F8 variant is not sulfonated at Y1699

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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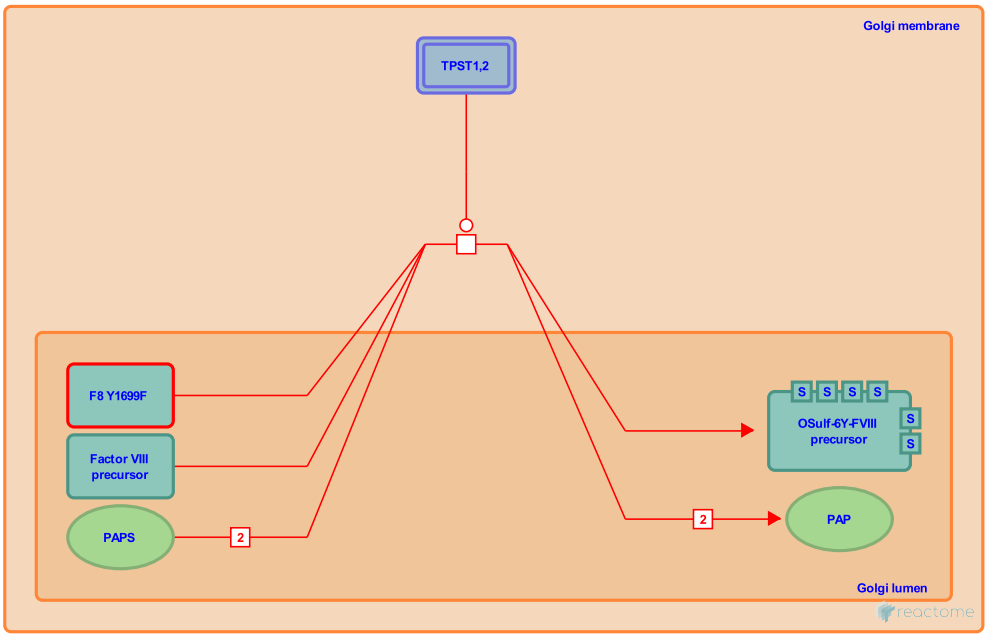
Stable identifier: R-HSA-9668148

Type: transition

Compartments: Golgi lumen, Golgi membrane

Diseases: factor VIII deficiency



Post-translational cellular processing of the factor VIII (FVIII or F8) precursor enables O-sulfation of tyrosine residues (Pittman DD et al. 1992; Michnick DA et al. 1994). Biochemical and structural studies demonstrated that human FVIII contains six potential tyrosine sulfation sites on the FVIII molecule, ie, four on the heavy chain (at amino acid residues 365, 737, 738, and 742) and two in the a3 subdomain of the light chain (residues 1683 and 1699) (Pittman DD et al. 1992; Michnick DA et al. 1994; Severs JC et al. 1999; Schmidbauer S et al. 2015). Site-directed mutagenesis of individual or multiple tyrosine residues showed that all the six sulfation sites are required to modulate FVIII activity (Pittman DD et al. 1992; Michnick DA et al. 1994). Further, mutagenesis of Tyr1699 to Phe (Y1699F) demonstrated that sulfation at that residue was required for high affinity interaction of FVIII with von Willebrand factor (vWF) (Leyte A et al. 1991). In the absence of tyrosine sulfation at 1699 in FVIII, the affinity for vWF was reduced by 5-fold (Leyte A et al. 1991). Nuclear magnetic resonance (NMR) spectrum studies of the complex between FVIII and vWF showed significantly larger residue-specific chemical shift changes when Y1699 was sulfated further highlighting the importance of FVIII sulfation at Y1699 for the binding affinity to vWF (Dagil L et al. 2019). The significance of the sulfation of FVIII at Y1699 in vivo is made evident by the presence of a Y1699F mutation that causes a moderate hemophilia A, likely due to reduced interaction with vWF and decreased plasma half-life (Higuchi M et al. 1990; van den Biggelaar M et al. 2011). The Reactome event describes defective O-sulfation of FVIII precursor due to mutation at Y1699.

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Editions

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