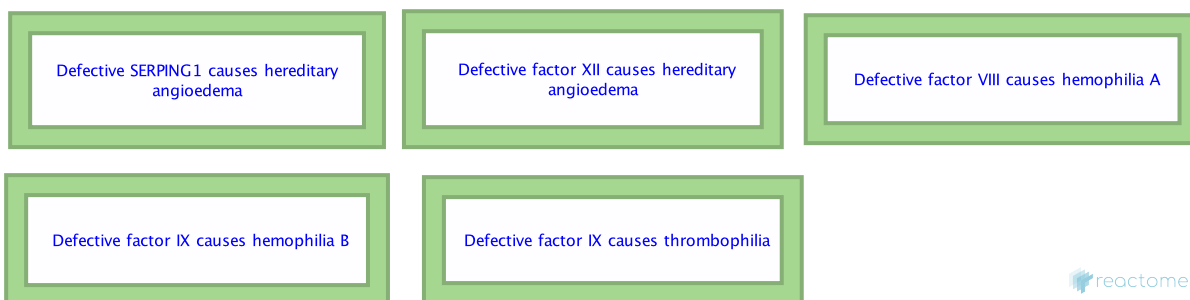


Defects of contact activation system (CAS) and kallikrein/kinin system (KKS)



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.

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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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Reactome database release: 77

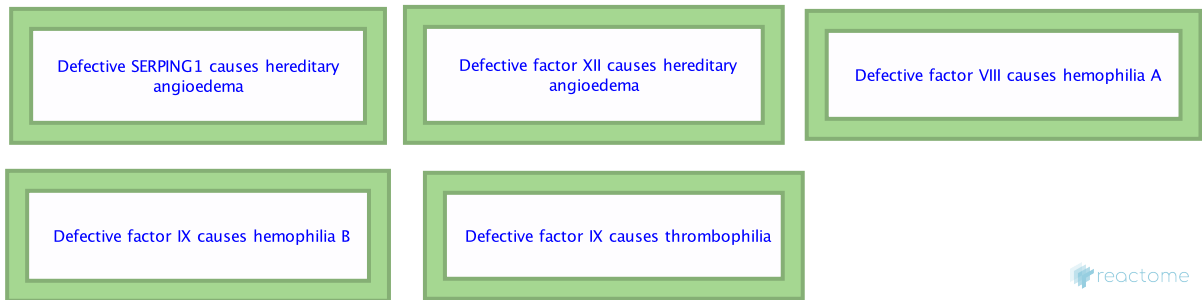
This document contains 6 pathways ([see Table of Contents](#))

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

Stable identifier: R-HSA-9651496

Compartments: extracellular region

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



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). 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. 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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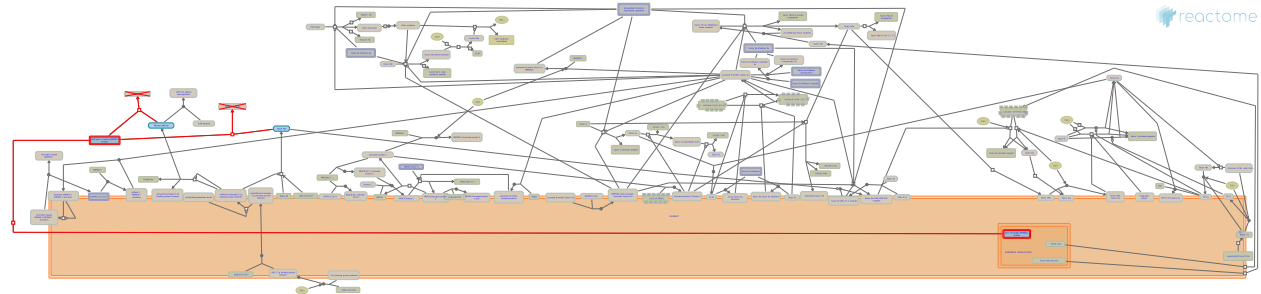
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Defective SERPING1 causes hereditary angioedema ↗

