BACKGROUND:
von Willebrand disease (VWD) is a common inherited bleeding disorder with a reported incidence ranging from 0.01% to 1%. VWD is classified by quantitative (types 1 and 3) and qualitative (type 2) defects in von Willebrand factor (VWF). The defects observed in type 2 VWD include defects in multimerization (type 2A), increased susceptibility of VWF to degradation by proteases (type 2A), abnormal interaction of VWF with platelets (types 2B, 2M and platelet-type), decreased interaction with factor VIII (type 2N), and decreased interaction with collagen (a rare form of type 2M). Type 2B, type 2M, and the majority of type 2A cases are inherited as autosomal dominant traits, while type 2N and some cases of type 2A are autosomal recessive disorders. Sequence variations in exon 28 are found in the majority of types 2A, 2B and 2M VWD. A minority of type 1 sequence variations are also found in exon 28. Molecular analysis of VWF exon 28 is useful in the diagnosis and classification of patients in whom there is evidence of an abnormal plasma VWF multimer distribution (with or without thrombocytopenia) or there is evidence of an abnormal interaction of platelets with VWF (as suggested by a low ratio of VWF ristocetin cofactor activity to VWF antigen level, thrombocytopenia, or an abnormal low dose ristocetin-induced platelet aggregation result).

METHOD:
Assay Principle:
PCR amplification and bi-directional DNA sequence analysis are performed. Complete coding region and splice junction of VWF exon 28 is compared to the NM_000552 reference sequence. Functional implications are classified using data from the HGMD and the ISTH VWD database (http://www.vwf.group.shef.ac.uk). Sequence variations are reported using standard nomenclature recommendations of the Human Variation Society. Sequence variations designated as benign are not reported, but those results are available upon request.

Analytical sensitivity/Specificity:
Analytical sensitivity is >99% for sequence variations in exon 28. Rare polymorphisms within primer or probe regions may interfere with detection of gene variants. Mutations that are outside the regions sequenced will not be detected. Large deletions and duplications are not detected. Clinical sensitivity for type 2B VWD and type 2M VWD with abnormal interaction of VWF with platelets is >99% for reported mutations. Sensitivity for type 2A VWD is approximately 70-80% and sequencing of VWF exons 11-16, 24-26 and 51-52 will detect the vast majority of other type 2A mutations. Exon 28 sequence analysis will distinguish type 2B from platelet-type VWD, but sequence analysis of GP1BA is required to genetically confirm a diagnosis of platelet-type VWD. Type 1 and type 3 VWD mutations have been identified throughout the VWF gene; only a minority reside within exon 28.
REASONS FOR REFERRAL:
- Confirm diagnosis of variant von Willebrand Disease (VWD).
- Diagnose difficult cases of Type 2A, 2B and 2M VWD.
- Facilitate genetic counseling and prenatal diagnosis.

REFERENCE RANGE:
Normal - Normal DNA sequence.
Abnormal - Presence of mutation known to cause Type 2A, 2B, or 2M VWD.

SPECIMEN REQUIREMENTS:
Sample must be less than one month old when received by our laboratory.
Parental/Patient: 3-5 ml EDTA (lavender top) whole blood.
Fetal: 7-15 ml Amniotic Fluid or 5-10 mg CVS, backup culture of Amniocytes or CVS is highly recommended; Two T25 flasks Cultured Amniocytes or CVS (2x10^6 minimum).

SHIPPING REQUIREMENTS:
Ship on an ice pack or at room temperature. Place the specimen and the requisition into plastic bags and seal. Insert into a Styrofoam container; 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
800-245-3117, ext. 6250

TURNAROUND TIME: 21 days

CPT CODES: 81403

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