

Mutation Awareness of von Willebrand's Disease in Medical and Genetic Differences Screening: A Systematic Review

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Abstract

There were hospitalized patients diagnosed with Von Willebrand disorders (vWD) in this population medical base study. PubMed search bibliographies extracted applicable studies. Ten studies of 3296 patients diagnosed with vWD have been included in numerous research orders, ranging from 29.7% to 100%. The overall prevalence turned was 83.7% (95% CI 29.7-100%). The prevalence was 99.7 % (95 percent CI 99.3-100 %) higher in African and French research studies compared to 29.7% in America. This variation was pleasing to be as the results of different in these studies, which included the recruitment approach to population evaluation methods, blood loss, ethnic composition, and vWD mutation screening techniques criteria. The objective of this systematic review research was to evaluate the techniques of vWD mutation's screening. The mutation screening and its separate subtypes became a recommendation to use next - generation sequencing (NGS) and multiplex ligation - dependent probe amplification (MLPA) across the globe to check for analytical techniques that needed to be considered specifically for those of Caucasian origin and those with no obvious signs of pathological bleeding.

Keywords: mutation, screening techniques, genome, vWD

1. Introduction

Global efforts have been made over the past six years to evaluate the vWD screening mutations (Sadler et al., 2006). It is the maximum not unusual bleeding disorder with the aforementioned prevalence of 0.01% to 1%. (Sadler et al., 2006; Ruggeri, 2003) The situation is due to abnormalities associated with the Von Willebrand factor (vWF) protein that has a critical function in primary hemostasis (Ruggeri, 2003; Vlot et al., 1996). The vWF glycoprotein is encoded by a VWF giant gene of approximately 178 kb consisting of 52 exons. It is highly polymorphic (> 100 coding unmarried - nucleotide polymorphisms (cSNPs)) with relatively homologous partial pseudogene (VWFP; exons 23 - 34) (Mancuso et al., 1991), these characteristics make it difficult to amplify and sequence vWF for this reason, the molecular evaluation of vWF is an undertaking (Corrales et al., 1991; Irene et al., 2012). The classic Sanger sequencing of the entire vWF is too expensive for standard use in all patients, so this technique has been completed with moderate variations, predominantly VWF exons, depending on the vWD subtype. Exon 28 is sequenced for patients of type 2A, 2B, 2 M and type 2A, but if a mutation is not always found in exon 28 genes, we should check its prolonged exons 50 to 52 and Exons 18 to 20 are like the FVIII-binding site in 2N cases. (Irene et al., 2012; Goodeve, 2010; Desai & Jere, 2012; Rodeghiero et al., 2009; Dunham et al., 2012; Lillicrap et al., 2009; Vidal et al., 2005). Ultimately, Type 1 and Type 3 patients need to analyze the coding collection as capability mutations can be spread throughout vWF (Goodeve, 2010). The next - technology sequencing (NGS) makes the molecular analysis of vWD faster and grade - by - grade through complete vWF sequencing and simplifies and optimizes this evaluation (Irene et al., 2012; Desai & Jere, 2012). Based on the results of previous research that explained the difficulties of diagnosing vWD and inclusion of NGS screening of vWD mutations would be an excellent way to identify this disease and would provide an in - intensive explanation of the technical components of the vWF characterization supported by NGS for the analysis of Von Willebrand. The purpose of this writing was to present a systematic overview of all the studies that vWD's mutation screening techniques. It's far - reaching expectation that the evaluation will help determine whether or not the screening of these mutations will form part of routine laboratory analysis.

2. Methods

2.1 Data Sources

Figure 1 summarizes an outline of the methodology. Briefly, we collected bibliographies of abstract articles published on mutations in PUBMED's vWD mutation screening. Key phrases for this search were the PUBMED extracted abstracts; vWD, mutations, polymorphisms, and screening techniques. For articles published in English language proceedings, bibliographies of recognized articles were considered.

2.2 Study Eligibility

The search was designed and included to evaluate the vWD screening mutations. Studies that searched exclusively for vWD mutation screenings were covered, and no attempts were made to contact for information the authors of the original articles.

