Genetic Loci Associated with Platelet Traits and Platelet Disorders

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Semin Thromb Hemost 2013;39:291–305.

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 A_2 (TXA_2) and platelet storage granule release.[1–3] Platelets then undergo further activation, with intracellular signaling triggered by their released TXA_2, 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

published online March 6, 2013

Issue Theme Quality in Hemostasis and Thrombosis, Part II; Guest Editors, Giuseppe Lippi, MD, Mario Plebani, MD, and Emmanuel J. Favaloro, PhD, FFSc (RCPA).

DOI http://dx.doi.org/10.1055/s-0033-1334466.
ISSN 0094-6176.

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

Table 1 (*Continued*)

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

[a]The 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 g subunit of phosphoinositol-4,5-biphosphate 3-kinase,[38] the α-2A adrenergic receptor,[39] platelet endothelial aggregation receptor 1,[40] dynamin 3,[41] multidrug 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	*KIF1B*	Kinesin-like protein KIF1B	E	rs17396340	1p36.22	22
Count	*MFN2*	Mitofusin-2	E	rs2336384	1p36.22	22
ADP and epinephrine aggregation	*PEAR1*	Platelet endothelial aggregation receptor 1	E	rs12566888 (epinephrine)	1q23.1	25
			AA	rs12041331 (ADP)		
Count, MPV	*DNM3*	Dynamin 3	E	rs10914144	1q24.3	22,23
Count, MPV	*TMCC2*	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	*TRIM58*	Tripartite motif-containing protein 58	E	rs3811444	1q44	22
Count	*THADA*	Thyroid adenoma-associated protein	E	rs17030845	2p21	22
Count, MPV	*EHD3*	EH domain-containing protein 3	E	rs649729 (MPV), rs625132 (count)	2p21	22,23
Count	*GCKR*	Glucokinase regulatory protein	E	rs1260326	2p23	22
MPV	*ANKMY1*	Ankyrin repeat and MYND domain-containing protein 1	E	rs4305276	2q37.3	22
Count, MPV	*ARHGEF3*	Rho guanine nucleotide exchange factor 3	E	rs1354034 (count), rs12485738 (MPV)	3p14.3	22,23
Count	*SATB1*	DNA-binding protein SATB1	E	rs7641175	3p23	22
Count	*SYN2*	Synapsin-2	E	rs7616006	3p25	22
Count	*PDIA5*	Protein disulfide-isomerase A5	E	rs3792366	3q21.1	22
MPV	*KALRN*	Kalirin	E	rs10512627	3q21.1	22
Count	*THPO*	Thrombopoietin	E	rs6141	3q27.1	22
MPV	*KIAA0232*	Uncharacterized protein KIAA0232	E	rs11734132	4p16.1	22
Count	*HSD17B13*	17-β-hydroxysteroid dehydrogenase 13	E	rs7694379	4q22.1	22
Count, MPV	*F2R*	Proteinase-activated receptor 1	E	rs2227831 (MPV), rs17568628 (count)	5q13.3	22
Count, MPV	*MEF2C*	Myocyte-specific enhancer factor 2C	E	rs700585	5q14.3	22
Count	*IRF1*	Interferon regulatory factor 1	E	rs2070729	5q31.1	22
MPV	*RNF145*	RING finger protein 145	E	rs10076782	5q33.3	22
Count	*BAK1*	Bcl-2 homologous antagonist/killer	E	rs1330066	6p21.31	22–24
			AA	rs210134		
Count	*HLA-DOA*	HLA class II histocompatibility antigen, DO α chain	E	rs399604	6p21.32	22
