Genetic Loci Associated with Platelet Traits and Platelet Disorders

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Abstract

Genetic investigations have led to important advances in our knowledge of genes, proteins, and microRNA that influence circulating platelet counts, platelet size, and function. The application of genome-wide association studies (GWAS) to platelet traits has identified multiple loci with a significant association to platelet number, size, and function in aggregation and granule secretion assays. Moreover, the genes altered by disease-causing mutations have now been identified for several platelet disorders, including X-linked recessive, autosomal dominant, and autosomal recessive platelet disorders. Some mutations that cause inherited platelet disorders involve genes that GWAS have associated to platelet traits. Although disease-causing mutations in many rare and syndromic causes of platelet disorders have now been characterized, the genetic mutations that cause common inherited platelet disorders, and impair platelet aggregation and granule secretion, are largely unknown. This review summarizes current knowledge on the genetic loci that influence platelet traits, including the genes with well-characterized mutations in certain inherited platelet disorders.

Keywords

- ▶ platelet function
- ▶ inherited platelet disorders
- ▶ genome-wide association studies
- ▶ platelet aggregation
- ▶ platelet secretion

Platelets play an important role in hemostasis and their function traits are emerging to have important genetic influences. Platelet function is complex: with vascular injury, normal platelets adhere to exposed collagen and to von Willebrand factor bound to collagen.^{1–3} This triggers the generation and secretion of thromboxane A₂ (TXA₂) and platelet storage granule release.^{1–3} Platelets then undergo further activation, with intracellular signaling triggered by their released TXA₂, adenosine diphosphate (ADP), serotonin, and other agonists (such as thrombin) that are generated at the sites of vessel injury.^{1–3} Genetic defects can impair platelet hemostatic function in many ways, from modifying platelet–vessel wall interactions, through changes in the number of circulating platelets, and/or their size, adhesive properties, responses to agonists, intracellular signaling, granule release, and the feedback that signaling and secretion have on platelet activation and prohemostatic function.^{1–3}

The purpose of this review is to summarize the current state of knowledge on the genetic loci that influence platelet functions and traits, including the genes that may contain disease-causing mutations in those characterized forms of inherited platelet disorders and other conditions that modify platelets.

Inheritance of Platelet Traits and Platelet Disorders

Megakaryocytes transcribe a huge number of genes, and platelets are estimated to contain more than 1,000 proteins.^{4–11} Twin studies have provided evidence that platelet traits and function are influenced by genetic factors.¹² Studies of families and candidate genes have led to the identification of several genetic loci that are strongly associated with platelet physiologic and pathologic function.^{13–29} Genome-wide

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Table 1 Human single nucleotide polymorphisms that have been associated with platelet count, volume, and function as measured by light-transmission platelet aggregation or secretion assays^a

Trait	Gene	Protein	Population	SNP with lowest p value for locus (associated trait)	Cytoband	Reference
Count	<i>HSPB7</i>	Heat shock 27 kDa protein family, member 7	AU, D	rs1763611	1p36.23	14
MPV	<i>LAPTM4A, SDC1</i>	Lysosomal-associated transmembrane protein 4A, syndecan-1	E	rs11686303	2p24.1	15
Count	<i>KCNJ3</i>	G protein-activated inward rectifier potassium channel 1	AU, D	rs11682195	2q24.1	14
Collagen-induced secretion	<i>MAGI1</i>	Membrane-associated guanylate kinase, WW and PDZ domain containing protein 1	SA	rs1318477	3p14.1	16
Count, MPV	<i>ARHGEF3</i>	Rho guanine nucleotide exchange factor 3	AU, D	rs1354034 (count)	3p14.3	14,15
			E	rs12485738 (MPV)		
Aggregation with collagen/thromboxane	<i>MME</i>	Neprilysin	E	rs1436634	3q25.2	17
Count	<i>THPO</i>	Thrombopoietin	J	rs6141	3q27.1	18
Count	<i>KCNIP4</i>	Kv channel-interacting protein 4	AU, D	rs13150985	4p15.32	14
MPV	<i>UNC5C</i>	Netrin receptor UNC5C	E	rs265013	4q22.3	15
Count	<i>CDH10</i>	Cadherin-10	AU, D	rs10043237	5p14.2	14
Count	<i>BAK1</i>	Bcl-2 homologous antagonist/killer	J	rs5745568	6p21.31	18
Count	<i>PHACTR1</i>	Phosphatase and actin regulator	AU, D	rs12212807	6p24.1	14
Count	<i>GMDS</i>	GDP-mannose 4,6 dehydratase	SA	rs4463305	6p25.3	16
Count	<i>HBS1L, MYB</i>	HBS1-like protein, transcriptional activator Myb	AU, D	rs9399137	6q23.3	14,18
			J	rs7775698		
Aggregation with collagen/thromboxane	<i>IPCEF1</i>	Interactor protein for cytohesin exchange factors 1	E	rs1534446	6q25.2	17
MPV	<i>PIK3CG</i>	Phosphoinositol-4,5-bisphosphate 3-kinase (g subunit)	E	rs342293	7q22.3	19
Aggregation with ristocetin	<i>C8orf86</i>	Uncharacterized protein C8orf86	SA	rs7845393	8p11.22	16
Aggregation with ristocetin	<i>FGFR1</i>	Fibroblast growth factor receptor 1	SA	rs7845393	8p11.22	16
MPV	<i>C8orf22</i>	Chromosome 8 open reading frame 22	E	rs12056729	8q11.21	15
MPV	<i>CPQ, TSPYL5</i>	Carboxypeptidase Q, testis-specific Y-encoded-like protein 5	E	rs1835742	8q22.1	15
Aggregation with collagen/thromboxane	<i>GLIS3</i>	Zinc finger protein GLIS3	E	rs10116901	9p24.2	17
Count	<i>RCL1</i>	RNA 3'-terminal phosphate cyclase-like protein	E	rs385893	9q24.1	18
Count	<i>ABCA1</i>	ATP-binding cassette subfamily A member 1	AU, D	rs11999261	9q31.1	14
Aggregation with AA	<i>LPAR1</i>	Lysophosphatidic acid receptor 1	SA	rs4366150	9q31.3	16
Aggregation with ristocetin	<i>CACNB2</i>	Voltage-dependent L-type calcium channel subunit β -2	SA	rs6415964	10p12.33	16

Table 1 (Continued)

Trait	Gene	Protein	Population	SNP with lowest <i>p</i> value for locus (associated trait)	Cytoband	Reference
Aggregation with ristocetin	<i>SLC39A12</i>	Zinc transporter ZIP12	SA	rs6415964	10p12.33	16
MPV	<i>PFKP</i>	Platelet phosphofructokinase	E	rs1574318	10p15.2	15
Aggregation with ADP	<i>LDHAL6A</i>	L-lactate dehydrogenase A-like 6A	AA	rs11024665	11p15.1	17
Aggregation (collagen-induced)	<i>MIR100HG</i>	mir-100-let-7a-2 cluster host gene	F	rs565229	11q24.1	20
Count	<i>NFE2, COPZ1</i>	Transcription factor NF-E2 45 kDa subunit, coatomer subunit zeta-1	E	rs10876550	12q13.13	21
Aggregation with ADP	<i>ANKS1B</i>	Ankyrin repeat and sterile α motif domain-containing protein 1B	AA	rs17029861	12q23.1	17
Count	<i>SH2B3</i>	SH2B adapter protein 3	J	rs739496	12q24.21	18
Count, MPV	<i>WDR66</i>	WD repeat-containing protein 66	E	rs7961894 (count, MPV)	12q24.31	15
Aggregation with AA	<i>RPP25</i>	Ribonuclease P protein subunit p25	SA	rs1867153	15q24.2	16
Count, aggregation with AA	<i>SCAMP5</i>	Secretory carrier-associated membrane protein 5	SA	rs1867153 (aggregation)	15q24.2	14,16
			AU, D	rs2289583 (count)		
Count	<i>GPIBA</i>	Glycoprotein Iba α	J	rs6065	17pter-p12	18
Count, MPV	<i>TAOK1</i>	Serine/threonine-protein kinase TAO1	E	rs2138852	17q11.2	15
Count, MPV	<i>TPM4</i>	Tropomyosin 4	E, AA	rs8109288	19p13.12	21

Abbreviations: AA, African American; AU, Australian; D, Dutch; E, European; F, Framingham Heart Study population; J, Japanese; MPV, mean platelet volume; SA, South American.

