CPSI) enzyme, the first and rate-limiting enzyme of the urea cycle. Biochemically NAGS deficiency and CPSI deficiency are characterized by elevated plasma ammonia and glutamine with low to normal concentrations of the other urea cycle intermediates. Urine orotic acid is not elevated. Discrimination between NAGS deficiency and CPSI deficiency requires liver enzyme studies or molecular testing; however, open liver biopsy is technically difficult and is not completely reliable. The majority of patients presenting as neonates have less than 5% residual NAGS activity while late-onset patients have greater levels of enzyme activity. The NAGS gene is located on chromosome 17q21.31 and has 7 exons.

Test Methods:
Variant analysis of the NAGS gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the NAGS gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.
Test Sensitivity:
Very few patients with NAGS deficiency and variants in the NAGS gene have been described; therefore, the sensitivity of variant analysis cannot be established at this time. However, variants are expected to be identified in the NAGS gene in the majority of patients with NAGS deficiency.²

References: