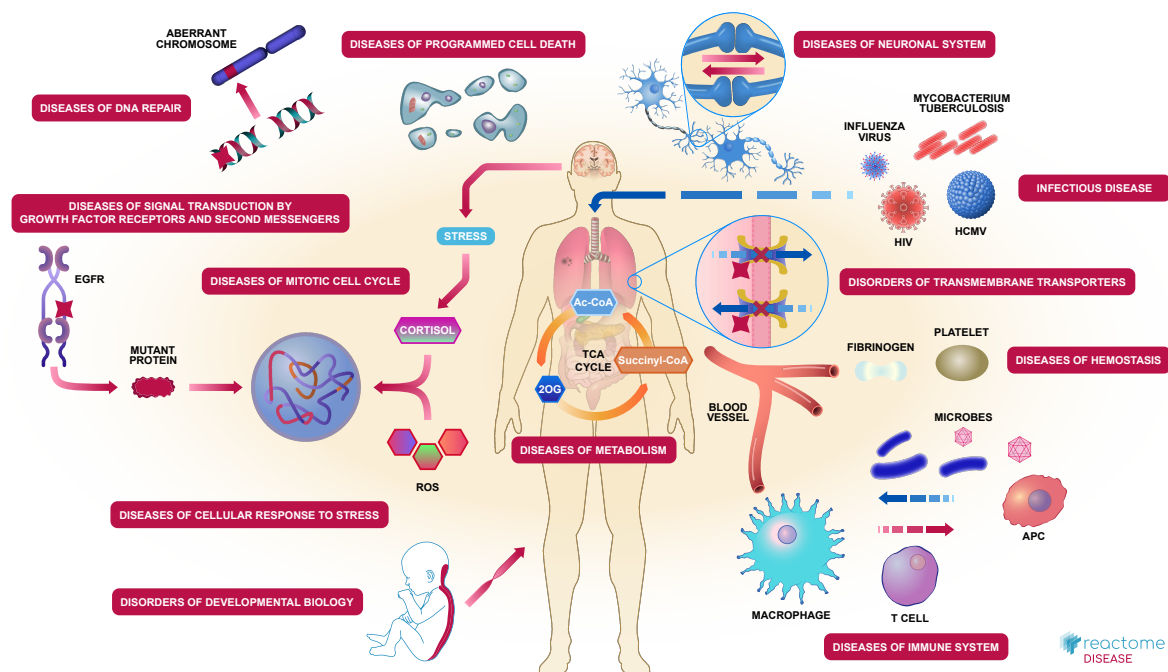


# Disease



D'Eustachio, P., Jassal, B., Matthews, L., Moitra, K., Orlic-Milacic, M., 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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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/about-us).

17/09/2024

## 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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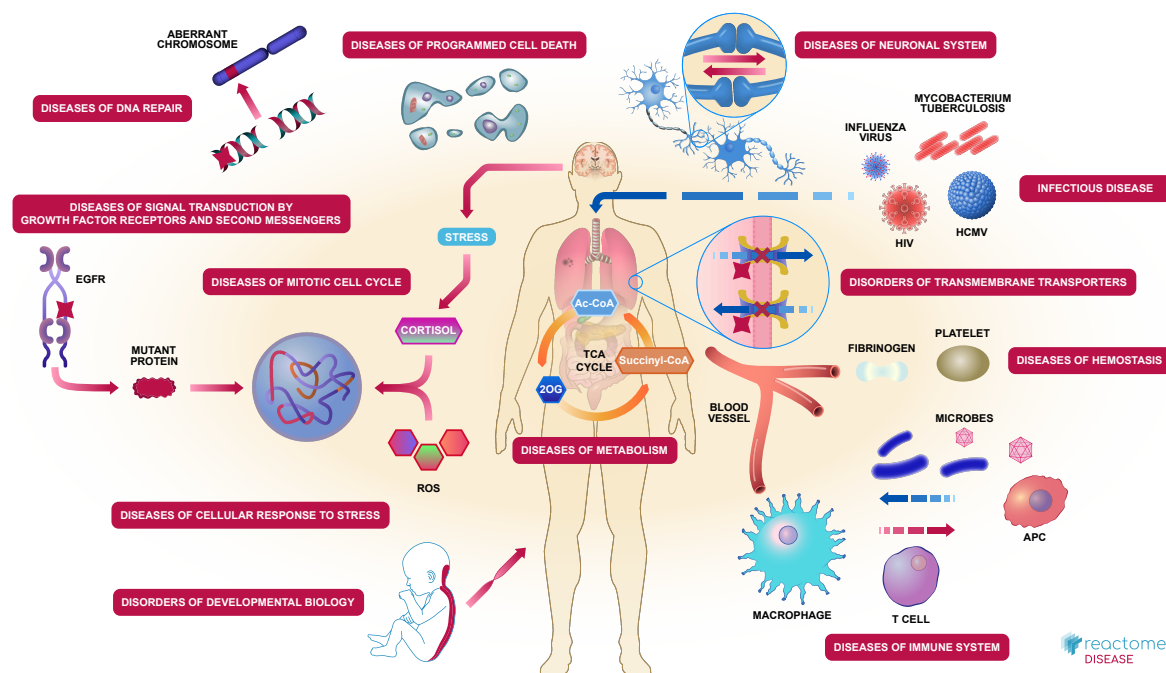
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Reactome database release: 89

This document contains 13 pathways ([see Table of Contents](#))

## Disease ↗

**Stable identifier:** R-HSA-1643685



Biological processes are captured in Reactome by identifying the molecules (DNA, RNA, protein, small molecules) involved in them and describing the details of their interactions. From this molecular viewpoint, human disease pathways have three mechanistic causes: the inclusion of microbially-expressed proteins, altered functions of human proteins, or changed expression levels of otherwise functionally normal human proteins.

The first group encompasses the infectious diseases such as influenza, tuberculosis and HIV infection. The second group involves human proteins modified either by a mutation or by an abnormal post-translational event that produces an aberrant protein with a novel function. Examples include somatic mutations of EGFR and FGFR (epidermal and fibroblast growth factor receptor) genes, which encode constitutively active receptors that signal even in the absence of their ligands, or the somatic mutation of IDH1 (isocitrate dehydrogenase 1) that leads to an enzyme active on 2-oxoglutarate rather than isocitrate, or the abnormal protein aggregations of amyloidosis which lead to diseases such as Alzheimer's.