^aThe chromosome positions and gene(s) closest to the single nucleotide polymorphism are shown, along with the respective proteins encoded by the genes. All associations shown were reported have a *p* value $\leq 1 \times 10^{-5}$.

association studies (GWAS) of different populations have expanded the list of genetic loci that show significant associations to platelet traits (**►Table 1** summarizes information on the associations with *p* values $\leq 1 \times 10^{-5}$).^{14–25} Although there are uncertainties about the degree to which these loci predict normal or pathological platelet variability, the heritability of platelet traits, including platelet “reactivity” to agonists in function tests, offers an attractive explanation for the significant correlation of platelet responses to different agonists in clinical aggregation and secretion assays, for individuals with and without bleeding problems.^{30–34}

Among the heritable markers associated with platelet traits, some show associations with size, count, and/or function, and some are associated with more than one platelet trait. Some associations do not clearly map to a single gene and/or show an association to multiple loci (see **►Table 1**). Some single nucleotide polymorphisms (SNPs) have been associated with a platelet characteristic in multiple populations, consistent with an influence upon different genetic backgrounds^{14–16,18,35} (see **►Table 1**). Meta-analyses, which increase the power for detecting associations, have found additional associations for platelet traits (**►Table 2** summarizes data for associations with *p* values $\leq 1 \times 10^{-5}$).

GWAS have associated some noncoding regions of the genome with platelet traits, which indirectly suggests that transcriptional or posttranscriptional regulatory mechanisms are involved in regulating platelet function.³⁶ Given that both platelets and megakaryocytes contain unique regulatory microRNA (miRNA),²⁹ some GWAS have explored if the genes encoding these short RNA sequences are associated with platelet function traits.¹⁶ Although strong associations of platelet traits with genes encoding miRNA have not been established by GWAS, this possibility needs to be tested with larger numbers of subjects.

At present, there is small but important overlap between genetic loci that are mutated in platelet disorders (**►Table 3**) and those that are known to influence platelet traits (**►Tables 1** and **2**). Among the genes that show associations to platelet traits by GWAS (**►Tables 1** and **2**)^{13–32,36} but are not yet implicated as causing platelet function disorders, a number have known or implicated importance to platelet function, production, or other traits, including the genes for the following: thrombopoietin,³⁷ the γ subunit of phosphoinositol-4,5-bisphosphate 3-kinase,³⁸ the α -2A adrenergic receptor,³⁹ platelet endothelial aggregation receptor 1,⁴⁰ dynamin 3,⁴¹ multi-drug resistance protein 4,⁴² tropomyosin 4,⁴³ proteinase-

Table 2 Human single nucleotide polymorphisms that have been associated with platelet function through meta-analysis of genome-wide association studies^a

Trait	Gene	Protein	Population	SNP with lowest p value for locus (associated trait)	Cytoband	Reference
MPV	<i>KIF1B</i>	Kinesin-like protein KIF1B	E	rs17396340	1p36.22	22
Count	<i>MFN2</i>	Mitofusin-2	E	rs2336384	1p36.22	22
ADP and epinephrine aggregation	<i>PEAR1</i>	Platelet endothelial aggregation receptor 1	E	rs12566888 (epinephrine)	1q23.1	25
			AA	rs12041331 (ADP)		
Count, MPV	<i>DNM3</i>	Dynamin 3	E	rs10914144	1q24.3	22,23
Count, MPV	<i>TMCC2</i>	Transmembrane and coiled-coil domains protein 2	E	rs1668871 (count), rs1172130 (MPV)	1q32.1	22,23
Count	LOC148824	Uncharacterized miscellaneous RNA gene	E	rs7550918	1q44	22
Count	<i>TRIM58</i>	Tripartite motif-containing protein 58	E	rs3811444	1q44	22
Count	<i>THADA</i>	Thyroid adenoma-associated protein	E	rs17030845	2p21	22
Count, MPV	<i>EHD3</i>	EH domain-containing protein 3	E	rs649729 (MPV), rs625132 (count)	2p21	22,23
Count	<i>GCKR</i>	Glucokinase regulatory protein	E	rs1260326	2p23	22
MPV	<i>ANKMY1</i>	Ankyrin repeat and MYND domain-containing protein 1	E	rs4305276	2q37.3	22
Count, MPV	<i>ARHGEF3</i>	Rho guanine nucleotide exchange factor 3	E	rs1354034 (count), rs12485738 (MPV)	3p14.3	22,23
Count	<i>SATB1</i>	DNA-binding protein SATB1	E	rs7641175	3p23	22
Count	<i>SYN2</i>	Synapsin-2	E	rs7616006	3p25	22
Count	<i>PDIA5</i>	Protein disulfide-isomerase A5	E	rs3792366	3q21.1	22
MPV	<i>KALRN</i>	Kalirin	E	rs10512627	3q21.1	22
Count	<i>THPO</i>	Thrombopoietin	E	rs6141	3q27.1	22
MPV	<i>KIAA0232</i>	Uncharacterized protein KIAA0232	E	rs11734132	4p16.1	22
Count	<i>HSD17B13</i>	17- β -hydroxysteroid dehydrogenase 13	E	rs7694379	4q22.1	22
Count, MPV	<i>F2R</i>	Proteinase-activated receptor 1	E	rs2227831 (MPV), rs17568628 (count)	5q13.3	22
Count, MPV	<i>MEF2C</i>	Myocyte-specific enhancer factor 2C	E	rs700585	5q14.3	22
Count	<i>IRF1</i>	Interferon regulatory factor 1	E	rs2070729	5q31.1	22
MPV	<i>RNF145</i>	RING finger protein 145	E	rs10076782	5q33.3	22
Count	<i>BAK1</i>	Bcl-2 homologous antagonist/killer	E	rs1330066	6p21.31	22–24
			AA	rs210134		
Count	<i>HLA-DOA</i>	HLA class II histocompatibility antigen, DO α chain	E	rs399604	6p21.32	22
Count	<i>HLA-B</i>	HLA class I histocompatibility antigen, B-82 α chain	E	rs3819299	6p22.2	22
Count	<i>LRRC16A</i>	Leucine-rich repeat containing 16A	AA, E, HA	rs441460	6p22.2	22,24
Count	<i>HBS1L, MYB</i>	HBS1-like protein, transcriptional activator Myb	E	rs9399137	6q23.3	22,24
			AA	rs9494145		
Count	<i>CD36</i>	Platelet glycoprotein IV (thrombospondin receptor)	AA, E, HA	rs13236689	7q21.11	24
Count, MPV, aggregation with epinephrine	<i>PIK3CG</i>	Phosphoinositol-4,5-bisphosphate 3-kinase (g subunit)	E	rs342293 (MPV)	7q22.3	22,23,25
			AA	rs342293 (count)		
			AA	rs342296 (MPV)		
			E	rs342275 (count)		
			E	rs342286 (aggregation)		

Table 2 (Continued)

Trait	Gene	Protein	Population	SNP with lowest <i>p</i> value for locus (associated trait)	Cytoband	Reference
Count	<i>WASL</i>	Wiskott-Aldrich syndrome-like protein	E	rs4731120	7q31.3	22
Aggregation with ADP	<i>SHH</i>	Sonic hedgehog protein	E	rs2363910	7q36.3	25
			AA	rs6943029		
Count	<i>ZFPM2</i>	Zinc finger protein ZFPM2	E	rs6993770	8q23.1	22
Count	<i>PLEC1</i>	Plectin	E	rs6995402	8q24.3	22
Count	<i>CDKN2A</i>	Cyclin-dependent kinase inhibitor 2A, isoform 4	E	rs3731211	9p21.3	22
MPV	<i>DOCK8</i>	Dedicator of cytokinesis protein 8	E	rs10813766	9p24.3	22
Count	<i>AK3</i>	GTP:AMP phosphor-transferase, mitochondrial	E	rs409801	9q24.1	22
Count	<i>RCL1</i>	RNA 3'-terminal phosphate cyclase-like protein	E	rs13300663	9q24.1	22
Count	<i>BRD3</i>	Bromodomain-containing protein 3	E	rs11789898	9q34.2	22
Count, MPV, aggregation with epinephrine	<i>JMJD1C</i>	Probable JmjC domain-containing histone demethylation protein 2C	E	rs7075195 (MPV)	10q21.2–10q21.3	22–25
			E	rs10761731 (count)		
			AA	rs7896518 (count)		
			E	rs10761741 (aggregation)		
			AA	rs2893923 (aggregation)		
Aggregation with epinephrine	<i>ADRA2A</i>	Alpha-2A adrenergic receptor	E	rs4311994	10q25.2	25
			AA	rs869244		
Aggregation with ADP	<i>MRVI1</i>	Protein MRVI1	E	rs7940646	11p15.4	25
			AA	rs1874445		
MPV	<i>BET1L</i>	BET1-like protein	E	rs11602954	11p15.5	23
Count, MPV	<i>PSMD13</i>	26S proteasome non-ATPase regulatory subunit 13	E	rs17655730 (MPV), rs505404 (count)	11p15.5	22
Count	<i>FEN1</i>	Flap endonuclease 1	E	rs4246215	11q12.2	22
Count	<i>BAD</i>	Bcl2 antagonist of cell death	AA, E, HA	rs477895	11q13.1	24
Count	<i>CBL</i>	E3 ubiquitin-protein ligase CBL	E	rs4938642	11q23.3	22
MPV	<i>MLSTD1</i>	Fatty acyl-CoA reductase 2	E	rs2015599	12p11.22	22
Count, MPV	<i>CD9, VWF</i>	CD9 antigen, von Willebrand factor	E	rs1558324 (MPV), rs7342306 (count)	12p13.31	22
Count, MPV	<i>PTGES3, BAZ2A</i>	Prostaglandin E synthase 3, bromodomain adjacent to zinc finger domain protein 2A	E	rs2950390 (MPV), rs941207 (count)	12q13.3	22
MPV	<i>COPZ1, NFE2, CBX5</i>	Coatmer subunit zeta-1, transcription factor NF-E2 45 kDa subunit, chromobox protein homolog 5	E	rs10876550	12q13.13	22
Count	<i>ATXN2</i>	Ataxin 2	E	rs11065987	12q24.1	23
Count	<i>PTPN11</i>	Tyrosine-protein phosphatase non-receptor type 11	E	rs11066301	12q24.1	22,23
Count	<i>RPH3A, PTPN11</i>	Rabphilin-3A, tyrosine-protein phosphatase nonreceptor type 11	E	rs17824620	12q24.1	22
Count	<i>ACAD10</i>	Acyl-CoA dehydrogenase family member 10	AA	rs6490294	12q24.12	24
Count	<i>SH2B3</i>	SH2B adapter protein 3	E	rs3184504	12q24.12	22
Count, MPV	<i>WDR66</i>	WD repeat-containing protein 66	E	rs7961894 (count, MPV)	12q24.31	22,23

