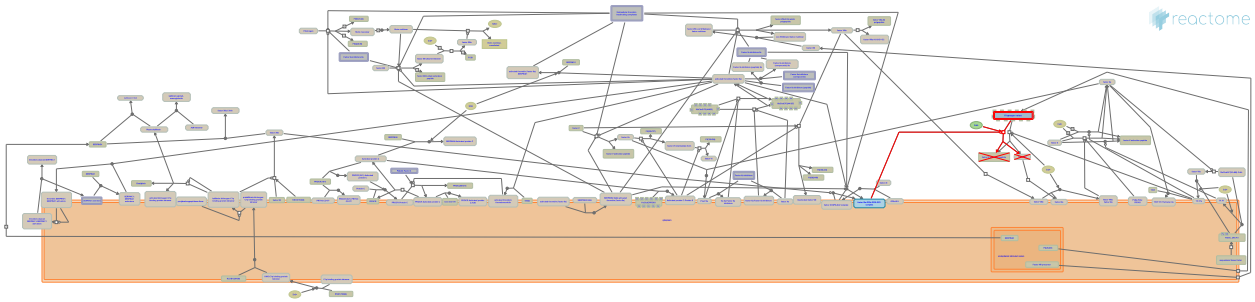
Defective F9 activation



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.

20/05/2024

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. ↗

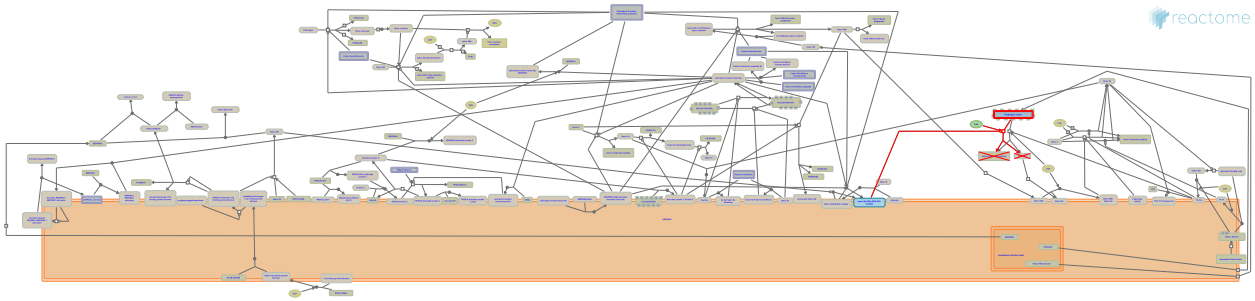
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 F9 activation ↗

Stable identifier: R-HSA-9673221

Diseases: hemophilia B



Deficiency or dysfunction of FIX leads to hemophilia B (HB), an X-linked, recessive, bleeding disorder. On a molecular basis, HB is due to a heterogeneous spectrum of mutations spread throughout the F9 gene (Rallapalli PM et al. 2013).

The Reactome event describes the defective proteolytic activation of FIX by factor XIa due to the presence of HB-associated point mutations R191C, R191H, R226Q and R226W in the cleavage sites of FIX (Liddell MB et al. 1989; Monroe DM et al. 1989; Suehiro K et al. 1989; Diuguid DL et al. 1989; Bertina RM et al.1990). In addition, naturally occurring point mutations in the FIX propeptide sequence such as N43Q, N43L or N46S are also annotated here. These FIX variants are secreted into the circulation with a mutant 18-amino acid propeptide still attached (Bentley AK et al. 1986; Galeffi P & Brownlee GG 1987). The unprocessed FIX variants were found to affect the function of the protein by destabilizing the calcium-induced conformation of FIX (Wojcik EG et al. 1997) and showed delayed activation by FXIa (Liddell MB et al. 1989; Ware J et al. 1989; de la Salle C et al. 1993; Wojcik EG et al. 1997; Bristol JA et al. 1993).

