BLOODCENTER of WISCONSIN™

ADAMTS13 SEQUENCE ANALYSIS

BloodCenter of Wisconsin offers DNA sequencing of the ADAMTS13 gene for diagnosis of congenital thrombotic thrombocytopenic purpura (TTP).

BACKGROUND:
Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening condition characterized by consumption of platelets, hemolytic anemia, and varying degrees of organ dysfunction. Diagnosis of TTP is made clinically; however, differentiation from other thrombotic microangiopathies is often difficult.[1,2]

ADAMTS13 is a plasma protein that regulates the interaction of platelets with von Willebrand factor. Severe deficiency of ADAMTS13 allows formation of platelet microthrombi, which in turn obstruct arterioles and capillaries, generating the clinical sequelae of TTP. In adults, severe ADAMTS13 deficiency is usually an acquired abnormality caused by autoantibody.

Congenital severe ADAMTS13 deficiency is a rare autosomal recessive disorder (Upshaw-Schulman syndrome). Patients usually present as children, but adult presentations are reported, often triggered by stress events such as pregnancy. Patients are at risk for recurrent episodes of TTP. Antibody to ADAMTS13 is usually not detected, and patients generally improve with plasma transfusion therapy for ADAMTS13 replacement.[3]

Disease causing mutations have been identified throughout the coding sequence of the ADAMTS13 gene including missense, nonsense and splice site alterations, as well as nucleotide deletions and insertions. No specific mutation appears to predominate.[4] DNA sequence analysis with mutation detection will confirm a diagnosis of congenital ADAMTS13 deficiency.[3] For family members of patients with known ADAMTS13 mutations, sequencing of the appropriate exons can be used for diagnosis, carrier status or prenatal testing.

REASONS FOR REFERRAL:
- Confirmation of diagnosis of congenital ADAMTS13 deficiency
- Evaluation of family members
- Prenatal diagnosis

METHOD:
PCR and bidirectional DNA sequence analysis. The complete coding region and splice junction of each of the 29 exons is compared to the reference sequence (NC_000009.11), and functional implications of sequence variations are characterized. In family members of patients with known mutations, selective analysis of 1 or 2 exons may be requested.

LIMITATIONS:
Analytical sensitivity is >99%. Rare polymorphisms within primer regions may interfere with detection of gene variants. Large deletions or duplications and novel mutations that are outside the regions sequenced will not be detected. Clinical sensitivity is >99% for all known mutations.

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REPORTABLE RANGE:
Sequence variations are reported as heterozygous or homozygous and are classified according to the following system:

I. Sequence variation is previously reported and is a recognized cause of the disorder.
II. Sequence variation is previously unreported and is of the type which is expected to cause the disorder.
III. Sequence variation is previously unreported and is of the type which may or may not be causative of the disorder.
IV. Sequence variation is previously unreported and is probably not causative of disease.
V. Sequence variation is previously reported and is a recognized neutral variant.
VI. Sequence variations that are not known or expected to be causative of disease, but have been found to be associated with a clinical presentation.

Known polymorphisms are not reported but are available upon request.

SPECIMEN REQUIREMENTS:
3-5 mL EDTA (lavender top) whole blood.
Contact the laboratory for prenatal sample requirements.
Contact the laboratory about testing for known familial ADAMTS13 mutations.

TURNAROUND TIME: 21 days

CPT CODES: 81479

SHIPPING REQUIREMENTS:
Ship at room temperature. Place the specimen and the requisition into plastic bags and seal. Insert into a Styrofoam container, seal and place into a sturdy cardboard box, and tape securely. Ship the package in compliance with your overnight carrier guidelines. Label with the following address:

Client Services/Hemostasis Reference Laboratory
BloodCenter of Wisconsin
638 N. 18th St.
Milwaukee, WI 53233
Phone: 800-245-3117, ext. 6250

REFERENCES:
1. Sadler JE. Von Willebrand Factor, ADAMTS13 and thrombotic thrombocytopenic purpura. Blood 2008:112:11-18.
2. Kremer Hovinga JA, Meyer SC. Current management of thrombotic thrombocytopenic purpura. Curr Opin Hematol15:445-450, 2008.
3. Savasan, S., Lee, S.-K., Ginsburg, D., Tsai, H.-M. ADAMTS13 gene mutation in congenital thrombotic thrombocytopenic purpura with previously reported normal VWF cleaving protease activity. Blood 101: 4449-4451, 2003.
4. Lotta LA, Garagiola I, Palla R, Cairo A, Peyvandi F. ADAMTS13 mutations and polymorphisms in congenital thrombotic thrombocytopenic purpura. Hum Mutat 31:11-19, 2010.

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