JAK3 Gene Analysis in Autosomal Recessive Severe Combined Immune Deficiency (SCID)

Clinical Features:
JAK3 variants cause an autosomal recessive form of severe combined immune deficiency (SCID) that is clinically indistinguishable from the more common X-linked SCID where the deficient gene encodes the interleukin-2 receptor common gamma chain. Both present early in life with persistent severe viral, bacterial, protozoan or fungal infections and are distinguished from some other types of SCID by the lymphocyte profile which is usually T–, NK–, and B+. In both X-linked and JAK3 deficiency SCID, the interleukin signaling pathways in lymphocytes are defective. JAK3 deficiency can be confirmed by tests demonstrating either the absence of the JAK3 protein or, in the presence of a normal common gamma chain, the failure of lymphoid cells to phosphorylate downstream mediators of activation, such as STAT5, in vitro. Detection of deleterious JAK3 gene variants on both alleles by sequence analysis also is confirmatory.

Genetics:
Autosomal Recessive Severe Combined Immune Deficiency (SCID) involving JAK3 has an autosomal recessive inheritance pattern.

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions and splice sites of the 23 exons of the JAK3 gene. If sequencing identifies a variant on only one allele, focused array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or 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:
Roughly 10% of cases of T–B+NK– SCID are due to JAK3 deficiency. If variants are present in JAK3, the strategy used by GeneDx is expected to detect one or both variants in about 98% of patients.

Variant Spectrum:
Published variants in JAK3 are distributed throughout the gene. Missense, nonsense, and frameshift variants are predominant but whole exon deletions have been reported.²

References: