

Thrombotic Thrombocytopenic Purpura (TTP) via Sequencing of the *ADAMTS13* Gene (Test #430)

Brief Description of Clinical Features: Thrombotic Thrombocytopenic Purpura (TTP) (OMIM 274150), often described as Upshaw-Schulman syndrome (USS), is a rare blood condition characterized by frequent relapses of fever, hemolytic anemia, thrombocytopenic purpura, neurologic symptoms, renal disease, and possible organ failure. TTP is caused by mutations in the *ADAMTS13* gene (Levy et al. *Nature* 413:488-494, 2001) and differs from the more common idiopathic platelet disorder Immune Thrombocytopenia Purpura (ITP) which is an autoimmune disease that causes thrombocytopenia. TTP preferentially affects the microvasculature of the brain and kidneys, and initial symptoms may include hypertension, headache, numbness or transient paralysis, confusion, and difficulty speaking. In a related disorder, hemolytic uremic syndrome (HUS), neurologic symptoms are less common while renal failure is more predominant. In unaffected individuals, large multimers of the platelet-adhesive protein von Willebrand Factor (vWF) are secreted from platelet stores into blood plasma where they are cleaved by the metalloprotease ADAMTS13 during a key step of thrombosis (Furlan et al. *Blood* 87:4223-4234, 1996). In patients with TTP, cleavage of vWF multimers is diminished or absent due to either loss-of-function mutations in *ADAMTS13*, or to lack of ADAMTS13 secretion from storage granules in platelets and megakaryocytes (Mannucci et al. *Blood* 74:978-983, 1989; Kokame et al. *Proc. Natl. Acad. Sci. U.S.A.* 99:11902-11907, 2002). Deficiencies in vWF cleavage result in the formation of damaging microvascular thrombi, comprising platelets and vWF multimers, that cause erythrocyte lysis and other symptoms of TTP (Moake et al. *N. Engl. J. Med.* 307:1432-1435, 1982). TTP affects males and females equally and may present at any age. Without preventative treatment, episodes of TTP typically recur every 21 to 28 days and are often precipitated by other stressors including infection, surgery, or pregnancy (Furlan and Lämmle *Best Pract Res Clin Haematol.* 14:437-454, 2001).

Genetics: Mutations in *ADAMTS13* are inherited in an autosomal recessive manner, although individuals heterozygous for pathogenic mutations often display mild deficiencies of ADAMTS13 activity (Levy et al. *Nature* 413:488-494, 2001; Kokame et al. *Proc. Natl. Acad. Sci. U.S.A.* 99:11902-11907, 2002). Causative mutations in *ADAMTS13* have been identified throughout the coding sequence. No predominant *ADAMTS13* mutations have been identified, but the phenotypes resulting from secretion-deficient *ADAMTS13* mutations appear to be more severe than the phenotypes resulting from secreted ADAMTS13 with diminished function (Kokame et al. *Proc. Natl. Acad. Sci. U.S.A.* 99:11902-11907, 2002).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the 29 coding exons in the *ADAMTS13* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000009.11 mRNA: NM_139025.3 Protein: NP_620594.1 (CCDS 6970.1)

Indications for Test: Patients with clinical features of TTP, or a family history of TTP or hemolytic uremic syndrome.

Sensitivity of Test: Mutations in *ADAMTS13* account for nearly 100% of cases of congenital TTP.

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

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of *ADAMTS13* Gene \$1290

CPT Codes							
Test	83890	83891	83898	83904	83894	83912	Total
<i>ADAMTS13</i>	\$30 (x1)	\$40 (x1)	\$390 (x29)	\$590 (x29)	\$110 (x1)	\$130 (x1)	\$1290

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

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