

Development of Consensus on Standardized Nomenclature for PT-VWD

Subcommittee: Joint project Platelet Physiology SSC & VWF SSC

Persons responsible:

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Description Abstract

State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

History and nomenclature of diseases are important issues particularly in rare diseases. Some guidance can be driven from Orphanet database (www.orpha.net), which defines a set of rules to be used to promote a correct nomenclature. Nomenclature is generally based on clinical practice and validated by experts of the field, self-sufficient and aims to avoid ambiguity. Consistency and stability are important, but due consideration must be given to the evolution of scientific knowledge.

A guidance on the diagnosis and management of platelet-type von Willebrand Disease (PT-VWD) by the Subcommittee of the ISTH on Platelet Physiology has recently been reported [1].

The first description of this bleeding disorder in four members of one family was made in 1982 by when Dr. Weiss and coworkers identified the basic defect leading to reduced high-molecular-weight VWF forms in plasma in this family in their platelets and proposed the name pseudo-von Willebrand disease [2]. Independently and in the same year Drs. Miller and Castello described another family with the same phenotype and named it Platelet-type von Willebrand disease (PT-VWD) [3]. It is interesting to note that a Japanese group led by Dr. Takahashi began to describe a similar phenotype and indicated the possibility of a new disorder, without naming it, in 1981 [4-5]. In addition to pseudo-VWD [2] and PT-VWD [3], other names have been proposed over the years, including 'VWD-mimic' disorder [6], and 'platelet type pseudo VWD' [7]. Of these, Platelet-type VWD has probably gained the widest acceptance.

The issue of nomenclature in PT-VWD has been discussed on several occasions [8-10]. In a 2007 review [11], we stated that "until a final agreement on nomenclature is reached, we will continue to use the term

platelet-type VWD, since this is the name that attained most popularity”. The first confirmatory evidence this is a genetic platelet bleeding defect was made in 1991 where a gain-of-function- mutation was identified within the VWF binding region of the platelet GPIBA gene [12]; 4 years following the cloning of that gene by Lopez et al, 1987 [13]. GPIba is the major subunit of the platelet GPIb-IX-V complex [14,15]. The name PT-VWD has indeed gained popularity since the description of the first gene mutation. The ISTH PT-VWD registry www.pt-vwd.com has listed 5 single nucleotide mutations within the VWF-binding domain of the GPIb alpha and 1 deletion further down in the macroglycopeptide region, which are likely involved in the pathology of the disease [16]. A 7th mutation also outside the VWF-binding region (in the leucine rich repeats) was just described and functionally characterised [17].

Although the term PT-VWD is in common use, this nomenclature is potentially problematic. The diagnostic pathway of patients with PT-VWD often starts with VWF assays but, as outlined, the disorder is due to a platelet *GPIBA* gain-of-function defect rather than a *VWF* mutation. The therapeutic approaches for patients with PT-VWD are accordingly quite different and management appropriate for those with VWD can be detrimental to patients with PT-VWD, or require extra caution (e.g. DDAVP). For physicians less experienced in haemostasis this subtlety may be lost, resulting in inappropriate use of VWD directed therapies. Through reconsideration of the nomenclature of this condition we hope to delineate the disease as distinct from VWD, with specific diagnostic and management considerations, while recognizing that most PT-VWD are diagnosed following a VWF work up pathway. Ultimately, we hope that this approach will increase awareness, diagnosis and management of this condition and improving patient care.

Another important issue is the mutation nomenclature. This potentially requires re-visiting. Historically and more widely used in literature, an old naming system where numbering starts from the first aa of the mature protein without taking into account the 16 aa signal peptide. This numbering system is also used in all crystal structure and molecular modelling studies. This has created confusion in literature with the standard and ideal name where the Met; the first translated aa, is the first aa. It is also interesting to note, the more common platelet function defect Bernard–Soulier syndrome results from loss-of-function mutations within the same protein; some of which are close to same residues where PT-VWD gain-of-function mutations reside [18]. Whether the disease’ new name needs to accommodate the protein name, or the nature of the functional defect, may require some thoughtful discussion and consideration.

There is a clear need to re-visit the disease’ nomenclature, in view of the evolving scientific landscape. It is also important that we seek contribution from ISTH members and the scientific community particularly since PT-VWD has become a widely used term, before a standardized nomenclature can be established.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

We are planning to launch an expert consensus panel involving the Platelet Physiology and VWF ISTH SSCs to re-examine the nomenclature of the disease. The ISTH registry for this disease has been supported initially by the SSC for VWF and over the years, projects and reporting on this disease have been completed with support from the Platelet physiology SSC (given that the disease is a platelet functional defect). We plan to seek input on a new, widely shared name from the scientific community and ensure to obtain global consensus.

SSC Subcommittee Project/Collaborative Project

Our proposed method involves:

- 1- Establish a working group of both SSCs, and expert collaborators worldwide, to explore issues around nomenclature and synthesize current use and rationale for various names;
- 2- Propose a unified name and definition (disease and mutations) by the working group;
- 3- Design and administer a survey to capture the ISTH members' and scientific community's views;
- 4- Publicise the survey at the next ISTH meeting (ISTH 2021 in Philadelphia / virtual meeting) to encourage broad participation
- 5- Present the findings in both a joint manuscript and at the 2022 ISTH Congress

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Suggested length 2-3 paragraphs

All members of both ISTH SSCs will be involved in developing the consensus. Additionally, several experts named above will be also included as collaborators

Expected timeline:

- 1- Project discussion: virtual meeting (cochairs of both SSCs): Dec 2020 - Apr 2021
- 2- Survey design: May - July 2021
- 3- Discussion: ISTH SSC meeting 2021
- 4- Launch survey - July 2021
- 5- Tabulate results - Sept 2021

Expected outcomes (ie. publications):

Presentation at the ISTH 2021
Joint statement from both SSCs

Publication type (SSC Communication, Guidance document or original article):

SSC Communication

Description of project set/up and management, needed infrastructure and resources (summary):

We would like to set-up 1-2 virtual meetings with chairs and cochairs of both SSCs and collaborators to discuss the nomenclature issues, present the historically debatable issue, proposed names and discuss the pros and cons of each and rationale behind the proposed name (s). Then seek input from the scientific community at ISTH 2021 SSC meetings (Platelet SSC and VWF SSC or a joint session if possible) and via email survey.

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