

Wiskott-Aldrich Syndrome, X-linked Thrombocytopenia, and X-linked Congenital Neutropenia, via WAS Gene Sequencing (Test #440)

Brief Description of Clinical Features: Wiskott-Aldrich Syndrome (WAS; OMIM 301000) and X-linked thrombocytopenia (XLT; OMIM 313900) are characterized by thrombocytopenia (platelet counts 5,000-50,000/ μ l) with markedly small-sized platelets. WAS is often detected in infancy through bleeding problems such as easy bruising, petechiae, and excessive bleeding during circumcision. Other features may include eczema, recurrent bacterial and viral infections, severe hemorrhaging, autoimmune disease such as hemolytic anemia or immune thrombocytopenic purpura, and lymphomas. Severity of WAS varies from lethal infantile forms to adult intermittent thrombocytopenia. X-linked Congenital Neutropenia (XLN; OMIM 300299) is characterized by absolute neutrophil counts (ANC) consistently below 500/ μ l and severe systemic bacterial infections that may begin in early infancy or during adolescence (Ancliff et al. Blood 108:2182-2189, 2006). For more information on WAS-related disorders, see Filipovich et al. GeneReviews (www.genetests.org 2007).

Genetics: WAS and related disorders exhibit X-linked recessive inheritance. Nearly all affected individuals are male. Female carriers are usually asymptomatic. The WAS gene (OMIM 300392) encodes a major regulator of actin polymerization in hematopoietic cells. Over 250 causative mutations in WAS have been reported (<http://homepage.mac.com/kohsukeimai/wasp/WASbase.html>; <http://bioinf.uta.fi/WASbase/>). The causative mutations are roughly 35% missense, 25% frameshift, 20% splicing, 15% nonsense and 5% other. Although there are exceptions, patients carrying missense mutations are generally less severely affected than those carrying nonsense, frameshift or splicing mutations (Jin et al. Blood 104:4010-4019, 2004; Imai et al. Blood 103:456-464, 2004; Lutskiy et al. J Immunol 175:1329-1336, 2005). In the outbred U.S. population, no mutations are common. A fraction of patients are mosaic for blood cells with revertant WAS genes (Ariga et al. J Immunol 166:5245-5249, 2001; Wada et al. PNAS 98:8697-8702, 2001). Three mutations in exon 9 (i.e. p.Leu270Pro, p.Ser272Pro, and p.Ile294Thr) have been shown to result in constitutively active WAS protein which is known to cause XLN with normal platelet counts (Devriendt et al. Nature 27:313-317, 2001; Ancliff et al. Blood 108:2182-2189, 2006).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 12 exons of the WAS gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will also sequence any single exon in family members of patients with known mutations, and to confirm research results (Test #100, \$190).

Reference Sequences: Genomic: NC_000023.10 mRNA: NM_000377.2 Protein: NP_000368.1 (CCDS 14303.1)

Indications for Test: All male patients with symptoms of WAS or related disorders and with a family history of X-linked inheritance are candidates for this test. Female patients should only be considered if they have affected fathers, and/or if they have a strong family history (Lutskiy et al. Blood 100:2763-2768, 2002). Males with congenital neutropenia and evidence of X-linked familial inheritance are also candidates. PreventionGenetics also offers tests for several other thrombocytopenia genes.

Sensitivity of Test: Approximately 95% of causative WAS mutations are detectable by DNA sequencing (Imai et al. 2004; Lutskiy et al. 2005). If the diagnosis of WAS is distinguished from other severe immunodeficiency disorders and also from immune thrombocytopenic purpura, the overall sensitivity of this test will be high (Filipovich et al. 2007).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of WAS \$ 540

CPT Codes							
Test	83890	83891	83898	83904	83894	83912	Total
WAS	\$30	\$40	\$140	\$200	\$50	\$80	\$540

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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