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ORIGINAL ARTICLE

A Compound Heterozygosis of Two Novel Mutations in vWF Exacerbates vWD in a Chinese Pedigree

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SUMMARY

Background: **von Willebrand disease (vWD), caused by mutations in the von Willebrand factor (vWF) coding gene, is a disease characterized by abnormal coagulation activity and a severe tendency for hemorrhage. Therefore, identifying mutations in *vWF* is important for diagnosing congenital vWD.**
Methods: **We studied a 23-year-old male vWD patient and his parents. Clotting methods were used to determine activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen (FIB) levels, FVIII activity. Chromogenic substrate method was used to determine vWF antigen and activity. The platelet count was determined. Mutations were searched using whole-exome sequencing and certified by Sanger sequencing. Clinical data, including activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen levels, FX activity, FX antigen levels, and the platelet count were collected. A mixing study was performed to eliminate the presence of coagulation factor inhibitors and lupus anticoagulants. Mutations were screened by using whole-exome sequencing (WES) and were verified by using Sanger sequencing.**
Results: **The proband showed severely decreased vWF antigen, vWF activity, and FVIII activity. RIPA (RISTOCETIN-induced platelet aggregation) was 0%. Data from WES showed that the proband carried compound heterozygous variants vWF: NM_000552.5 (c.3213C>A p.Cys1071Ter) and vWF: NM_000552.5 (c.6598+2T>C). The proband's mother carried variant vWF: NM_000552.5 (c.3213C>A p.Cys1071Ter) while the proband's father carried variant vWF: NM_000552.5 (c.6598+2T>C). All laboratory test indexes of the proband's parents, including vWF antigen, vWF activity, and FVIII activity, were within the normal ranges.**
Conclusions: **We identified a compound heterozygosis with two novel mutations in vWF (c.3213C>A, c.6598+2T >C) in a family pedigree, and our results demonstrate that the compound heterozygous mutations probably exacerbate vWD.**
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Supplementary Data

Table S1. All coding sequence and exonic boundaries ± 10 base pairs (bp) of 68 relevant genes.

Input	Match type	Approved symbol	Approved name	HGNC ID	Location
ABCG5	approved symbol	ABCG5	ATP binding cassette subfamily G member 5	HGNC:13886	2p21
ABCG8	approved symbol	ABCG8	ATP binding cassette subfamily G member 8	HGNC:13887	2p21
ACVRL1	approved symbol	ACVRL1	activin A receptor like type 1	HGNC:175	12q13.13
ANKRD26	approved symbol	ANKRD26	ankyrin repeat domain containing 26	HGNC:29186	10p12.1
AP3B1	approved symbol	AP3B1	adaptor related protein complex 3 subunit beta 1	HGNC:566	5q14.1
BLOC1S3	approved symbol	BLOC1S3	biogenesis of lysosomal organelles complex 1 subunit 3	HGNC:20914	19q13.32
CYCS	approved symbol	CYCS	cytochrome c, somatic	HGNC:19986	7p15.3
DTNBP1	approved symbol	DTNBP1	dystrobrevin binding protein 1	HGNC:17328	6p22.3
ENG	approved symbol	ENG	endoglin	HGNC:3349	9q34.11
F10	approved symbol	F10	coagulation factor X	HGNC:3528	13q34
F11	approved symbol	F11	coagulation factor XI	HGNC:3529	4q35.2
F13A1	approved symbol	F13A1	coagulation factor XIII A chain	HGNC:3531	6p25.1
F13B	approved symbol	F13B	coagulation factor XIII B chain	HGNC:3534	1q31.3
F2	approved symbol	F2	coagulation factor II, thrombin	HGNC:3535	11p11.2
F5	approved symbol	F5	coagulation factor V	HGNC:3542	1q24.2
F7	approved symbol	F7	coagulation factor VII	HGNC:3544	13q34
F8	approved symbol	F8	coagulation factor VIII	HGNC:3546	Xq28
F9	approved symbol	F9	coagulation factor IX	HGNC:3551	Xq27.1
FGA	approved symbol	FGA	fibrinogen alpha chain	HGNC:3661	4q31.3
FGB	approved symbol	FGB	fibrinogen beta chain	HGNC:3662	4q31.3
FGG	approved symbol	FGG	fibrinogen gamma chain	HGNC:3694	4q32.1
FLI1	approved symbol	FLI1	Fli-1 proto-oncogene, ETS transcription factor	HGNC:3749	11q24.3
FLNA	approved symbol	FLNA	filamin A	HGNC:3754	Xq28
GATA1	approved symbol	GATA1	GATA binding protein 1	HGNC:4170	Xp11.23
GGCX	approved symbol	GGCX	gamma-glutamyl carboxylase	HGNC:4247	2p11.2
GP1BA	approved symbol	GP1BA	glycoprotein Ib platelet subunit alpha	HGNC:4439	17p13.2
GP1BB	approved symbol	GP1BB	glycoprotein Ib platelet subunit beta	HGNC:4440	22q11.21
GP6	approved symbol	GP6	glycoprotein VI platelet	HGNC:14388	19q13.42
GP9	approved symbol	GP9	glycoprotein IX platelet	HGNC:4444	3q21.3
HOXA11	approved symbol	HOXA11	homeobox A11	HGNC:5101	7p15.2
HPS1	approved symbol	HPS1	HPS1 biogenesis of lysosomal organelles complex 3 subunit 1	HGNC:5163	10q24.2
HPS3	approved symbol	HPS3	HPS3 biogenesis of lysosomal organelles complex 2 subunit 1	HGNC:15597	3q24
HPS4	approved symbol	HPS4	HPS4 biogenesis of lysosomal organelles complex 3 subunit 2	HGNC:15844	22q12.1
HPS5	approved symbol	HPS5	HPS5 biogenesis of lysosomal organelles complex 2 subunit 2	HGNC:17022	11p15.1
HPS6	approved symbol	HPS6	HPS6 biogenesis of lysosomal organelles complex 2 subunit 3	HGNC:18817	10q24.32
HRG	approved symbol	HRG	histidine rich glycoprotein	HGNC:5181	3q27.3
ITGA2B	approved symbol	ITGA2B	integrin subunit alpha 2b	HGNC:6138	17q21.31
ITGB3	approved symbol	ITGB3	integrin subunit beta 3	HGNC:6156	17q21.32
JAK2	approved symbol	JAK2	Janus kinase 2	HGNC:6192	9p24.1

