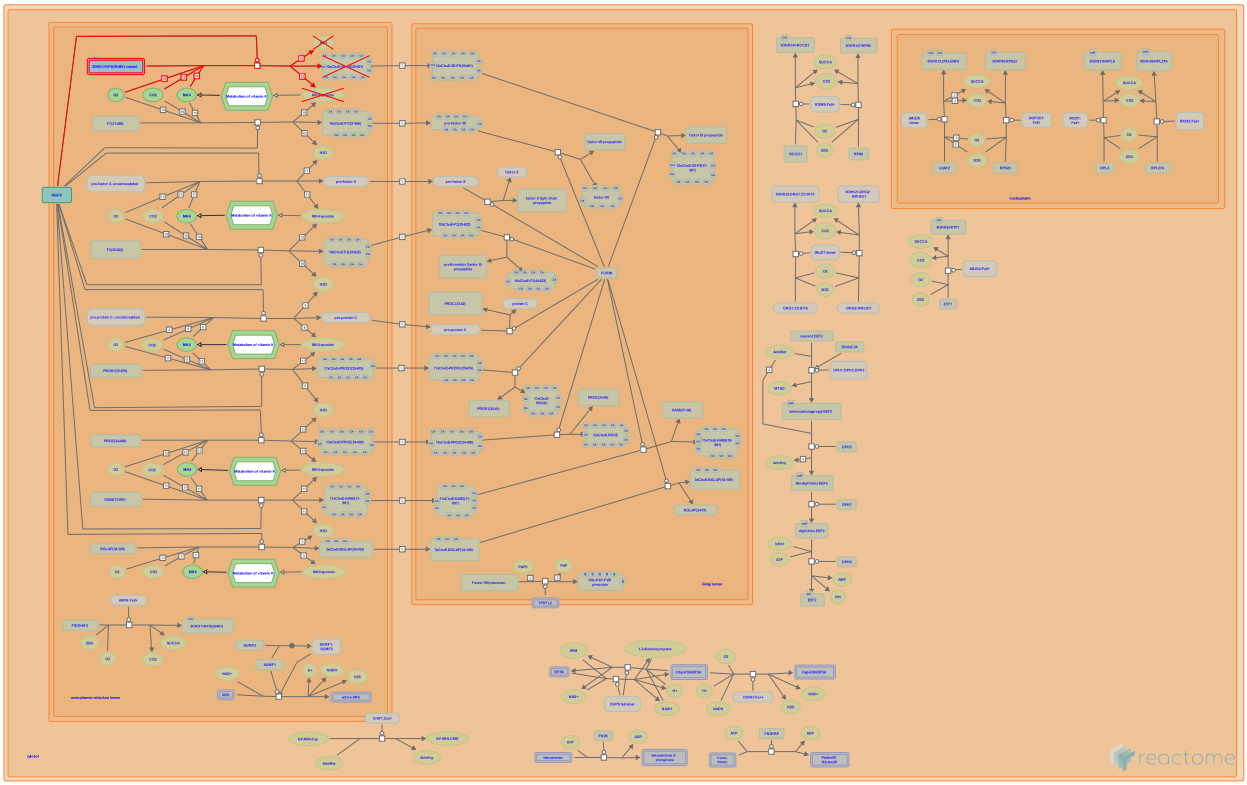
Defective gamma-carboxylation of F9



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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.

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.

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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. ↗

