

Platelet Disorders Gene Sequencing Panel

<i>ABCG5</i>	<i>ABCG8</i>	<i>ACBD5</i>	<i>ACTN1</i>	<i>ANKRD26</i>
<i>ANO6 (TMEM16F)</i>	<i>AP3B1</i>	<i>BLOC1S3</i>	<i>BLOC1S6</i>	<i>CYCS</i>
<i>DTNBP1</i>	<i>ETV6</i>	<i>FLI1</i>	<i>FLNA</i>	<i>GATA1</i>
<i>GFI1B</i>	<i>GP1BA</i>	<i>GP1BB</i>	<i>GP6</i>	<i>GP9</i>
<i>HOXA11</i>	<i>HPS1</i>	<i>HPS3</i>	<i>HPS4</i>	<i>HPS5</i>
<i>HPS6</i>	<i>ITGA2B</i>	<i>ITGB3</i>	<i>LYST (CHS1)</i>	<i>MASTL</i>
<i>MPL</i>	<i>MYH9</i>	<i>NBEAL2</i>	<i>ORAI1</i>	<i>P2RX1</i>
<i>P2RY12</i>	<i>PLA2G4A</i>	<i>PRKACG</i>	<i>RASGRP2</i>	<i>RBM8A</i>
<i>RUNX1</i>	<i>STIM1</i>	<i>STX11</i>	<i>STXBP2</i>	<i>TBXA2R</i>
<i>TBXAS1</i>	<i>THPO</i>	<i>TUBB1</i>	<i>UNC13D</i>	<i>VIPAS39</i>
<i>VPS33B</i>	<i>VPS45</i>	<i>WAS</i>		

Description:

The Platelet Disorders Gene Sequencing Panel utilizes Whole Exome Sequencing (WES) technology to identify inherited forms of platelet dysfunction. Utilizing a predefined list of 53 clinically significant genes, this panel analyzes mutations related to adhesion and activation receptor genes, secretion and membrane regulation genes, and platelet production genes related to genetically inherited platelet disorders. Compared to WES, this targeted approach results in fewer sequence changes identified: allowing for a shorter turnaround time and decreased cost of testing. This test will be performed on the proband only and will not include the identification of incidental findings.

Indications:

- Platelet dysfunction/defect
- Abnormal bleeding
- Unexplained Thrombocytopenia
- Easy bruising/spontaneous ecchymoses
- Positive family history of bleeding disorders or platelet function disorders

What Is Reported?

Variants that will be discussed in detail in the report:

- **Pathogenic/likely pathogenic variants:** Variants that are known to be pathogenic or for which the laboratory has sufficient evidence suggesting pathogenicity.

Variants that will be listed in the report:

- Variants of uncertain clinical significance.

What is not reported?

- Variants in genes not included in the predefined gene list
- Variants where there is currently no evidence of association with the disease and that are identified in healthy individuals (benign or likely benign variants)
- Variants that predict an increased risk of diseases, but do not cause a disease by themselves (risk alleles).

Genetic Conditions Commonly Associated with Platelet Disorders

Gene	Inheritance	Condition
<i>ABCG5</i>	AR	Macrothrombocytopenia and sitosterolemia
<i>ABCG8</i>	AR	Macrothrombocytopenia and sitosterolemia
<i>ACBD5</i>	AD	Autosomal Dominant Thrombocytopenias
<i>ACTN1</i>	AD	Congenital Macrothrombocytopenia
<i>ANKRD26</i>	AD	Autosomal Dominant Thrombocytopenias
<i>ANO6 (TMEM16F)</i>	AR	Scott Syndrome
<i>AP3B1</i>	AR	Hermansky-Pudlak syndrome
<i>BLOC1S3</i>	AR	Hermansky-Pudlak syndrome
<i>BLOC1S6</i>	AR	Hermansky-Pudlak syndrome
<i>CYCS</i>	AD	Autosomal Dominant Thrombocytopenias
<i>DTNBP1</i>	AR	Hermansky-Pudlak syndrome
<i>ETV6</i>	AD	Thrombocytopenia and cancer susceptibility
<i>FLI1</i>	AD/AR	Paris-Trousseau (Jacobson) Syndrome, bleeding disorder
<i>FLNA</i>	X linked	X-linked thrombocytopenia with PVNH
<i>GATA1</i>	X linked	X-linked thrombocytopenia
<i>GFI1B</i>	AD/AR	Gray platelet syndrome, bleeding disorder
<i>GP1BA</i>	AD/AR	Bernard-Soulier syndrome, Platelet-type von Willebrand's disease
<i>GP1BB</i>	AR	Bernard-Soulier syndrome, giant platelet disorder
<i>GP6</i>	AR	GPVI deficiency
<i>GP9</i>	AR	Bernard-Soulier syndrome
<i>HOXA11</i>	AD	Amegakaryocytic thrombocytopenia radio-ulnar synostosis
<i>HPS1</i>	AR	Hermansky-Pudlak syndrome
<i>HPS3</i>	AR	Hermansky-Pudlak syndrome
<i>HPS4</i>	AR	Hermansky-Pudlak syndrome
<i>HPS5</i>	AR	Hermansky-Pudlak syndrome
<i>HPS6</i>	AR	Hermansky-Pudlak syndrome
<i>ITGA2B</i>	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
<i>ITGB3</i>	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
<i>LYST (CHS1)</i>	AR	Chediak-Higashi syndrome
<i>MASTL</i>	AD	Autosomal Dominant Thrombocytopenias
<i>MPL</i>	AD/AR	Congenital amegakaryocytic thrombocytopenia
<i>MYH9</i>	AD	MYH9 Disorders
<i>NBEAL2</i>	AR	Gray platelet syndrome
<i>ORAI1</i>	AD/AR	Stormorken Syndrome
<i>P2RX1</i>	n/a	ADP receptor defects