Infectious diseases are represented in Reactome as microbial-human protein interactions and the consequent events. The existence of variant proteins and their association with disease-specific biological processes is represented by inclusion of the modified protein in a new or variant reaction, an extension to the 'normal' pathway. Diseases which result from proteins performing their normal functions but at abnormal rates can also be captured, though less directly. Many mutant alleles encode proteins that retain their normal functions but have abnormal stabilities or catalytic efficiencies, leading to normal reactions that proceed to abnormal extents. The phenotypes of such diseases can be revealed when pathway annotations are combined with expression or rate data from other sources.

Depending on the biological pathway/process immediately affected by disease-causing gene variants, non-infectious diseases in Reactome are organized into diseases of signal transduction by growth factor receptors and second messengers, diseases of mitotic cell cycle, diseases of cellular response to stress, diseases of programmed cell death, diseases of DNA repair, disorders of transmembrane transporters, diseases of metabolism, diseases of immune system, diseases of neuronal system, disorders of developmental biology, disorders of extracellular matrix organization, and diseases of hemostasis.

## Editions

2020-08-24

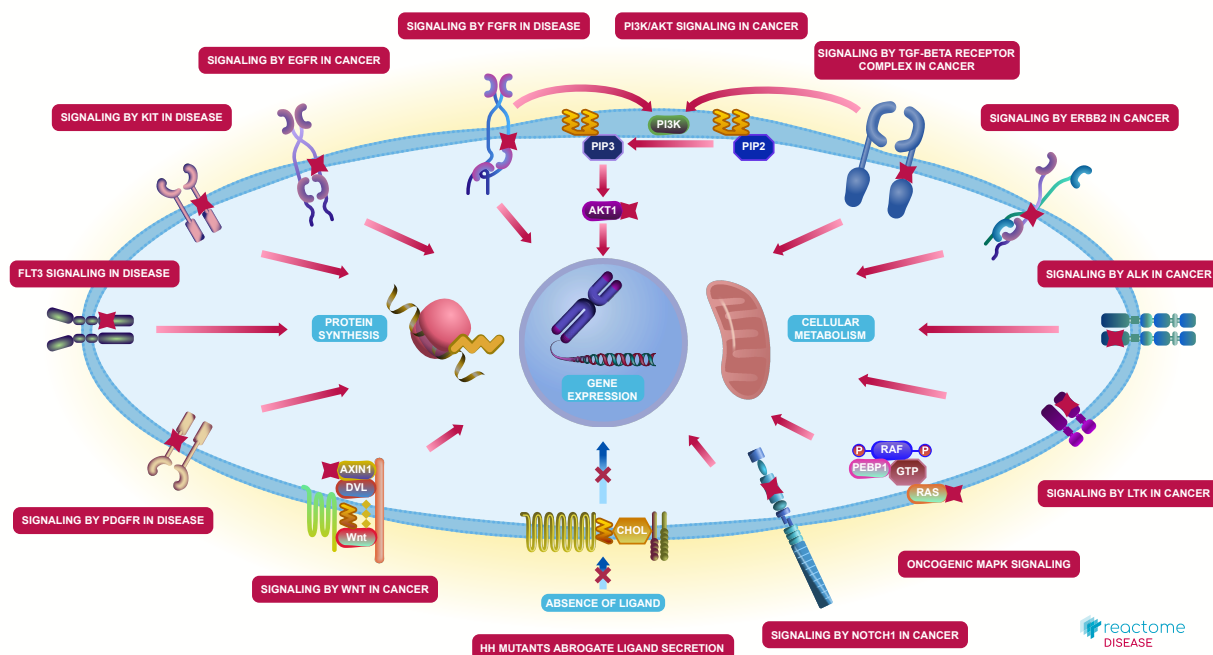
Edited

Orlic-Milacic, M.

# Diseases of signal transduction by growth factor receptors and second messengers ↗

Location: Disease

Stable identifier: R-HSA-5663202



Signaling processes are central to human physiology (e.g., Pires-da Silva & Sommer 2003), and their disruption by either germ-line and somatic mutation can lead to serious disease. Here, the molecular consequences of mutations affecting visual signal transduction and signaling by diverse growth factors are annotated.

## Literature references

Pires-daSilva, A., Sommer, R.J. (2003). The evolution of signalling pathways in animal development. *Nat. Rev. Genet.*, 4, 39-49. ↗

## Editions

2023-12-08

Reviewed

D'Eustachio, P.

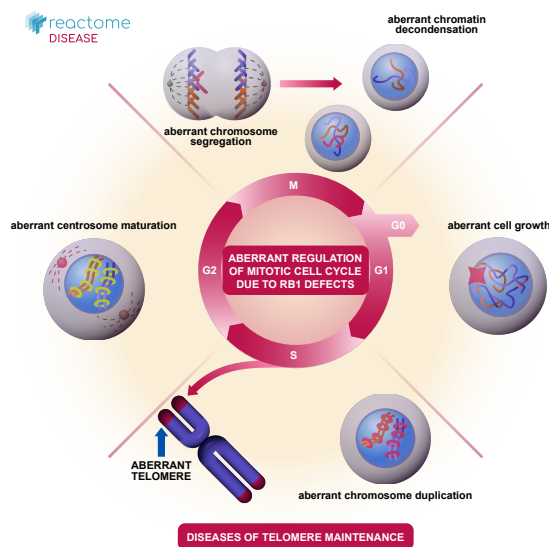


Diseases of mitotic cell cycle ↗

Location: Disease

Stable identifier: R-HSA-9675126

Diseases: disease of cellular proliferation



Diseases of mitotic cell cycle are caused by mutations in cell cycle regulators (Collins and Garrett 2005, Diaz-Moralli et al. 2013), such as retinoblastoma protein RB1 (Classon and Harlow 2002), as well as proteins involved in telomere maintenance, such as ATRX and DAXX (Sarek et al. 2015). These diseases mainly include different types of cancer, hereditary syndromes such as dyskeratosis congenita that may predispose affected patients to cancer, and neurodegenerative diseases (Webber et al. 2005).

