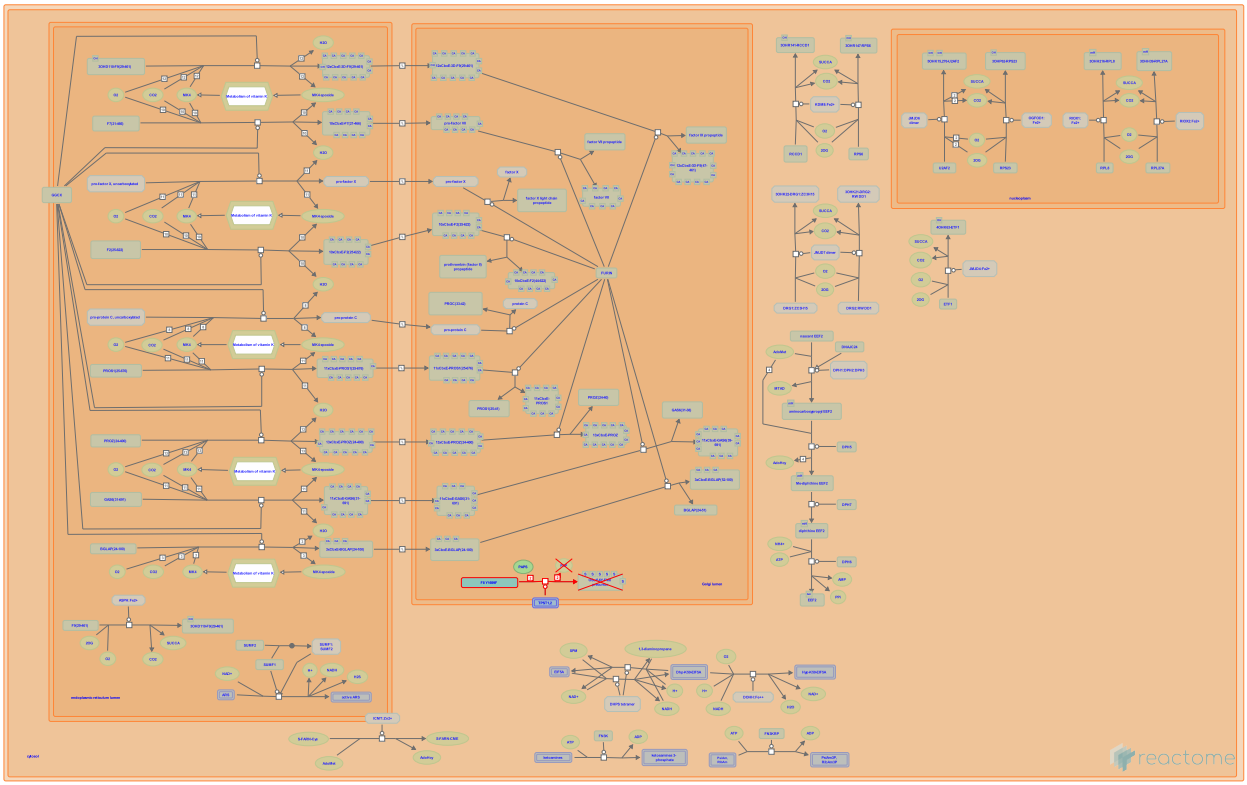
Defective F8 sulfation at Y1699



D'Eustachio, P., Shamovsky, V., Zhang, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

