Platelet Disorders Gene Sequencing Panel

ABCG5	*ABCG8*	*ACTB*	*ACTN1*	*ANKRD26*	*ANO6 (TMEM16F)*
AP3B1	*AP3D1*	*ARPC1B*	*BLOC1S3*	*BLOC1S6*	*CDC42*
CYCS	*DIAPH1*	*DTNBP1*	*ETV6*	*FERMT3*	*FLI1*
FLNA	*FYB1*	*GALE*	*GATA1*	*GFI1B*	*GNE*
GP1BA	*GP1BB*	*GP6*	*GP9*	*HOXA11*	*HPS1*
HPS3	*HPS4*	*HPS5*	*HPS6*	*IKZF5*	*ITGA2*
ITGA2B	*ITGB3*	*KDSR*	*MECOM*	*LYST (CHS1)*	*MASTL*
MPIG6B	*MPL*	*MYH9*	*NBEA*	*NBEAL2*	*ORAI1*
P2RX1	*P2RY1*	*P2RY12*	*PLA2G4A*	*PRKACG*	*PTGS1*
PTPRJ	*RASGRP2*	*RBM8A*	*RUNX1*	*SLFN14*	*SRC*
STIM1	*STX11*	*STXBP2*	*TBXA2R*	*TBXAS1*	*THPO*
TPM4	*TUBB1*	*UNC13D*	*VIPAS39*	*VPS33B*	*VPS45*
WAS					

Description:

The Platelet Disorders Gene Sequencing Panel utilizes Exome Sequencing (ES) technology to identify inherited forms of platelet dysfunction. Utilizing a predefined list of 73 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 ES, this targeted approach results in fewer sequence changes identified: allowing for a shorter turn-around 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).

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Note: Platelet Disorders Panel cases with negative or uncertain findings can be reflexed to Whole Exome Sequencing (WES). A separate test order is required for WES testing. In addition, including biological parental samples is strongly encouraged to assist with the analysis of WES and to increase test yield. Reflex to WES orders can either be placed simultaneously or separately. Separate reflex to WES orders are subject to review prior to the initiation of testing. Please see our website at www.cincinnatichildrens.org/exome to obtain a WES test requisition.

Genetic Conditions Commonly Associated with Platelet Disorders

Gene	Inheritance	Condition
ABCG5	AR	Macrothrombocytopenia and sitosterolemia
ABCG8	AR	Macrothrombocytopenia and sitosterolemia
ACTB	AD	*ACTB*-associated syndromic thrombocytopenia
ACTN1	AD	Congenital Macrothrombocytopenia
ANKRD26	AD	Autosomal Dominant Thrombocytopenias
ANO6 (TMEM16F)	AR	Scott Syndrome
AP3B1	AR	Hermansky-Pudlak syndrome
AP3D1	AR	Hermansky-Pudlak syndrome 10
ARPC1B	AR	Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease
BLOC1S3	AR	Hermansky-Pudlak syndrome
BLOC1S6	AR	Hermansky-Pudlak syndrome
CDC42	AD	Takenouchi-Kosaki syndrome with macrothrombocytopenia
CYCS	AD	Autosomal Dominant Thrombocytopenias
DIAPH1	AD	Macrothrombocytopenia and hearing loss
DTNBP1	AR	Hermansky-Pudlak syndrome
ETV6	AD	Thrombocytopenia and cancer susceptibility
FERMT3	AR	Leukocyte adhesion deficiency, type III
FLI1	AD/AR	Paris-Trousseau (Jacobson) Syndrome, bleeding disorder
FLNA	X linked	X-linked thrombocytopenia with PVNH
FYB1	AR	Thrombocytopenia 3
GALE	AR	*GALE*-related thrombocytopenia
GATA1	X linked	X-linked thrombocytopenia
GFI1B	AD/AR	Gray platelet syndrome, bleeding disorder
GNE	AR	*GNE*-related thrombocytopenia
GP1BA	AD/AR	Bernard-Soulier syndrome, Platelet-type von Willebrand's disease
GP1BB	AR	Bernard-Soulier syndrome, giant platelet disorder
GP6	AR	GPVI deficiency
GP9	AR	Bernard-Soulier syndrome
HOXA11	AD	Amegakaryocytic thrombocytopenia radio-ulnar synostosis
HPS1	AR	Hermansky-Pudlak syndrome
HPS3	AR	Hermansky-Pudlak syndrome

Genetic Conditions Commonly Associated with Platelet Disorders (continued)