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

Stable identifier: R-HSA-9657689

Diseases: C1 inhibitor deficiency, hereditary angioedema



The reciprocal activation is initiated when zymogen factor XII (F12 or FXII) binds to a negatively charged surface, which induces FXII autoactivation. Activated FXII (FXIIa) converts prekallikrein (PK) to kallikrein, which proteolytically liberates bradykinin from high molecular weight kininogen (HK) (Renne T 2012; Renne T et al. 2012; Maas C et al. 2011). Kallikrein also activates FXII to produce more FXIIa (initially). FXIIa and kallikrein reciprocally activate their zymogens and thus generate a positive feedback loop. In the presence of sufficient amounts of active enzyme, FXIIa also generates active factor XI (FXIa) to potentiate the intrinsic coagulation pathway. All of these enzymatic steps are normally inhibited by C1-esterase inhibitor (C1-INH, encoded by the SERPING1 gene).

Binding of the proinflammatory peptide hormone bradykinin to the bradykinin B2 receptor (B2R) activates various proinflammatory signaling pathways that increase vascular permeability and fluid efflux. An excessive formation of bradykinin due to uncontrolled activation of the coagulation factor XII (FXII)-dependent kallikrein-kinin system causes increased vascular permeability at the level of the postcapillary venule and results in hereditary angioedema (HAE) (Bossi F et al. 2009; Kaplan AP 2010; Suffritti C et al. 2014; Zuraw BL & Christiansen SC 2016). HAE is a rare life-threatening inherited edema disorder that is characterized by recurrent episodes of localized edema of the skin or of the mucosa of the gastrointestinal tract or upper airway. Angioedema initiated by bradykinin is usually associated with SERPING1 (C1-INH) deficiency. Thus, a major role of SERPING1 (C1-INH) is to prevent the development of excessive vascular permeability. More rarely, HAE occurs in individuals with normal SERPING1 activity, linked to mutations in other proteins, including FXII, plasminogen, and angiopoietin (Magerl M et al. 2017; Zuraw BL 2018; Ivanov I et al. 2019). Patients with HAE are heterozygous for deficiency of SERPING1. The disease, therefore, has an autosomal dominant inheritance and may result from lack of expression of SERPING1 from one allele (type 1 HAE) or from expression of a nonfunctional SERPING1 protein (type 2 HAE). This classification has however been challenged by observations of intermediary HAE types, that can arise, when small amounts of dysfunctional SERPING1 is present in the blood stream (Eldering E et al. 1995; Verpy E et al. 1995; Madsen DE et al. 2014).

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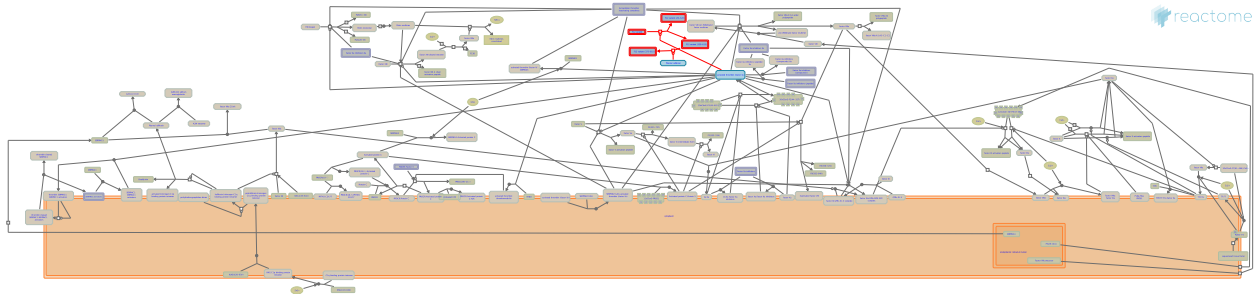
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Defective factor XII causes hereditary angioedema ↗