10/10/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

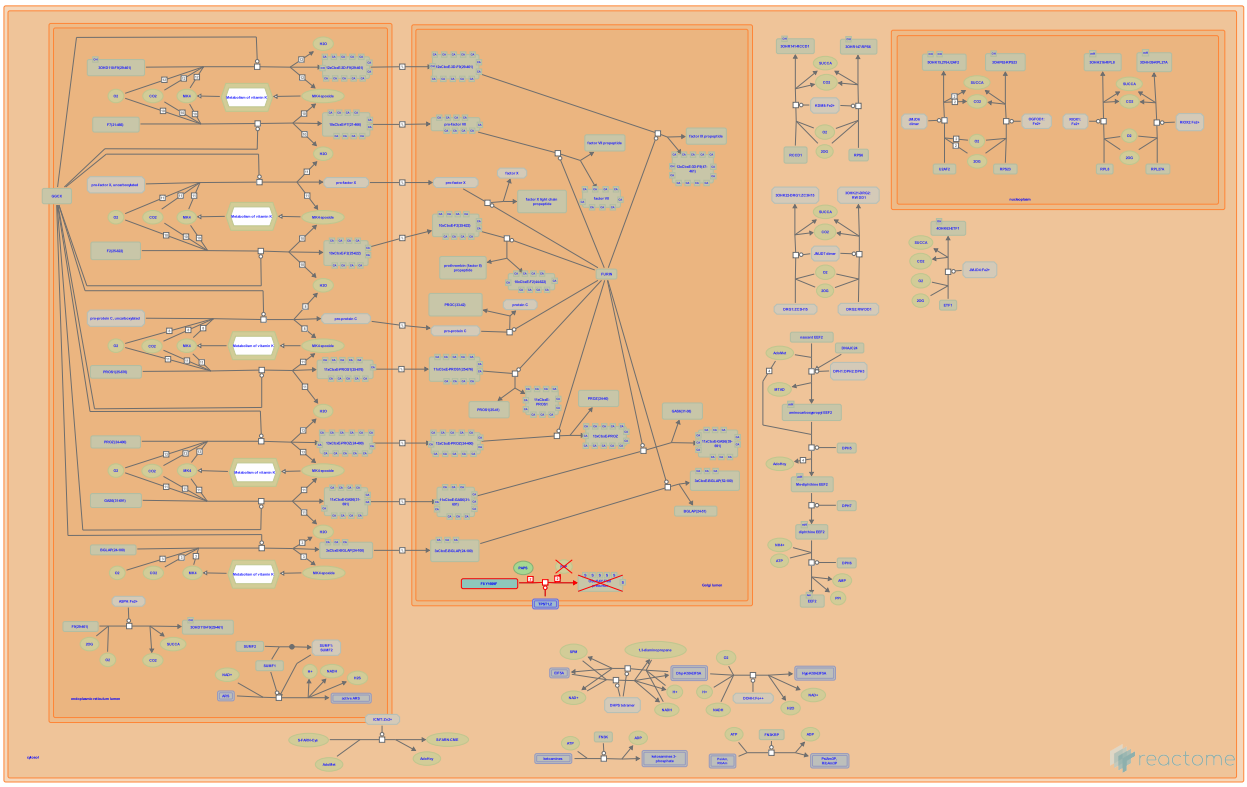
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Defective F8 sulfation at Y1699 ↗

Stable identifier: R-HSA-9674519

Diseases: factor VIII deficiency



Hemophilia A (HA) is a bleeding disorder caused by lack of or a defective factor VIII (FVIII) protein and results from defects in the F8 gene (Peyvandi F et al. 2016).

In healthy individuals, FVIII is synthesized as a large glycoprotein of 2351 amino acids with a discrete domain structure: A1-A2-B-A3-C1-C2 (Wood WI et al. 1984; Vehar GA et al. 1984; Toole JJ et al. 1984). Upon synthesis, FVIII is translocated into the lumen of the endoplasmic reticulum (ER), where it undergoes extensive processing including cleavage of a signal peptide and N-linked glycosylation at asparagine residues (Kaufman RJ et al. 1988, 1997; Kaufman RJ 1998). In the ER lumen of mammalian cells FVIII interacts with the protein chaperones calnexin (CNX), calreticulin (CRT), and immunoglobulin-binding protein (BiP or GRP78) that facilitate proper folding of proteins prior to trafficking to the Golgi compartment (Marquette KA et al. 1995; Swaroop M et al. 1997; Pipe SW et al. 1998; Kaufman RJ et al. 1997; Kaufman RJ 1998). Trafficking from the ER to the Golgi compartment is facilitated by LMAN1 and multiple combined factor deficiency 2 (MCFD2) cargo receptor complex (Zhang B et al. 2005; Zheng, C et al. 2010, 2013). Within the Golgi apparatus, FVIII is subject to further processing, including modification of the N-linked oligosaccharides to complex-type structures, O-linked glycosylation, and sulfation of specific Tyr-residues (Kaufman RJ 1998). Upon secretion from the cell, FVIII is cleaved at two sites in the B-domain to form a heterodimer consisting of the heavy chain containing the A1-A2-B domains in a metal ion-dependent complex with the light chain consisting of the A3-C1-C2 domains (Kaufman RJ et al. 1997; Kaufman RJ 1998).

