News Release

Title

Identification of a novel pathogenetic variant in von Willebrand disease (VWD)
—p.Gly2752Ser produces a new molecular pathology of type 3 VWD—

Key Points

- A novel missense variant, *VWF* c8254G→A (p.Gly2752Ser), was identified in a type3 VWD patient.
- VWF-Gly2752Ser is a deleterious variant that impairs dimer formation and causes type 3 VWD by severely impairing VWF secretion. The molecular pathology of VWF-Gly2752Ser involves VWF dimerization failure, resulting in abnormal VWF retention in the endoplasmic reticulum.
- This results suggest that type 3 VWD involves a complex molecular pathogenesis that, cannot be explained by the currently accepted concept of the complete deficiency of VWF.

Summary

The research team led by Professor Tadashi Matsushita has identified a novel pathogenic gene variant, Gly2752Ser, in type 3 von Willebrand disease (VWD), and has investigated its molecular pathogenesis.

von Willebrand factor (VWF) is a large glycoprotein that is mainly synthesized in vascular endothelial cells. It plays a role in platelet adhesion to subendothelial tissues, and acts as a carrier protein of coagulation factor VIII.

VWD is a congenital bleeding disorder caused by qualitative or quantitative abnormalities of VWF due to *VWF* gene variations. It is classified into three major groups according to its etiology. The severest type, type 3 VWD, is characterized by the virtually complete deficiency of VWF. Patients with type 3 VWD need frequent replacement therapy of VWF-containing products frequently.

Prof. Matsushita and his colleagues have noted that the bleeding scores of type 3 VWD patients vary widely, with some patients having mild bleeding symptoms and not requiring frequent replacement therapy. To investigate the reason for this variation, they examined the molecular pathogenesis in a type3 VWD patient with mild bleeding symptoms. As a result, a novel pathological variant, VWF p.Gly2752Ser, was identified. The patient's plasma VWF level was approximately 1.2% of that of normal pooled plasma. In addition, a tiny amount of VWF was detected in the patient's endothelial cells. Overexpression studies of VWF-Gly2752Ser were also conducted to examine the pathogenesis in more detail.

Although type 3 VWD is currently considered to be due to a complete deficiency of VWF, the

study results suggest that it actually involves a more complex and diverse pathogenesis that does not necessarily converge with the notion of a complete deficiency of VWF. It was speculated that this pathogenetic diversity causes a wide range of bleeding symptoms. The results of this study have been published in the *Journal of Thrombosis and Haemostasis.*

Research Background

von Willebrand factor (VWF) is a large glycoprotein that is mainly synthesized in vascular endothelial cells. It plays a role in platelet adhesion to subendothelial tissues, and acts as a carrier protein of coagulation factor VIII. von Willebrand disease (VWD) is a congenital bleeding disorder caused by qualitative or quantitative abnormalities of VWF due to *VWF* gene variations. VWD is classified into three major groups according to its etiology. The severest type, type 3 VWD, is characterized by the virtually complete deficiency of VWF, which is caused by genetic variations with a null phenotype.

Most type 3 VWD patients need to receive replacement therapy with VWF concentrates for their bleeding symptoms. However, some patients have mild bleeding symptoms and do not need frequent infusions. The variation in bleeding symptoms is an interesting point that needs to be considered for the optimization of replacement therapy. Therefore, the molecular characteristics of a type 3 VWD patient with mild bleeding symptoms were investigated.

Research Results

VWF-Gly2752Ser was identified as a novel pathological variant of type 3 VWD. This variant is a missense variant in the CK domain located at the end of the VWF molecule.

The VWF antigen level of the patient in whom VWF-Gly2752Ser was identified was 1.2% of the level of healthy subjects. To examine the expression of VWF in vascular endothelial cells, endothelial colony forming cells (ECFC) were established from the patient's blood. A tiny amount of VWF was detected identified in the ECFC. In addition, a carrier (vector) was created to express the VWF-Gly2752Ser variant in model cell lines such as COS-7 and HEK293. Recombinant VWF-Gly2752Ser was recovered, and its molecular behaviors were analyzed.

Physiologically, VWF monomers dimerize in the endoplasmic reticulum (ER), and the dimers subsequently are multimerize in the Golgi apparatus. The study results revealed that VWF-Gly2752Ser causes impairment in dimerization, resulting in abnormal VWF retention in the ER, which led to defects in the extracellular secretion of VWF.

This study reported on the pathological diversity of type 3 VWD. Only a tiny amount of VWF was produced in the patient with the VWF-Gly2752Ser variant, which may have accounted for the mild hemorrhagic characteristics in this case.

Research Summary and Future Perspective

The results of this study suggest that type 3 VWD does not necessarily involve a complete deficiency of VWF and may include more diverse pathological conditions.

Prof. Matsushita and his colleagues have continued to collect pathophysiological data on type

3 VWD in Japan, including data on bleeding symptoms, variant genes and their products. By utilizing these data, they aim to develop individualized hemostatic treatments by adjusting the applied dose and dosage interval based on the pathological condition of each patient. In the future, Prof. Matsushita and his colleagues plan to identify risk factors of VWF inhibitors, that counteract the effect of supplemented VWF, and to find ways to avoid them. They hope their findings can be applied to help improve the lives of patients with VWD.

Publication

Journal

Journal of Thrombosis and Haemostasis

Title

VWF-Gly2752Ser, a novel non-cysteine substitution variant in the CK domain, exhibits severe secretory impairment by hampering C-terminal dimer formation

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