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 effectively treated with N-carbamylglutamate.[1]

Genetics:
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 I (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.[1] 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.

Inheritance Pattern:
Autosomal Recessive

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:
In 41 unrelated patients with NAGS deficiency, variants were found on 79/82 alleles via sequencing of exons and intron/exons boundaries. Many of these individuals were homozygous for a variant. Three individuals were found to harbor a single *NAGS* variant; no variant in the enhancer region was identified in these individuals. Somatic mosaicism or a dominant negative effect of the identified variant cannot be excluded for these inidividuals with a single variant detected.[2] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
Reported *NAGS* variants include missense, nonsense, splicing, regulatory, and small deletions and insertions.[3,4] Patients presenting in the neonatal period have been frequently found to harbor frameshift or nonsense variants, while later-onset patients have frequently been found to harbor missense variants.[2]

References:

1. Caldovic et al. (2007) Human Mutation 28 (8):754-9 (PMID: 17421020)
2. Sancho-Vaello et al. (2016) Hum. Mutat. 37 (7):679-94 (PMID: 27037498)
3. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)
4. Heibel et al. (2011) Hum. Mutat. 32 (10):1153-60 (PMID: 21681857)