Autosomal Dominant Thrombocytopenia Panel

BloodCenter of Wisconsin offers a specifically designed Autosomal Dominant Thrombocytopenia Panel (test code 4865) optimized for detection of germline variants in 14 genes known to cause thrombocytopenia—specifically inherited in an autosomal dominant manner.

Inherited thrombocytopenia is a heterogeneous group of disorders characterized by low platelet counts typically less than 150,000/uL, but often can vary with age, gender, and ethnic background. Symptoms of thrombocytopenia may include purpura, petechiae, prolonged bleeding from cuts, epistaxis, gum bleeding, excessive bleeding after surgery, hemoptysis, hematuria, and menorrhagia in women. Severe inherited thrombocytopenias can present in the newborn period, while mild thrombocytopenia may remain undiagnosed until incidental detection on routine blood testing in adulthood. While some inherited types of thrombocytopenia can have distinctive hematologic features of platelet structure, platelet function, or granulocyte inclusions, many have no other distinguishing findings. Certain types of inherited thrombocytopenia cause predisposition to acute myelogenous leukemia or myelodysplastic syndromes, while some types are associated with mild to severe syndromic findings.

Misdiagnosis of inherited thrombocytopenia as autoimmune thrombocytopenia (ITP) can result in inappropriate therapies and inadequate surveillance for additional medical complications, underscoring the importance of accurate diagnosis. Advances in genetic testing through next generation sequencing allow for identification of underlying genetic defects and for distinguishing inherited cases from immune thrombocytopenia. Accurate diagnosis provides information about the phenotype and prognosis, guides medical management decisions, assists with the identification of affected family members, and allows for accurate genetic recurrence risk assessment.

Well-known and underrecognized types of autosomal dominant thrombocytopenia, with low platelet counts as the primary presenting feature, will be identified with this panel; some of these conditions carry variable risk for myeloid neoplasm or development other non-hematologic features.

This panel evaluates for single nucleotide variants and small deletions and duplications, which are most commonly responsible for genetic disease. However, large deletions and duplications, also referred to as copy number variation (CNV), are a known cause of genetic disorders, but can escape detection by next generation sequence analysis. Separate testing with aCGH Deletion/Duplication Analysis is available for some of the genes on this panel to evaluate for large deletions and duplications within a single exon of a given gene, encompassing one or more exons, or affecting an entire gene; please refer to the aCGH Deletion/Duplication Analysis test description for more information about specific genes included in this array.

For evaluation of inherited thrombocytopenia without a recognized autosomal dominant family history, the Inherited Thrombocytopenia Panel, which includes genes associated with dominant, recessive and X-linked conditions, is recommended. Inherited platelet disorders associated with platelet dysfunction are evaluated in the Platelet Function Disorder Panel. For broader evaluation of unspecified platelet problems, both the Inherited Thrombocytopenia Panel and Platelet Function Disorder Panel can be ordered together as part of the Comprehensive Platelet Disorder Panel.

Refer to the table inside for further information about each gene in the Autosomal Dominant Thrombocytopenia Panel, including the clinical phenotype, OMIM numbers and inheritance pattern.