Gene	Inheritance	Condition
HPS4	AR	Hermansky-Pudlak syndrome
HPS5	AR	Hermansky-Pudlak syndrome
HPS6	AR	Hermansky-Pudlak syndrome
IKZF5	AD	*IKZF5*-related thrombocytopenia
ITGA2	AD	Glycoprotein Ia deficiency
ITGA2B	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
ITGB3	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
KDSR	AR	*KDSR*-related thrombocytopenia
LYST (CHS1)	AR	Chediak-Higashi syndrome
MASTL	AD	Autosomal Dominant Thrombocytopenias
MECOM	AD	Radioulnar synostosis with amegakaryocytic thrombocytopenia 2
MPIG6B	AR	Thrombocytopenia, anemia, and myelofibrosis
MPL	AD/AR	Congenital amegakaryocytic thrombocytopenia
MYH9	AD	*MYH9* Disorders
NBEA	AD	Autism and dense granule deficiency
NBEAL2	AR	Gray platelet syndrome
ORAI1	AD/AR	Stormorken Syndrome
P2RX1	n/a	ADP receptor defects
P2RY1	AR?	Moderate platelet-related bleeding phenotype with diminished platelet responsiveness to thrombin and thrombin-mimetic peptides in vitro
P2RY12	AR	ADP receptor defects, bleeding disorder
PLA2G4A	AR	Cytosolic phospholipase A2, Deficiency of phospholipase A2 group IVA
PRKACG	AR	Congenital Macrothrombocytopenia
PTGS1	AD/AR	Platelet-type bleeding disorder 12; Prostaglandin-endoperoxide synthase 1 deficiency
PTPRJ	AR	*PTPRJ*-related thrombocytopenia
RASGRP2	AR	Impaired RAP1 activation and $\alpha_{IIb}\beta_3$ signaling, bleeding disorder
RBM8A	AR	Thrombocytopenia absent radius (TAR) syndrome
RUNX1	AD	Thrombocytopenia and AML susceptibility
SLFN14	AD	Bleeding disorder, platelet-type, 20
SRC	AD	*SRC*-related thrombocytopenia
STIM1	AD/AR	Stormorken Syndrome
STX11	AR	Familial HLH types 4
STXBP2	AR	Familial HLH types 5
TBXA2R	AD	Thromboxane A2 receptor deficiency
TBXAS1	AD/AR	Thromboxane A synthase (Ghosal syndrome), Thromboxane Synthase deficiency
THPO	AD	Cyclic Thromboctyopenia

Genetic Conditions Commonly Associated with Platelet Disorders (continued)

Gene	Inheritance	Condition
TPM4	AD	*TPM4*-related thrombocytopenia
TUBB1	AD	Congenital Macrothrombocytopenia
UNC13D	AR	Familial HLH types 3
VIPAS39	AR	ARC Syndrome, Arthrogryposis-renal dysfunction-cholestasis syndrome
VPS33B	AR	Arthrogryposis-renal dysfunction-cholestasis syndrome
VPS45	AR	Congenital neutropenia & platelet α granule defect
WAS	X linked	Wiskott-Aldrich syndrome

Methodology:

Procedure: Platelet disorders gene sequencing panel uses Human Comprehensive Exome kit from Twist Bioscience to capture the exonic regions of genes from the genomic DNA extracted from the patient. Targeted regions are sequenced using an Illumina sequencing system with paired-end reads. Sequence reads are aligned to the human reference genome (build UCSC hg19). Variants within exons and flanking sequences are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline that includes the usage of GATK and Fabric Genomic Analysis platform. 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 or in regions with suboptimal data due to homologous issue, poly-nucleotides, or nucleotide repeats, and therefore may not be identified. Thus, the absence of identified pathogenic variants does not exclude the possibility of a genetic etiology for the patient's symptoms.
- 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, repeat expansions, low level mosaicism and many epigenetic defects may not be detected by this test.

Regions of Homology

These gene regions with homology may generate suboptimal data with potential false negative results.

GENE	TRANSCRIPT	EXON	CHROM	EXON_START	EXON_END
CDC42	NM_001791	6	1	22417920	22418010
RBM8A	NM_005105	6	1	145509165	145509211
TPM4	NM_003290	8	19	16212073	16212156

Low coverage (<20X) regions

GENE	TRANSCRIPT	EXON	CHROM	EXON_START	EXON_END
GP6	NM_001083899	8	19	55525449	55526533
VPS45	NM_001279353	13	1	150115015	150115109

Please note: *These regions represent the low coverage (<20X) regions identified during our test validation. For specific patient cases, these regions may vary.*

Note: Targeted deletion and duplication analysis of every gene on this panel except *ACTB, CDC42, FERMT3, GALE, GNE, GP6, GP9, HPS5, HPS6, IKZF5, KDSR, MPIG6B, P2RY1, PTGS1, PTPRJ, SRC* and *TPM4* 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 or saliva in an Oragene saliva kit . Please call the lab at 513-636-4474 for a free saliva collection kit. Label the tube with the patient's name, birth date, and date of collection. Alternatively, 10 mcg of DNA may be submitted.

We are unable to accept blood samples collected within two (2) weeks of a transfusion**.**

CPT Codes:

- **Platelet Disorders Gene Sequencing Panel:** 81443
- **Deletion and duplication analysis of any single Gene on the Platelet Disorders Gene Sequencing Panel except *GP1BB* and *WAS:*** 81479
- **Deletion and duplication analysis of *GP1BB:*** 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 Saturday.

Ship to:

Genetics and Genomics Diagnostic Laboratory
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

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