The Reactome event describes defects within the secretory pathway due to mutations in the F8 gene that can impair FVIII synthesis, folding, intracellular processing and transport which result in a lack or reduced levels of the plasma FVIII protein. The module includes also an event of defective post-translational tyrosine sulfonation of FVIII in the Golgi apparatus that is required for the optimal interaction between the secreted FVIII and the von Willebrand factor (VWF).

Literature references

Huttner, WB., Leyte, A., van Mourik, JA., van Schijndel, HB., Niehrs, C., Verbeet, MP. et al. (1991). Sulfation of Tyr1680 of human blood coagulation factor VIII is essential for the interaction of factor VIII with von Willebrand factor. *J. Biol. Chem., 266*, 740-6. ↗

Editions

2019-09-09	Authored	Shamovsky, V.
2020-01-09	Reviewed	D'Eustachio, P.
2020-04-02	Reviewed	Zhang, B.
2020-05-26	Edited	Shamovsky, V.

F8 variant is not sulfonated at Y1699 ↗

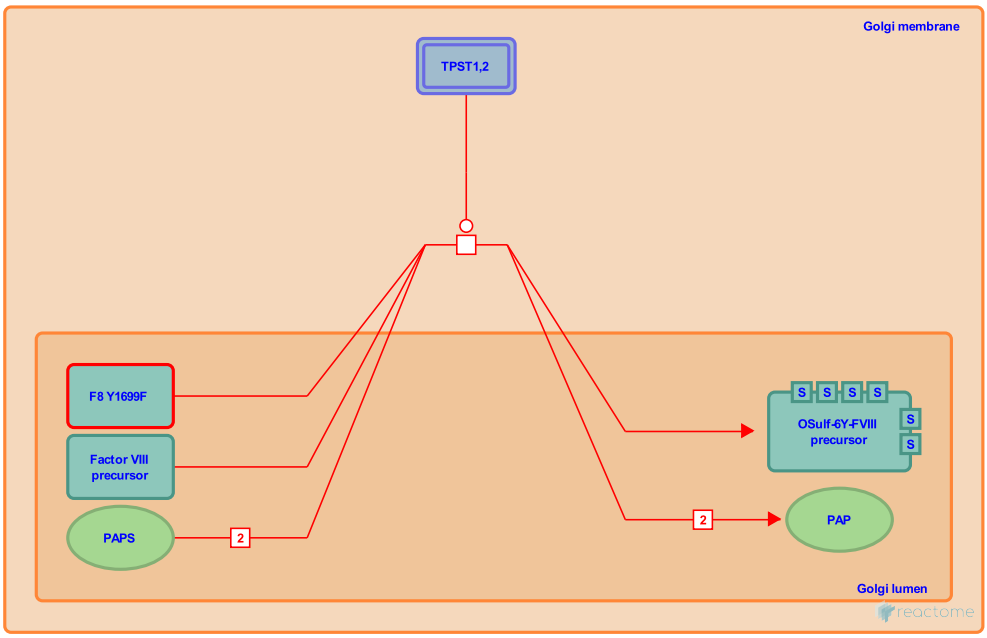
Location: Defective F8 sulfation at Y1699

Stable identifier: R-HSA-9668148

Type: transition

Compartments: Golgi membrane, Golgi lumen

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.

Literature references

Pittman, DD., Kaufman, RJ., Wang, JH. (1992). Identification and functional importance of tyrosine sulfate residues within recombinant factor VIII. *Biochemistry, 31*, 3315-25. ↗

Huttner, WB., Leyte, A., van Mourik, JA., van Schijndel, HB., Niehrs, C., Verbeet, MP. et al. (1991). Sulfation of Tyr1680 of human blood coagulation factor VIII is essential for the interaction of factor VIII with von Willebrand factor. *J. Biol. Chem., 266*, 740-6. ↗

Pittman, DD., Kaufman, RJ., Wise, RJ., Michnick, DA. (1994). Identification of individual tyrosine sulfation sites within factor VIII required for optimal activity and efficient thrombin cleavage. *J. Biol. Chem., 269*, 20095-102. ↗

Editions

2019-09-09	Authored	Shamovsky, V.
2020-01-09	Reviewed	D'Eustachio, P.
2020-04-02	Reviewed	Zhang, B.
2020-05-26	Edited	Shamovsky, V.

Table of Contents