UKE Paper of the Month Januar 2019

The von Willebrand factor Tyr2561 allele is a gain-of-function variant and a risk factor for early myocardial infarction

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ABSTRACT: The frequent von Willebrand factor (VWF) variant p.Phe2561Tyr is located within the C4 domain, which also harbors the platelet GPIIb/IIIa-binding RGD sequence. To investigate its potential effect on hemostasis, we genotyped 865 patients with coronary artery disease (CAD), 915 with myocardial infarction (MI) and 417 controls (Ludwigshafen Risk and Cardiovascular Health Study (LURIC)) and performed functional studies of this variant. A univariate analysis of male and female carriers of the Tyr2561 allele ≤55 years revealed an elevated risk for repeated MI (odds ratio: 2.53, 95% CI:1.07-5.98). The odds ratio was even higher in females ≤55 years at a value of 5.93 (95% CI:1.12–31.24). Cone and plate aggregometry showed that, compared to Phe2561, Tyr2561 was associated with increased platelet aggregate size both in probands' blood and with the recombinant variants. Microfluidic assays revealed that the critical shear rate for inducing aggregate formation was decreased to 50% by Tyr2561 compared to Phe2561. Differences in C-domain circular dichroism spectra resulting from Tyr2561 suggest an increased shear sensitivity of VWF as a result of altered association of the C-domains that disrupts the normal dimer interface. In summary, our data emphasize the functional impact of the VWF C4-domain for VWF-mediated platelet aggregation in a shear-dependent manner and provide the first evidence that a functional variant of VWF plays a role in arterial thromboembolism.

STATEMENT: *Our paper, which is one of the outputs of our interdisciplinary DFG Research Group FOR1543 has several novel aspects: This is the first time a gain of function (GOF) variant of von Willebrand factor (VWF), a key player in haemostasis and thromboembolism, has been identified, which increases the hemostatic activity of VWF. All previously described VWF-GOF variants were associated with von Willebrand disease, and thus induced bleeding. We have characterized this variant, p.Phe2561Tyr, both functionally and structurally and showed that it is the first variant with increased force sensitivity. At the same time we were able to show that p.Phe2561Tyr is as a novel risk factor for myocardial infarction and probably other arterial thrombotic events through a new force-dependent mechanism. Finally, this variant, located in the VWF C4 domain, harbouring the binding site for the platelet GPIIb/IIIa receptor, emphasizes the VWF C domain region as a new target to prevent*

thromboembolism. Its extended impact on other forms of arterial embolism, in particular on stroke but possibly also on metastasis in cancer is a matter of future research. Our paper was highlighted in BLOOD by a respective commentary.

BACKGROUND: This work was performed at the Laboratories of Pediatric Hematology and Oncology in the group of Reinhard Schneppenheim, who held a professorship at UKE since 1998 and the group of Stefan Schneider, Prof. of Dermatology since 2017. It was carried out in cooperation with Prof. Matthias Wilmanns from the EMBL/DESY associated with the UKE, the LURIC study group and other national and international partners including researchers from INSERM, France and the Mayo Clinic, Rochester, USA. Assessment of the LURIC genetic data was performed by Dr. Hellermann as subject of her thesis at our institution. All groups have a strong interest in the biomechanical mechanisms of VWF in bleeding and thromboembolism.