## Modulation of von Willebrand Factor Function by Domain C4 Mutations

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von Willebrand factor (VWF) contains functionally critical domains which have been extensively studied in hemostasis and bleeding via molecular and genetic approaches. Flowbased assays have unraveled the importance of the A1A2A3 cluster for VWF function and have validated loss-of-function and gain-of-function VWF variants.<sup>1</sup> Various VWF mutations causing deficient shear stress-regulated unfolding of this cluster showed the importance of the three-dimensional interaction of the VWF A1 domain with its platelet receptor, the glycoprotein Ib (GPIb) complex. Recently, Schneppenheim et al clarified why the common p.Phe2561Tyr VWF variant displays prothrombotic properties at low shear stress, due to a mutation in the VWF C4 domain.<sup>2</sup> In the absence of flow, the mutated domain binds normally to platelet  $\alpha$ IIb $\beta$ 3 via its RGD sequence, the prothrombotic properties of p.Phe2561Tyr VWF being elicited only in response to shear stress. In this issue, Huck et al further elucidated this mechanism, via an elegant study of p. Pro2555Arg VWF, which shear-dependently doubled platelet aggregate size during Cone and Plate aggregometry.<sup>3</sup> The underlying mutation again impacted on dimeric VWF C4 domain interactions with *α*IIbβ3, via a mechanism dictated by more sensitive opening of the zipped VWF stem under increasing shear forces, allowing more pronounced binding of p.Pro2555Arg VWF to allbβ3, which in turn increased platelet aggregate formation. Extensive biochemical and biophysical study of p.Pro2555Arg VWF indeed demonstrated mutant-induced modifications in the dimeric structure of the C-terminal region, triggering increased flexibility in the stem region. Defective VWF function can be compensated for by fibrinogen (fg), but elegant shear stress-dependent assays in the absence or presence of fg and  $\alpha$ IIb $\beta$ 3 neutralization experiments defined the prothrombotic properties for p. Pro2555Arg VWF as a gain-of-function mutant, requiring flow to become operational.<sup>3</sup> In addition to earlier mutations affecting  $k_{on}$  and  $k_{off}$  for VWF A1–GPIb $\alpha$  interactions, this interesting study identifies the VWF C4 domain as a new source of clinically relevant VWF variants.

Conflict of Interest None declared.

## References

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- 2 Schneppenheim R, Hellermann N, Brehm MA, et al. The von Willebrand factor Tyr2561 allele is a gain-of-function variant and a risk factor for early myocardial infarction. Blood 2019; 133(04):356–365
- 3 Huck V, Chen PC, Xu ER, et al. Gain-of-function variant p. Pro2555Arg of von Willebrand factor increases aggregate size through altering stem dynamics. Thromb Haemost 2021. Doi: 10.1055/a-1344-440

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