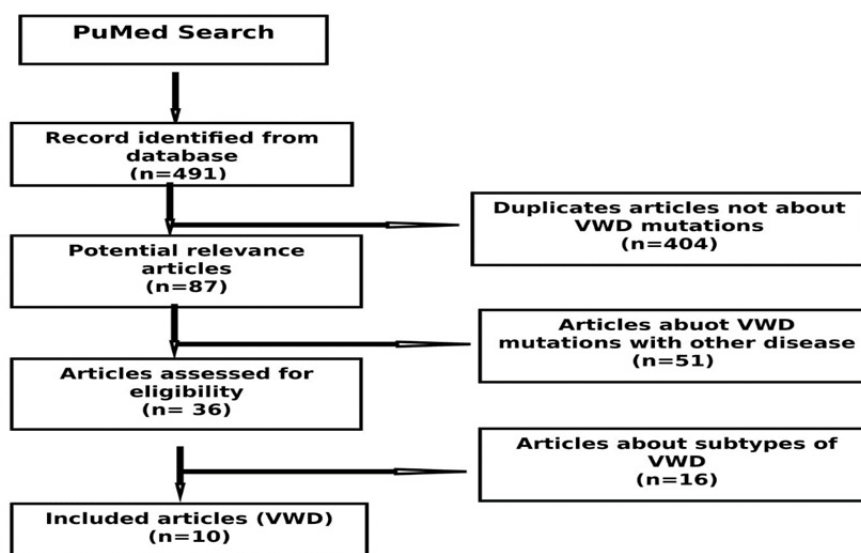


Figure 1. A schematic overview of the systematic review

3. Results

Ten studies were identified from 2012 to 2017; 491 abstracts recognized by our electronic search cover various screenings for vWD mutations. Figure 1 shows the flow from the abstracts to the categorization of the mutation. The list was shortened from the completed studies to 10 after filtering the results to consider only vWD screening techniques. These techniques of screening mutations were sorted using the number of abstracts associated with them. Depending on their corresponding number of abstracts, there was a clear difference in screening techniques for gene mutations. These 10 abstracts mentioned the well-known vWD susceptible mutation screening techniques; more occurrences in the abstracts and some of them were clearly recognized in vWD for their biological functions. These mutations included all vWD family types. Information on the reviewed studies included was presented in Table 1 and Table 2. In table 1, the studies done in African, French and Chinese's populations conclude a higher vWD prevalence when compared with other populations. Table 2 summarized vWD subtypes, mutation types and the diagnostic testing in the studies reviewed. Even though there were some similarities, the designs of the studies were compared; the researches within the study recruitment approach, demographic characteristics (especially ethnic composition) and evaluation requirements (look at the diagnosis and its cutoff values).

Table 1. Prevalence rates of VWF mutations distribution of the studies reviewed

Study	No. of Patients	No. VWF mutations	Prevalence, % (95% CI)	Populations
Battle, <i>et.al.</i> 2016	480	463	96.5	Spanish
Boylan, <i>et.al.</i> , 2015	37	11	29.7	USA
Fidalgo, <i>et.al.</i> 2016	92	62	67.3	Portuguese
Hampshire, <i>et.al.</i> 2013	26	25	96.2	Turkey
Jiang, <i>et.al.</i> 2012	3	3	100	Chinese
Kasatkar, <i>et.al.</i> 2014	85	77	90.6	Indian
Liang, <i>et.al.</i> 2017	200	195	97.5	Chinese
Veyradier, <i>et.al.</i> 2016	1167	1159	99.3	French
Wang, <i>et.al.</i> 2013	1092	1092	100	African
Yadegari, <i>et.al.</i> 2012	114	68	59.6	Germany

Table 2. VWD subtypes, mutation types and the diagnostic testing in the studies reviewed

Study	Definition of vWD	Mutation	Diagnostic test
Battle, <i>et.al.</i> 2016	vWD 1, vWD 2A, vWD 2B, vWD3	different types	NGS
Boylan, <i>et.al.</i> , 2015	vWD 1, VWD 3	heterozygous	CSS
Fidalgo, <i>et.al.</i> 2016	vWD 2B , vWD 2N	different types	CSS and NGS
Hampshire, <i>et.al.</i> 2013	vWD 1, vWD 2A	homozygous and heterozygous	MLPA
Jiang, <i>et.al.</i> 2012	vWD 1, vWD 2A, vWD 2M	Heterozygous	CSS
Kasatkar, <i>et.al.</i> 2014	VWD 3	different types	MLPA
Liang, <i>et.al.</i> 2017	vWD 1, vWD 2A, vWD 2M	vWD 3	CSS
Veyradier, <i>et.al.</i> 2016	All types	different types	CSS
Wang, <i>et.al.</i> 2013	vWD 1 , vWD 2N	CSS	CSS
Yadegari, <i>et.al.</i> 2012	All types	different types	CSS and MLPA

CSS; Classical Sanger sequencing, NGS; Next-generation sequencing, MLPA; Multiplex ligation-dependent probe amplification (MLPA).

