

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.^{1,10} The progression of intellectual disability is slow at first but increases with age.¹⁰ 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.^{1,10} The average life span of patients is usually less than 50 years.^{2,10} 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.³

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:

Variant analysis of the *AGA* 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 single variant in the *AGA* gene, and if clinically indicated, reflex 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 two small studies including 7 and 12 patients with AGU from diverse ethnic backgrounds, sequence analysis of the *AGA* gene identified variants in 12 of 14 alleles (86%) and in 22 of 24 alleles (92%), respectively.^{4,5} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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.^{4,11} Large deletions have also been reported.^{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.^{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.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.⁹ Most patients with AGU are homozygous for a single *AGA* variant.⁵

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