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Genotype Characteristics of Von Willebrand Disease in Taiwan

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OBJECTVES

- Genetic study of von Willebrand factor (VWF) gene may provide more information for von Willebrand disease (VWD) diagnosis, classification and effective management.
- The reports of the genetic study on VWD from Asian countries are rarely described.
- The aim of this study was to analyze the genotype characteristics in a Taiwanese cohort of VWD patients.

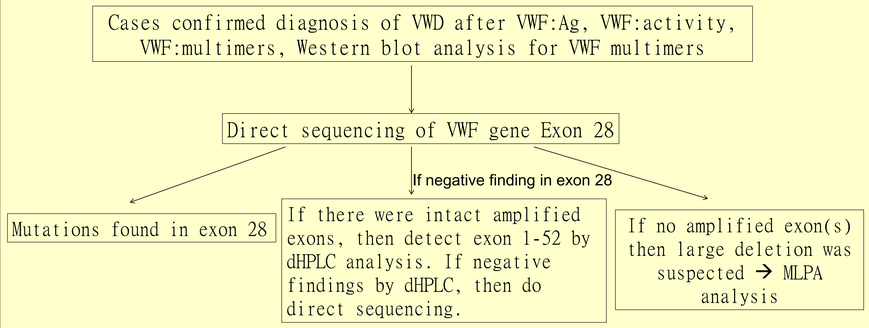
METHODS

- We analyzed the genetic defects of 62 patients with diagnosed VWD from 37 unrelated families enrolled from 2008 to 2016 in two hemophilia centers (TSGH, TMUH).
- 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.

RESULTS

- Totally 62 patients：from 37 unrelated families, Sex：30 male / 32 female. Age：35.3 ± 15.5 y/o, ranging from 1 to 64.
- Among 62 patients, 50 were type 1 VWD, five type 2 VWD and 7 type 3 VWD.
- VWF gene mutations were identified in 36 (58.1%) patients. Mutation detection rate was 50%, 80% and 100% for type 1, 2 and 3 VWD patients, respectively.
- There were totally 23 different genotypes, including 14 missense mutations (60.9%), three nonsense mutations (13.0%), two small deletions (8.7%), two large deletions (8.7%), one splice-site mutation (4.3%) and one small insertion (4.3%). [Fig.1]
- Nine of the 36 (25%) patients have an exon 28 mutation of VWF gene. All of them: non-type 3 VWD patients. Exon 28 mutations: the most common mutation exon.[Fig.2]
- 21 putative mutations are novel mutations. In type 1 and type 2 VWD, the majority of mutations (80% and 100%, respectively) were missense mutations.
- Type 1 VWD : 25 detectable, the most common mutations : E28: c.4499C>T (n=5)
- Frequency of mutation numbers in type 1, 2, & 3 VWD: summaried as Table 1.
- We compared our mutation analysis data with that of Germany and China, and similar mutation distributions were found. (Table 2A and 2B)

Mutation analysis of VWD



Type	Patient Num.	Patient found Mut.	Mutation in Exon28		Mutation in other Exon		Patient not found Mut.
Type 1	50	25 (50%)	5	c.4499C>T, A1500V; **X5**	20	E4: c.311delGA; **X1** E6: c.646 G>A,E216K **X2** E12: c.1400A>G, D467G; **X1** E13: c.1519A>G, R507G; **X3** E14: c.1613C>T, P538L; **X2** E18: c.2308C>T, P770S; **X1** E30: c.5173 del C; **X2** E31: c.5336G>A, R1779Q; **X3** E36: c.6104G>A, G2035D; **X1** E37: c.6352C>T, R2118W; **X1** E37: c.6547C>T, L2173F; **X1** E37: c.6596 G>A, R2199Y; **X1** E44: c.7548T>A, S2516R; **X1**	25 (50%)
Type 2	5	4 (80%)	4	c.4883T>C, I1628T; **X2** c.3814T>G, C1272G; **X2**	0	-	1 (20%)
Type 3	7	7 (100%)	0		7	E31: c.5335 C>T, R1779X; & E7: c.691dupGC; (Compound Heterozygous) **X1** E32: c.5503C>T, Q1835X; & IVS27+2T>C; (Compound Heterozygous) **X1** E7-E16 deletion & E6-E52 deletion; or E6-E16 deletion & E7-E52 deletion (Compound Heterozygous) **X1** E6: c.646 G>A, GAA>AAA, E216K (Homo, missense mutation) **X2** E14: c.1658 G>A; TGG>TAG; Trp(W)>Ter(X) (Homo, nonsense mutation) **X2**	0