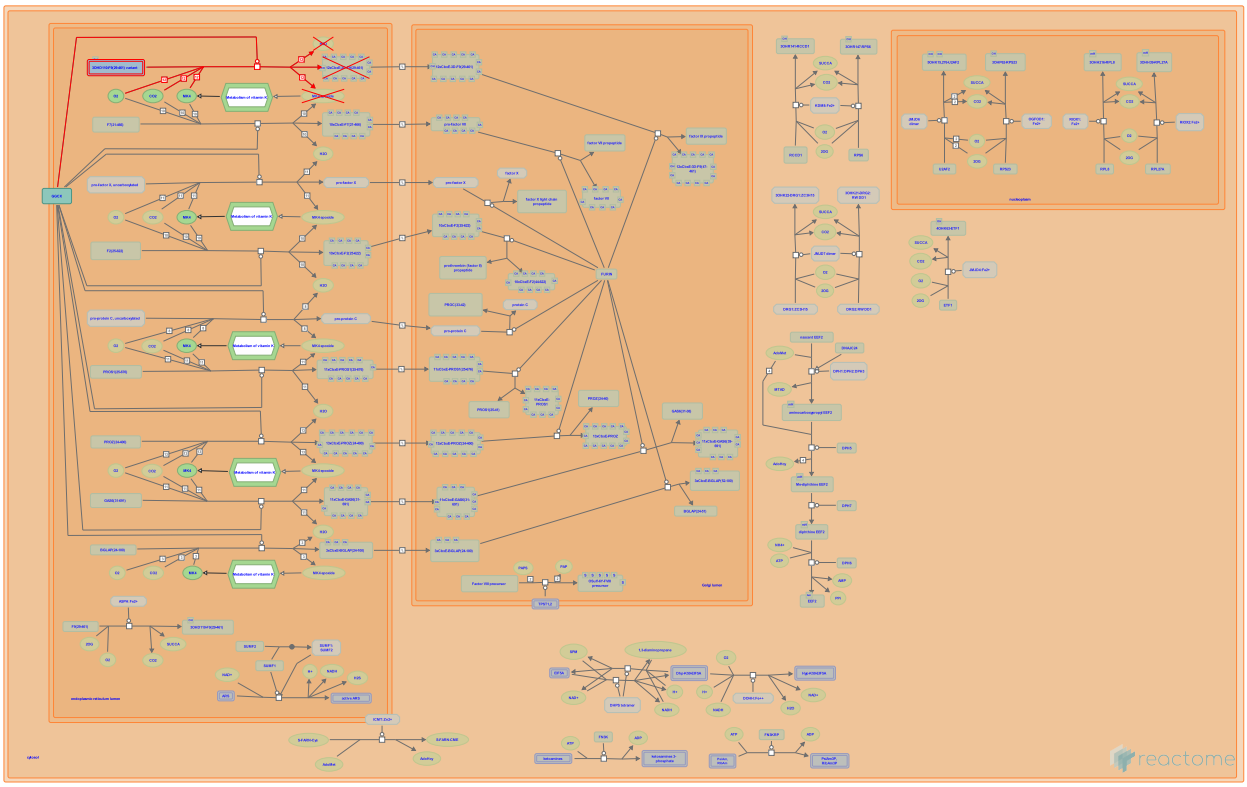
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 gamma-carboxylation of F9 ↗

Stable identifier: R-HSA-9673240

Diseases: hemophilia B



Naturally occurring hemophilia B (HB)-associated point mutations in the FIX propeptide sequence reduce affinity to gamma-glutamyl carboxylase (GGCX) resulting in reduced γ-carboxylation and aberrant propeptide processing (Bentley AK et al. 1986; Rabiet MJ et al. 1987; Diuguid DL et al. 1986; Ware J et al. 1989; de la Salle C et al. 1993). Unprocessed FIX variants such as F9 N43Q/L or F9 N46S, circulate with the attached propeptide and show delayed FIX activation (Bentley AK et al. 1986; Diuguid DL et al. 1986; Ware J et al. 1989; de la Salle C 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. ↗

Jorgensen, MJ., Furie, BC., Rabiet, MJ., Furie, B. (1987). Effect of propeptide mutations on post-translational processing of factor IX. Evidence that beta-hydroxylation and gamma-carboxylation are independent events. *J. Biol. Chem., 262*, 14895-8. ↗

Bischoff, R., Charmantier, JL., Hartmann, ML., Roecklin, D., de la Salle, C., Ohlmann, P. et al. (1993). The Arg-4 mutant factor IX Strasbourg 2 shows a delayed activation by factor XIa. *Nouv Rev Fr Hematol, 35*, 473-80. ↗

Van Den Berg, M., Wojcik, EG., Poort, SR., Bertina, RM. (1997). Modification of the N-terminus of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation: effects on phospholipid binding and activation by factor XIa. *Biochem. J., 323*, 629-36. ↗

Bloom, AL., Peake, IR., Lillicrap, DP., Liddell, MB. (1989). Defective propeptide processing and abnormal activation underlie the molecular pathology of factor IX Troed-y-Rhiw. *Br. J. Haematol., 72*, 208-15. ↗

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2020-05-26	Edited	Shamovsky, V.

