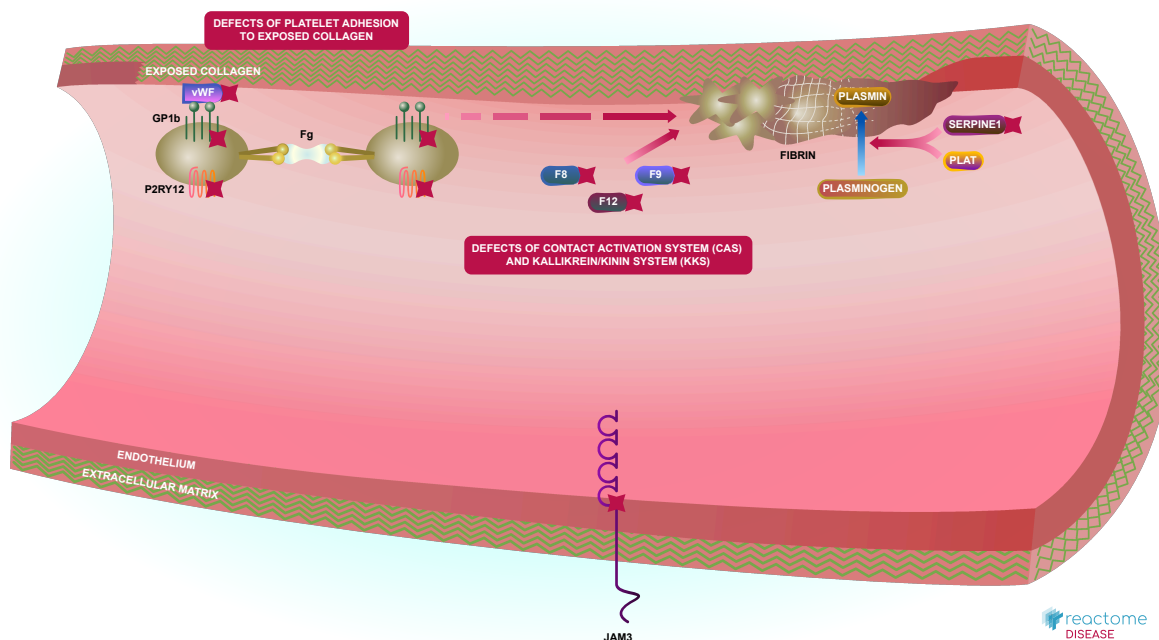


Diseases of hemostasis



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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](https://reactome.org/page/faq).

16/10/2024

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).

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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. [↗](#)

Reactome database release: 90

This document contains 3 pathways ([see Table of Contents](#))

Kumar, R., Carcao, M. (2013). Inherited abnormalities of coagulation: hemophilia, von Willebrand disease, and beyond. *Pediatr. Clin. North Am.*, 60, 1419-41. [↗](#)

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.
2023-11-09	Reviewed	Matthews, L.

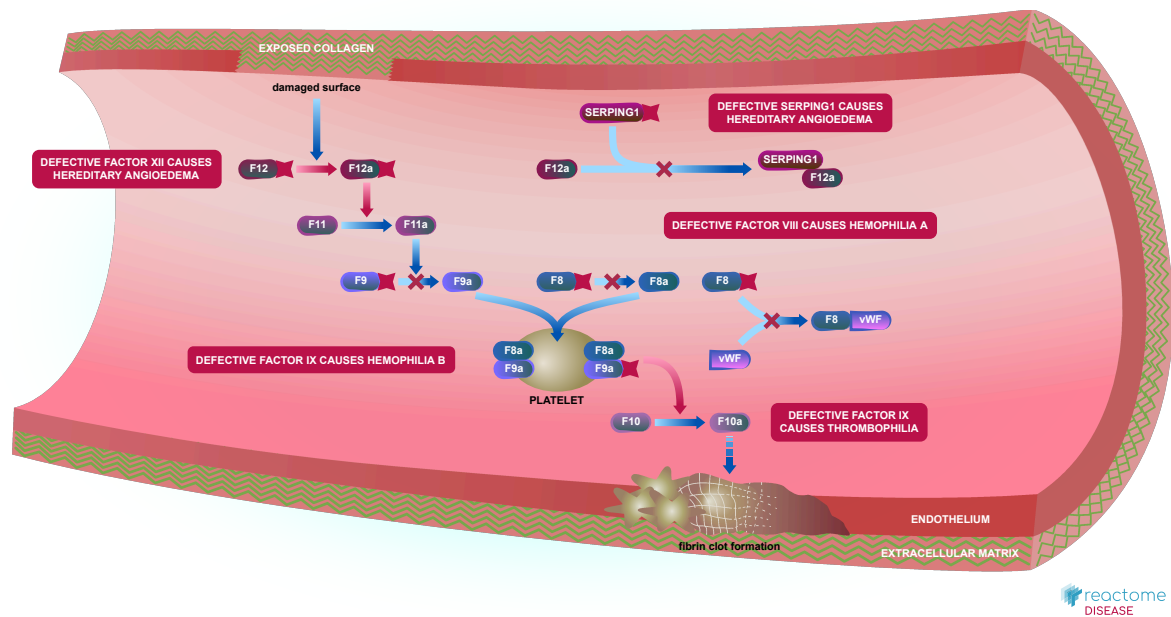
Defects of contact activation system (CAS) and kallikrein/kinin system (KKS) ↗