Literature references

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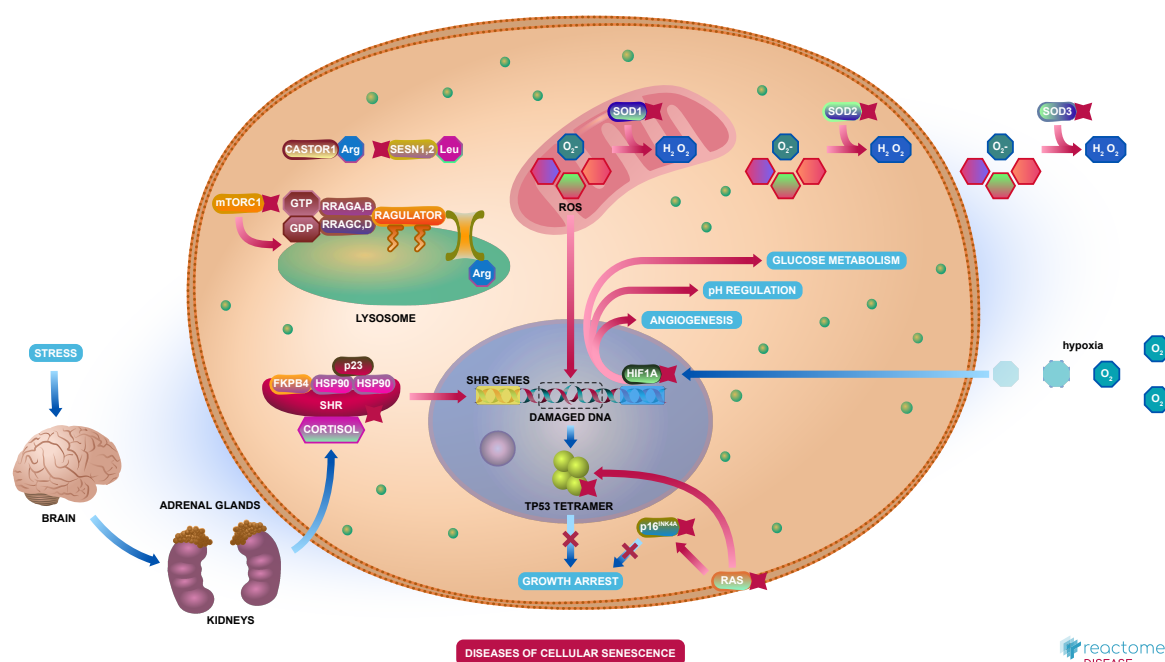
Editions

2020-05-07	Authored	Orlic-Milacic, M.
2020-05-27	Reviewed	Matthews, L.
2020-05-27	Edited	Orlic-Milacic, M.

## Diseases of cellular response to stress ↗

**Location:** Disease

**Stable identifier:** R-HSA-9675132



Cells are subject to external and internal stressors, such as foreign molecules that perturb metabolic or signaling processes, cellular respiration-generated reactive oxygen species that can cause DNA damage, oxygen and nutrient deprivation, and changes in temperature or pH. The ability of cells and tissues to respond to stress is essential to the maintenance of tissue homeostasis (Kultz 2005) and dysregulation of cellular response to stress is involved in disease.

So far, we have captured diseases of cellular senescence.

Impaired cellular senescence contributes to malignant transformation and cancer development by enabling continuous proliferation of damaged cells. On the other hand, presence of an excessive number of senescent cells that are not cleared by the immune system promotes tissue inflammation and creates a microenvironment suitable for growth of neighboring malignant cells. In addition to cancer, senescence is also involved in other age-related diseases such as atherosclerosis, osteoarthritis, chronic obstructive lung disease, and diabetes (Childs et al. 2015, He and Sharpless 2017, Hamsanathan et al. 2019, Faget et al. 2019, Gorgoulis et al. 2019, Rhinn et al. 2019). Senotherapy is a new field of pharmacology that aims to therapeutically target senescence to improve healthy aging and age-related diseases (Schmitt 2017, Gorgoulis et al. 2019).

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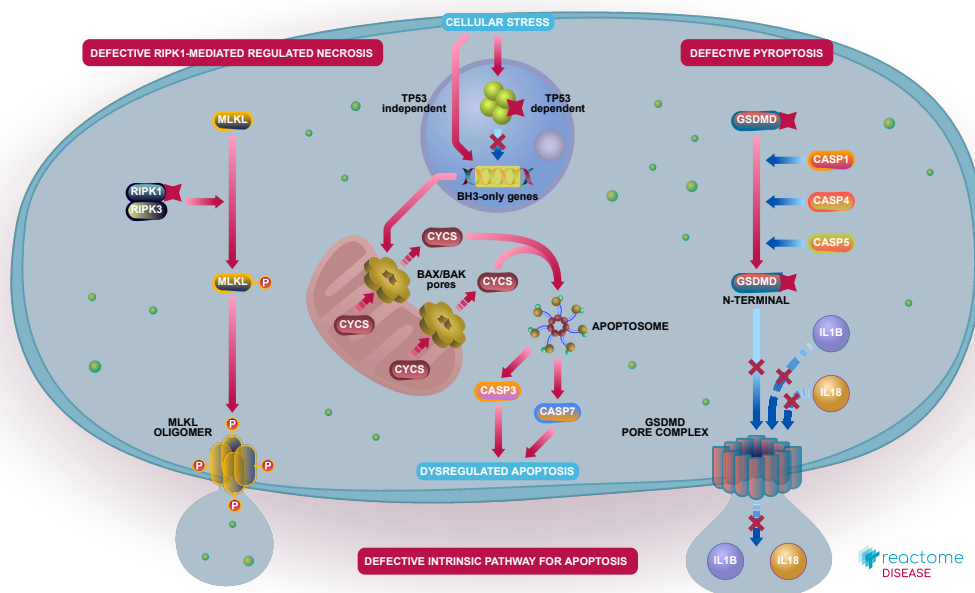
2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.