GGCX does not gamma-carboxylate 3D-F9(29-461) (pro-factor IX) ↗

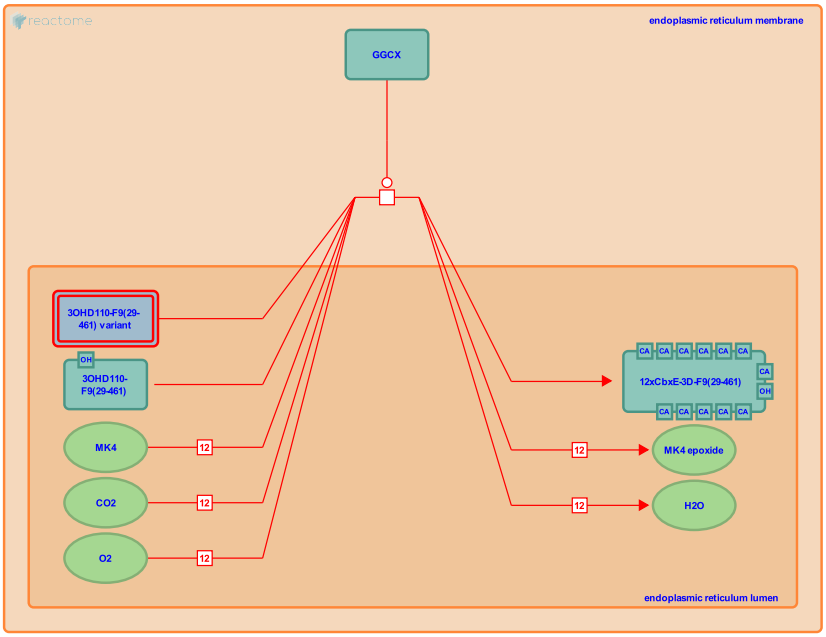
Location: Defective gamma-carboxylation of F9

Stable identifier: R-HSA-9673231

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen

Diseases: hemophilia B



Being a vitamin K-dependent (VKD) glycoprotein, factor IX (FIX) is synthesized first as a precursor protein which then undergoes extensive posttranslational modification including γ-carboxylation. The precursor FIX protein has the following parts, starting with a signal peptide at the amino-terminal end, which directs the protein to the endoplasmic reticulum (ER), and continuing with the 18 residue length propeptide. The propeptide contains the γ-carboxylase recognition site (γ-CRS) in the N-terminal part of the propeptide for connecting substrate to the gamma-glutamyl carboxylase (GGCX), and a peptidase recognition site in the C-terminal for cleaving by PACE/furin (Higgins-Gruber SL et al. 2010). GGCX in the ER γ-carboxylates twelve glutamate residues on F9(29-461) (pro-factor IX) converting the specific glutamic acids in the GLA domain to γ-carboxyglutamic acid residues. MK4 (vitamin K hydroquinone) is oxidized to MK4 epoxide in the process (Berkner KL 2000; Furie B et al. 1999; Stenina O et al. 2001; Morris DP et al. 1995; Ware J et al. 1989). The signal peptide and the propeptide sequence of FIX are removed before the protein is secreted into the circulation,

Naturally occurring hemophilia B (HB)-associated point mutations in the FIX propeptide sequence such as F9 N43Q/L or F9 N46S reduce affinity to GGCX resulting in reduced γ-carboxylation and aberrant propeptide processing (Bentley AK et al. 1986; Rabiet MJ et al. 1987; Diuguid DL et al. 1986; Ware J et al. 1989; de la Salle C et al. 1993). 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). However, unprocessed FIX variants showed altered phospholipid binding properties and delayed activation by factor XIa (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, 1994). In addition, beta-hydroxylation of aspartic acid 110 (D110) is an independent process which does not require vitamin K and is mediated through a hydroxylation recognition site in the mature Factor IX, not in the propeptide (Rabiet MJ et al. 1987).

The Reactome event describes defective γ-carboxylation of FIX variants due to HB-associated genetic defects in the propeptide sequence of the F9 gene.

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. ↗

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