(Continued)

Table 2 (Continued)

Trait	Gene	Protein	Population	SNP with lowest <i>p</i> value for locus (associated trait)	Cytoband	Reference
Count	<i>ABCC4</i>	Multidrug resistance-associated protein 4	E	rs4148441	13q32	22
MPV	<i>GRTF1</i>	Growth hormone-regulated TBC protein 1	E	rs7317038	13q34	22
Count	<i>RAD51L1</i>	DNA repair protein RAD51 homolog 2	E	rs8022206	14q24.1	22
Count	<i>ITPK1</i>	Inositol-tetrakisphosphate 1-kinase	E	rs8006385	14q31	22
Count	<i>C14orf70</i> , <i>DLK1</i>	Putative uncharacterized protein encoded LINC00523, protein delta homolog 1	E	rs7149242	14q32.2	22
Count	<i>RCOR1</i>	REST corepressor 1	E	rs11628318	14q32.31	22
Count, MPV	<i>C14orf73</i>	Exocyst complex component 3-like protein 4	E	rs2297067 (count), rs944002 (MPV)	14q32.32	22
MPV	<i>BRF1</i>	Transcription factor IIIB 90 kDa subunit	E	rs3000073	14q32.33	22
Count, MPV	<i>TPM1</i>	Tropomyosin α -1 chain	E	rs11071720 (MPV), rs3809566 (count)	15q22.1	22,23
Count	<i>ANKDD1A</i>	Ankyrin repeat and death domain-containing protein 1A	E	rs1719271	15q22.31	22
Count	<i>GPIBA</i>	Glycoprotein Iba	E	rs6065	17pter-p12	22
Count	<i>AKAP10</i>	A-kinase anchor protein 10, mitochondrial	E	rs397969	17p11.1	22
Count, MPV	<i>TAOK1</i>	Serine/threonine-protein kinase TAO1	E	rs8076739 (MPV)	17q11.2	22,24
			AA	rs11653144 (MPV)		
			E	rs559972 (count)		
Count, MPV	<i>SNORD7</i> , <i>AP2B1</i>	Small nucleolar RNA C/D box 7, AP-2 complex subunit β	E	rs10512472 (count), rs16971217 (MPV)	17q12	22
Count	<i>FAM171A2</i> , <i>ITGA2B</i>	Protein FAM171A2, integrin α -IIb	E	rs708382	17q21.31	22
Count	<i>CABLES1</i>	CDK5 and ABL1 enzyme substrate 1	E	rs11082304	18q11.2	22
MPV	<i>CD226</i>	CD226 antigen	E	rs12969657	18q22.3	22,23
Count, MPV	<i>TPM4</i>	Tropomyosin 4	E, AA, HA	rs8109288 (count, MPV)	19p13.12	22,24
Count	<i>EXOC3L2</i>	Exocyst complex component 3-like protein 2	E	rs17356664	19q13.32	22
Aggregation with collagen	<i>GP6</i>	Platelet glycoprotein VI	E, AA	rs1671152	19q13.42	25
MPV	<i>SIRPA</i>	Tyrosine-protein phosphatase nonreceptor type substrate 1	E	rs13042885	20p13	22,23
Count, MPV	<i>TUBB1</i> , <i>CTS2</i> , <i>SLMO2</i>	Tubulin β -1 chain, cathepsin Z, protein slowmo homolog 2	E	rs4812048 (MPV)	20q13.32	22,24
			AA, E, HA	rs151361 (count)		
Count	<i>ARVCF</i>	Armadillo repeat protein deleted in velocardiiofacial syndrome	E	rs1034566	22q11.21	22

Abbreviations: AA, African Americans; ADP, adenosine diphosphate; CRP, collagen-related peptide; E, European; HA, Hispanic American; MPV, mean platelet volume; SNP, single nucleotide polymorphism.

^aThe chromosome positions and gene(s) closest to SNP are shown, along with the respective proteins encoded by the genes. SNPs with $p \leq 1 \times 10^{-5}$ for associations are shown.

Table 3 Summary of the genetic causes of characterized inherited platelet disorders^a

Type of defect	Name of disorder or affected protein	Mode of inheritance	Gene(s)	Protein(s)	Locus	Description of defect and reference
Activation	GPVI	Autosomal recessive	GP6	Platelet GPVI	19q13.42	Impaired platelet activation by collagen because of mutations of GPVI, which mediates collagen-induced platelet activation ^{61,62}
Activation	P2Y ₁₂	Autosomal recessive	P2RY12	P2Y purinoceptor 12	3q25.1	Impaired platelet activation by ADP ⁸¹
Activation	P2X ₁	Autosomal dominant	P2RX1	P2X purinoceptor 1	17p13.2	Impaired platelet activation by ADP ⁸²
Activation	Thromboxane A ₂ receptor	Autosomal dominant	TBXA2R	Thromboxane A ₂ receptor	19p13.3	Defective function of the platelet receptor for thromboxane A ₂ ^{83–87}
Activation	Prostaglandin G/H synthase deficiency	Unproven as deficiencies have been reported, but not mutations	PTGS1	Prostaglandin G/H synthase 1 (cyclo-oxygenase 1)	9q33.2	Defective platelet function because of impaired production of thromboxane A ₂ ¹³²
Activation	Thromboxane synthase deficiency	Autosomal recessive	TBXA51	Thromboxane-A synthase	7q34	Defective platelet functions because of impaired production of thromboxane A ₂ . Some associated with increased bone density with Ghosal hematodiaphyseal syndrome ¹³³
Adhesion	Platelet-type VWD	Autosomal dominant	GP1BA	Platelet GPIIb chain	17p13.2	Gain-of-function defect in VWF binding to GPIIbIXV, because of a mutation in GPIIb α ¹¹⁹
Adhesion	Bernard-Soulier syndrome	Autosomal recessive, some forms autosomal dominant	GP9 GP1BA GP1BB	Platelet GPIX, platelet GPIIb chain, or platelet GPIIb β chain	3q21.3 17p13.222 22q11.21	Deficiency or functional defect in GPIIbIXV ¹³⁴
Adhesion	α 2 β 1	Autosomal dominant	ITGA2	Integrin α 2 subunit of α 2 β 1	5q11.2	Thrombocytopenia associated with deficiency of the platelet integrin receptor for collagen ⁸⁰
Adhesion	GPIV	Autosomal recessive	CD36	Platelet GPIV (thrombospondin receptor)	7q21.11	Deficiency of platelet CD36 affecting thrombospondin binding and associated with metabolic syndrome, atherosclerotic cardiovascular diseases and cardiomyopathy ⁶⁶
Aggregation	Glanzmann thrombasthenia	Autosomal recessive	ITGA2B ITGB3	Integrin, α IIb or integrin β 3 subunits of α IIb β 3	17q21.31 17q21.32	Impaired platelet aggregation because of loss or dysfunction of α IIb β 3, the platelet integrin that binds fibrinogen ^{63,79}
Aggregation	Leukocyte adhesion deficiency type III (LAD3)	Autosomal recessive	FERMT3	Fermitin family homolog 3 (kindlin-3)	11q13.1	Defective integrin activation involving platelets and leukocytes, because of defects in kindlin ^{3,109,111}
Fibrinolysis	Quebec platelet disorder	Autosomal dominant	PLAU	Urokinase-type plasminogen activator	10q22.2	Gain-of-function defect in fibrinolysis from increased platelet urokinase plasminogen activator ^{102–104}

(Continued)

Table 3 (Continued)

