Update on Platelet-type von Willebrand Disease Registry and Proposed Mechanisms for Newly Reported Mutations

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INTRODUCTION

Gain-of-function mutations in the platelet *GP1BA gene* create a hyper-responsive GPIbα protein- the receptor for von Willebrand factor (VWF) - and cause platelet type von Willebrand disease (PT-VWD); a rare bleeding disorder. Bleeding symptoms are variable and life threatening bleeding may occur during surgeries, pregnancy and child-birth. Correct diagnosis is critical for treatment decision and is negatively influenced by poorly applied/interpreted laboratory tests. Confirmation is made by DNA analysis of the *GP1BA gene.*

AIM

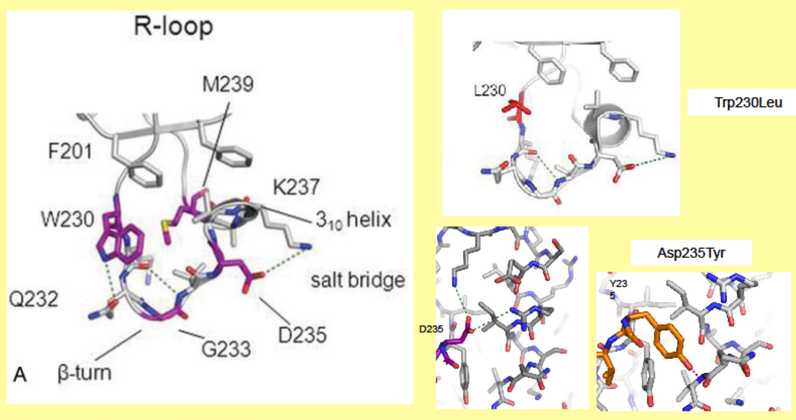
- To provide an update on PT-VWD worldwide registry
- To propose mechanisms to help understand the newly reported mutations

METHODS

- PT-VWD online registry-database created in 2007, supported by the ISTH and available online *www.pt-vwd.org.*
- An open call for participation and submission of mutations and sharing information about diagnosed cases is currently on ISTH website. *https://www.isth.org/?page=collaboration.*
- LOVD mutation submission database *http://www.lovd.nl/3.0/home* is available for submission of new *GP1BA gene* mutations causing PT-VWD.
- Using the crystal structure of GPIbα from the GPIbα-VWFA1 complex as a template, the effects of introducing each of the two new mutations Asp235Tyr (Asp251Tyr) and Trp230Leu (Trp246Leu) mutations into the complex structure were examined. The coordinates for the GPIbα-VWFA1 complex structure were downloaded from the pdb database (pdb code: 1SQ0). (Emsley and Cowtan 2004).

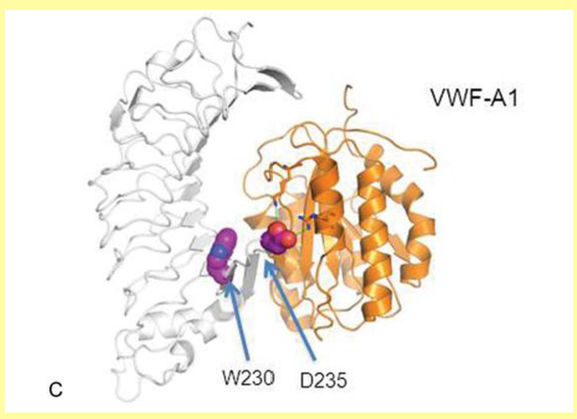
RESULTS

Compact triangular conformation of the R-loop is disrupted in PT-VWD



- *Residues affected by PT-VWD mutations are shown in purple with the β-turn hydrogen bond and the D235-K237 salt bridge shown as green-dotted lines.*
- *The newly characterized PT-VWD residue Trp230Leu (Trp246Leu) may act by disrupting the interactions formed by Trp230 in the R-loop including the hydrogen bond to Gln232 and packing against Met239 thus promote destabilization of the R-Loop*
- *The newly characterized PT-VWD residue Asp235Tyr (Asp251Tyr) mutation acts by disrupting the salt bridge normally existing between Lys237 and Asp235 and thus reducing the stability of the compact triangular form of the R-loop*

GPIbα-VWFA1 complex crystal structure



- *The positions of the residues Trp230 and Asp235 are shown as spheres colored purple.*
- *Residue Trp230 is similar to Met239 in that it does not contact VWF, whereas Asp235 makes direct contacts with the VWFA1 domain shown as green-dotted lines*

PT-VWD Registry 2014

Affected individuals	Gender	GP1BA Nucleotide change	GP1BA Amino acid change	Country	References
7	1F, 6M	G>T 746	Gly 249 Val	USA	Miller et al, 1991
3	2F, 1M	A>G 763	Met 255 Val	Puerto Rico	Russell and Roth 1993 Weiss et al, 1983
4	2F, 2M	A>G 763	Met 255 Val	Japan	Takahashi et al, 1995
2	2M	G>A 746	Gly 249 Ser	Japan	Matsubara et al, 2003
3	3F	1306 del 27	436-444 del 9	UK	Othman et al, 2005
9	9F	G>T 746	Gly 249 Val	UK	Enayat et al, 2006
8	7F, 1M	G>T 746	Gly 249 Val	UK	Whalley and Perry, 2006
2	2F	G>A 746	Gly 249 Ser	France	Nurden et al, 2007
3	3F	G>A 746	Gly 249 Ser	Australia/ New Zealand	Favaloro et al, 2007
1	1F	A>G 763	Met 255 Val	Italy	Giannini et al, 2010
3	2F, 1M	G>T 746	Gly 249 Val	UK	Hamilton et al, 2011
2	2F	G>T 746	Gly 249 Val	Canada	Hamilton et al, 2011
2	1F, 1M	G>T 793	Asp 251 Tyr	Iran	Enayat et al., 2012
1	1F	G>T 746	Gly 249 Val	Ireland UK	O'Donnell, NCC 2011, Unpublished
1	1F	G>T 746	Gly 249 Val	Canada	Rydz 2014, unpublished
1	1M	G>T 3805	Trp 246 Leu	Argentina	Woods et al, 2014
1	1M	A>G 763	Met 255 Val	USA	Acharya 2014, unpublished

Total cases reported so far: 53

Males:16 Females:37

Most frequent mutation: Gly 249 Val (31) Least frequent mutation: Trp 246 Leu (1)

CONCLUSIONS

- Collection of clinical and laboratory data remains challenging.
- Further worldwide collaboration is required for studying phenotypes/genotype relationships.
- Examination of crystal structures provides a framework for forming hypotheses relating to the "sticky" mode of action of PT-VWD missense mutations
- Protein expression studies and kinetic analysis in functional assays

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