

WAS Gene Analysis in Wiskott-Aldrich Syndrome (WAS), X-linked Thrombocytopenia (XLT), and X-linked Neutropenia (XLN)

Clinical Features:

Pathogenic variants in the WAS gene have been associated with three clinical presentations: Wiskott-Aldrich syndrome and X-linked thrombocytopenia, which are associated with loss-of-function variants, and X-linked neutropenia, which is associated with activating variants. Wiskott-Aldrich syndrome, the most severe presentation, is classically characterized by thrombocytopenia (with small platelet size), eczema, increased susceptibility to pyogenic and opportunistic infections, and increased risk of autoimmune disease and cancer, specifically lymphomas. If untreated, this syndrome typically leads to death in early childhood or adolescence. Individuals with X-linked thrombocytopenia have thrombocytopenia (which can present intermittently), and mild or no eczema or immune deficiency. Though individuals with XLT typically have a normal lifespan, they are still at increased risk for severe disease-related complications. Individuals with XLN have a persistent neutropenia due to a promyelocyte/myelocytic maturation arrest and recurrent bacterial infections.

Inheritance Pattern:

X-linked inheritance

Test Sensitivity:

Greater than 99% of variants present in the WAS gene are expected to be detectable by the methods used at GeneDx. Approximately 95% of reported variants are detectable by sequencing analysis, and the remaining 5% are gross deletions detectable by deletion/duplication analysis.⁵ No gross duplications of exons have been reported to our knowledge.

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

References:

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3. Imai et al., (2003) WASP (Wiskott-Aldrich syndrome protein) gene mutations and phenotype. *Curr Opin Allergy Clin Immunol*. 6:427-436.
4. Ancliff et al., (2006) Two novel activating mutations in the Wiskott-Aldrich syndrome protein result in congenital neutropenia. *Blood*. 108(7): 2182-218
5. Chandra S, Bronicki L, Nagaraj CB, et al. WAS-Related Disorders. 2004 Sep 30 [Updated 2016 Sep 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1178/>