Type of defect	Name of disorder or affected protein	Mode of inheritance	Gene(s)	Protein(s)	Locus	Description of defect and reference
Platelet numbers	Glanzmann thrombasthenia-like syndromes	Autosomal dominant	<i>ITGA2B</i>	Integrin, α IIb or	17q21.31	Macrothrombocytopenia associated with activating mutations in $\alpha_{IIb}\beta_3$ ⁶³
			<i>ITGB3</i>	integrin β_3 subunits of $\alpha_{IIb}\beta_3$	17q21.32	
Platelet numbers	Thrombocytopenia associated with absent radii syndrome (TAR)	Autosomal recessive	<i>RBM8A</i>	RNA-binding protein 8A	1q21.1	Thrombocytopenia associated with the absence of radii and the presence of thumbs ^{116,135}
Platelet numbers	Thrombocytopenia with or without syndromic features	X-linked recessive	<i>FLNA</i>	Filamin A	Xq28	Thrombocytopenia, with or without peritricular nodular heterotopia or otopalatodigital syndromes, because of defects in filamin A ⁸⁸
Platelet numbers	Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	<i>MPL</i>	Thrombopoietin receptor	1p34.2	Thrombocytopenia because of a deficiency of the thrombopoietin receptor ³⁷
Platelet numbers	Wiskott-Aldrich syndrome, X-linked thrombocytopenia	X-linked recessive	<i>WAS</i>	Wiskott-Aldrich syndrome protein	Xp11.23	Related disorders, associated with thrombocytopenia, small platelets, and often eczema, recurrent infections and immune deficiency ¹¹⁸
Platelet numbers	MYH9-related disorders	Autosomal dominant	<i>MYH9</i>	Myosin-9	22q12.3	Macrothrombocytopenia, leukocyte inclusions (Döhle-like bodies), with or without deafness, cataracts and nephritis ^{77,78}
Platelet numbers	Thrombocytopenia (THC2)	Autosomal dominant	<i>MASTL</i> , <i>ANKRD26</i>	Serine/threonine-protein kinase great wall or ankyrin repeat domain-containing protein 2	10p12.1	Thrombocytopenia ^{113,123}
Platelet numbers	Thrombocytopenia Cargeeg	Autosomal dominant	<i>CYCS</i>	Cytochrome C	7p15.3	Thrombocytopenia from a gain-of-function defect in cytochrome C that increases apoptosis and dysregulates megakaryopoiesis ⁸⁹
Platelet numbers	GATA-1	X-linked recessive	<i>GATA-1</i>	Erythroid transcription factor	Xp11.23	Thrombocytopenic platelet disorder, that can be associated with thalassemia, neutropenia and megakaryoblastic leukemia, with or without Down syndrome ⁹²
Platelet numbers	Macrothrombocytopenia	Autosomal dominant	<i>TUBB1</i>	Tubulin β -1 chain	20q13.32	Thrombocytopenia with giant platelets ^{64,65}
Platelet numbers	Congenital amegakaryocytic thrombocytopenia associated with synostosis of the radius and ulna	Autosomal dominant	<i>HOXA11</i> and possibly other genes	Homeobox protein Hox-A11	7p15.2	Thrombocytopenia associated with bilateral or unilateral proximal synostosis of the radius and ulna ⁹³
Platelet numbers aggregation and secretion	Familial platelet disorder with propensity to myeloid malignancy	Autosomal dominant	<i>RUNX1</i>	Runx-related transcription factor 1	21q22.12	Thrombocytopenia associated with impaired platelet function and hereditary predisposition

Table 3 (Continued)

Type of defect	Name of disorder or affected protein	Mode of inheritance	Gene(s)	Protein(s)	Locus	Description of defect and reference
Platelet numbers and α-granules	Paris-Trousseau-Jacobsen syndrome	Autosomal dominant	Deletion includes <i>FLI1</i>	Friend leukemia integration 1 transcription factor	11q23	to myelodysplastic syndrome and myeloid leukemia ^{91,120}
Procoagulant function	Scott syndrome	Autosomal recessive	<i>TMEM16F</i>	Anoctamin-6 (transmembrane protein 16F)	12q12	Thrombocytopenia, giant platelets and α-granules, mental retardation, cardiac and facial defects ¹²²
Signaling	Signaling defects involving G-protein pathways	Not well documented	<i>GNAS1</i> <i>GNAQ</i>	Guanine nucleotide-binding protein G(s) subunit α isoforms XLas or guanine nucleotide-binding protein G(q) subunit α	20q13.32 9q21.2	Impaired expression of procoagulant phospholipids on activated platelets for coagulation ^{114,105} Defective G-protein coupled signaling ^{105–107}
Signaling	Impaired platelet G-protein signaling	Autosomal dominant	<i>RGS2</i>	Regulator of G-protein signaling 2	1q31.2	Platelets showed reduced sensitivity to Gs stimulation and reduced cAMP production after Enlarged, round platelets with abnormal α-granules. ¹⁰⁸
α-granule storage	Gray platelet syndrome	Autosomal recessive	<i>NBEAL2</i>	Neurobeachin-like protein 2	3p21.31	Thrombocytopenia associated with severe α-granule protein deficiency ^{94–96,113}
α-granule storage	ARC Syndrome	Autosomal recessive	<i>VPS33B</i>	Vacuolar protein sorting-associated protein 33B	15q26.1	Arthrogryposis, renal dysfunction, cholestasis associated with platelet α-granule deficiency ⁹⁷
δ-granule storage	Hemansky–Pudlak syndrome	Autosomal recessive	<i>HPS1</i> <i>AP3B1</i> <i>HPS3</i> <i>HPS4</i> <i>HPS5</i> <i>HPS6</i> <i>DTNBP1</i> <i>BLOC1S3</i> <i>PLDN</i>	Defects in Hermansky–Pudlak syndrome proteins 1–6, AP-3 complex subunit β-1, dysbindin, Biogenesis of lysosome-related organelles complex 1 subunit 3, or palladin	10q24.2 5q14.1 3q24 22q12.1 11p15.1 10q24.32 6p22.3 19q13.32 15q21.1	Dense granule deficiency associated with defects of lysosomes and melanosomes with albinism ^{60,98–101}
δ-granule storage	Chédiak–Higashi syndrome	Autosomal recessive	<i>LYST</i>	Lysosomal trafficking regulator	1q42.3	Dense granule deficiency associated with hypopigmentation, neutropenia, inclusion bodies in myeloblasts and promyelocytes, susceptibility to infection and lymphoma ^{99,136}
δ-granule storage	Griscelli syndrome	Autosomal recessive	<i>MYO5A</i> <i>RAB27A</i> <i>MILPH</i>	Unconventional myosin-Va, ras-related protein Rab-27A, or melanophilin	15q21.2 15q21.3 2q37.3	Dense granule deficiency associated with hypopigmentation, immunological defects, lymphohistiocytosis and central nervous system defects ^{128,136}

Abbreviations: ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; GP, glycoprotein.

^aMore than one gene or protein is shown if there are multiple causes.

Fig. 1 Schematic representation of the genetic mutations that have been identified to cause platelet function disorders. Affected proteins and resulting disorders are indicated on the diagram, at the point along the pathway of platelet function (from platelet birth to adhesion, activation, and aggregation) that is disrupted.

activated receptor 1 (the thrombin receptor),⁴⁴ the transcriptional activator Myb,⁴⁵ the ATP-binding cassette transporter A1 ABCA1,⁴⁶ the transcription factor NF-E2,⁴⁷ secretory carrier-associated membrane protein 5,⁴⁸ von Willebrand factor, the tetraspanin CD9,^{49,50} CD226,⁵¹ myocyte-specific enhancer factor 2C,⁵² protein MRV1,⁵³ E3 ubiquitin-protein ligase CBL,⁵⁴ tyrosine-protein phosphatase nonreceptor type 11,⁵⁵ tyrosine-protein phosphatase nonreceptor type substrate 1,⁵⁶ and Bcl-2 homologous antagonist/killer.⁵⁷ For many of the genes showing association, there is a need to validate the GWAS data by other experimental models, to verify that the candidate genes influence platelet traits, as has been done for supervillin.²⁸ Once characterized, candidate genes that are verified to influence platelet traits will provide attractive targets for investigations of the causes of unidentified bleeding disorders.

At present, the knowledge on associations has not reached the point where genotyping can be used to predict an individual's platelet "reactivity" in function tests. It is also important to recognize that GWAS provides information on the genetic causes of variability, but this technique is unlikely to identify rare causes of variability and it will not identify the genes or miRNA with important roles in platelet function if the genetic sequence has little or no variability between subjects.

Gene Defects in Characterized Hereditary Disorders of Platelet Numbers and/or Function

There has been significant progress in finding the molecular defect of inherited platelet disorders, particularly for rare

disorders, including those associated with syndromic features, as summarized in ►Table 3 and illustrated in ►Fig. 1.^{58–60} Nonetheless, only a few of the genes identified to contain mutations in persons with inherited defects of platelet function overlap the genes that show a significant association to platelet "reactivity" in other subjects (►Tables 1–3). Such an overlap is evident in the platelet disorders that are associated with mutations in the genes encoding glycoprotein (GP) VI,^{61,62} platelet GPIb α ,^{59,60} integrin α IIb,^{59,60,63} tubulin β -1 chain,^{64,65} and the thrombospondin receptor.⁶⁶ Nonetheless, there may be important associations with a disease that are not yet discovered, as recent prospective cohort studies indicate that most individuals with bleeding problems from suspected inherited platelet function disorders (>90%) and impaired platelet aggregation and/or dense granule release have uncharacterized defects.^{33,67,68} There are many potential candidate genes for uncharacterized, inherited platelet disorders, given the many genes transcribed by megakaryocytes and the large number of proteins found in platelets.^{6,8–11,69–74}

Genetic mutations resulting in characterized inherited platelet disorders have been identified to alter various aspects of platelets, including their circulating numbers and hemostatic function (►Fig. 1). Perhaps not surprisingly, most of the mutations are in the genes that have well-known, and important roles in regulating platelet numbers and/or function.^{59,60} Some are associated with thrombocytopenias, with or without changes to platelet shape and volume.^{75,76} As a comprehensive review of the diagnosis and management of all characterized inherited platelet disorders is beyond the scope of this review, readers interested in information on

specific disorders are encouraged to read the references cited for different conditions.