## Diseases of programmed cell death ↗

**Location:** Disease

**Stable identifier:** R-HSA-9645723

**Diseases:** neurodegenerative disease, cancer



Programmed cell death is frequently impaired in cancer and is thought to significantly contribute to resistance to chemotherapy. Mutations and perturbations in expression of different proteins involved in programmed cell death, such as TP53 (p53), BH3-only family proteins, caspases and their regulators enable malignant cells to evade apoptosis (Ghavami et al. 2009, Chao et al. 2011, Wong 2011, Fernald and Kurokawa 2013, Ichim and Tait 2016).

### Literature references

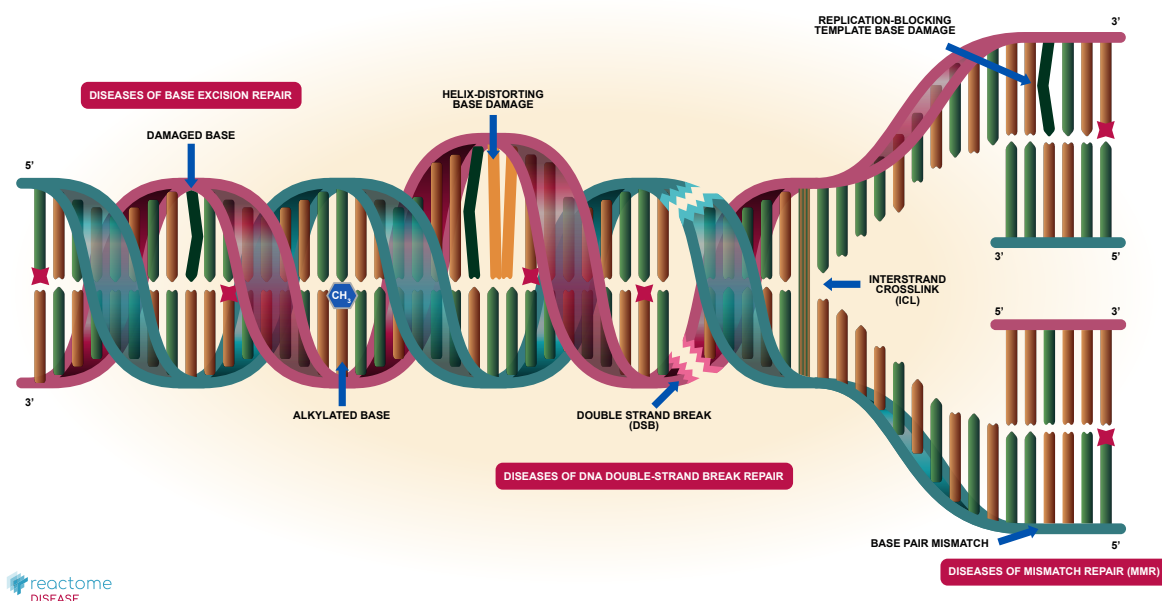
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## Diseases of DNA repair ↗

**Location:** Disease

**Stable identifier:** R-HSA-9675135

**Diseases:** genetic disease



Germline and somatic defects in genes that encode proteins that participate in DNA repair give rise to genetic instability that can lead to malignant transformation or trigger cellular senescence or apoptosis. Germline defects in DNA repair genes are an underlying cause of familial cancer syndromes and premature ageing syndromes. Somatic defects in DNA repair genes are frequently found in tumors. For review, please refer to Tiwari and Wilson 2019.

We have so far annotated diseases of mismatch repair, diseases of base excision repair and diseases of DNA double-strand break repair.

Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) result in microsatellite instability (MSI) and reduced fidelity during replication and repair steps. Defective variants of MMR genes are associated with sporadic cancers with hypermutation phenotypes as well as hereditary cancer syndromes such as Lynch syndrome (hereditary non-polyposis colorectal cancer) and constitutional mismatch repair deficiency syndrome (CMMRD). MSI is an important predictor of sensitivity to cancer immunotherapy as the high mutational burden renders MSI tumors immunogenic and sensitive to programmed cell death-1 (PD-1) immune checkpoint inhibitors (Mandal et al. 2019). For review, please refer to Pena-Diaz and Rasmussen 2016, Sijmons and Hofstra 2016, Tabori et al. 2017, Baretti and Le 2018.

Germline mutations, single nucleotide polymorphisms (SNPs) and somatic mutations in several genes involved in base excision repair (BER), a DNA repair pathway where a damaged DNA base is excised and replaced with a correct base, are involved in the development of cancer and several oxidative stress-related diseases. For review, please refer to Fu et al. 2012, Fletcher and Houlston 2010, Brennerman et al. 2014, Patrono et al. 2014, and D'Errico et al. 2017.

Germline mutations in genes involved in repair of DNA double-strand breaks (DSBs) are the underlying cause of several cancer predisposition syndromes, some of which also encompass developmental disorders associated with immune dysfunction, radiosensitivity and neurodegeneration. Somatic mutations in genes involved in DSB repair also occur in sporadic cancers. For review, please refer to McKinnon and Caldecott 2007, Keijzers et al. 2017, and Jachimowicz et al. 2019.

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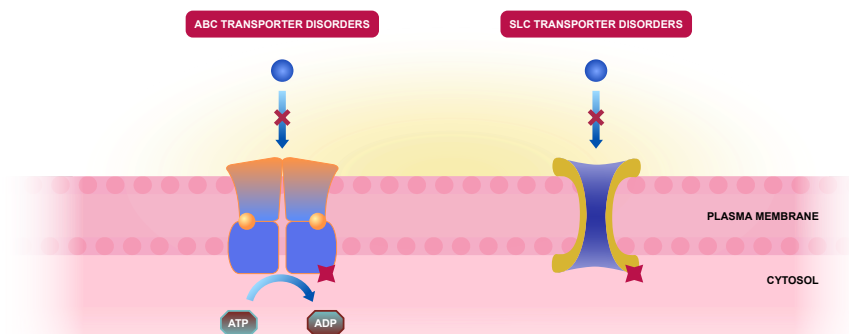
## Editions

2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.
2020-11-11	Reviewed	D'Eustachio, P.
2020-11-12	Edited	Orlic-Milacic, M.