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

Stable identifier: R-HSA-9657688

Diseases: hereditary angioedema



Hereditary angioedema (HAE) is a rare life-threatening inherited edema disorder that is characterized by recurrent episodes of localized edema of the skin or of the mucosa of the gastrointestinal tract or upper airway. The edema formation in patients with HAE is primarily caused by a transient increased bradykinin release from high molecular weight kininogen (HK) due to uncontrolled activation of the coagulation factor XII (FXII)-dependent kallikrein kinin system (KKS) (Bossi F et al. 2009; Kaplan AP 2010; Suffritti C et al. 2014; Zuraw BL & Christiansen SC 2016). Angioedema initiated by bradykinin is usually associated with SERPING1 (C1-INH) deficiency. SERPING1 is the major regulator of the contact system. More rarely, HAE occurs in individuals with normal SERPING1 activity, and has been linked to mutations in other proteins, including FXII, plasminogen, and angiopoietin (Magerl M et al. 2017; Zuraw BL 2018; Ivanov I et al. 2019). Substitution of threonine 328 by either a lysine or an arginine residue (T328K or T328R) in the FXII proline-rich region has been identified in several families with HAE and normal SERPING1. FXII T328K or T328R variants change protein glycosylation and introduce a new site that is sensitive to enzymatic cleavage by fibrinolytic and coagulation proteases such as plasmin, thrombin, or FXIa (de Maat S et al. 2016; Ivanov I et al. 2019). The intrinsic capacity of the truncated form of FXII (329-615) (also known as δ FXII) to convert prekallikrein to kallikrein is greater than that of FXII leading to more kallikrein generated early during reciprocal activation (Ivanov I et al. 2019). Second, FXII (329-615) is a better kallikrein substrate than is FXII. The accelerated kallikrein/FXII activation with truncated FXII (329-615) appears to overwhelm the regulatory function of SERPING1 at normal plasma levels leading to uncontrolled bradykinin formation (de Maat S et al. 2016; Ivanov I et al. 2019). Binding of the proinflammatory peptide hormone bradykinin to the bradykinin B2 receptor (B2R) activates various proinflammatory signaling pathways that increase vascular permeability and fluid efflux. An excessive formation of bradykinin due to uncontrolled activation of FXII-dependent KKS causes increased vascular permeability at the level of the postcapillary venule and results in HAE (Zuraw BL & Christiansen SC 2016; de Maat S et al. 2016; Ivanov I et al. 2019).

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Ivanov, I., Matafonov, A., Sun, MF., Mohammed, BM., Cheng, Q., Dickeson, SK. et al. (2019). A mechanism for hereditary angioedema with normal C1 inhibitor: an inhibitory regulatory role for the factor XII heavy chain. *Blood*, 133, 1152-1163. ↗

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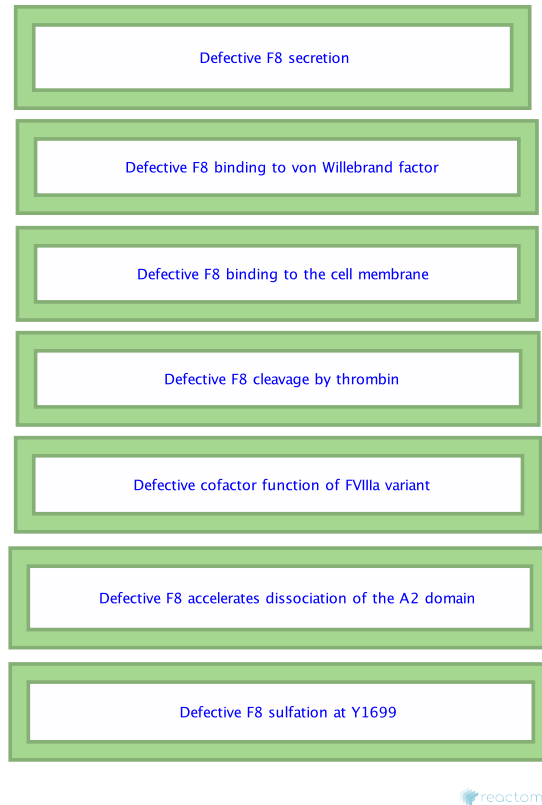
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Defective factor VIII causes hemophilia A ↗