Count	*HLA-B*	HLA class I histocompatibility antigen, B-82 α chain	E	rs3819299	6p22.2	22
Count	*LRRC16A*	Leucine-rich repeat containing 16A	AA, E, HA	rs441460	6p22.2	22,24
Count	*HBS1L, MYB*	HBS1-like protein, transcriptional activator Myb	E	rs9399137	6q23.3	22,24
			AA	rs9494145		
Count	*CD36*	Platelet glycoprotein IV (thrombospondin receptor)	AA, E, HA	rs13236689	7q21.11	24
Count, MPV, aggregation with epinephrine	*PIK3CG*	Phosphoinositol-4,5-biphosphate 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 *p* value for locus (associated trait)	Cytoband	Reference
Count	*WASL*	Wiskott–Aldrich syndrome-like protein	E	rs4731120	7q31.3	22
Aggregation with ADP	*SHH*	Sonic hedgehog protein	E	rs2363910	7q36.3	25
			AA	rs6943029		
Count	*ZFPM2*	Zinc finger protein ZFPM2	E	rs6993770	8q23.1	22
Count	*PLEC1*	Plectin	E	rs6995402	8q24.3	22
Count	*CDKN2A*	Cyclin-dependent kinase inhibitor 2A, isoform 4	E	rs3731211	9p21.3	22
MPV	*DOCK8*	Dedicator of cytokinesis protein 8	E	rs10813766	9p24.3	22
Count	*AK3*	GTP:AMP phosphor-transferase, mitochondrial	E	rs409801	9q24.1	22
Count	*RCL1*	RNA 3′-terminal phosphate cyclase-like protein	E	rs13300663	9q24.1	22
Count	*BRD3*	Bromodomain-containing protein 3	E	rs11789898	9q34.2	22
Count, MPV, aggregation with epinephrine	*JMJD1C*	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	*ADRA2A*	Alpha-2A adrenergic receptor	E	rs4311994	10q25.2	25
			AA	rs869244		
Aggregation with ADP	*MRVI1*	Protein MRVI1	E	rs7940646	11p15.4	25
			AA	rs1874445		
MPV	*BET1L*	BET1-like protein	E	rs11602954	11p15.5	23
Count, MPV	*PSMD13*	26S proteasome non-ATPase regulatory subunit 13	E	rs17655730 (MPV), rs505404 (count)	11p15.5	22
Count	*FEN1*	Flap endonuclease 1	E	rs4246215	11q12.2	22
Count	*BAD*	Bcl2 antagonist of cell death	AA, E, HA	rs477895	11q13.1	24
Count	*CBL*	E3 ubiquitin-protein ligase CBL	E	rs4938642	11q23.3	22
MPV	*MLSTD1*	Fatty acyl-CoA reductase 2	E	rs2015599	12p11.22	22
Count, MPV	*CD9, VWF*	CD9 antigen, von Willebrand factor	E	rs1558324 (MPV), rs7342306 (count)	12p13.31	22
Count, MPV	*PTGES3, BAZ2A*	Prostaglandin E synthase 3, bromodomain adjacent to zinc finger domain protein 2A	E	rs2950390 (MPV), rs941207 (count)	12q13.3	22
MPV	*COPZ1, NFE2, CBX5*	Coatomer subunit zeta-1, transcription factor NF-E2 45 kDa subunit, chromobox protein homolog 5	E	rs10876550	12q13.13	22
Count	*ATXN2*	Ataxin 2	E	rs11065987	12q24.1	23
Count	*PTPN11*	Tyrosine-protein phosphatase non-receptor type 11	E	rs11066301	12q24.1	22,23
Count	*RPH3A, PTPN11*	Rabphilin-3A, tyrosine-protein phosphatase nonreceptor type 11	E	rs17824620	12q24.1	22
Count	*ACAD10*	Acyl-CoA dehydrogenase family member 10	AA	rs6490294	12q24.12	24
Count	*SH2B3*	SH2B adapter protein 3	E	rs3184504	12q24.12	22
Count, MPV	*WDR66*	WD repeat-containing protein 66	E	rs7961894 (count, MPV)	12q24.31	22,23

(*Continued*)

Table 2 (*Continued*)