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Autosomal Dominant Thrombocytopenia Panel: gene, clinical phenotype, OMIM number and inheritance pattern.			
Gene	Clinical Phenotype	Phenotype/Gene MIM number	Inheritance
ACTN1	*ACTN1*-related thrombocytopenia (bleeding disorder, platelet-type 15, BDPT15): macrothrombocytopenia or platelet anisocytosis with mild or absent bleeding tendency.	615193/102575	Autosomal Dominant
ANKRD26	*ANKRD26*-related thrombocytopenia (thrombocytopenia-2, THC2) mild bleeding tendency with normal platelet function and morphology with increased predisposition to hematologic myeloid malignancies.	188000/610855	Autosomal Dominant
CYCS	*CYCS* -associated thrombocytopenia (thrombocytopenia-4, THC4): mild or absent bleeding tendency with normal platelet size and morphology.	612004/123970	Autosomal Dominant
ETV6	*ETV6*-related thrombocytopenia (thrombocytopenia-5, THC5): onset is typically in early childhood with mild or absent bleeding tendency and increased predisposition to hematologic malignancies, particularly ALL.	616216/600618	Autosomal Dominant
FLI1	*FLI1*-related thrombocytopenia (bleeding disorder, platelet-type bleeding disorder-21, BDPLT21): variable bleeding tendency, increased platelet size and mild thrombocytopenia, with platelet counts that can increase with age. (Deletions of *FLI1* also account for the thrombocytopenia phenotype in the 11q23 contiguous gene deletion syndrome, also known as Paris-Trousseau thrombocytopenia and Jacobsen syndrome.)	188025/193067	Autosomal Dominant
GFI1B	Bleeding disorder, platelet-type 17 (Gray Platelet-like syndrome): variable bleeding symptoms due to disorder of platelet alpha granules with moderate macrothrombocytopenia and red cell anisopoikilocytosis.	187900/604383	Autosomal Dominant
GP1BA	Platelet-type von Willebrand disease (also known as pseudo-von Willebrand disease): thrombocytopenia and mucosal bleeding due to dominant pathogenic variants in *GP1BA* that cause excessive binding of the GPIb-IX-V complex to von Willebrand factor.	177820/606672 153670/606672	Autosomal Dominant Autosomal Dominant
GP1BB	Autosomal dominant macrothrombocytopenia (Autosomal dominant/monoallelic Bernard-Soulier syndrome, BSSA2): mild thrombocytopenia, variable large platelets, and mild to absent bleeding tendency, due to specific heterozygous variants, including the *GP1BA* "Bolzano" variant.	153670/138720	Autosomal Dominant
GP9	(Homozygous or compound heterozygous pathogenic variants in *GP1BA*, *GP1BB* and *GP9* cause autosomal recessive Bernard-Soulier syndrome (BSS) characterized by giant platelets, thrombocytopenia and severe bleeding.)	153670/173515	Autosomal Dominant
ITGA2B	Autosomal dominant macrothrombocytopenia (Bleeding disorder, platelet-type 16, BDPLT16): congenital macrothrombocytopenia associated with platelet anisocytosis with mild to or absent symptoms due to specific heterozygous dominant activating mutations in *ITGA2B* or *ITGB3*.	187800/607759	Autosomal Dominant
ITGB3	(Homozygous or compound heterozygous pathogenic variants in ITGA2B or ITGB3 cause autosomal recessive Glanzmann thrombasthenia, a mild to severe bleeding disorder with platelet aggregation abnormalities due to quantitative or qualitative defects of platelet glycoproteins IIb and /or IIIa.)	187800/173470	Autosomal Dominant
MYH9	***MYH9*-related disorders: large platelets and thrombocytopenia at birth with variable later onset of non-hematologic manifestations including progressive sensorineural hearing loss, glomerulonephritis, presenile cataracts and elevation of liver enzymes.** ***MYH9*-related disorders includes previously characterized disorders:** May-Hegglin anomaly: thrombocytopenia, giant platelets, and Dohle body-like inclusions. Epstein syndrome: thrombocytopenia, giant platelets, nephritis, and deafness. Fechtner syndrome: thrombocytopenia, giant platelets, and Dohle body-like inclusions in peripheral blood leukocytes, with nephritis, hearing loss, and eye abnormalities, mostly cataracts. Sebastian syndrome: thrombocytopenia, giant platelets, and leukocyte inclusions composed of highly dispersed filaments and few ribosomes. DNFA17: nonsyndromic progressive hearing loss with onset in childhood or later; hearing loss progressed from high frequency to moderate-severe deafness over time.	see below/ 160775 155100/160775 155100/160775 155100/160775 155100/160775 603622/160775	Autosomal Dominant
RUNX1	Familial platelet disorder with associated myeloid malignancy (FPDMM): characterized by mild to moderate thrombocytopenia, qualitative platelet defects and a predisposition to development of myeloid malignancies.	601399/151385	Autosomal Dominant
TUBB1	*TUBB1*-related macrothrombocytopenia: mild to absent bleeding symptoms and enlarged platelets.	613112/612901	Autosomal Dominant

Indications for testing

Autosomal Dominant Thrombocytopenia Panel:

Clarification and/or confirmation of diagnosis in a patient with thrombocytopenia in the context of family history of thrombocytopenia in a parent or child, consistent with autosomal dominant inheritance.