Literature references

Furie, B., Stafford, DW., Diuguid, DL., Liebman, HA., Rabiet, MJ., Ware, J. et al. (1989). Factor IX San Dimas. Substitution of glutamine for Arg-4 in the propeptide leads to incomplete gamma-carboxylation and altered phospholipid binding properties. *J Biol Chem, 264*, 11401-6. ↗

Giddings, JC., Bloom, AL., Peake, IR., Lillicrap, DP., Taylor, SA., Liddell, MB. (1989). Factor IX Cardiff: a variant factor IX protein that shows abnormal activation is caused by an arginine to cysteine substitution at position 145. *Br. J. Haematol., 72*, 556-60. ↗

Lundblad, RL., Roberts, HR., McCord, DM., High, KA., Huang, MN., Kasper, CK. et al. (1989). Functional consequences of an arginine180 to glutamine mutation in factor IX Hilo. *Blood, 73*, 1540-4. ↗

Niho, Y., Suehiro, K., Saito, H., Ogata, K., Takeya, H., Kawabata, S. et al. (1989). Blood clotting factor IX BM Nagoya. Substitution of arginine 180 by tryptophan and its activation by alpha-chymotrypsin and rat mast cell chymase. *J. Biol. Chem., 264*, 21257-65. ↗

Bentley, AK., Brownlee, GG., Rizza, C., Rees, DJ. (1986). Defective propeptide processing of blood clotting factor IX caused by mutation of arginine to glutamine at position -4. *Cell, 45*, 343-8. ↗

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.

FIX(29-461) variant is not activated (factor XIa catalyst)