Trait	Gene	Protein	Population	SNP with lowest *p* value for locus (associated trait)	Cytoband	Reference
Count	*ABCC4*	Multidrug resistance-associated protein 4	E	rs4148441	13q32	22
MPV	*GRTP1*	Growth hormone-regulated TBC protein 1	E	rs7317038	13q34	22
Count	*RAD51L1*	DNA repair protein RAD51 homolog 2	E	rs8022206	14q24.1	22
Count	*ITPK1*	Inositol-tetrakisphosphate 1-kinase	E	rs8006385	14q31	22
Count	*C14orf70, DLK1*	Putative uncharacterized protein encoded LINC00523, protein delta homolog 1	E	rs7149242	14q32.2	22
Count	*RCOR1*	REST corepressor 1	E	rs11628318	14q32.31	22
Count, MPV	*C14orf73*	Exocyst complex component 3-like protein 4	E	rs2297067 (count), rs944002 (MPV)	14q32.32	22
MPV	*BRF1*	Transcription factor IIIB 90 kDa subunit	E	rs3000073	14q32.33	22
Count, MPV	*TPM1*	Tropomyosin α-1 chain	E	rs11071720 (MPV), rs3809566 (count)	15q22.1	22,23
Count	*ANKDD1A*	Ankyrin repeat and death domain-containing protein 1A	E	rs1719271	15q22.31	22
Count	*GPIBA*	Glycoprotein Ibα	E	rs6065	17pter-p12	22
Count	*AKAP10*	A-kinase anchor protein 10, mitochondrial	E	rs397969	17p11.1	22
Count, MPV	*TAOK1*	Serine/threonine-protein kinase TAO1	E	rs8076739 (MPV)	17q11.2	22,24
			AA	rs11653144 (MPV)		
			E	rs559972 (count)		
Count, MPV	*SNORD7, AP2B1*	Small nucleolar RNA C/D box 7, AP-2 complex subunit β	E	rs10512472 (count), rs16971217 (MPV)	17q12	22
Count	*FAM171A2, ITGA2B*	Protein FAM171A2, integrin α-IIb	E	rs708382	17q21.31	22
Count	*CABLES1*	CDK5 and ABL1 enzyme substrate 1	E	rs11082304	18q11.2	22
MPV	*CD226*	CD226 antigen	E	rs12969657	18q22.3	22,23
Count, MPV	*TPM4*	Tropomyosin 4	E, AA, HA	rs8109288 (count, MPV)	19p13.12	22,24
Count	*EXOC3L2*	Exocyst complex component 3-like protein 2	E	rs17356664	19q13.32	22
Aggregation with collagen	*GP6*	Platelet glycoprotein VI	E, AA	rs1671152	19q13.42	25
MPV	*SIRPA*	Tyrosine-protein phosphatase nonreceptor type substrate 1	E	rs13042885	20p13	22,23
Count, MPV	*TUBB1, CTSZ, SLMO2*	Tubulin β-1 chain, cathepsin Z, protein slowmo homolog 2	E	rs4812048 (MPV)	20q13.32	22,24
			AA, E, HA	rs151361 (count)		
Count	*ARVCF*	Armadillo repeat protein deleted in velocardiofacial 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.