4. Discussion

All research has demonstrated the completion of mutation detection for vWD using separate techniques. However, the variance within the studies must provide an explanation for the superiority rates of gene mutation screening techniques, highly altered analysis and reduced detection restriction, especially vWF: RCo, unavailability for checks such as; vWF: FVIII B or multimeric evaluation may also lead to misdiagnosis or inefficient vWD diagnosis. In other studies, the study groups were recovered from the common populations where patients were previously recognized with vWD and were asked to collaborate on the medical database control system with or patients with vWD. Analysis of vWD was made second-hand truthful by CSS techniques in most research (Boylan et al., 2015; Jiang et al., 2012; Liang et al., 2017; Veyradier et al., 2016; Wang et al., 2013). Only one research was used the NGS (Battle et al., 2016), even as those studies used MLPT (Hampshire et al., 2013; Kasatkar et al., 2014) but others used CSS in addition to NGS (Fidalgo et al., 2016) or MLPT (Yadegari et al., 2012) to screen VWD mutations. Within the analysis of vWD in research with one exclusion, some consistencies are outstanding having utilization vWF activity and suggested analysis while the patient's genetic evidence is supported on the evaluation of the vWF gene.

At the sub-classifies, the difference in testing in vWD serves; it is highly valuable for discriminating evaluation and finishes proper management in type 2 vWD patients. It would be useful to sort out the distinction between type 2NvWD and hemophilia A, possibly by analyzing the exons that encode the binding region of FVIII (exons 17 to 25). Genetic finding may also be valuable in distinguishing type 2BvWD from blood platelet-type, which is supported by analyzing real exon 28 within the vWF gene. For the best analysis of type 2A and type 2 M vWD, further hereditary finding is critical if multimer evaluation was difficult to perform. Type 2A and type 2 M vWD

genetic analysis may also be helpful in dealing with type 2A that affected the reaction of the person to DDAVP compared to type 2 M patients. Type 3 diagnoses are effectively made based on phenotypic evidence because there is a complete lack of vWF within the plasma. However, hereditary checking out of type three patients may be a necessity for genetic analysis, prenatal diagnosis, and inhibitor form predicting as the gene for mutations should be analyzed is diffuse alongside the vWF gene. On the other hand, the correct diagnosis of type 1 vWD is clinically questionable due to insecure molecular analysis, complication and mutational distinction of the vWF gene due to inadequacy biased of vWF. In some in vitro statement studies, the mutations of many patients have been diagnosed as type 1 to determine whether or not pathogenic variations are crucial as a result of expression analysis for these mutations may be appropriate to distinguish the polymorphisms. The presence of a particular haplotype is probably responsible for the disease phenotype for a few result variations along with R924Q. In addition, it is similar that some 35% of patients in type 1 do not have any alternative vWF gene. Subsequently, in type 1 vWD patients, the presence of defective penetration and complicated pathogenesis are greater barriers to making an association of genotype-phenotype. Although the usefulness of genetic inspection in type 1 vWD is of usefulness, it may be necessary in patients with vWF: Ag < 30 percent and in patients with mutations involving vWF clearing that includes R1205H mutation for type 1 vWD of type 2 vWD (Keeney et al., 2008; Peake et al., 2010; Flavaloro, 2011). Because the results of this gene's incomplete penetration and variable expression were more limited to the mutation analysis for screening techniques in vWD detection research, next technology sequencing and multiplex ligation - dependent sample amplification must be used in the common population in addition to the starting stages of the prognosis as supported by various previous studies (Batlle et al., 2016; Fidalgo et al., 2016).

5. Conclusion

In summary, the VWD gene mutations screening listing we provided, in mixture with recent sequencing techniques and larger studies, may also contribute to appropriately estimate the usage of mutation screening techniques and genome-wide linkage in vWD of complete genome or exome (a part of genome formed with the aid of exons) sequencing (modern technology) might recognize different hereditary determinants of vWD and guide to best our knowledge of vWD by the genotype-phenotype relationship demonstration. This will enhance understanding of vWD in terms of genetic counseling, early analysis, mutation occurrence, clinical evaluation, therapeutic approach, and disease diagnosis. A future study should validate these gene screening techniques for checking in patients and would be useful in interpreting vWD's molecular pathogenesis, which can also more accurately determine the outcome of gene mutations of the affected person.

Conflict of Interest

We declared that they have no conflict of interest

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Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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