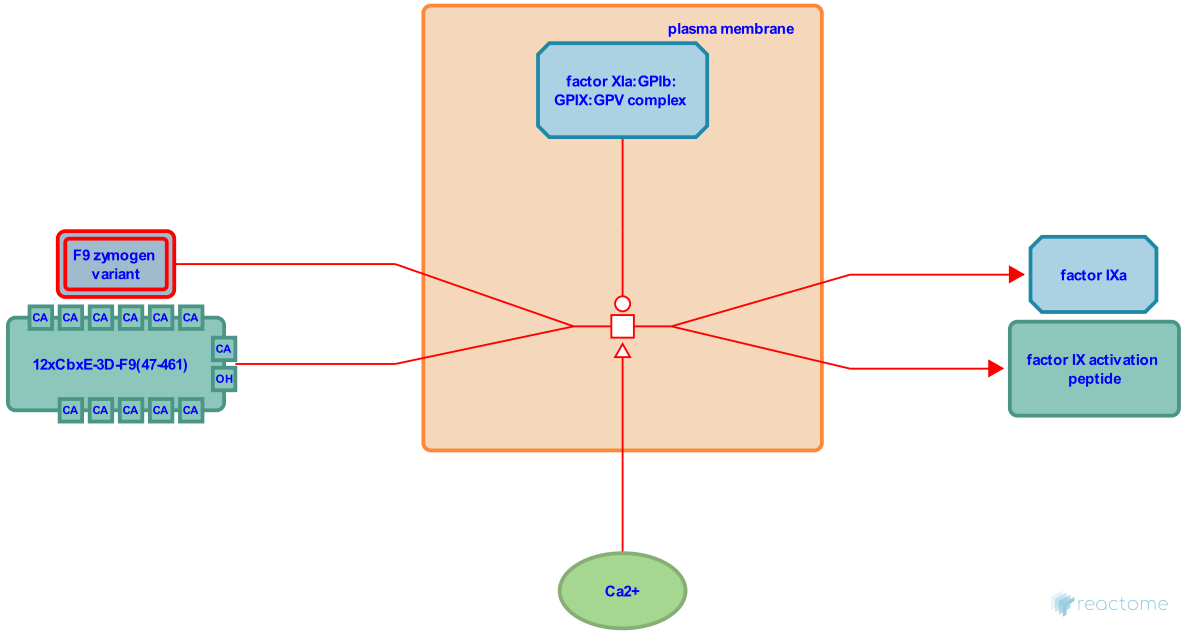
Location: Defective F9 activation

Stable identifier: R-HSA-9673223

Type: transition

Compartments: plasma membrane, extracellular region

Diseases: hemophilia B



In healthy individuals, conversion of factor IX (FIX) to the activated FIX is a calcium-dependent process catalyzed by factor VIIa (FVIIa) in the presence of tissue factor and phosphatidyl serine-rich phospholipid (Vadivel K & Bajaj SP 2012) or by factor XIa (FXIa) in a phospholipid-independent reaction (Wolberg AS et al. 1997; Smith SB et al. 2008; Geng Y et al. 2012). Regardless of the activating protease, FIX is cleaved first after Arg191 (R191-A192, the α-cleavage) forming the intermediate FIX product, then after the residue 226 (R226-V227, the β-cleavage) to form the activated FIXa (FIXaβ) (Smith SB et al. 2008; Geng Y et al. 2012; Mohammed BM et al. 2018). Deficiency or dysfunction of FIX leads to hemophilia B (HB), an X-linked, recessive, bleeding disorder. On a molecular level, HB is due to a heterogeneous spectrum of mutations spread throughout the F9 gene (Rallapalli PM et al. 2013).

The Reactome event describes the defective proteolytic activation of FIX by factor XIa due to the presence of HB-associated point mutations R191C, R191H, R226Q and R226W in the cleavage sites of FIX (Liddell MB et al. 1989; Monroe DM et al. 1989; Suehiro K et al. 1989; Diuguid DL et al. 1989; Bertina RM et al.1990). In addition, naturally occurring point mutations in the FIX propeptide sequence such as R43Q, R43L or R46S are also annotated here. These FIX variants are secreted into the circulation with a mutant 18-amino acid propeptide still attached (Bentley AK et al. 1986; Galeffi P & Brownlee GG 1987). The unprocessed FIX variants were found to affect the function of the protein by destabilizing the calcium-induced conformation of FIX (Wojcik EG et al. 1997) and showed delayed activation by FXIa (Liddell MB et al. 1989; Ware J et al. 1989; de la Salle C et al. 1993; Wojcik EG et al. 1997; Bristol JA et al. 1993).

Literature references

Furie, B., Bristol, JA., Furie, BC. (1993). Propeptide processing during factor IX biosynthesis. Effect of point mutations adjacent to the propeptide cleavage site. *J Biol Chem, 268*, 7577-84.

Furie, B., Stafford, DW., Diuguid, DL., Liebman, HA., Rabiet, MJ., Ware, J. et al. (1989). Factor IX San Dimas. Substitution of glutamine for Arg-4 in the propeptide leads to incomplete gamma-carboxylation and altered phospholipid binding properties. *J Biol Chem, 264*, 11401-6.

Giddings, JC., Bloom, AL., Peake, IR., Lillicrap, DP., Taylor, SA., Liddell, MB. (1989). Factor IX Cardiff: a variant factor IX protein that shows abnormal activation is caused by an arginine to cysteine substitution at position 145. *Br. J. Haematol., 72*, 556-60. ↗

Diuguid, DL., Furie, BC., Rabiet, MJ., Furie, B. (1989). Molecular defects of factor IX Chicago-2 (Arg 145----His) and prothrombin Madrid (Arg 271----cys): arginine mutations that preclude zymogen activation. *Blood, 74*, 193-200. ↗

Reitsma, PH., Poort, SR., Mannucci, PM., van der Linden, IK., Bertina, RM., Reinalda-Poot, HH. et al. (1990). Mutations in hemophilia Bm occur at the Arg180-Val activation site or in the catalytic domain of factor IX. *J. Biol. Chem., 265*, 10876-83. ↗

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