[a]The 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	*TBXAS1*	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 GPIbα chain	17p13.2	Gain-of-function defect in VWF binding to GPIbIXV, because of a mutation in GPIbα[119]
Adhesion	Bernard–Soulier syndrome	Autosomal recessive, some forms autosomal dominant	*GP9*	Platelet GPIX, platelet GPIbα chain, or platelet GPIbβ chain	3q21.3	Deficiency or functional defect in GPIbIXV[134]
			GPIBA		17p13.222	
			GPIBB		22q11.21	
Adhesion	α2β1	Autosomal dominant	*ITGA2*	Integrin α2 subunit of $\alpha_2\beta_1$	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*	Integrin, αIIb or	17q21.31	Impaired platelet aggregation because of loss or dysfunction of $\alpha IIb\beta_3$, the platelet integrin that binds fibrinogen[63,79]
			ITGB3	integrin β3 subunits of $\alpha IIb\beta_3$	17q21.32	
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	*ITGA2B*	Integrin, αIIb or	17q21.31	Macrothrombocytopenia associated with activating mutations in $\alpha_{IIb}\beta_3$[63]
			ITGB3	integrin β3 subunits of $\alpha IIb\beta_3$	17q21.32	
Platelet numbers	Thrombocytopenia associated with absent radii syndrome (TAR)	Autosomal recessive	*RBM8A*	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	*FLNA*	Filamin A	Xq28	Thrombocytopenia, with or without periventricular nodular heterotopia or otopalatodigital syndromes, because of defects in filamin A[88]
Platelet numbers	Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	*MPL*	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	*WAS*	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	*MYH9*	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	*MASTL*, *ANKRD26*	Serine/threonine-protein kinase great wall or ankyrin repeat domain-containing protein 2	10p12.1	Thrombocytopenia[113,123]
Platelet numbers	Thrombocytopenia Cargeeg	Autosomal dominant	*CYCS*	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	*GATA-1*	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	*TUBB1*	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	*HOXA11* 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	*RUNX1*	Runt-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
						to myelodysplastic syndrome and myeloid leukemia[91,120]
Platelet numbers and α-granules	Paris-Trousseau-Jacobsen syndrome	Autosomal dominant	Deletion includes *FLI1*	Friend leukemia integration 1 transcription factor	11q23	Thrombocytopenia, giant platelets and α-granules, mental retardation, cardiac and facial defects[122]
Procoagulant function	Scott syndrome	Autosomal recessive	*TMEM16F*	Anoctamin-6 (transmembrane protein 16F)	12q12	Impaired expression of procoagulant phospholipids on activated platelets for coagulation[114,105]
Signaling	Signaling defects involving G-protein pathways	Not well documented	*GNAS1*	Guanine nucleotide-binding protein G(s) subunit α isoforms XLas or guanine nucleotide-binding protein G(q) subunit α	20q13.32	Defective G-protein coupled signaling[105–107]
			GNAQ		9q21.2	
Signaling	Impaired platelet G-protein signaling	Autosomal dominant	*RGS2*	Regulator of G-protein signaling 2	1q31.2	Platelets showed reduced sensitivity to Gs stimulation and reduced cAMP production after stimulation of Gs-coupled receptors. Enlarged, round platelets with abnormal α-granules.[108]
α-granule storage	Gray platelet syndrome	Autosomal recessive	*NBEAL2*	Neurobeachin-like protein 2	3p21.31	Thrombocytopenia associated with severe α-granule protein deficiency[94–96,113]
α-granule storage	ARC Syndrome	Autosomal recessive	*VPS33B*	Vacuolar protein sorting-associated protein 33B	15q26.1	Arthrogryposis, renal dysfunction, cholestasis associated with platelet α-granule deficiency[97]
δ-granule storage	Hermansky–Pudlak syndrome	Autosomal recessive	*HPS1*	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	Dense granule deficiency associated with defects of lysosomes and melanosomes with albinism[60,98–101]
			AP3B1		5q14.1	
			HPS3		3q24	
			HPS4		22q12.1	
			HPS5		11p15.1	
			HPS6		10q24.32	
			DTNBP1		6p22.3	
			BLOC1S3		19q13.32	
			PLDN		15q21.1	
δ-granule storage	Chédiak–Higashi syndrome	Autosomal recessive	*LYST*	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	*MYO5A*	Unconventional myosin-Va, ras-related protein Rab-27A, or melanophilin	15q21.2	Dense granule deficiency associated with hypopigmentation, immunological defects, lymphohistiocytosis and central nervous system defects[128,136]
			RAB27A		15q21.3	
			MLPH		2q37.3	

Abbreviations: ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; GP, glycoprotein.
[a]More than one gene or protein is shown if there are multiple causes.