# Disorders of transmembrane transporters ↗

Location: [Disease](#)

Stable identifier: R-HSA-5619115



reactome  
DISEASE

Proteins with transporting functions can be roughly classified into 3 categories: ATP hydrolysis-coupled pumps, ion channels, and transporters. Pumps utilize the energy released by ATP hydrolysis to power the movement of substrates across the membrane against their electrochemical gradient. Channels in their open state can transfer substrates (ions or water) down their electrochemical gradient at an extremely high efficiency (up to  $10^8$  s<sup>-1</sup>). Transporters facilitate the movement of a specific substrate either against or with their concentration gradient at a lower speed (about  $10^2$  -  $10^4$  s<sup>-1</sup>); as generally believed, conformational change of the transporter protein is involved in the transfer process. Diseases caused by defects in these transporter proteins are detailed in this section. Disorders associated with ABC transporters and SLC transporters are annotated here (Dean 2005).

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## Editions

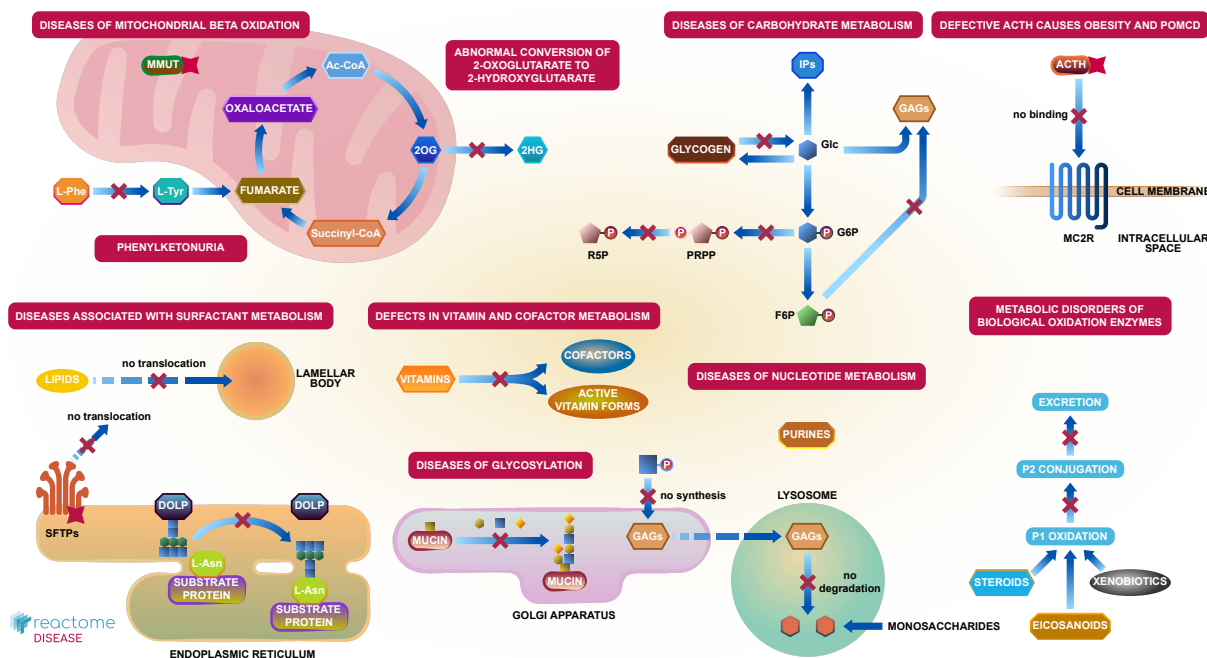
2014-08-22	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

## Diseases of metabolism ↗

**Location:** Disease

**Stable identifier:** R-HSA-5668914

**Diseases:** disease of metabolism



Metabolic processes in human cells generate energy through the oxidation of molecules consumed in the diet and mediate the synthesis of diverse essential molecules not taken in the diet as well as the inactivation and elimination of toxic ones generated endogenously or present in the extracellular environment. Mutations that disrupt these processes by inactivating a required enzyme or regulatory protein, or more rarely by changing its specificity can lead to severe diseases. Metabolic diseases annotated here involve aspects of carbohydrate, glycosylation, amino acid (phenylketonuria), surfactant and vitamin metabolism, and biological oxidations. One somatic mutation that affects cytosolic isocitrate metabolism, often found in glioblastomas and some lymphoid neoplasms, is also annotated. Also described are mutated forms of adrenocorticotrophic hormone (ACTH) that can lead to obesity, resulting in excessive accumulation of body fat.

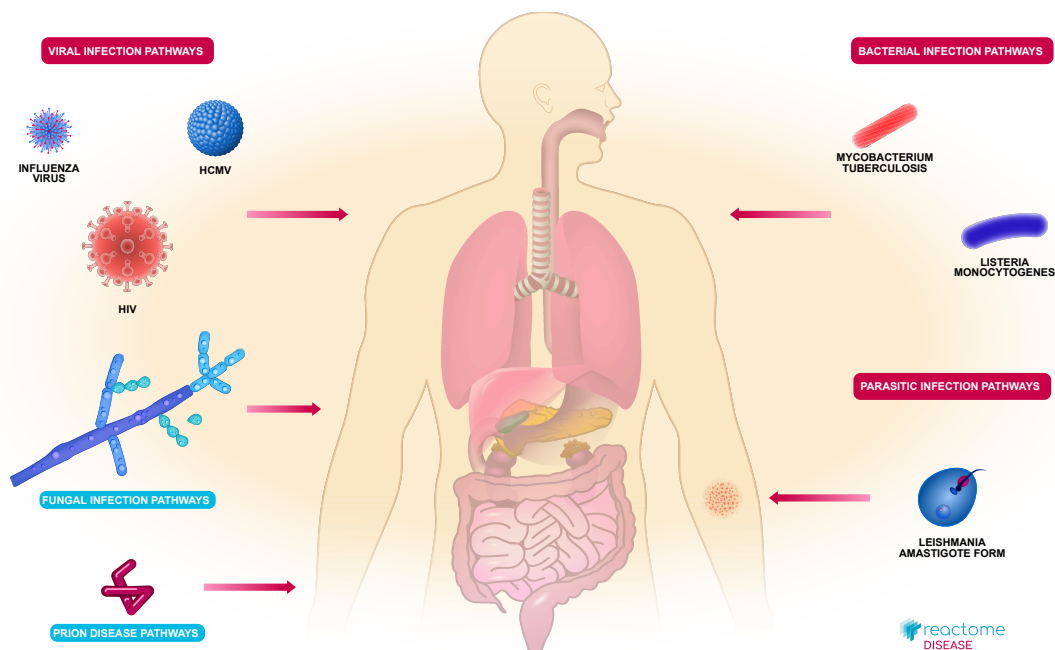


## Infectious disease ↗

**Location:** Disease

**Stable identifier:** R-HSA-5663205

**Diseases:** disease by infectious agent



Infectious diseases are ones due to the presence of pathogenic microbial agents in human host cells. Processes annotated in this category include bacterial, viral and parasitic infection pathways.