Location: Diseases of hemostasis

Stable identifier: R-HSA-9651496

Compartments: extracellular region

Diseases: C1 inhibitor deficiency, hereditary angioedema, thrombophilia, factor VIII deficiency, hemophilia B



The contact activation system (CAS) is a plasma protease cascade initiated by factor XII (FXII) that activates the pro-inflammatory kallikrein-kinin system (KKS) and the pro-coagulant intrinsic coagulation pathway (Renne T 2012; Renne T et al. 2012; Maas C et al. 2011; Schmaier AH 2016; Long AT et al. 2016). The CAS is initiated by the auto-activation of factor XII (FXII) on charged or neutral surfaces with conversion of plasma prekallikrein (PK) to plasma kallikrein (Samuel M et al. 1992; Ivanov I et al. 2017). These events are followed by reciprocal activation of FXII by kallikrein and amplification of each other's activation. Two branches of the CAS have been identified: (i) the inflammatory branch activates contact factors FXII and PK on the surface of endothelial cells resulting in release of the peptide bradykinin (BK) and (ii) the plasma coagulation branch activates FXII and FXI on the surface of platelets. The CAS is thought to be central to crosstalk between coagulation and inflammation and the underlying cause for various disorders affecting the cardiovascular system (Wu Y 2015; Long AT et al. 2016). Physiologically, a fine balance is normally maintained between blood flow and blood clotting, the dysfunction of which yields either hemorrhage or thrombosis. Defects in the intrinsic pathway coagulation factors (FVIII, FIX, and FXI) are associated with a significant bleeding tendency. The X-linked recessive disorders, hemophilia A (FVIII deficiency) and B (FIX deficiency), are associated with spontaneous and excessive hemorrhage, especially hemarthroses and muscle hematomas (Bowen DJ 2002; Goodeve AC 2015). A deficiency in FXI, which is encoded by a gene on chromosome 4, generally results in a less severe, but still significant, bleeding tendency (James P et al. 2014; Puy C et al. 2016). Although PK and FXIIa are recognized as upstream triggers for the intrinsic coagulation system, the clinical significance of these factors on thrombosis and hemorrhage is not fully understood. The CAS blockade results in prolonged coagulation times in the activated partial thromboplastin time (aPTT) assay. However, the absence of thrombotic and hemostatic abnormalities in individuals with genetic deficiencies of PK or FXII has suggested that the CAS plays a minimal role in physiological coagulation (Müller F et al. 2011). At the same time, excessive formation of bradykinin due to abnormal FXII-dependent KKS activation causes increased

vascular permeability at the level of the post capillary venule and results in hereditary angioedema (HAE). HAE initiated by bradykinin is usually associated with SERPING1 (C1-INH) deficiency (Suffritti C et al. 2014). More rarely, HAE occurs in individuals with normal SERPING1 activity, and has been linked to mutations in other proteins, including FXII, plasminogen, and angiopoietin (Cichon S et al. 2006; Magerl M et al. 2017; Zuraw BL 2016; Ivanov I et al. 2019). This Reactome module describes abnormal FXII-dependent KKS activation that leads to an excessive formation of bradykinin causing increased vascular permeability at the level of the post capillary venule and results in hereditary angioedema (HAE). HAE caused by defective function of SERPING1 is also covered here. The module also includes disorders that can cause abnormal bleeding due to a shortage (deficiency) of coagulation factor proteins, which are involved in blood clotting. This module also describes elevation of FIX activity associated with thrombophilia. Genetic variants are named following Human Genome Variation Society (HGVS) nomenclature with sequence numbering starting from the first methionine of the protein as +1.(Goodeve AC et al.2011).

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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.

Defects of platelet adhesion to exposed collagen ↗

Location: Diseases of hemostasis

Stable identifier: R-HSA-9823587

Diseases: blood platelet disease, autoimmune thrombocytopenic purpura



This Reactome module describes dysfunctions in platelet adhesion caused by mutations in different genes, including VWF, ADAMTS13 and GPIBA.

Editions

2023-01-07	Authored	Shamovsky, V.
2023-11-06	Reviewed	Gao, R.
2023-11-07	Edited	Shamovsky, V.

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