THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Thrombocytopenia

Clinical Features:
Inherited thrombocytopenias (IT) are a heterogeneous group of diseases characterized by variable expressivity of the bleeding tendency because of low platelet count sometimes associated with platelet dysfunction. IT identified over the last years were found to be more frequent than those previously known. At present, mutations in more than 30 different genes are known to cause ITs. These genes account for approximately 50% of the IT patients [1]. Making a molecular diagnosis is important for the correct patients' management [2].

Our Thrombocytopenia Panel includes sequence and deletion/duplication of analysis of all the genes listed below.

Thrombocytopenia Panel					
ABCG5	ABCG8	ACTN1	ADAMTS13	ANKRD26	C3
CD46 (MCP)	CFB	CFH	SRC	WAS	CFHR4
CFHR5	CFI	CYCS	DGKE	ETV6	FLI1
FLNA	FYB	GATA1	GATA2	GFI1B	GP1BA
GP1BB	GP9	HOXA11	ITGA2B	MPL	MYH9
NBEAL2	PRKACG	RBM8A	RUNX1	SLFN14	
TERC	TERT	THBD	TUBB1	VWF	

Gene	Disease	Main Clinical Features
ABCG5	Sitosterolemia (STSL)	Hemolytic anemia with stomatocytosis. Tendon and tuberous xanthomas. Premature atherosclerosis. [2, 3]
ABCG8	Sitosterolemia (STSL)	Hemolytic anemia with stomatocytosis. Large platelets. Tendon and tuberous xanthomas. Premature atherosclerosis. Also non-syndromic.[2, 3]
ACTN1	*ACTN1*-related thrombocytopenia	Large platelets.[2, 4]
ADAMTS13	Familial thrombotic thrombocytopenic purpura (TPP)	Hemolytic anemia with fragmentation of erythrocytes, diffuse and nonfocal neurologic findings, decreased renal function, and fever. [5]
ANKRD26	*ANKRD26*-related thrombocytopenia (THC2)	About 8% of patients acquire myeloid malignancies. Some patients have increased hemoglobin levels and/or leukocytosis.[2, 4]
C3	Atypical hemolytic uremic syndrome-5 (aHUS5)	Age at onset ranged from 8 months to 40 years. Most developed end-stage renal disease, and all had decreased serum C3. [6]
CD46	Atypical hemolytic uremic syndrome-2 (aHUS2)	Microangiopathic hemolytic anemia, thrombocytopenia, thrombotic microangiopathy, fragmented erythrocytes. decreased hemoglobin. [7, 8]
CFB	Atypical hemolytic uremic syndrome-4 (aHUS4)	Microangiopathy, persistent hypocomplementemia, decreased serum C3. [9]
CFH	Atypical hemolytic uremic syndrome-1 (aHUS1)	Acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia associated with distorted erythrocytes. [10]
CFHR4	Atypical hemolytic uremic syndrome	Acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia associated with distorted erythrocytes. [12]
CFHR5	Atypical hemolytic uremic syndrome	An autosomal dominant form of glomerulonephritis resulting in renal failure. [13]
CFI	Atypical hemolytic uremic syndrome-3 (aHUS3)	Thrombotic microangiopathy. microangiopathic hemolytic anemia, hypertension, and proteinuria. [14]
CYCS	*CYCS*-related thrombocytopenia	Reduced platelet size.[2, 4]
DGKE	Atypical hemolytic uremic syndrome-7 (aHUS7)	Acute onset in the first year of life of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. [15]
ETV6	*ETV6*-related thrombocytopenia	Increased risk of myeloid and lymphoid malignancies.[2]