Genetic Conditions Commonly Associated with Platelet Disorders, Continued

Gene	Inheritance	Condition
<i>P2RY12</i>	AR	ADP receptor defects, bleeding disorder
<i>PLA2G4A</i>	AR	Cytosolic phospholipase A2, Deficiency of phospholipase A2 group IVA
<i>PRKACG</i>	AR	Congenital Macrothrombocytopenia
<i>RASGRP2</i>	AR	Impaired RAP1 activation and $\alpha_{IIb}\beta_3$ signaling, bleeding disorder
<i>RBM8A</i>	AR	Thrombocytopenia absent radius (TAR) syndrome
<i>RUNX1</i>	AD	Thrombocytopenia and AML susceptibility
<i>STIM1</i>	AD/AR	Stormorken Syndrome
<i>STX11</i>	AR	Familial HLH types 4
<i>STXBP2</i>	AR	Familial HLH types 5
<i>TBXA2R</i>	AD	Thromboxane A2 receptor deficiency
<i>TBXAS1</i>	AD/AR	Thromboxane A synthase (Ghosal syndrome), Thromboxane Synthase deficiency
<i>THPO</i>	AD	Cyclic Thrombocytopenia
<i>TUBB1</i>	AD	Congenital Macrothrombocytopenia
<i>UNC13D</i>	AR	Familial HLH types 3
<i>VIPAS39</i>	AR	ARC Syndrome, Arthrogyrosis-renal dysfunction-cholestasis syndrome
<i>VPS33B</i>	AR	Arthrogyrosis-renal dysfunction-cholestasis syndrome
<i>VPS45</i>	AR	Congenital neutropenia & platelet a granule defect
<i>WAS</i>	X linked	Wiskott-Aldrich syndrome

Methodology:

Procedure: The Platelet Disorders Gene Sequencing Panel uses the Agilent SureSelect CRE V1 kit to capture the exonic regions of genes from the genomic DNA extracted from the patient. Targeted regions are sequenced using the Illumina HiSeq 2500 sequencing system with 125 base pair (bp) paired-end reads. Sequence reads are mapped and compared to human genome build UCSC hg19. Variants within exons and flanking sequences of +/- 5bps are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline that includes the usage of GATK 3.5 and Alamut Batch 1.4.4 software packages. Mutations in the promoter region of *ANKRD26* are analyzed; allele specific analysis for the 253kb inversion as well as targeted analysis of the c.118-308 region in *UNC13D* are performed. Data quality is assessed to confirm it has a minimum coverage of 20X for >95% of targets of interest.

Technical Limitations:

- Pathogenic variants may be present in a portion of the genes not covered by this test and therefore would not be identified. Thus, the absence of reportable findings for any gene does not mean there are no pathogenic variants.
- Certain types of mutations are not detected. Only single base pair changes or small insertions or deletions of DNA are detected. Large deletions, duplications, or rearrangements, mitochondrial genome mutations, trinucleotide repeat expansions, genes with pseudogenes, mutations in tri-allelic inheritance, and many epigenetic defects may not be detected by this test.

Note: Targeted deletion and duplication analysis of every gene on this panel except *ACBD5*, *ACTN1*, *ANKRD26*, *ANO6*, *CYCS*, *ETV6*, *FLII*, *GFIIB*, *GP6*, *HOXA11*, *MASTL*, *NBEAL2*, *P2RX1*, *P2RY12*, *PLA2G4A*, *PRKACG*, *RUNX1*, *TBXA2R*, *TBXAS1*, *THPO*, *TUBB1*, *VIPAS39* and *VPS33B* is clinically available at an additional charge.

Turn-Around Time: 56 days (8 weeks)

Specimen: At least 3 mls whole blood in a lavender top (EDTA) tube. Label the tube with the patient's name, birth date, and date of collection. Alternatively, 10 mcg of DNA may be submitted.

CPT Codes:

- **Platelet Disorders Gene Sequencing Panel:** 81404, 81406, 81479
- **Deletion and duplication analysis of any single Gene on the Platelet Disorders Gene Sequencing Panel except *GPIBB* and *WAS*:** 81479
- **Deletion and duplication analysis of *GPIBB*:** 81404
- **Deletion and duplication analysis of *WAS*:** 81406

Shipping Instructions:

Please enclose **test requisition** with sample.

All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References:

Bolton-Maggs, P.H.B., E.A. Chalmers, et al. (2006) A Review of Inherited Platelet Disorders with Guidelines for Their Management on Behalf of the UKHCDO. British Journal of Haematology 135(5): 603–33.

Dixon-Salazar TJ, Silhavy JL, et al. (2012) Exome sequencing can improve diagnosis and alter patient management. Sci Transl Med. 4(138):138ra78.

Handin, R.I. (2005) Inherited Platelet Disorders. Hematology. American Society of Hematology. Education Program: 396–402.

Nurden, A.T. and P. Nurden (2014) Congenital Platelet Disorders and Understanding of Platelet Function. British Journal of Haematology 165(2): 165–78.

Romasko, E.J., B. Devkota, et al. (2018) Utility and Limitations of Exome Sequencing in the Molecular Diagnosis of Pediatric Inherited Platelet Disorders. American Journal of Hematology 93(1):8-16.