Supplementary table S1

									Sequence identity	
Human	*Homo sapiens*	Q7LDG7	**F181**	**Y289**	**C296**	**G305**	**N330**	**A345**	**CalDAG-GEFI**	**Just CDC25**
Chimpanzee	*Pan troglodytes*	H2Q404	F181	Y289	C296	G305	N330	A345	99.67%	100%
Macaque	*Macaca mulatta*	H9ENK8	F181	Y289	C296	G305	N330	A345	99.84%	100%
Dog	*Canis lupus familiaris*	J9P904	F235	Y343	C350	G359	N384	A409	88.08%	98.30%
Cow	*Bos taurus*	F1MJ35	F181	Y289	C296	G305	N330	A345	96.55%	96.60%
Mouse	*Mus musculus*	Q9QUG9	F181	Y289	C296	G305	N330	A345	96.22%	97.00%
Rat	*Rattus norvegicus*	P0C643	F181	Y289	C296	G305	N330	A345	96.88%	97.90%
Zebrafish	*Danio rerio*	F1R763	F175	Y283	C290	G299	N324	A339	58.95%	69.70%
Xenopus	*Xenopus laevis*	Q32N25	F176	Y284	C291	G300	N325	T340	63.05%	70.50%
% conservation			100%	100%	100%	100%	100%	89%		

Conservation of the human CalDAG-GEFI residues F181, Y289, C296, G305, N330 and A345 in orthologs. The amino acid sequence of human CalDAG-GEFI was compared to orthologs using CLUSTAL Omega (http://www.ebi.ac.uk/Tools/msa/clustalo/). The CDC25 sequence is more conserved across orthologs when compared to the sequence across all of the CalDAG-GEFI domains. All the substituted residues predicted from the observed likely pathogenic missense variants in the study were completely conserved with the exception of human residue A345 which is a T residue in *Xenopus*.

Supplementary table S2

	A-II3	B-II1	C-II1	D-II2	E-II1	F-II1	G-II2	H-II4	I-II1	J-II2	K-II1
Variant	N67Lfs*24	E260* / C296R	N330K	R494Afs*54	R494Afs*54 / F181S	F497Sfs*22	F497Sfs*22	F497Sfs*22 / A345P	F497Sfs*22 / Y289C	G305D	P125*
Sex	F	F	F	M	M	F	M	M	M	M	F
Ethnicity*	European	Other	Other	European	European	European	African	European	European	South Asian	European
Recruiting country	France	France	Israel	France	USA	Belgium	France	UK	UK	Argentina	UK
Collection	NBR	NBR	NBR	NBR	NBR	NBR	NBR	NBR	TG	TG	TG
Year of birth	1994	1997	1996	1957	2004	1993	NK	1960	1956	NK	1993
Presentation age (y)	1	1	5	5	1	1	14	5	4	NK	2
Blood products	PLT	None	RBC, PLT	NK	RBC, PLT	RBC, PLT	NK	None	PLT	RBC	RBC, PLT
PLT (10^9/L)	226	443	304	282	223	209	NK	200	322	196	197
MPV (fL)	7.8	7.3	7.4	10.2	9.9	9.8	NK	9.1	10.4	9.7	12.3
ADP Agg	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
EPI Agg	↓	↓	↓	NK	↓	↓	NK	↓	↓	↓	↓
COL Agg	↓	↓	↓	↓	N	↓	↓	↓	↓	↓	↓
AA Agg	↓	↓	NK	↓	N	NK	↓	↓	↓	N	↓
TRAP Agg	N	N	NK	N	NK	NK	NK	NK	NK	↓	NK
RIST Agg	N	N	N	N	N	N	NK	N	NK	N	N
GPIIb (CD41)	N	N	N	N	N	N	N	N	N	NK	N
GPIIIa (CD61)	N	N	NK	N	N	N	N	N	N	NK	N
GPIX (CD42a)	N	NK	N	N	NK	NK	N	NK	NK	NK	NK

GP1bα (CD42b)	N	N	N	N	N	N	N	N	N	NK	N
P-selectin exposure (CD62P)	N	N	NK	N	NK	N	NK	NK	NK	NK	NK
CD63 exposure	N (TRAP14)	N (TRAP14)	NK	NK	NK	NK	NK	NK	NK	NK	NK
ATP secretion	NK	NK	NK	↓ (ADP) ↓ (collagen)	↓ (ADP) N (collagen)	NK	NK	N (ADP) N (collagen)	↓ (ADP) N (thrombin)	NK	NK
ATP:ADP ratio	NK	NK	NK	NK	1.7 (N)	NK	NK	1.57 (N)	NK	NK	NK
PFA100 (ADP/coll) (s)	NK	NK	NK	NK	279 (↑)	NK	NK	84 (N)	>300 (↑)	NK	NK
PFA100 (Epi/coll) (s)	NK	NK	NK	NK	300 (↑)	NK	NK	154 (N)	>300 (↑)	NK	NK
Electron microscopy	N	N	NK	Abnormal vacuoles	NK	N	N	NK	NK	NK	NK
Other clinical features reported	Immune thrombocyto-penia	Leucocytosis	Mental retardation, epilepsy, leucocytosis	GI angio-dysplasia	None	None	Keloid scarring, intracerebral meningioma	None	Ulcerative colitis	None	None

Clinical and laboratory characteristics of the 11 index cases with biallelic, likely pathogenic variants in *RASGRP2*. PLT- platelet count; MPV- mean platelet volume; GI- gastrointestinal; ADP- adenosine diphosphate; EPI-epinephrine; COL-collagen; AA-arachidonic acid; TRAP-thrombin receptor agonist peptide; RIST- ristocetin; Agg- aggregation; NK- not known; N- normal; ↓- reduced; ↑ increased when compared to reference interval. * Ethnicity was inferred from next generation sequencing data according to previously described methods. [1,2] The index cases from pedigrees A – H were unrelated (at least no closer than fourth degree relatives). This was determined using analysis of 30,000 common SNPs according to previously described methods.[3]

1. Simeoni I, Stephens JC, Hu F, et al. A high-throughput sequencing test for diagnosing inherited bleeding, thrombotic, and platelet disorders. *Blood*. 2016;127(23):2791-2803.
2. Conomos MP, Miller MB, Thornton TA. Robust inference of population structure for ancestry prediction and correction of stratification in the presence of relatedness. *Genet Epidemiol.* 2015; 39(4):276-93.
3. Conomos MP, Reiner AP, Weir BS, Thornton TA. Model-free estimation of recent genetic relatedness. *Am J Hum Genet* 2016; 98(1):127-148.