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

Stable identifier: R-HSA-9662001

Diseases: factor VIII deficiency



Hemophilia A is an X-chromosome-linked recessive bleeding disorder defined by a qualitative and/or quantitative factor VIII (FVIII, F8) deficiency (Salen P & Babiker HM 2019). Patients affected by the mild form of the disease (FVIII activity 0.05–0.4 IU/mL) suffer from bleedings occurring after trauma or surgery. In severe hemophilia A patients (FVIII activity <0.01 IU/mL) bleedings occur spontaneously, whereas moderate hemophilia A patients (FVIII activity 0.01–0.05 IU/mL) present with an intermediate bleeding phenotype (White GC 2nd et al. 2001). In healthy individuals, FVIII is synthesized as an ~300-kDa glycoprotein by hepatocytes, liver sinusoidal endothelial cells, and certain types of endothelial cells (Wion KL et al. 1995; Jacquemin M et al. 2006; Shahani T et al. 2009; Turner NA & Moake JL 2015). The FVIII protein contains a domain sequence A1-A2-B-ap-A3-C1-C2 and circulates as an A1-A2-B:ap-A3-C1-C2 heterodimer bound noncovalently to the von Willebrand factor (vWF) protein. vWF protects FVIII from rapid clearance (Lenting PJ et al. 2007). During the activation of FVIII by thrombin to FVIIIa, the B domain and an activation peptide (ap) are released, and cleavage between the A1 and A2 domains produces an A1:A2:A3-C1-C2 heterotrimer (Lollar P & Parker ET 1991; Nogami K et al. 2005; Newell JL & Fay PJ 2007; 2009). Once activated, FVIIIa dissociates from vWF and binds to the membrane of activated platelets to assemble with activated factor IX (FIXa) (Gilbert GE & Arena AA 1996; Ahmad SS et al. 2003; Panteleev MA et al. 2004; Ngo JC et al. 2008). At physiologic concentrations, the A2 subunit spontaneously dissociates, leading to loss of FVIIIa cofactor activity (Lollar P & Parker CG 1990).

Hemophilia A results from a broad spectrum of mutations that occur along the entire length of the F8 gene causing diverse molecular phenotypes that result in similar disease states (Peyvandi F et al. 2016). Together with missense mutations being the most common type of mutations in hemophilia A, a relat-

ively frequent cause is ascribable to nonsense and splice site mutations, deletions/insertions and promoter mutations (Hakeos WH et al. 2002; Wei W et al. 2017; Jacquemin M et al. 2000; Amano K et al. 1998; Gilbert GE et al. 2012; Pahl S et al. 2014; Peyvandi F et al. 2016). In addition, the inversion of intron 1 or 22 in the F8 gene is responsible for approximately half of severely affected hemophilia A patients (Antonarakis SE et al. 1995). Although specific FVIII missense mutations correlate with defects including decreased secretion or stability and specific functional impairment of FVIII, the mechanisms of the majority of missense mutations are poorly understood (Hakeos WH et al. 2002; Wei W et al. 2017, 2018; Jacquemin M et al. 2000; Amano K et al. 1998; Gilbert GE et al. 2012; Pahl S et al. 2014). The Reactome module describes several molecular mechanisms underlying hemophilia A which include: (1) low-level secretion of defective FVIII molecule as a result of impaired FVIII folding and intracellular processing, (2) reduced ability of FVIII variants to bind to von Willebrand factor (VWF) that leads to instability of FVIII variants in the plasma, (3) abnormal interaction of defective FVIII with FIXa. Defects in FVIII activity may also result in potentially slowing down FVIII activation by thrombin or altering stability of activated FVIIIa.

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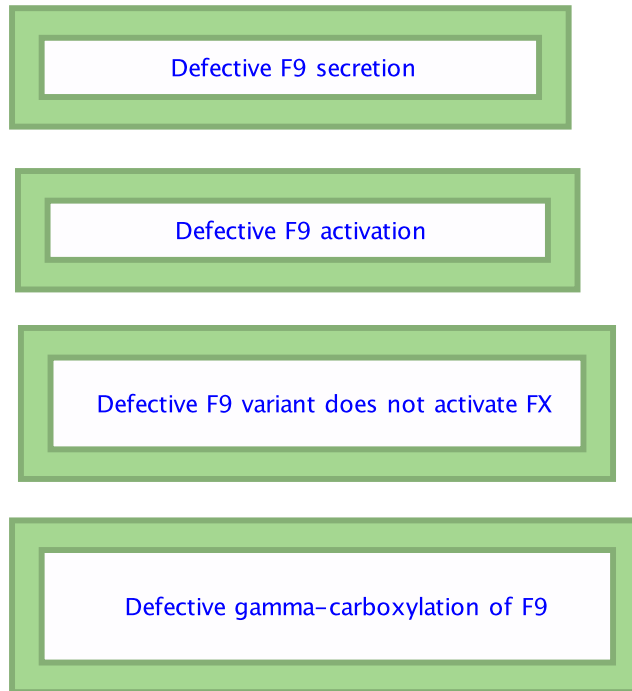
Defective factor IX causes hemophilia B ↗