FLI1	Mimics Paris-Trousseau thrombocytopenia but has no other features of the 11q23 deletion syndrome	Moderate thrombocytopenia; absent collagen-induced platelet aggregation; large, fused α-granules in 1% to 5% of circulating platelets[16]
FLNA	*FLNA*-related thrombocytopenia	Periventricular nodular heterotopia (OMIM 300049). Large platelets. Also non-syndromic. [2, 4]
FYB	Congenital autosomal recessive small-platelet thrombocytopenia	Remarkable small-platelet thrombocytopenia and a significant bleeding tendency. [17]
GATA1	*GATA1*-related diseases	Hemolytic anemia with laboratory abnormalities resembling beta-thalassemia, splenomegaly, or dyserythropoietic anemia. Congenital erythropoietic porphyria. [2, 4]
GATA2	*GATA2*-related diseases	Myelodysplastic syndrome, acute myeloid leukemia.[18]
GFI1B	*GFI1B*-related thrombocytopenia	Some pale platelets reflecting a variable alpha-granule deficiency. Large platelets.[2, 4]
GP1BA	Bernard-Soulier syndrome (BSS)	Giant platelets. Large platelets. Platelet count can decrease under stress. Moderate thrombocytopenia. [2, 4, 19]
GP1BB	Bernard-Soulier syndrome (BSS)	Giant platelets. Large platelets. Moderate thrombocytopenia. [2, 4, 19]
GP9	Bernard-Soulier syndrome (BSS)	Moderate thrombocytopenia with giant platelets and a bleeding tendency. [4, 19]
HOXA11	Congenital thrombocytopenia with radio-ulnar synostosis (CTRUS)	Bilateral radio-ulnar synostosis +/− other malformations. Reduced/absent megakaryocytes in bone marrow.[2, 4]
ITGA2B	*ITGA2/ITGB3*-related thrombocytopenia	Large platelets. [2, 4]
ITGB3	*ITGA2B/ITGB3*-related thrombocytopenia	Large platelets. [2, 4]
MPL	Congenital amegakaryocytic thrombocytopenia (CAMT)	Reduced/absent megakaryocytes in BM. Evolution to fatal bone marrow aplasia in infancy in all patients. [2, 4]
MYH9	*MYH9*-related disease	Sensorineural deafness, nephropathy, cataract, and/or elevated liver enzymes. Giant platelets. Döhle-like inclusions in granulocytes. Also non-syndromic. [2, 4]
NBEAL2	Gray platelet syndrome (GPS)	Platelet count decreases over time. Development of progressive myelofibrosis and splenomegaly. Large platelets. [2, 4]
PRKACG	*PRKACG*-related thrombocytopenia	Large platelets. [2, 4]
RBM8A	Thrombocytopenia with absent radii (TAR)	Bilateral radial aplasia +/− other upper and lower limb bone abnormalities. Kidney, cardiac, and/or CNS malformations. Reduced/absent megakaryocytes in BM. Platelet count tends to raise over time and often normalizes. [2, 4]
RUNX1	Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML)	Over 40% of patients acquire acute myelogenous leukemia or myelodysplastic syndromes. Increased risk of T acute lymphoblastic leukemia. [2, 4]
SLFN14	SLFN14-related disease	Moderate thrombocytopenia, macrothrombocytopenia. [20]
SRC	Autosomal dominant thrombocytopenia-6	Increased bleeding episodes due to reduced platelet count and abnormal platelet morphology resulting from defective megakaryopoiesis. [21]
TERC	Telomere biology disorder	Idiopathic pulmonary fibrosis, dyskeratosis congenital, bone marrow failure. [22-24]
TERT	Telomere biology disorder	Idiopathic pulmonary fibrosis, pancytopenia. [22-25]
THBD	atypical hemolytic uremic syndrome-6 (aHUS6)	One or more episodes of microangiopathic hemolytic anemia and thrombocytopenia associated with acute renal failure. [26]
TUBB1	*TUBB1*-related thrombocytopenia	Large platelets.[2, 4]
VWF	von Willebrand disease TYPE 2B (VWF)	Macrothrombocytopenia, spontaneous thrombocytopenia
WAS	Wiskott-Aldrich syndrome (WAS) X-linked thrombocytopenia	Severe immunodeficiency leading to early death. Eczema. Increased risk of malignancies and autoimmunity. Reduced platelet size.[2, 4] Mild immunodeficiency. Mild transient eczema. Increased risk of malignancies and autoimmunity. Reduced platelet size. Also non-syndromic. [2]

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99%

for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Thrombocytopenia Panel

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube.

NOTE: blood samples are not accepted if patient has a history of myelodysplastic syndrome or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.

Cost: $4000

Turn-around time: 6 weeks

Note: We cannot bill insurance for the comprehensive thrombocytopenia panel

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. All abnormal results are reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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