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.[1,2]

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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the NAGS gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

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.

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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 individuals with later onset have frequently been found to harbor missense variants.[5]

REFERENCES:

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