Bacterial infection pathways currently include some metabolic processes mediated by intracellular *Mycobacterium tuberculosis*, the actions of clostridial, anthrax, and diphtheria toxins, and the entry of *Listeria monocytogenes* into human cells.

Viral infection pathways currently include the life cycles of SARS-CoV viruses, influenza virus, HIV (human immunodeficiency virus), and human cytomegalovirus (HCMV).

Parasitic infection pathways currently include Leishmania infection-related pathways.

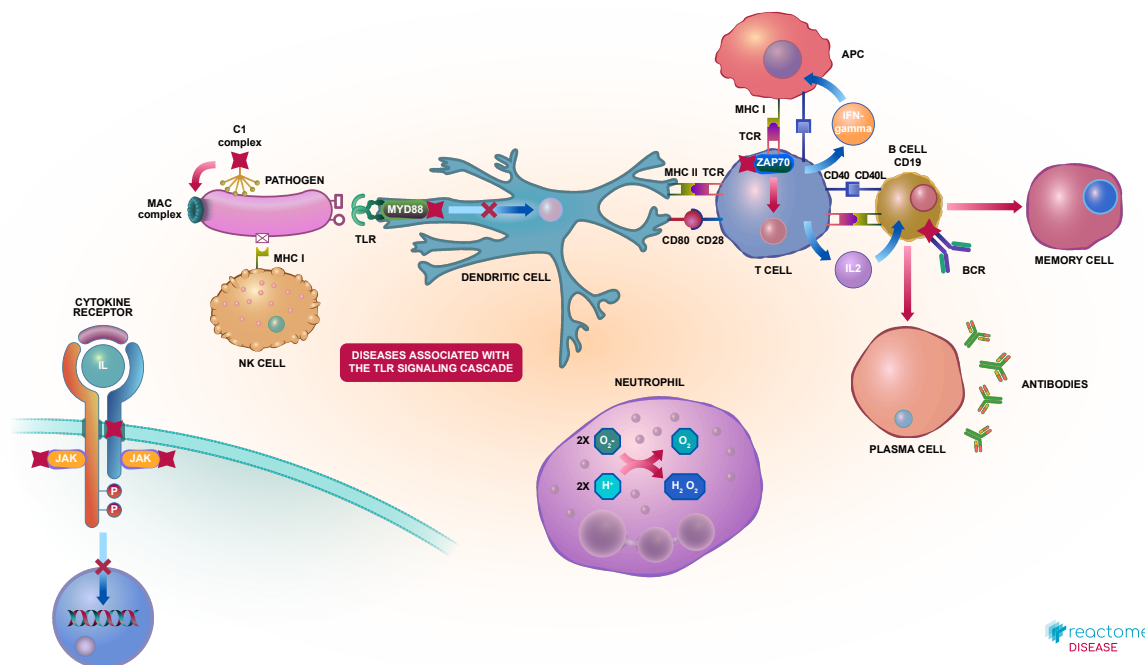
Fungal infection pathways and prion diseases have not been annotated.

## Diseases of Immune System ↗

**Location:** Disease

**Stable identifier:** R-HSA-5260271

**Diseases:** primary immunodeficiency disease



The immune system is a complex network of the biological processes that provide defense mechanisms during infection or in response to an intrinsic danger signal. Compromised immune response may present itself as either overactivity or underactivity of the immune system leading to a broad spectrum of clinical phenotypes that can be categorized into four main groups - autoimmunity, immunodeficiency (ID) with a greater susceptibility to infectious diseases, hypersensitivity to compounds that are usually not harmful and malignancy. Several host conditions may cause the dysfunctional immunity. Among them are inherited and somatic mutations found in the components of immune signaling pathways. In addition to genetic defects, infection with pathogen such as human immunodeficiency virus (HIV), or interaction of immune cells with immunosuppressive drugs result in non-genetic immunodeficiencies. Age-associated alterations in immunity may also contribute to pathogenesis of immunodeficiency .

The Reactome module represents selected defects of the immune system and provides a short description of their clinical phenotypes. The module also describes functional features of defective molecules by both providing a published source for experimental functional analysis data and linking to the corresponding normal process within the Reactome database.

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## Editions

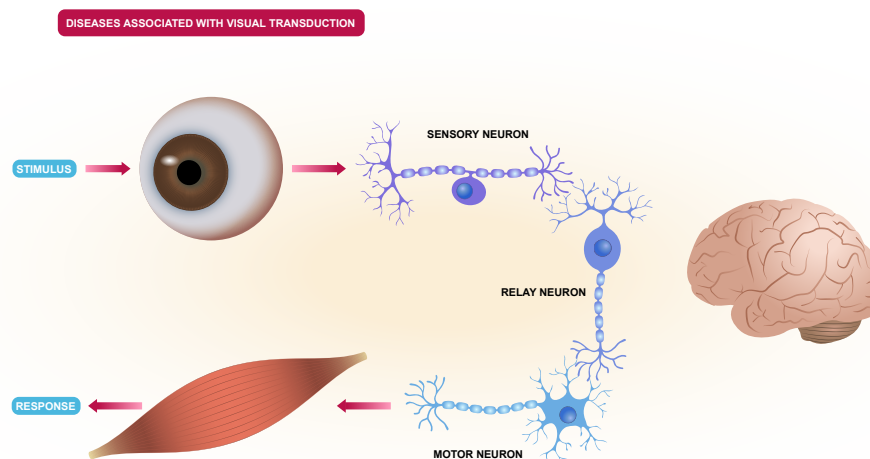
2014-05-21	Authored	Shamovsky, V.
2014-09-06	Reviewed	D'Eustachio, P.
2015-02-15	Edited	Shamovsky, V.