Mechanistically, the characterized defects are difficult to classify into disorders of number or function as some affect both. The defects involve proteins found in several different compartments within platelets, such as the following: (1) the cytoskeleton (e.g., MYH9-related disorders^{77,78} and β 1-tubulin defects^{64,65}); (2) platelet membranes (e.g., the membrane receptor for von Willebrand factor, GPIbIXV, in Bernard–Soulier syndrome and platelet type von Willebrand disease^{59,60}; the fibrinogen receptor α IIb β 3 in Glanzmann thrombasthenia and the thrombocytopenic disorders associated with gain-of-function defects in this receptor^{59,60,79}; the platelet integrin receptor for collagen, α 2 β 1⁸⁰; the thrombospondin receptor, GPIV⁶⁶; the membrane receptors for agonist stimulation, GPVI,^{61,62} P2Y₁₂,⁸¹ P2X₁,⁸² the TXA2 receptor,^{83–87} among others; the membrane receptor for thrombopoietin in congenital amegakaryocytic thrombocytopenia³⁷); (3) the region of platelets linking membrane receptors and cytoskeletal proteins (e.g., filamin A defects)⁸⁸; (4) mitochondria (e.g., cytochrome C, which influences platelet apoptosis)⁸⁹; (5) enzymes in the cytosol (e.g., thromboxane-A synthase⁹⁰); and (6) the nucleus, in the case of factors that regulate megakaryocyte gene expression, such as RUNX1,⁹¹ GATA-1,⁹² and HOXA11⁹³ (see ►Fig. 1 and ►Table 3). Additionally, some disorders are caused by mutations in the genes that affect the biogenesis of α -granules^{94–97} and dense granules.^{98–101} A unique copy number variation mutation, causing overexpression of the α -granule protein urokinase-type plasminogen activator by megakaryocytes in Quebec platelet disorder, leads to plasmin-mediated degradation of other stored α -granule proteins and a gain-of-function defect in clot lysis.^{102–104}

The disorders that alter platelet surface receptors can impair platelet function in adhesion or aggregation, alter platelet interactions with collagen, von Willebrand factor, or other ligands (►Fig. 1 and ►Table 3), or alter the process of platelet activation by ADP, collagen or TXA2, and agonist-induced signaling (►Fig. 1 and ►Table 3). Recently, a mutation of the transmembrane protein 16F, a Ca²⁺-activated chloride channel, was identified as the cause of the defective, agonist-induced scrambling of phospholipids and impaired membrane activation and procoagulant function of Scott syndrome. Platelet signaling, which is important for activation induced by agonists and platelet interactions with adhesive ligands, is impaired by mutations in genes encoding G proteins^{105–107} and in proteins that regulate G-protein signaling.¹⁰⁸ Inside-out integrin activation is impaired by mutation in the gene for kindlin-3, an intracellular protein that interacts with β integrins.¹⁰⁹

Inherited Platelet Disorders: Current Information on Modes of Inheritance

Among the characterized inherited platelet abnormalities, autosomal recessive platelet disorders represent a rare but important cause of bleeding (prevalence approximately 1:10⁶ or less).^{60,110} Some of these recessive platelet disorders derive from mutations in genes that encode proteins that are

important for platelet production (e.g., *MPL*, the thrombopoietin receptor),^{37,76} adhesion or aggregation (e.g., glycoprotein IbIX in Bernard–Soulier syndrome^{59,60}; α IIb β 3 in Glanzmann thrombasthenia^{59,60}; and kindlin-3 in persons with impaired platelet integrin function and leukocyte adhesion defects^{59,109,111}), agonist responses (e.g., ADP receptor P2Y₁₂, GPVI, and thromboxane synthase),^{61,62,81,90,112} and granule protein storage (e.g., *NBEAL2* in gray platelet syndrome)^{94–96,113} (►Table 3). The recessively inherited platelet disorders also include conditions such as Scott syndrome,^{114,115} thrombocytopenia with absent radii syndrome,¹¹⁶ and syndromic disorders associated with δ -granule deficiency (►Table 3).^{97–101,117}

X-linked platelet disorders are uncommon and include thrombocytopenia associated with GATA-1 mutations,⁹² Wiskott–Aldrich syndrome and the related condition, X-linked thrombocytopenia,¹¹⁸ in addition to the syndromic and nonsyndromic thrombocytopenias associated with filamin A defects^{59,88} (►Table 3).

Autosomal dominant platelet disorders are the most prevalent of inherited platelet disorders and their causes include mutations in diverse genes that are important for fibrinolysis (e.g., *PLAU* in Quebec platelet disorder),^{102–104} platelet adhesion (e.g., activating mutations of the gene for GP α IIb β 3, and GPIb α , and α 2 β 1 deficiency),^{60,63,80,119} agonist response (e.g., P2X₁⁸² and TXA2 receptor^{83,84,87}), the platelet cytoskeleton (e.g., MYH9-related disorders),^{77,78} transcriptional regulation (e.g., *RUNX1*),^{91,120} or other platelet traits,^{80,121–123} including apoptotic pathways that influence platelet numbers⁸⁹ (►Table 3). Defects in the platelet function from mutations in the gene encoding the TXA2 receptor have been reported in individuals heterozygous for receptor mutations,^{84,87} although some have been homozygous for mutations.⁸⁶

Most patients with uncharacterized inherited platelet function disorders have “secretion defects” (also called “release” or “activation” defects) that impair platelet function in aggregation and/or dense granule release assays, often with multiple (but not necessarily all) agonists.^{33,34,67,68,124–126} A comprehensive study of the genetic causes of inherited platelet secretion defects has never been undertaken. Inherited secretion defects include δ -granule deficiency, which can result from characterized, autosomal recessive, syndromic disorders associated with hypopigmentation (e.g., Hermansky–Pudlak syndrome, Chédiak–Higashi syndrome, and Griscelli syndrome)^{97,100,127,128} or uncharacterized, nonsyndromic autosomal dominant causes (^{79,80,127,129} and Hayward, unpublished observations). Impaired platelet secretion has been reported in individuals who are heterozygous for disease-causing *P2RY12* mutations (gene for the ADP receptor P2Y₁₂), who have impaired ADP aggregation.¹³⁰ However, *P2RY12* mutations could be an infrequent cause of hereditary secretion defects as many individuals with secretion defects have normal ADP aggregation responses.³⁴

Summary

In recent years, GWAS have become a powerful tool for identifying new genetic factors involved in human diseases

and variability in the general population, including platelet function.¹³ GWAS, and meta-analyses of GWAS data, have provided new information on the genes that influence platelet function and traits (refer to ► **Tables 1** and **2**). Nonetheless, some caution is advised as many of the associated genes have not been tested for influence on platelet traits using other models (e.g., mouse knockouts²⁸ and zebrafish morpholinos¹³¹) to validate their importance to platelet function and other platelet traits. It is likely that platelet function is influenced by many factors, including genetic background, ethnicity, gender and environment, and exposures to drugs that inhibit platelet function. Although the characterization of several disorders with an altered platelet phenotype has provided important new insights on the genes that influence platelet traits, the causes of most inherited platelet “secretion defects” still need to be thoughtfully characterized. Technical advances in molecular analysis of gene linkage and genomic sequences (e.g., full genome and exome sequencing) will facilitate the discovery of the disease-causing mutations of inherited platelet function disorders and increase our understanding of the genetic loci that influence platelet physiology and pathology.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

