

# 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 Genome Sequencing (GS) 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 GS, 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).

**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](http://www.cincinnatichildrens.org/exome) to obtain a WES test requisition.

## 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>ACTB</i>	AD	<i>ACTB</i> -associated syndromic thrombocytopenia
<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>AP3D1</i>	AR	Hermansky-Pudlak syndrome 10
<i>ARPC1B</i>	AR	Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease
<i>BLOC1S3</i>	AR	Hermansky-Pudlak syndrome
<i>BLOC1S6</i>	AR	Hermansky-Pudlak syndrome
<i>CDC42</i>	AD	Takenouchi-Kosaki syndrome with macrothrombocytopenia
<i>CYCS</i>	AD	Autosomal Dominant Thrombocytopenias
<i>DIAPH1</i>	AD	Macrothrombocytopenia and hearing loss
<i>DTNBP1</i>	AR	Hermansky-Pudlak syndrome
<i>ETV6</i>	AD	Thrombocytopenia and cancer susceptibility
<i>FERMT3</i>	AR	Leukocyte adhesion deficiency, type III
<i>FLI1</i>	AD/AR	Paris-Trousseau (Jacobson) Syndrome, bleeding disorder
<i>FLNA</i>	X linked	X-linked thrombocytopenia with PVNH
<i>FYB1</i>	AR	Thrombocytopenia 3
<i>GALE</i>	AR	<i>GALE</i> -related thrombocytopenia
<i>GATA1</i>	X linked	X-linked thrombocytopenia
<i>GF11B</i>	AD/AR	Gray platelet syndrome, bleeding disorder
<i>GNE</i>	AR	<i>GNE</i> -related thrombocytopenia
<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

## Genetic Conditions Commonly Associated with Platelet Disorders (continued)

Gene	Inheritance	Condition
<i>HPS4</i>	AR	Hermansky-Pudlak syndrome
<i>HPS5</i>	AR	Hermansky-Pudlak syndrome
<i>HPS6</i>	AR	Hermansky-Pudlak syndrome
<i>IKZF5</i>	AD	<i>IKZF5</i> -related thrombocytopenia
<i>ITGA2</i>	AD	Glycoprotein Ia deficiency
<i>ITGA2B</i>	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
<i>ITGB3</i>	AD/AR	Glanzmann's thrombasthenia, bleeding disorder
<i>KDSR</i>	AR	<i>KDSR</i> -related thrombocytopenia
<i>LYST (CHS1)</i>	AR	Chediak-Higashi syndrome
<i>MASTL</i>	AD	Autosomal Dominant Thrombocytopenias
<i>MECOM</i>	AD	Radioulnar synostosis with amegakaryocytic thrombocytopenia 2
<i>MPIG6B</i>	AR	Thrombocytopenia, anemia, and myelofibrosis
<i>MPL</i>	AD/AR	Congenital amegakaryocytic thrombocytopenia
<i>MYH9</i>	AD	<i>MYH9</i> Disorders
<i>NBEA</i>	AD	Autism and dense granule deficiency
<i>NBEAL2</i>	AR	Gray platelet syndrome
<i>ORAI1</i>	AD/AR	Stormorken Syndrome
<i>P2RX1</i>	n/a	ADP receptor defects
<i>P2RY1</i>	AR?	Moderate platelet-related bleeding phenotype with diminished platelet responsiveness to thrombin and thrombin-mimetic peptides in vitro
<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>PTGS1</i>	AD/AR	Platelet-type bleeding disorder 12; Prostaglandin-endoperoxide synthase 1 deficiency
<i>PTPRJ</i>	AR	<i>PTPRJ</i> -related thrombocytopenia
<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>SLFN14</i>	AD	Bleeding disorder, platelet-type, 20
<i>SRC</i>	AD	<i>SRC</i> -related thrombocytopenia
<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

## Genetic Conditions Commonly Associated with Platelet Disorders (continued)

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

### Methodology:

**Procedure:** Platelet disorders gene sequencing panel is performed on genomic DNA using a PCR-free genome sequencing preparation and sequenced on an Illumina sequencing system with paired-end reads to an average autosomal sequencing depth of at least 30X. Sequence reads are aligned to the human reference genome (build UCSC hg38) and variants are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline that includes the usage of Dragen Germline pipeline 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.

### 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, polynucleotides, 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.

### Low coverage (<10X) regions

GENE	TRANSCRIPT	CHROM	EXON	EXON_START	EXON_END
<i>RUNX1</i>	NM_001754.5	<i>chr21</i>	Exon9	34792306	34792318
<i>GATA1</i>	NM_002049.4	<i>chrX</i>	Exon5	48793268	48793302
<i>FLNA</i>	NM_001110556.2	<i>chrX</i>	Exon32	154354618	154354640
<i>FLNA</i>	NM_001110556.2	<i>chrX</i>	Exon23	154359816	154359832
<i>FLNA</i>	NM_001110556.2	<i>chrX</i>	Exon12	154364817	154364828
<i>FLNA</i>	NM_001110556.2	<i>chrX</i>	Exon3	154367885	154367904
<i>FLNA</i>	NM_001110556.2	<i>chrX</i>	Exon2	154370896	154370928

**Please note:** These regions represent the low coverage (<10X) 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. Alternatively, 10 mcg of DNA extracted from whole blood in a CLIA certified lab 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

## References:

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*Futterer, J., Dalby, et al. (2018). Mutation in GNE is associated with severe congenital thrombocytopenia. Blood, 132(17), 1855–1858.*

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*Takeichi, T., et al. (2017). Biallelic Mutations in KDSR Disrupt Ceramide Synthesis and Result in a Spectrum of Keratinization Disorders Associated with Thrombocytopenia. The Journal of investigative dermatology, 137(11), 2344–2353.*

*Turro, E., et al. (2016). A dominant gain-of-function mutation in universal tyrosine kinase SRC causes thrombocytopenia, myelofibrosis, bleeding, and bone pathologies. Science translational medicine, 8(328), 328ra30.*