## Diseases of the neuronal system ↗

**Location:** Disease

**Stable identifier:** R-HSA-9675143

**Diseases:** nervous system disease



reactome  
DISEASE

Diseases of the neuronal system can affect sensory cells and transmission of signals between sensory cells and sensory neurons (Martemyanov and Sampath 2017), transmission of signals across electrical and chemical synapses in the nervous system (Picconi et al. 2012, Yin et al. 2012, Kida and Kato 2015), and transmission of signals between motor neurons and muscle cells (Sine 2012, Engel et al. 2015).

We have so far annotated diseases of visual phototransduction due to retinal degeneration caused by defects in the genes involved in the retinoid cycle (Travis et al. 2007, Palczewski 2010, Fletcher et al. 2011, den Hollander et al. 2008).

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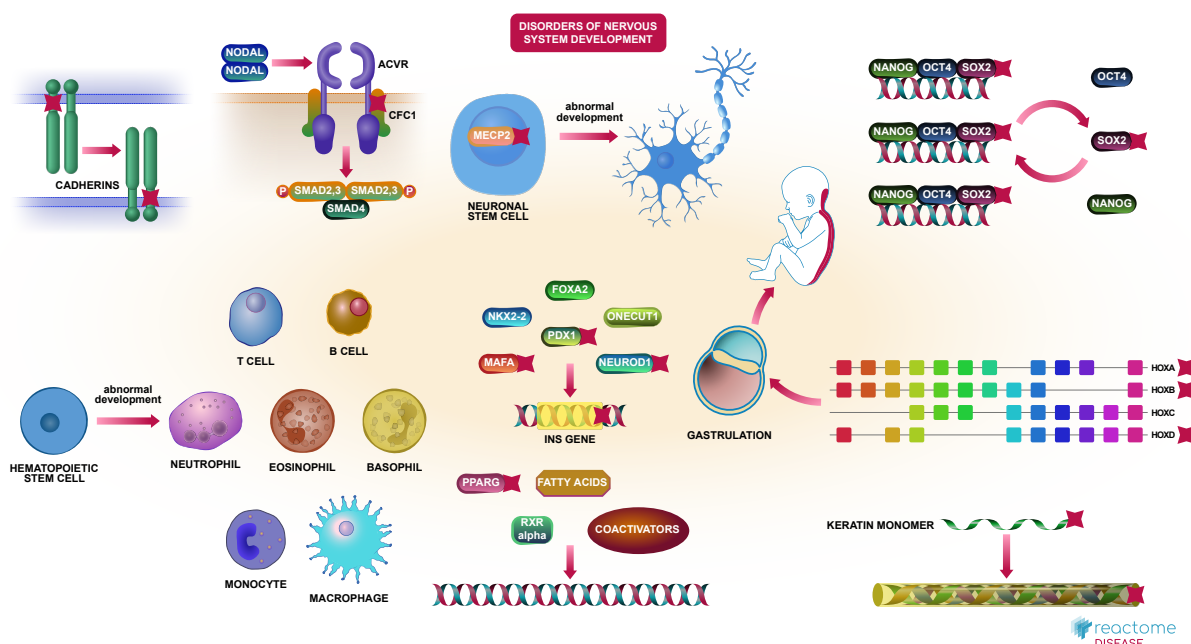
### Editions

2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.

## Disorders of Developmental Biology

**Location:** Disease

**Stable identifier:** R-HSA-9675151



Developmental disorders affect formation of body organs and organ systems. The causes of defects in human development are diverse and incompletely understood, and include environmental insults such as nutrient deficiency, exposure to toxins and infections (Gilbert 2000, National Research Council (US) Committee on Developmental Toxicology 2000, Taylor and Rogers 2005, Zilbauer et al. 2016, Izvolkskaia et al. 2018), as well as genetic causes such as aneuploidy and other chromosomal abnormalities, and germline mutations in genes that regulate normal development. It is estimated that about 40% of human developmental disabilities can be attributed to genetic aberrations (Sun et al. 2015), of which at least 25% are due to mutations affecting single genes (Chong et al. 2015), and this latter group of Mendelian developmental disorders is the focus of curation in Reactome.

Disorders of nervous system development affect the function of the central nervous system (CNS) and impair motor skills, cognition, communication and/or behavior (reviewed by Ismail and Shapiro 2019). So far, we have annotated the role of loss-of-function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, in Rett syndrome, a pervasive developmental disorder (Pickett and London 2005, Ferreri 2014).

Disorders of myogenesis are rare hereditary muscle diseases that in the case of congenital myopathies are defined by architectural abnormalities in the muscle fibres (Pelin and Wallgren-Pettersson 2019, Phadke 2019, Radke et al. 2019, Claeys 2020) and in the case of muscular dystrophies by increased muscle breakdown that progresses with age (Pasirja and Tadi 2020). Mutations in cadherin family genes are present in some types of muscular dystrophy (Puppo et al. 2015).

Disorders of pancreas development result in pancreatic agenesis, where a critical mass of pancreatic tissue is congenitally absent. For example, the PDX1 gene is a master regulator of beta cell differentiation and homozygous deletions or inactivating mutations in PDX1 gene cause whole pancreas agenesis. PDX1 gene haploinsufficiency impairs glucose tolerance and leads to development of diabetes mellitus (Hui and Perfetti 2002, Babu et al. 2007, Chen et al. 2008).

Left-right asymmetry disorders are caused by mutations in genes that regulate the characteristic asymmetry of internal organs in vertebrates. Normally, cardiac apex, stomach and spleen are positioned towards the left side, while the liver and gallbladder are on the right. Loss-of-function mutations in the CFC1 gene, whose protein product functions as a co-factor in Nodal signaling, result in heterotaxic phenotype in affected patients, manifested by randomized organ positioning (Bamford et al. 2000).

Congenital lipodystrophies are characterized by a lack of adipose tissue, which predisposes affected patient to development of insulin resistance and related metabolic disorders. The severity of metabolic complications is

correlates with the extent of adipose tissue loss. Loss-of-function mutations in the PPARG gene, encoding a key transcriptional regulator of adipocyte development and function, are a well-established cause of familial partial lipodystrophy type 3 (FPLD3) (Broekema et al. 2019).