References

- Gresele P, Page CP, Fuster V, Vermylen J. Platelets in Thrombotic and Non-thrombotic Disorders. Cambridge, UK: Cambridge University Press; 2002:1–1124
- Michelson AD. Platelets. 3rd ed. Philadelphia, PA: Elsevier/Academic Press; 2013 (in press)
- Marder VJ, Aird WC, Bennett JS, Schulman S, White GC II. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012:1–1592
- Rowley JW, Oler AJ, Tolley ND, et al. Genome-wide RNA-seq analysis of human and mouse platelet transcriptomes. *Blood* 2011;118(14):e101–e111
- Gnatenko DV, Dunn JJ, Schwedes J, Bahou WF. Transcript profiling of human platelets using microarray and serial analysis of gene expression (SAGE). *Methods Mol Biol* 2009;496:245–272
- Senzel L, Gnatenko DV, Bahou WF. The platelet proteome. *Curr Opin Hematol* 2009;16(5):329–333
- Bahou WF. Platelet systems biology using integrated genetic and proteomic platforms. *Thromb Res* 2012;129(Suppl 1):S38–S45
- García A, Prabhakar S, Brock CJ, et al. Extensive analysis of the human platelet proteome by two-dimensional gel electrophoresis and mass spectrometry. *Proteomics* 2004;4(3):656–668
- García A, Prabhakar S, Hughan S, et al. Differential proteome analysis of TRAP-activated platelets: involvement of DOK-2 and phosphorylation of RGS proteins. *Blood* 2004;103(6):2088–2095
- García A, Zitzmann N, Watson SP. Analyzing the platelet proteome. *Semin Thromb Hemost* 2004;30(4):485–489
- Watson SP, Bahou WF, Fitzgerald D, Ouwehand W, Rao AK, Leavitt AD; ISTH Platelet Physiology Subcommittee. Mapping the platelet proteome: a report of the ISTH Platelet Physiology Subcommittee. *J Thromb Haemost* 2005;3(9):2098–2101
- Gaxiola B, Friedl W, Propping P. Epinephrine-induced platelet aggregation. A twin study. *Clin Genet* 1984;26(6):543–548
- Kunicki TJ, Williams SA, Nugent DJ. Genetic variants that affect platelet function. *Curr Opin Hematol* 2012;19(5):371–379
- Ferreira MA, Hottenga JJ, Warrington NM, et al. Sequence variants in three loci influence monocyte counts and erythrocyte volume. *Am J Hum Genet* 2009;85(5):745–749
- Meisinger C, Prokisch H, Gieger C, et al. A genome-wide association study identifies three loci associated with mean platelet volume. *Am J Hum Genet* 2009;84(1):66–71
- Guerrero JA, Rivera J, Quiroga T, et al. Novel loci involved in platelet function and platelet count identified by a genome-wide study performed in children. *Haematologica* 2011;96(9):1335–1343
- Mathias RA, Kim Y, Sung H, et al. A combined genome-wide linkage and association approach to find susceptibility loci for platelet function phenotypes in European American and African American families with coronary artery disease. *BMC Med Genomics* 2010;3:22
- Kamatani Y, Matsuda K, Okada Y, et al. Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nat Genet* 2010;42(3):210–215
- Soranzo N, Rendon A, Gieger C, et al. A novel variant on chromosome 7q22.3 associated with mean platelet volume, counts, and function. *Blood* 2009;113(16):3831–3837
- Yang Q, Kathiresan S, Lin JP, Tofler GH, O'Donnell CJ. Genome-wide association and linkage analyses of hemostatic factors and hematological phenotypes in the Framingham Heart Study. *BMC Med Genet* 2007;8(Suppl 1):S12
- Lo KS, Wilson JG, Lange LA, et al. Genetic association analysis highlights new loci that modulate hematological trait variation in Caucasians and African Americans. *Hum Genet* 2011;129(3):307–317
- Gieger C, Radhakrishnan A, Cvejic A, et al. New gene functions in megakaryopoiesis and platelet formation. *Nature* 2011;480(7376):201–208
- Soranzo N, Spector TD, Mangino M, et al. A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the HaemGen consortium. *Nat Genet* 2009;41(11):1182–1190
- Qayyum R, Snively BM, Ziv E, et al. A meta-analysis and genome-wide association study of platelet count and mean platelet volume in African Americans. *PLoS Genet* 2012;8(3):e1002491
- Johnson AD, Yanek LR, Chen MH, et al. Genome-wide meta-analyses identifies seven loci associated with platelet aggregation in response to agonists. *Nat Genet* 2010;42(7):608–613
- Goodall AH, Burns P, Salles I, et al; Bloodomics Consortium. Transcription profiling in human platelets reveals LRRFIP1 as a novel protein regulating platelet function. *Blood* 2010;116(22):4646–4656
- Snoep JD, Gaussem P, Eikenboom JC, et al. The minor allele of GP6 T13254C is associated with decreased platelet activation and a reduced risk of recurrent cardiovascular events and mortality: results from the SMILE-Platelets project. *J Thromb Haemost* 2010;8(11):2377–2384
- Edelstein LC, Luna EJ, Gibson IB, et al. Human genome-wide association and mouse knockout approaches identify platelet supervillin as an inhibitor of thrombus formation under shear stress. *Circulation* 2012;125(22):2762–2771
- Nagalla S, Shaw C, Kong X, et al. Platelet microRNA-mRNA coexpression profiles correlate with platelet reactivity. *Blood* 2011;117(19):5189–5197