Table S1. All coding sequence and exonic boundaries ± 10 base pairs (bp) of 68 relevant genes (continued).

Input	Match type	Approved symbol	Approved name	HGNC ID	Location
KLKB1	approved symbol	KLKB1	kallikrein B1	HGNC:6371	4q35.2
KNG1	approved symbol	KNG1	kininogen 1	HGNC:6383	3q27.3
LMAN1	approved symbol	LMAN1	lectin, mannose binding 1	HGNC:6631	18q21.32
LYST	approved symbol	LYST	lysosomal trafficking regulator	HGNC:1968	1q42.3
MCFD2	approved symbol	MCFD2	multiple coagulation factor deficiency 2, ER cargo receptor complex subunit	HGNC:18451	2p21
MPL	approved symbol	MPL	MPL proto-oncogene, thrombopoietin receptor	HGNC:7217	1p34.2
MYH9	approved symbol	MYH9	myosin heavy chain 9	HGNC:7579	22q12.3
NBEA	approved symbol	NBEA	neurobeachin	HGNC:7648	13q13.3
NBEAL2	approved symbol	NBEAL2	neurobeachin like 2	HGNC:31928	3p21.31
P2RY12	approved symbol	P2RY12	purinergic receptor P2Y12	HGNC:18124	3q25.1
PLA2G4A	approved symbol	PLA2G4A	phospholipase A2 group IVA	HGNC:9035	1q31.1
PLAT	approved symbol	PLAT	plasminogen activator, tissue type	HGNC:9051	8p11.21
PLAU	approved symbol	PLAU	plasminogen activator, urokinase	HGNC:9052	10q22.2
PLG	approved symbol	PLG	plasminogen	HGNC:9071	6q26
PROC	approved symbol	PROC	protein C, inactivator of coagulation factors Va and VIIIa	HGNC:9451	2q14.3
PROS1	approved symbol	PROS1	protein S	HGNC:9456	3q11.1
RBM8A	approved symbol	RBM8A	RNA binding motif protein 8A	HGNC:9905	1q21.1
RUNX1	approved symbol	RUNX1	RUNX family transcription factor 1	HGNC:10471	21q22.12
SERPINC1	approved symbol	SERPINC1	serpin family C member 1	HGNC:775	1q25.1
SERPIND1	approved symbol	SERPIND1	serpin family D member 1	HGNC:4838	22q11.21
SERPINE1	approved symbol	SERPINE1	serpin family E member 1	HGNC:8583	7q22.1
TBXA2R	approved symbol	TBXA2R	thromboxane A2 receptor	HGNC:11608	19p13.3
TBXAS1	approved symbol	TBXAS1	thromboxane A synthase 1	HGNC:11609	7q34
THBD	approved symbol	THBD	thrombomodulin	HGNC:11784	20p11.21
THPO	approved symbol	THPO	thrombopoietin	HGNC:11795	3q27.1
TUBB1	approved symbol	TUBB1	tubulin beta 1 class VI	HGNC:16257	20q13.32
VKORC1	approved symbol	VKORC1	vitamin K epoxide reductase complex subunit 1	HGNC:23663	16p11.2
VWF	approved symbol	VWF	von Willebrand factor	HGNC:12726	12p13.31
WAS	approved symbol	WAS	WASP actin nucleation promoting factor	HGNC:12731	Xp11.23