Single gene sequencing or custom gene panel:

Analysis of genes included in the Autosomal Dominant Thrombocytopenia Panel may also be ordered as a stand-alone single gene sequencing test or as a Custom Blood Disorder Panel (2-10 genes) as dictated by the patient's clinical and laboratory phenotype.

Targeted familial variant analysis:

Targeted variant analysis for clinical diagnosis or prenatal diagnosis can also be performed on any gene in the panel when the pathogenic variant(s) is known in the family (test code: 4970).

For clinical questions about laboratory tests and test utilization support, contact BloodCenter Client Services: (414) 937-6396 or 800-245-3117, Option 1, to be directed to our genetic counselors and clinical support team.

Test method

This next generation sequencing assay analyzes 14 genes, spanning the full coding regions plus a minimum 30bp of non-coding DNA including intron-exon junctions, and to approximately 200bp upstream of the *ANKRD26* coding region (5' UTR). These targeted regions are captured by hybridization, amplified and sequenced by massively parallel sequencing. Regions will have a minimum coverage of 50x and those regions with less than 50 sequencing reads or low quality coverage are supplemented with Sanger sequencing. All regions are covered by bi-directional analysis. Variants are identified by a customized bioinformatics pipeline, analyzed and comprehensively interpreted by our team of directors, scientists, and genetic counselors. All reported variants, including pathogenic, likely pathogenic, and variants of uncertain significance, are confirmed by Sanger sequencing.

For prenatal testing, analysis of variable number tandem repeats (VNTR) is used to confirm results are not affected by maternal cell contamination.

Assay sensitivity and limitations

The analytical sensitivity of this test is >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our analysis does not detect large deletions or duplications (>20 bp), or deletions, duplications or variants that are outside the regions sequenced. To order the analysis of copy number variation at the exon or gene level, please refer to the aCGH Deletion/Duplication Analysis test, or contact Client Services before placing your order.

Reporting of results

While this assay is designed to detect germline genetic variants associated with autosomal dominant thrombocytopenia, variants unrelated to the indication for testing, but with other clinical and/or reproductive implications, may also be detected. A comprehensive database of gene-phenotype relationships listed by gene name can be found at http://www.omim.org.

Results are classified and reported in accordance with ACMG next-generation sequencing standards. Variants predicted to be pathogenic, likely pathogenic, and of uncertain significance will be reported; variants classified as likely benign or benign are typically not reported but such data are available upon request.

Sequence variants are described using standard Human Genome Variation Society (HGVS) nomenclature (http://hgvs.org).

Specimen requirements

Parental/Patient/Pediatric: 3-5 mL Whole blood (EDTA tube, lavender top), 2-5 mL Bone marrow (EDTA tube, lavender top), 3-4 Buccal swabs, or ≥1ug of DNA at ≥50ng/uL of High Quality DNA.

Fetal: 7-15 mL Amniotic fluid, 5-10 mg Chorionic villi; back up culture of amniocytes or chorionic villi is highly recommended. Cultured: Two T25 flasks cultured amniocytes or chorionic villi ($2x10^6$ minimum). Maternal blood sample of 3-5 mL Whole blood (EDTA tube, lavender top) is requested for all prenatal samples for maternal cell contamination studies.

If questions please contact the laboratory to discuss sample requirements.

SHIP

Shipping requirements

Ship on an ice pack or at room temperature. Protect from freezing. 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/Diagnostic Laboratory
BloodCenter of Wisconsin
638 N. 18th St.
Milwaukee, WI 53233

ORDER

Required forms

Please complete all pages of the requisition form. Clinical history (including patient's ethnicity, clinical diagnosis, family history and relevant laboratory findings) is necessary for optimal interpretation of genetic test results and recommendations. Clinical and laboratory history can either be recorded on the requisition form or clinical and laboratory reports can be submitted with the sample.

CPT Codes/Billing/Turnaround time

Test Code: 4865

CPT codes: 81404, 81479

Turnaround time: 21 days

The CPT codes provided are subject to change as more information becomes available. CPT codes are provided only as guidance to assist clients with billing.

For additional information related to shipping, billing or pricing, please contact, BloodCenter Client Services: (414) 937-6396 or 800-245-3117, Option 1, or LabInfo@bcw.edu.

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