AGA Gene Analysis in Aspartylglucosaminuria

Clinical Features:
Aspartylglucosaminuria (AGU) is a lysosomal storage disorder. The intrauterine and early development of individuals with AGU is usually normal but progressive intellectual disability develops from early childhood, speech and motor skills tend to be affected early, and affected individuals have dysmorphic features and abnormal skin. The progression of intellectual disability is slow at first but increases with age. Adults have severe/profound intellectual disability, seizures are present in 30% of affected individuals and psychiatric disorders in 20%. Affected adults may have seizures, movement disorders, osteoporosis, hypermobility, and loose skin. Macrocephaly may be present in children, while adults have microcephaly. The average life span of patients is usually less than 50 years. AGU is extremely rare except in the Finnish population where the carrier frequency is as high as 1 in 40 in some areas of the country.

Genetics:
AGU is caused by variants in the AGA gene that encodes the lysosomal aspartylglucosaminidase enzyme that catalyzes one of the final steps in the breakdown of glycoproteins, specifically the hydrolysis of the amide bond of the GlcNAc-Asn carbohydrate to protein linkage. Deficiency of aspartylglucosaminidase results in the accumulation of aspartylglucosamine, the major end-product of glycoprotein degradation, and elevated levels in urine. The AGA gene is located on chromosome 4q34.3 and has 9 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 AGA 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.

Variant Spectrum:
More than 30 variants have been identified in the AGA gene including missense, nonsense, splicing
and small deletions/insertions that are spread throughout the gene.\textsuperscript{4,11} Large deletions have also
been reported.\textsuperscript{6,7} The high incidence of AGU in the Finnish population is due to a p.Cys163Ser
founder mutation that is present on approximately 98% of alleles in affected patients.\textsuperscript{1,10} A 2 bp
deletion (c.200_201delAG) has been identified as a less common variant on approximately 1.5% of
alleles in Finnish individuals affected with AGU.\textsuperscript{8} The majority of variants outside of the Finnish
population appear to be private; however, a p.Ser72Pro missense variant was identified in four Arab
families with AGU.\textsuperscript{9} Most patients with AGU are homozygous for a single AGA variant.\textsuperscript{5}

References:
   (PMID: 1722323)
10. Arvio et al. (2016) Orphanet J Rare Dis 11 (1):162 (PMID: 27906067)