Congenital stem cell disorders are caused by mutations in genes that regulate the balance between stem cells maintenance and commitment to differentiated lineages. Loss-of-function mutations in the SOX2 gene, which encodes a transcription factor involved in the maintenance of totipotency during embryonic preimplantation period, pluripotency of embryonic stem cells, and multipotency of neural stem cells, are the cause of anophthalmia (the absence of an eye) and microphthalmia (the presence of a small eye within the orbit (Verma and Fitzpatrick 2007, Sarlak and Vincent 2016).

HOX-related structural birth defects are caused by loss-of-function mutations in HOX family genes. HOX transcription factors play a fundamental role in body patterning during embryonic development, and HOX mutation are an underlying cause of many congenital limb malformations (Goodman 2002).

Congenital keratinization disorders are caused by dominant negative mutation in keratin genes and depending on where the affected keratin gene is expressed, they affect epithelial tissues such as skin, cornea, hair and/or nails (McLean and Moore 2011).

Disorders of immune system development are caused by mutations in genes that regulate differentiation of blood cell lineages involved in immune defense, leading to immune system defects. For example, mutations in the gene encoding CSF3R, a receptor for the granulocyte-colony stimulating factor, result in congenital neutropenia, characterized by a maturation arrest of granulopoiesis at the level of promyelocytes. Patients with severe congenital neutropenia are prone to recurrent, often life-threatening infections from an early age and may be predisposed to myelodysplastic syndromes or acute myeloid leukemia (Germeshausen et al. 2008; Skokowa et al. 2017).

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## Editions

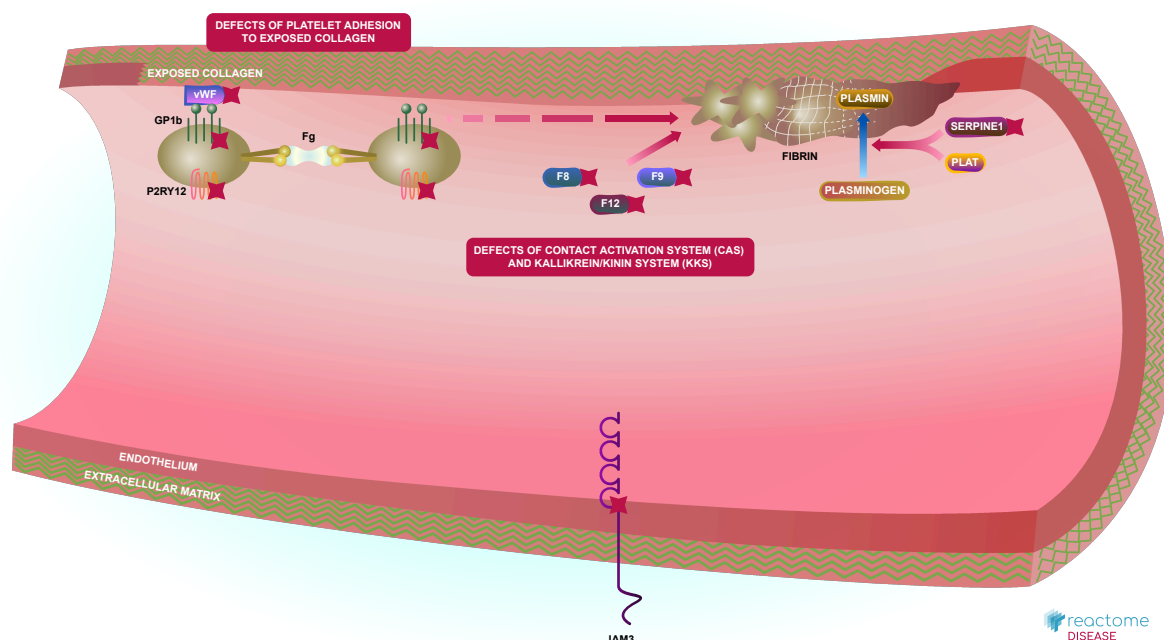
2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.
2020-08-18	Reviewed	D'Eustachio, P.
2020-08-24	Edited	Orlic-Milacic, M.

## Diseases of hemostasis ↗

**Location:** Disease

**Stable identifier:** R-HSA-9671793

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



Hemostasis is a complex process that leads to the formation of a blood clot at the site of vessel injury. Three phases can be distinguished: primary hemostasis or formation of a platelet plug, secondary hemostasis, or coagulation and fibrinolysis (Kriz N et al. 2009). Defects in hemostasis cause an imbalance between the coagulation and fibrinolytic systems and may lead either to hypercoagulation, which can result in thrombosis, or to hypocoagulation and increased susceptibility to bleeding (also known as hemorrhagic diathesis) (van Herrewegen F et al. 2012a,b; Kumar R & Carcao M 2013). Abnormalities can result from disorders of the platelets (primary hemostasis defect), coagulation factors defects (secondary hemostasis defect), or a combination of both (van Herrewegen F et al. 2012a,b; Kumar R & Carcao M 2013). Coagulation disorders may be inherited or acquired. Further, abnormalities of the coagulation and fibrinolytic systems are coupled to the inflammatory response, which aggravates blood vessel permeability, inflammation, and cell damage in tissues (Sandra Margetic 2012; Kaplan AP & Joseph K 2016).

This Reactome module describes abnormalities of the coagulation cascade (secondary hemostasis) due to defects of coagulation factor proteins such as factor VIII (FVIII), FIX or FXII. The module also describes an abnormal FXII-mediated activation of the pro-inflammatory kallikrein-kinin system (KKS) 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).

## Literature references

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

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# Table of Contents

Introduction	1
 Disease	2
 Diseases of signal transduction by growth factor receptors and second messengers	3
 Diseases of mitotic cell cycle	4
 Diseases of cellular response to stress	5
 Diseases of programmed cell death	7
 Diseases of DNA repair	8
 Disorders of transmembrane transporters	10
 Diseases of metabolism	11
 Infectious disease	12
 Diseases of Immune System	13
 Diseases of the neuronal system	14
 Disorders of Developmental Biology	15
 Diseases of hemostasis	17
Table of Contents	19