- 30 Bray PF, Mathias RA, Faraday N, et al. Heritability of platelet function in families with premature coronary artery disease. *J Thromb Haemost* 2007;5(8):1617–1623
- 31 Herrera-Galeano JE, Becker DM, Wilson AF, et al. A novel variant in the platelet endothelial aggregation receptor-1 gene is associated with increased platelet aggregability. *Arterioscler Thromb Vasc Biol* 2008;28(8):1484–1490
- 32 Faraday N, Yanek LR, Yang XP, et al. Identification of a specific intronic PEAR1 gene variant associated with greater platelet aggregability and protein expression. *Blood* 2011;118(12):3367–3375
- 33 Hayward CP, Pai M, Liu Y, et al. Diagnostic utility of light transmission platelet aggregometry: results from a prospective study of individuals referred for bleeding disorder assessments. *J Thromb Haemost* 2009;7(4):676–684
- 34 Pai M, Wang G, Moffat KA, et al. Diagnostic usefulness of a lumi-aggregometer adenosine triphosphate release assay for the assessment of platelet function disorders. *Am J Clin Pathol* 2011;136(3):350–358
- 35 Lo KA, Bauchmann MK, Baumann AP, et al. Genome-wide profiling of H3K56 acetylation and transcription factor binding sites in human adipocytes. *PLoS ONE* 2011;6(6):e19778
- 36 Kunicki TJ, Nugent DJ. The genetics of normal platelet reactivity. *Blood* 2010;116(15):2627–2634
- 37 Ballmaier M, Germeshausen M. Congenital amegakaryocytic thrombocytopenia: clinical presentation, diagnosis, and treatment. *Semin Thromb Hemost* 2011;37(6):673–681
- 38 Hirsch E, Bosco O, Tropol P, et al. Resistance to thromboembolism in PI3Kgamma-deficient mice. *FASEB J* 2001;15(11):2019–2021
- 39 Pozgajová M, Sachs UJ, Hein L, Nieswandt B. Reduced thrombus stability in mice lacking the alpha2A-adrenergic receptor. *Blood* 2006;108(2):510–514
- 40 Kauskot A, Di Michele M, Luyen S, Freson K, Verhamme P, Hoylaerts MF. A novel mechanism of sustained platelet $\alpha IIb\beta 3$ activation via PEAR1. *Blood* 2012;119(17):4056–4065
- 41 Wang W, Gilligan DM, Sun S, Wu X, Reems JA. Distinct functional effects for dynamin 3 during megakaryocytopoiesis. *Stem Cells Dev* 2011;20(12):2139–2151
- 42 Jedlitschky G, Cattaneo M, Lubenow LE, et al. Role of MRP4 (ABCC4) in platelet adenosine nucleotide-storage: evidence from patients with delta-storage pool deficiencies. *Am J Pathol* 2010;176(3):1097–1103
- 43 Côté GP. Structural and functional properties of the non-muscle tropomyosins. *Mol Cell Biochem* 1983;57(2):127–146
- 44 Lang NN, Guðmundsdóttir IJ, Newby DE. Vascular PAR-1: activity and antagonism. *Cardiovasc Ther* 2011;29(6):349–361
- 45 García P, Berlanga O, Vegiopoulos A, Vyas P, Frampton J. c-Myb and GATA-1 alternate dominant roles during megakaryocyte differentiation. *J Thromb Haemost* 2011;9(8):1572–1581
- 46 Schmitz G, Schambeck CM. Molecular defects in the ABCA1 pathway affect platelet function. *Pathophysiol Haemost Thromb* 2006;35(1–2):166–174
- 47 Fock EL, Yan F, Pan S, Chong BH. NF-E2-mediated enhancement of megakaryocytic differentiation and platelet production in vitro and in vivo. *Exp Hematol* 2008;36(1):78–92
- 48 Castermans D, Volders K, Crepel A, et al. SCAMP5, NBEA and AMISYN: three candidate genes for autism involved in secretion of large dense-core vesicles. *Hum Mol Genet* 2010;19(7):1368–1378
- 49 Israels SJ, McMillan-Ward EM. Platelet tetraspanin complexes and their association with lipid rafts. *Thromb Haemost* 2007;98(5):1081–1087
- 50 Mangin PH, Kleitz L, Boucheix C, Gachet C, Lanza F. CD9 negatively regulates integrin $\alpha IIb\beta 3$ activation and could thus prevent excessive platelet recruitment at sites of vascular injury. *J Thromb Haemost* 2009;7(5):900–902
- 51 Kojima H, Kanada H, Shimizu S, et al. CD226 mediates platelet and megakaryocytic cell adhesion to vascular endothelial cells. *J Biol Chem* 2003;278(38):36748–36753
- 52 Gekas C, Rhodes KE, Gereige LM, et al. Mef2C is a lineage-restricted target of Scl/Tal1 and regulates megakaryopoiesis and B-cell homeostasis. *Blood* 2009;113(15):3461–3471
- 53 Antl M, von Brühl ML, Eiglsperger C, et al. IRAG mediates NO/cGMP-dependent inhibition of platelet aggregation and thrombus formation. *Blood* 2007;109(2):552–559
- 54 Buitrago L, Tsygankov A, Sanjay A, Kunapuli SP. Cbl proteins in platelet activation. *Platelets* 2012;(August):29
- 55 Derbent M, Öncel Y, Tokel K, et al. Clinical and hematologic findings in Noonan syndrome patients with PTPN11 gene mutations. *Am J Med Genet A* 2010;152A(11):2768–2774
- 56 Catani L, Sollazzo D, Ricci F, et al. The CD47 pathway is deregulated in human immune thrombocytopenia. *Exp Hematol* 2011;39(4):486–494
- 57 Josefsson EC, James C, Henley KJ, et al. Megakaryocytes possess a functional intrinsic apoptosis pathway that must be restrained to survive and produce platelets. *J Exp Med* 2011;208(10):2017–2031
- 58 Hayward CP, Favaloro EJ. Diagnostic evaluation of platelet disorders: the past, the present, and the future. *Semin Thromb Hemost* 2009;35(2):127–130
- 59 Nurden A, Nurden P. Advances in our understanding of the molecular basis of disorders of platelet function. *J Thromb Haemost* 2011;9(Suppl 1):76–91
- 60 Nurden AT, Freson K, Seligsohn U. Inherited platelet disorders. *Haemophilia* 2012;18(Suppl 4):154–160
- 61 Dumont B, Lasne D, Rothschild C, et al. Absence of collagen-induced platelet activation caused by compound heterozygous GPVI mutations. *Blood* 2009;114(9):1900–1903
- 62 Hermans C, Wittevrongel C, Thys C, Smethurst PA, Van Geet C, Freson K. A compound heterozygous mutation in glycoprotein VI in a patient with a bleeding disorder. *J Thromb Haemost* 2009;7(8):1356–1363
- 63 Nurden AT, Pillois X, Fiore M, Heilig R, Nurden P. Glanzmann thrombasthenia-like syndromes associated with Macrothrombocytopenias and mutations in the genes encoding the $\alpha IIb\beta 3$ integrin. *Semin Thromb Hemost* 2011;37(6):698–706
- 64 Navarro-Núñez L, Teruel R, Antón AI, et al. Rare homozygous status of P43 $\beta 1$ -tubulin polymorphism causes alterations in platelet ultrastructure. *Thromb Haemost* 2011;105(5):855–863
- 65 Kunishima S, Kobayashi R, Itoh TJ, Hamaguchi M, Saito H. Mutation of the beta1-tubulin gene associated with congenital macrothrombocytopenia affecting microtubule assembly. *Blood* 2009;113(2):458–461
- 66 Hirano K, Kuwasako T, Nakagawa-Toyama Y, Janabi M, Yamashita S, Matsuzawa Y. Pathophysiology of human genetic CD36 deficiency. *Trends Cardiovasc Med* 2003;13(4):136–141
- 67 Castilloux JF, Moffat KA, Liu Y, Seecharan J, Pai M, Hayward CP. A prospective cohort study of light transmission platelet aggregometry for bleeding disorders: is testing native platelet-rich plasma non-inferior to testing platelet count adjusted samples? *Thromb Haemost* 2011;106(4):675–682
- 68 Hayward CP, Moffat KA, Castilloux JF, et al. Simultaneous measurement of adenosine triphosphate release and aggregation potentiates human platelet aggregation responses for some subjects, including persons with Quebec platelet disorder. *Thromb Haemost* 2012;107(4):726–734
- 69 Gnatenko DV, Perrotta PL, Bahou WF. Proteomic approaches to dissect platelet function: Half the story. *Blood* 2006;108(13):3983–3991
- 70 Gnatenko DV, Zhu W, Bahou WF. Multiplexed genetic profiling of human blood platelets using fluorescent microspheres. *Thromb Haemost* 2008;100(5):929–936
- 71 O'Neill EE, Brock CJ, von Kriegsheim AF, et al. Towards complete analysis of the platelet proteome. *Proteomics* 2002;2(3):288–305
- 72 Perrotta PL, Bahou WF. Proteomics in platelet science. *Curr Hematol Rep* 2004;3(6):462–469