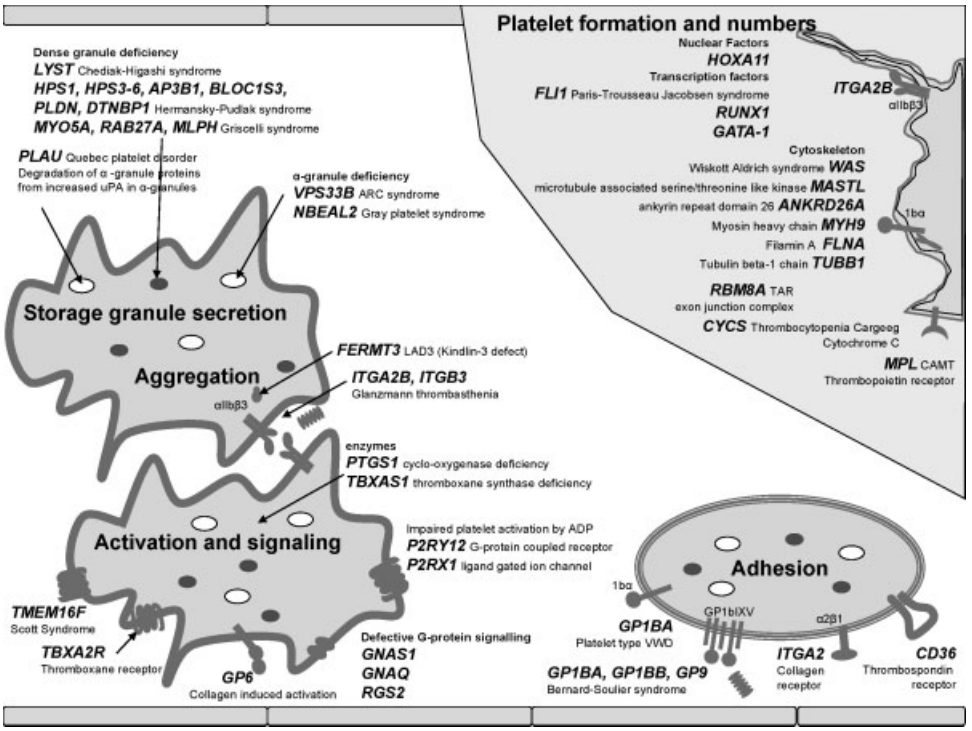

Fig. 1 Schematic representation of the genetic mutations that have been identified to cause platelet function disorders. Affected proteins and resulting disorders are indicated on the diagram, at the point along the pathway of platelet function (from platelet birth to adhesion, activation, and aggregation) 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 MRVI1,[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 GPIbα,[59,60] integrin αIIb,[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 β1-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 αIIbβ3 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, α2β1[80]; the thrombospondin receptor, GPIV[66]; the membrane receptors for agonist stimulation, GPVI,[61,62] $P2Y_{12}$,[81] $P2X_1$,[82] the TXA2 receptor,[83–87] among others; the membrane receptor for thrombopoietin in congenital amegakaryocytic thrombocytopenia[37]); (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 synthase[90]); and (6) the nucleus, in the case of factors that regulate megakaryocyte gene expression, such as RUNX1,[91] GATA-1,[92] and HOXA11[93] (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 protein16F, a Ca^{2+}-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 $1:10^6$ 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]; $\alpha IIb\beta_3$ 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 $P2Y_{12}$, 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 $GP\alpha IIb\beta_3$, and GPIbα, and $\alpha_2\beta_1$ deficiency),[60,63,80,119] agonist response (e.g., $P2X_1$[82] 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 numbers[89] (►**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 $P2Y_{12}$), 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 knockouts[28] and zebrafish morpholinos[131]) 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.

Funding
Catherine Hayward is the recipient of a Heart and Stroke Foundation of Ontario Career Investigator Award. The work was supported by grants from the Canadian Institutes for Health Research (MOP 97942) and the Canadian Hemophilia Society.

Conflict of Interest
The authors have no conflicts of interest to disclose.

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