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

Stable identifier: R-HSA-9668250

Compartments: endoplasmic reticulum lumen

Diseases: hemophilia B



 reactome

The F9 gene encodes coagulation factor IX (FIX), a vitamin K-dependent plasma protease that participates in the intrinsic blood coagulation pathway. FIX circulates as a zymogen, and is proteolytically activated to FIXa by activated FXIa or tissue factor-bound FVIIa. After being activated, FIXa forms a complex with Ca²⁺ ions, membrane phospholipids and coagulation factor VIIIa to activate coagulation factor X. Mutations within F9 gene that lead to quantitative and/or qualitative deficiencies in the circulating FIX protein are associated with hemophilia B (HB), a rare X-linked, recessively transmitted bleeding disorder (White GC et al. 2001; Rallapalli PM et al. 2013; Goodeve AC 2015). The disease severity in hemophilia is classified according to the plasma procoagulant levels of FIX activity. The severe form is defined as a factor level <1% of normal, the moderate form as a factor level of 1-5%, and the mild form with a factor level >5 and <40%. Patients with severe hemophilia frequently develop hemorrhages into joints, muscles or soft tissues without any apparent cause. They can also suffer from life-threatening bleeding episodes such as intracranial hemorrhages. Persons with mild and moderate factor deficiency rarely experience spontaneous hemorrhages, and excessive bleeding mostly occurs only following trauma or in association with invasive procedures.

A wide range of different genetic alterations are spread throughout the F9 gene, including single nucleotide substitutions, small and large deletions (Rallapalli PM et al. 2013). However functional consequences of most F9 mutations are poorly studied. The Reactome event describes altered functions of HB-associated FIX variants such as reduced FIX protein secretion due to defective expression and/or processing, failed proteolysis of factor X to Xa by defective FIX and failed formation of a membrane complex

in the presence of Ca²⁺ ions, phospholipid, and cofactor VIIIa. The annotated HB-associated FIX variants are supported with data from functional studies (Usharani P et al. 1985; Spitzer SG et al. 1990; Ludwig M et al. 1992; Kurachi S et al. 1997; Branchini A et al. 2013).

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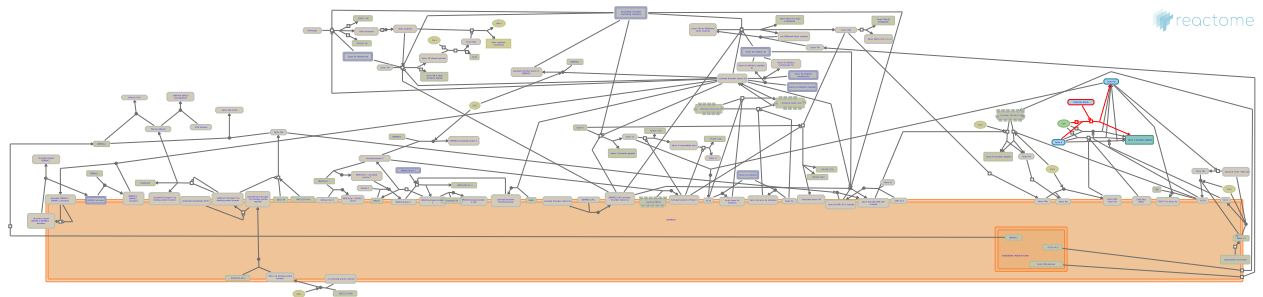
Defective factor IX causes thrombophilia [↗](#)

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

Stable identifier: R-HSA-9672383

Compartments: extracellular region, plasma membrane

Diseases: thrombophilia



In healthy individuals factor IXa (FIXa), in a complex with factor VIIIa on the surfaces of activated platelets, catalyzes the formation of activated factor X with high efficiency. A substitution of leucine for arginine at residue 384 in FIX (FIX R384L, also known as FIX Padua) is a gain-of-function mutation that resulted in elevated FIX clotting activity in a patient with venous thrombosis (Simioni P et al. 2009).

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