Table 1. Frequency of mutation number in different exons in type 1 and 2 VWD

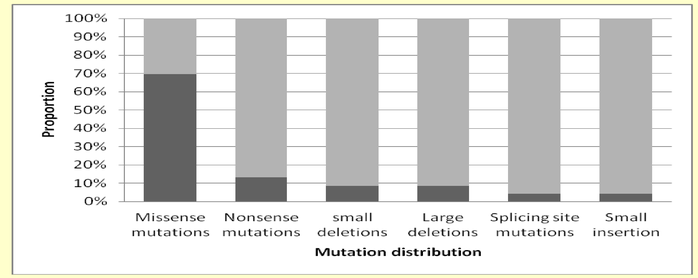


Fig 1. Mutation distributions in our cohort

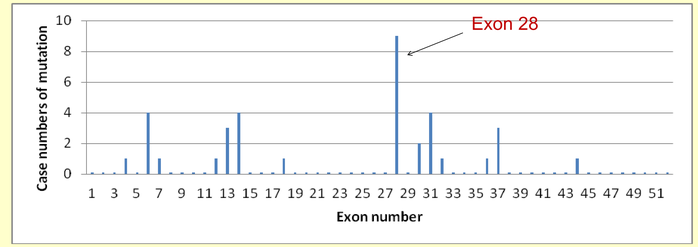


Fig 2. Frequency of mutation number in different exons

Table. 2A. Comparision of mutation distributions among different countries

Variables	*Taiwan* ~ 2016 WHF Poster	*Germany* ~ 2012 Thromb Haemost	*China* ~ 2015 Oral present
Case number : Total	***n=62 in 37 families***	***n=114 in 78 families***	***n=72 in ? families***
Type 1	***80.6%***	-	*27.8%*
Type 2	***8.1%***	-	*43%*
Type 3	***11.3%***	-	*29.2%*
Detection rate (total)	*58.1%*	*84.6%*	*80.5%*
Type 1	*50%*	*68%*	*65%*
Type 2	*80%*	*94%*	*83.9%*
Type 3	*100%*	*94%*	*90.5%*

Table. 2B. Comparision of mutation distributions among different countries

Variables	*Taiwan* ~ 2016 Oral present	*Germany* [1] ~ 2012 Thromb Haemost	*China* [2] ~ 2015 Oral present
Different putative mutations	*23*	*68*	*62*
Missense mutations	*60.9%*	*54.4%*	*54.8%*
Nonsense mutations	13.0%	10.3%	19.4%
Small deletions	8.7%	14.7%	12.9%*
Large deletions	8.7%	8.8%	1.6%
Splicing site	4.3%	7.4%	6.5%
Small insertion	4.3%	2.9%	*
Others	0	1 silent mutation	1 point mutation in 5'UTR

CONCLUSION

- Our study demonstrates that 58.1% of VWD patients had detectable VWF genetic defect. 50% of type 1 VWD, 80% of type 2 VWD and 100% of type 3 VWD patients were found to have mutation of VWF gene.
- Exon 28 is the highest number of mutation. Mutation distribution is similar to that of other countries.
- Missense mutations were the most common mutation, esp in type 1 and type 2 VWD.
- Totally 23 putative mutations are found out. All of them are novel mutations, with 14 and 2 novel mutations found in our type 1 & 2 VWD patients, respectively.

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