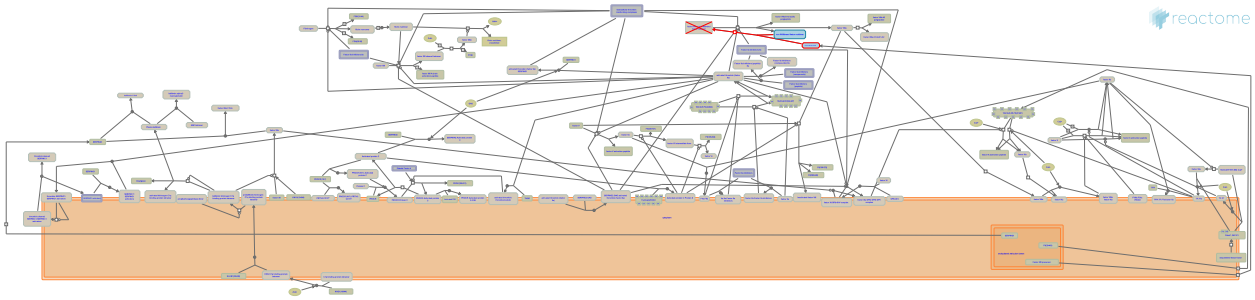
Defective F8 binding to von Willebrand factor



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.

14/10/2024

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. ↗

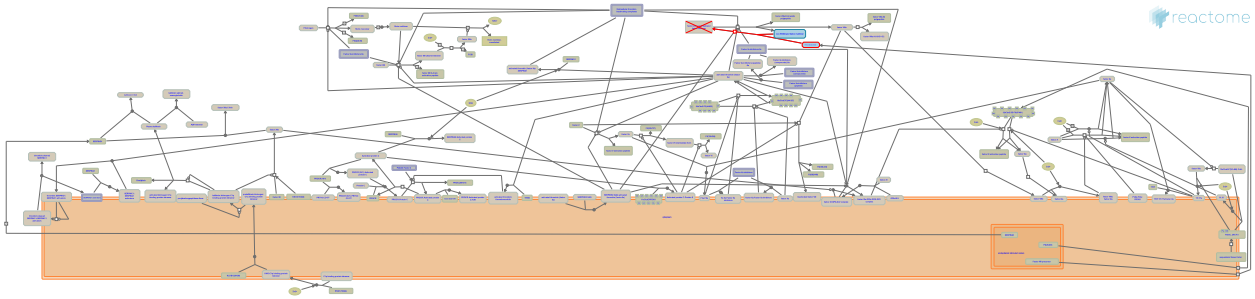
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Defective F8 binding to von Willebrand factor ↗

Stable identifier: R-HSA-9672393

Compartments: extracellular region

Diseases: factor VIII deficiency



Upon secretion from the cell, FVIII circulates in a tight complex with the multimeric glycoprotein von Willebrand Factor (vWF), which is essential for maintaining stable levels of FVIII in the circulation (reviewed by Pipe SW et al. 2016). Genetic mutations in the F8 gene can compromise FVIII binding to vWF thus decreasing FVIII values in the plasma causing hemophilia A (HA), an X-linked recessive bleeding disorder.

Literature references

Spiegel, PC., Stoddard, BL., Murphy, P. (2004). Surface-exposed hemophilic mutations across the factor VIII C2 domain have variable effects on stability and binding activities. *J. Biol. Chem., 279*, 53691-8. ↗

d'Oiron, R., Lavend'homme, R., Lavergne, JM., Jacquemin, M., Vermylen, J., Negrier, C. et al. (2004). Deletion of alanine 2201 in the FVIII C2 domain results in mild hemophilia A by impairing FVIII binding to VWF and phospholipids and destroys a major FVIII antigenic determinant involved in inhibitor development. *Blood, 103*, 155-7. ↗

Saint-Remy, JM., Gilles, JG., Schwaab, R., Jacquemin, M., Peerlinck, K., Vanzieleghem, B. et al. (2000). A novel cause of mild/moderate hemophilia A: mutations scattered in the factor VIII C1 domain reduce factor VIII binding to von Willebrand factor. *Blood, 96*, 958-65. ↗

Voorberg, J., Bouwens, EA., van den Biggelaar, M., Mertens, K. (2011). Storage of factor VIII variants with impaired von Willebrand factor binding in Weibel-Palade bodies in endothelial cells. *PLoS ONE, 6*, e24163. ↗

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 does not bind von Willebrand factor ↗

