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Clinical Features and Novel Mutations of 7 Taiwanese Patients with Type 3 von Willebrand Disease

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OBJECTIVES

- von Willebrand disease (VWD) is the most common inherited bleeding disorders.
- Type 3 VWD is the least but most severe type VWD, with incidence of 0.1–5.3 per million. Its inheritance is compound heterozygous or homozygous mutation of von Willebrand factor (VWF) gene.
- Most reports are from the West. The studies from Asian countries are limited. We aim to investigate the clinical features and genotypes of type 3 VWD in Taiwanese patients.

METHODS

- We retrospective collected total 7 Taiwanese patients diagnosed with type 3 VWD and reviewed their clinical presentation, bleeding scores, and genotypes from two hemophilia centers.
- Mutation analysis was performed from the 7 patients. Exon 28 of VWF gene was amplified using polymerase chain reaction followed by direct sequencing first, then mutations in the other 51 exons were detected by Denaturing High-Performance Liquid Chromatography analysis followed by direct sequencing.

Table 1. Patient Characteristics

Patient Characteristics	Sex	Age (y/o)	ABO grouping	Bleeding scores	VWF:Ag (%)	VWF:activity (%)	FVIII:C (%)
Patient 1	F	1	A	4	1.6	NA	4.3
Patient 2	M	16	AB	16	3.4	2.1 (VWF:Rco)	3.9
Patient 3	M	39	O	18	10.6	0	4
Patient 4	M	11	O	26	< 1	< 1	3.1
Patient 5	F	6	O	8	< 1	< 1	< 1
Patient 6	F	25	O	20	< 13.5	< 11.3	2.1
Patient 7	M	20	B	5	< 13.5	< 11.3	3.4

CONCLUSIONS

- Our study demonstrates clinical features and genotypes of 7 type 3 VWD Taiwanese patients. Hemarthrosis, bruising, and muscle hematoma were most common symptoms.
- All (100%) were found to have mutation of VWF gene. Total 8 different mutations were identified, including 3 nonsense mutations, 2 large deletions, 1 missense mutation, 1 splicing site and 1 insertion.
- There were 7 novel mutations on VWF gene identified, which has never been reported.
- Our report revealed the detected rate of VWF gene is as high as that of other countries. Mutation distribution showed small differences, compared with that of other countries.

RESULTS

- The 7 patients were from 5 unrelated families. Four patients were blood type O. Their mean age was 16.9 years old, from 1 to 39.Table 1
- The most common symptoms were bruising (85.7%),hemarthrosis (85.7%),and muscle hematoma(85.7%). The mean bleeding score was 13.9 ± 8.3 points, ranging from 4 to 26.(Fig.1 & 2)
- All patients' FVIII:C were lesser than 5%, with near absence of VWF multimers. All (100%) were found to have mutation of VWF gene.
- Five patients were autosomal recessive, among whom 3 were compound heterozygous inheritance and 2 homozygous inheritance.
- The other 2 siblings were autosomal co-dominant with homozygous mutation from the same consanguineous family, with the novel mutation of E6:c.646G>A. Their parents had the same heterozygous mutation in E6 and both were confirmed as type 1 VWD.
- Total 8 different mutations were identified, including 3 nonsense mutations, 2 large deletions, 1 missense mutation, 1 splicing site and 1 insertion. There were 7 novel mutations on VWF gene identified.
- We compared our data with that of UK and India.(Table 3)

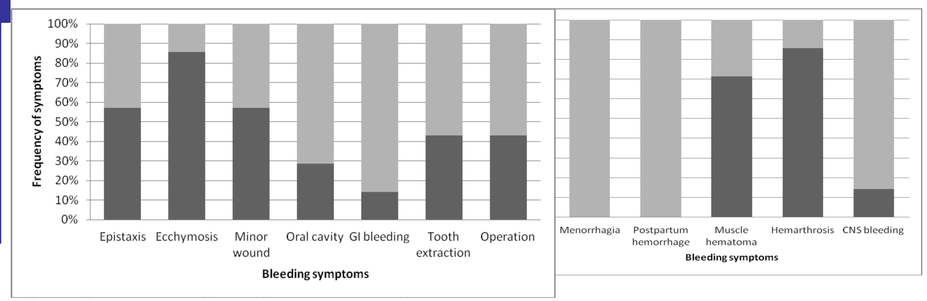

Fig 1. Frequency of bleeding symptoms in our cohort.

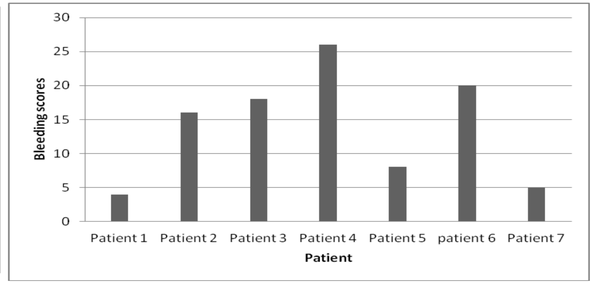

Fig.2 VWD bleeding scores.

Table 2. Genotypes of type 3 VWD in our cohort. (red color words mean novel mutations)

Cases	One allele	Another allele	Mutation
Patient 1	E7: c.691dupGC	E31: c.5335 C>T	Compound heterozygous Insertion + nonsense mutation
Patient 2	IVS27+2T>C	E32: c.5503C>T	Compound heterozygous Splicing site + nonsense mutation
Patient 3	E7-E16 deletion	E6-E52 deletion	Compound heterozygous large deletions
Patient 4	E6: c.646 G>A	E6: c.646 G>A	Homozygous missense mutation
Patient 5	E6: c.646 G>A	E6: c.646 G>A	Homozygous missense mutation
Patient 6	E14: c.1658 G>A	E14: c.1658 G>A	Homozygous nonsense mutation
Patient 7	E14: c.1658 G>A	E14: c.1658 G>A	Homozygous nonsense mutation

Table 3. Comparision of mutations of type 3 VWD in different countries.

	Taiwan (n=7) *~ 2016 WFH Poster*	***UK [1](n=20)*** *~ 2009 Haemophilia*	***India[2](n=19)*** *~ 2013 Thromb Haemost*
Detection rate	*100%*	*90%*	*89.5%*
Total mutation No.	*8*	*15*	*21*
Large deletions	25%	26.7%	33.3%
Missense mutations	12.5%	6.7%	36.8%
Nonsense mutations	37.5%	20%	23.8%
A putative splice site	12.5%	13.3%	5%
Frame shift	0	20%	0
Others	1 insertion	2 conversion	0
Novel mutations	7 (87.5%)	Not mentioned	15 (71.4%)

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