- 73 Maynard DM, Heijnen HF, Horne MK, White JG, Gahl WA. Proteomic analysis of platelet alpha-granules using mass spectrometry. *J Thromb Haemost* 2007;5(9):1945–1955
- 74 Parguina AF, Rosa I, García A. Proteomics applied to the study of platelet-related diseases: aiding the discovery of novel platelet biomarkers and drug targets. *J Proteomics* 2012;76(Spec No): 275–286
- 75 Balduini CL, Pecci A, Norris P. Diagnosis and management of inherited thrombocytopenias. *Semin Thromb Hemost* 2013; doi: <http://dx.doi.org/10.1055/s-0032-1333540>
- 76 Hayward CP, Bunimov N. Thrombocytopenic platelet disorders. *Semin Thromb Hemost* 2011;37(6):617–620
- 77 Althaus K, Greinacher A. MYH9-related platelet disorders. *Semin Thromb Hemost* 2009;35(2):189–203
- 78 Balduini CL, Pecci A, Savoia A. Recent advances in the understanding and management of MYH9-related inherited thrombocytopenias. *Br J Haematol* 2011;154(2):161–174
- 79 Nurden AT, Fiore M, Nurden P, Pillois X, Glanzmann thrombasthenia: a review of ITGA2B and ITGB3 defects with emphasis on variants, phenotypic variability, and mouse models. *Blood* 2011; 118(23):5996–6005
- 80 Noris P, Guidetti GF, Conti V, et al. Autosomal dominant thrombocytopenias with reduced expression of glycoprotein Ia. *Thromb Haemost* 2006;95(3):483–489
- 81 Cattaneo M. The platelet P2Y₁₂ receptor for adenosine diphosphate: congenital and drug-induced defects. *Blood* 2011; 117(7):2102–2112
- 82 Oury C, Toth-Zsamboki E, Van Geet C, et al. A natural dominant negative P2X1 receptor due to deletion of a single amino acid residue. *J Biol Chem* 2000;275(30):22611–22614
- 83 Kamae T, Kiyomizu K, Nakazawa T, et al. Bleeding tendency and impaired platelet function in a patient carrying a heterozygous mutation in the thromboxane A2 receptor. *J Thromb Haemost* 2011;9(5):1040–1048
- 84 Mumford AD, Dawood BB, Daly ME, et al. A novel thromboxane A2 receptor D304N variant that abrogates ligand binding in a patient with a bleeding diathesis. *Blood* 2010;115(2):363–369
- 85 Fuse I, Higuchi W, Aizawa Y. Pathogenesis of a bleeding disorder characterized by platelet unresponsiveness to thromboxane A2. *Semin Thromb Hemost* 2000;26(1):43–45
- 86 Higuchi W, Fuse I, Hattori A, Aizawa Y. Mutations of the platelet thromboxane A2 (TXA2) receptor in patients characterized by the absence of TXA2-induced platelet aggregation despite normal TXA2 binding activity. *Thromb Haemost* 1999;82(5):1528–1531
- 87 Hirata T, Kakizuka A, Ushikubi F, Fuse I, Okuma M, Narumiya S. Arg60 to Leu mutation of the human thromboxane A2 receptor in a dominantly inherited bleeding disorder. *J Clin Invest* 1994; 94(4):1662–1667
- 88 Nurden P, Debili N, Coupry I, et al. Thrombocytopenia resulting from mutations in filamin A can be expressed as an isolated syndrome. *Blood* 2011;118(22):5928–5937
- 89 Cramer Bordé E, Ouzegdough Y, Ledgerwood EC, Morison IM. Congenital thrombocytopenia and cytochrome C mutation: a matter of birth and death. *Semin Thromb Hemost* 2011;37(6): 664–672
- 90 Geneviève D, Proulle V, Isidor B, et al. Thromboxane synthase mutations in an increased bone density disorder (Ghosal syndrome). *Nat Genet* 2008;40(3):284–286
- 91 Michaud J, Wu F, Osato M, et al. In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. *Blood* 2002; 99(4):1364–1372
- 92 Millikan PD, Balamohan SM, Raskind WH, Kacena MA. Inherited thrombocytopenia due to GATA-1 mutations. *Semin Thromb Hemost* 2011;37(6):682–689
- 93 Thompson AA, Nguyen LT. Amegakaryocytic thrombocytopenia and radio-ulnar synostosis are associated with HOXA11 mutation. *Nat Genet* 2000;26(4):397–398
- 94 Kahr WH, Hinckley J, Li L, et al. Mutations in NBEAL2, encoding a BEACH protein, cause gray platelet syndrome. *Nat Genet* 2011; 43(8):738–740
- 95 Gunay-Aygun M, Falik-Zaccai TC, Vilboux T, et al. NBEAL2 is mutated in gray platelet syndrome and is required for biogenesis of platelet α -granules. *Nat Genet* 2011;43(8):732–734
- 96 Albers CA, Cvejic A, Favier R, et al. Exome sequencing identifies NBEAL2 as the causative gene for gray platelet syndrome. *Nat Genet* 2011;43(8):735–737
- 97 Abu-Sa'da O, Barbar M, Al-Harbi N, Taha D. Arthrogryposis, renal tubular acidosis and cholestasis (ARC) syndrome: two new cases and review. *Clin Dysmorphol* 2005;14(4):191–196
- 98 Meng R, Wang Y, Yao Y, et al. SLC35D3 delivery from megakaryocyte early endosomes is required for platelet dense granule biogenesis and is differentially defective in Hermansky-Pudlak syndrome models. *Blood* 2012;120(2):404–414
- 99 Masliah-Planchon J, Darnige L, Bellucci S. Molecular determinants of platelet delta storage pool deficiencies: an update. *Br J Haematol* 2013;160(1):5–11
- 100 Wei ML. Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. *Pigment Cell Res* 2006; 19(1):19–42
- 101 Badolato R, Prandini A, Caracciolo S, et al. Exome sequencing reveals a pallidin mutation in a Hermansky-Pudlak-like primary immunodeficiency syndrome. *Blood* 2012;119(13): 3185–3187
- 102 Blavignac J, Bunimov N, Rivard GE, Hayward CP. Quebec platelet disorder: update on pathogenesis, diagnosis, and treatment. *Semin Thromb Hemost* 2011;37(6):713–720
- 103 Hayward CP, Rivard GE. Quebec platelet disorder. *Expert Rev Hematol* 2011;4(2):137–141
- 104 Paterson AD, Rommens JM, Bharaj B, et al. Persons with Quebec platelet disorder have a tandem duplication of PLA2, the urokinase plasminogen activator gene. *Blood* 2010;115(6):1264–1266
- 105 Van Geet C, Izzi B, Labarque V, Freson K. Human platelet pathology related to defects in the G-protein signaling cascade. *J Thromb Haemost* 2009;7(Suppl 1):282–286
- 106 Gabbeta J, Vaidyula VR, Dhanasekaran DN, Rao AK. Human platelet Galphq deficiency is associated with decreased Galphq gene expression in platelets but not neutrophils. *Thromb Haemost* 2002;87(1):129–133
- 107 Freson K, Thys C, Wittevrongel C, et al. Pseudohypoparathyroidism type Ib with disturbed imprinting in the GNAS1 cluster and Gsalpha deficiency in platelets. *Hum Mol Genet* 2002;11(22): 2741–2750
- 108 Noé L, Di Michele M, Giets E, et al. Platelet Gs hypofunction and abnormal morphology resulting from a heterozygous RGS2 mutation. *J Thromb Haemost* 2010;8(7):1594–1603
- 109 Jurk K, Schulz AS, Kehrel BE, et al. Novel integrin-dependent platelet malfunction in siblings with leukocyte adhesion deficiency-III (LAD-III) caused by a point mutation in FERMT3. *Thromb Haemost* 2010;103(5):1053–1064
- 110 Hayward CP. Diagnostic evaluation of platelet function disorders. *Blood Rev* 2011;25(4):169–173
- 111 Kuipers TW, van de Vijver E, Weterman MA, et al. LAD-1/variant syndrome is caused by mutations in FERMT3. *Blood* 2009; 113(19):4740–4746
- 112 Defreyn G, Machin SJ, Carreras LO, Dauden MV, Chamone DA, Vermeylen J. Familial bleeding tendency with partial platelet thromboxane synthetase deficiency: reorientation of cyclic endoperoxide metabolism. *Br J Haematol* 1981;49(1):29–41
- 113 Di Paola J, Johnson J. Thrombocytopenias due to gray platelet syndrome or THC2 mutations. *Semin Thromb Hemost* 2011; 37(6):690–697
- 114 Lhermusier T, Chap H, Payrastre B. Platelet membrane phospholipid asymmetry: from the characterization of a scramblase activity to the identification of an essential protein mutated in Scott syndrome. *J Thromb Haemost* 2011;9(10):1883–1891

- 115 Weiss HJ. Impaired platelet procoagulant mechanisms in patients with bleeding disorders. *Semin Thromb Hemost* 2009;35(2): 233–241
- 116 Albers CA, Paul DS, Schulze H, et al. Compound inheritance of a low-frequency regulatory SNP and a rare null mutation in exon-junction complex subunit RBM8A causes TAR syndrome. *Nat Genet* 2012;44(4):435–439, S1–S2
- 117 Huizing M, Parkes JM, Helip-Wooley A, White JG, Gahl WA. Platelet alpha granules in BLOC-2 and BLOC-3 subtypes of Hermansky-Pudlak syndrome. *Platelets* 2007;18(2):150–157
- 118 Thrasher AJ. New insights into the biology of Wiskott-Aldrich syndrome (WAS). *Hematology (Am Soc Hematol Educ Program)* 2009;1:132–138
- 119 Othman M. Platelet-type Von Willebrand disease: three decades in the life of a rare bleeding disorder. *Blood Rev* 2011;25(4): 147–153
- 120 Owen C. Insights into familial platelet disorder with propensity to myeloid malignancy (FPD/AML). *Leuk Res* 2010;34(2):141–142
- 121 Raslova H, Komura E, Le Couédic JP, et al. FLI1 monoallelic expression combined with its hemizygous loss underlies Paris-Trousseau/Jacobsen thrombopenia. *J Clin Invest* 2004;114(1): 77–84
- 122 Favier R, Jondeau K, Boutard P, et al. Paris-Trousseau syndrome : clinical, hematological, molecular data of ten new cases. *Thromb Haemost* 2003;90(5):893–897
- 123 Noris P, Perrotta S, Seri M, et al. Mutations in ANKRD26 are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families. *Blood* 2011;117(24): 6673–6680
- 124 Mezzano D, Quiroga T, Pereira J. The level of laboratory testing required for diagnosis or exclusion of a platelet function disorder using platelet aggregation and secretion assays. *Semin Thromb Hemost* 2009;35(2):242–254
- 125 Quiroga T, Goycoolea M, Matus V, et al. Diagnosis of mild platelet function disorders. Reliability and usefulness of light transmission platelet aggregation and serotonin secretion assays. *Br J Haematol* 2009;147(5):729–736
- 126 Hayward CP, Moffat KA, Liu Y. Laboratory investigations for bleeding disorders. *Semin Thromb Hemost* 2012;38(7): 742–752
- 127 Gunay-Aygun M, Huizing M, Gahl WA. Molecular defects that affect platelet dense granules. *Semin Thromb Hemost* 2004; 30(5):537–547
- 128 Sandrock K, Zieger B. Current Strategies in Diagnosis of Inherited Storage Pool Defects. *Transfus Med Hemother* 2010;37(5): 248–258
- 129 Corral J, González-Conejero R, Pujol-Moix N, Domenech P, Vicente V. Mutation analysis of HPS1, the gene mutated in Hermansky-Pudlak syndrome, in patients with isolated platelet dense-granule deficiency. *Haematologica* 2004;89(3):325–329
- 130 Cattaneo M, Lecchi A, Lombardi R, Gachet C, Zighetti ML. Platelets from a patient heterozygous for the defect of P2CYC receptors for ADP have a secretion defect despite normal thromboxane A2 production and normal granule stores: further evidence that some cases of platelet 'primary secretion defect' are heterozygous for a defect of P2CYC receptors. *Arterioscler Thromb Vasc Biol* 2000;20(11):E101–E106
- 131 Jagadeeswaran P. Zebrafish: a tool to study hemostasis and thrombosis. *Curr Opin Hematol* 2005;12(2):149–152
- 132 Dubé JN, Drouin J, Aminian M, Plant MH, Laneuville O. Characterization of a partial prostaglandin endoperoxide H synthase-1 deficiency in a patient with a bleeding disorder. *Br J Haematol* 2001;113(4):878–885
- 133 Isidor B, Dagoneau N, Huber C, et al. A gene responsible for Ghosal hemato-diaphyseal dysplasia maps to chromosome 7q33–34. *Hum Genet* 2007;121(2):269–273
- 134 Pham A, Wang J. Bernard-Soulier syndrome: an inherited platelet disorder. *Arch Pathol Lab Med* 2007;131(12):1834–1836
- 135 Toriello HV. Thrombocytopenia-absent radius syndrome. *Semin Thromb Hemost* 2011;37(6):707–712
- 136 Huizing M, Helip-Wooley A, Westbroek W, Gunay-Aygun M, Gahl WA. Disorders of lysosome-related organelle biogenesis: clinical and molecular genetics. *Annu Rev Genomics Hum Genet* 2008; 9:359–386