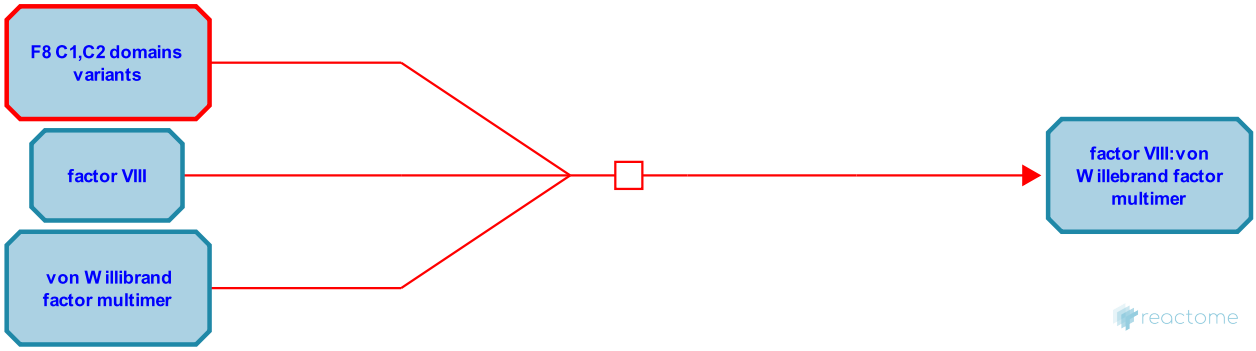
Location: Defective F8 binding to von Willebrand factor

Stable identifier: R-HSA-9665809

Type: transition

Compartments: extracellular region

Diseases: factor VIII deficiency



Coagulation factor VIII (FVIII) encoded by the F8 gene is synthesized as a 19 amino acid signal peptide followed by 2332 amino acids and includes the A1-A2-B-A3-C1-C2 structural domains (Toole JJ et al. 1984; Wood WI et al. 1984). 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 heterodimer circulates in a tight complex with the multimeric glycoprotein von Willebrand Factor (vWF), which is essential for maintaining stable levels of FVIII in the circulation (reviewed by Pipe SW et al. 2016). The structurally homologous C1 and C2 domains of FVIII are believed to have specific functions in interactions with vWF (Pratt KP et al. 1999; Jacquemin M et al. 2000a,b; Ebberink EH et al. 2017). The acidic subdomain a3 of the light chain also controls FVIII binding to vWF (Saenko EL & Scandella D 1997; Dagil L et al. 2019). Sulfation at Tyr1699 in the a3 subdomain was required for high affinity interaction with vWF (Leyte A et al. 1991).

Genetic mutations in the F8 gene can compromise FVIII binding to vWF thus decreasing FVIII values in the plasma causing hemophilia A (HEMA), an X-linked recessive bleeding disorder (Higuchi M et al. 1990; Liu ML et L. 2000; Jacquemin M et al. 2000b; Spiegel PC et al. 2004; d'Oiron R et al. 2004; van den Biggelaar M et al. 2011; Yada K et al. 2015). This Reactome event describes reduced FVIII interaction with vWF caused by the defective Tyr1699 sulfation site (Y1699F) in a3 of FVIII or by mutations in the C domains of FVIII (S2138Y, P2319L, R2169H, R2323H etc.) found in HEMA patients.

Literature references

Spiegel, PC., Stoddard, BL., Murphy, P. (2004). Surface-exposed hemophilic mutations across the factor VIII C2 domain have variable effects on stability and binding activities. *J. Biol. Chem., 279*, 53691-8. ↗

d'Oiron, R., Lavend'homme, R., Lavergne, JM., Jacquemin, M., Vermylen, J., Negrier, C. et al. (2004). Deletion of alanine 2201 in the FVIII C2 domain results in mild hemophilia A by impairing FVIII binding to VWF and phospholipids and destroys a major FVIII antigenic determinant involved in inhibitor development. *Blood, 103*, 155-7. ↗

Saint-Remy, JM., Gilles, JG., Schwaab, R., Jacquemin, M., Peerlinck, K., Vanzieleghem, B. et al. (2000). A novel cause of mild/moderate hemophilia A: mutations scattered in the factor VIII C1 domain reduce factor VIII binding to von Willebrand factor. *Blood, 96*, 958-65. ↗

Voorberg, J., Bouwens, EA., van den Biggelaar, M., Mertens, K. (2011). Storage of factor VIII variants with impaired von Willebrand factor binding in Weibel-Palade bodies in endothelial cells. *PLoS ONE, 6*, e24163. ↗

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