GBA Gene Analysis in Gaucher Disease

Clinical Features:
Gaucher disease (GD) is the most common lysosomal storage disease with an incidence of 1/40,000-1/60,000 in the general population and as high as 1/800 in the Ashkenazi Jewish population. GD can be divided into three major clinical types, based on the presence or absence of central nervous system abnormalities, age of onset, symptom severity and disease progression. Most individuals of American or European descent present with type 1 or non-neuronopathic GD which accounts for greater than 90% of GD in these populations. Type I GD is characterized by cytopenia, splenomegaly, hepatomegaly, and bone lesions without central nervous system involvement. Type 2 or acute neuronopathic GD, presents with hepatosplenomegaly and neurological involvement in the first months of life and is rapidly progressive resulting in death in infancy or early childhood. Type 3 or chronic neuronopathic GD, is associated with visceral and bone disease with more slowly progressive neurological symptoms with survival into early adulthood. There is wide variation in disease severity, even reported among affected siblings, and some individuals with biallelic GD pathogenic variants remain asymptomatic throughout their lifetime.

Pathogenic variants in GD are a risk factor for Parkinson disease. Although most individuals with GBA pathogenic variants do not develop Parkinson disease, individuals with GD, and to a lesser extent GD carriers who have a single GD variant, are at an increased risk for late onset PD compared to the general population risk.

Genetics:
GD is caused by pathogenic variants in the GBA gene which encodes beta-glucocerebrosidase. Deficient enzyme activity results in the accumulation of glucosylceramide and other glycolipids in the lysosomes of macrophages resulting in the characteristic “Gaucher cells” which are present in various tissues and lead to hepatosplenomegaly and bone disease. The mechanism for central nervous system involvement in GD, characterized by neuronal cell death, is not clear. The GBA gene is located on chromosome 1q22 and has 11 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the GBA gene is complicated by the presence of a highly homologous pseudogene, GBAP1. Testing at GeneDx is performed on genomic DNA from the submitted specimen using long range PCR to specifically amplify the GBA gene and bi-directional
sequence analysis of the coding exons 1-11 of GBA, and corresponding intron/exon boundaries. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing or another appropriate method.

Test Sensitivity:
Sequence analysis of the GBA gene at GeneDx is expected to be greater than 99% sensitive at detecting variants and recombinant alleles identifiable by sequencing. This method is not designed to detect large exon-level deletions of GBA.

Variant Spectrum:
The majority of pathogenic variants in GBA are missense variants, although nonsense, small deletions/insertions, frameshift, splice site variants and several large deletions have also been reported. The N409S variant (previously called N370S) is associated with Type I GD and is the most common pathogenic variant in GBA in Ashkenazi Jewish and European populations, accounting for 75-80% of alleles in Ashkenazi Jewish and approximately 30% of alleles in non-Jewish European patients with GD, although it is extremely rare in Asian and African populations.\(^1,2,5,6,7,8\) Other founder variants in the Ashkenazi Jewish population include c.84dupG, c.115+1G>A, and L483P (aka L444P).\(^2\) Approximately 12% of pathogenic alleles in the GBA gene arise from recombination events between the GBA gene and the GBAP1 pseudogene.\(^9,10\)

References: