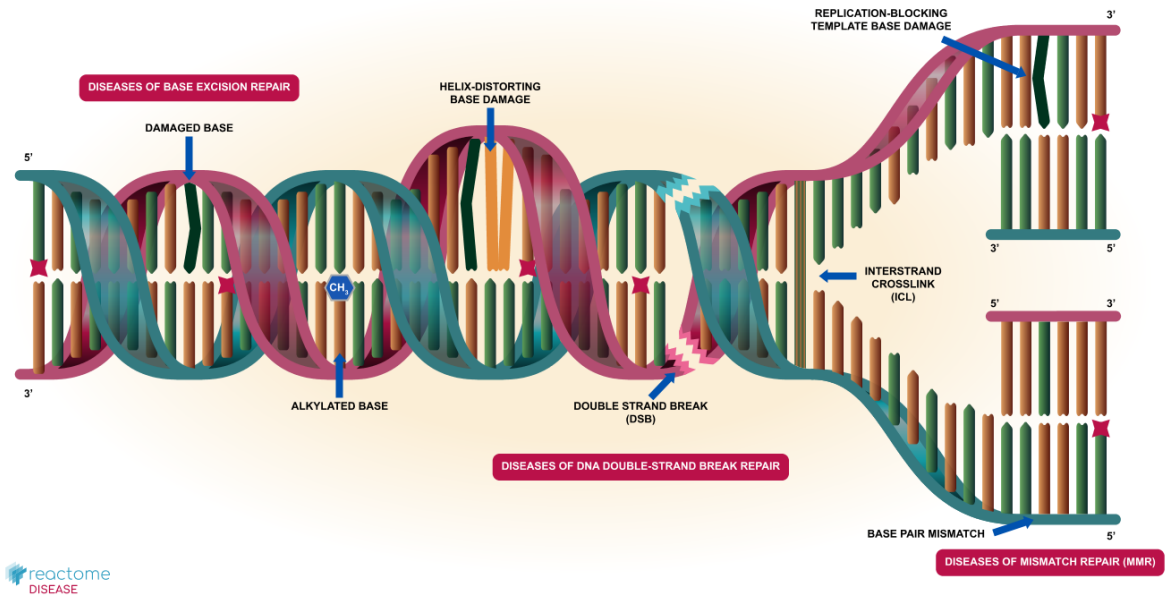
Diseases of DNA repair



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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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Literature references

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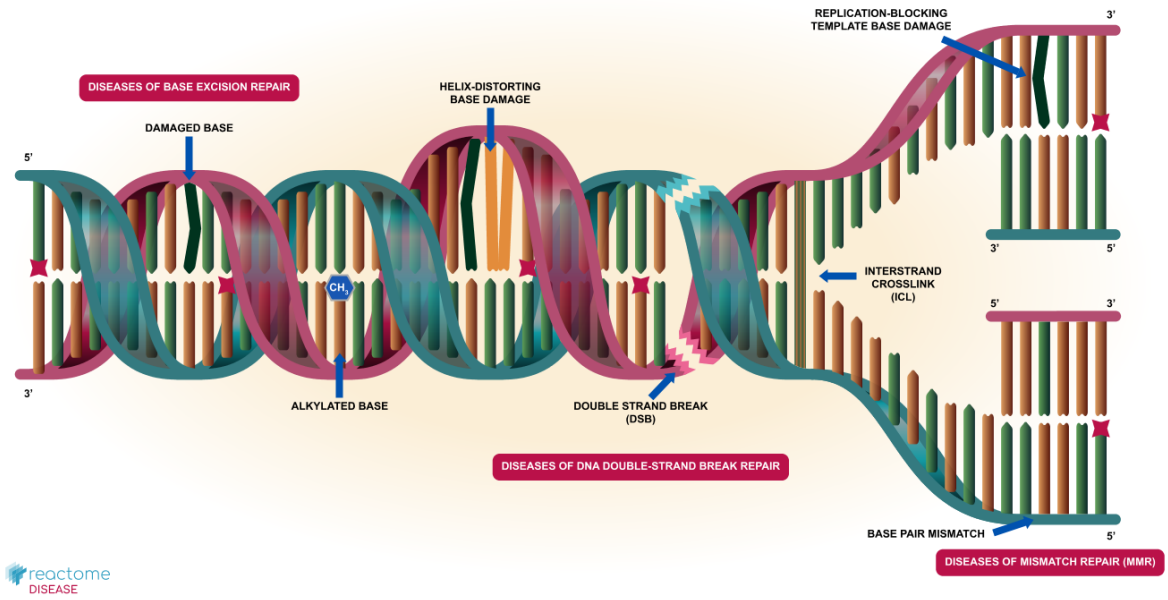
Diseases of DNA repair ↗

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, Brenerman 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 dis-

orders 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

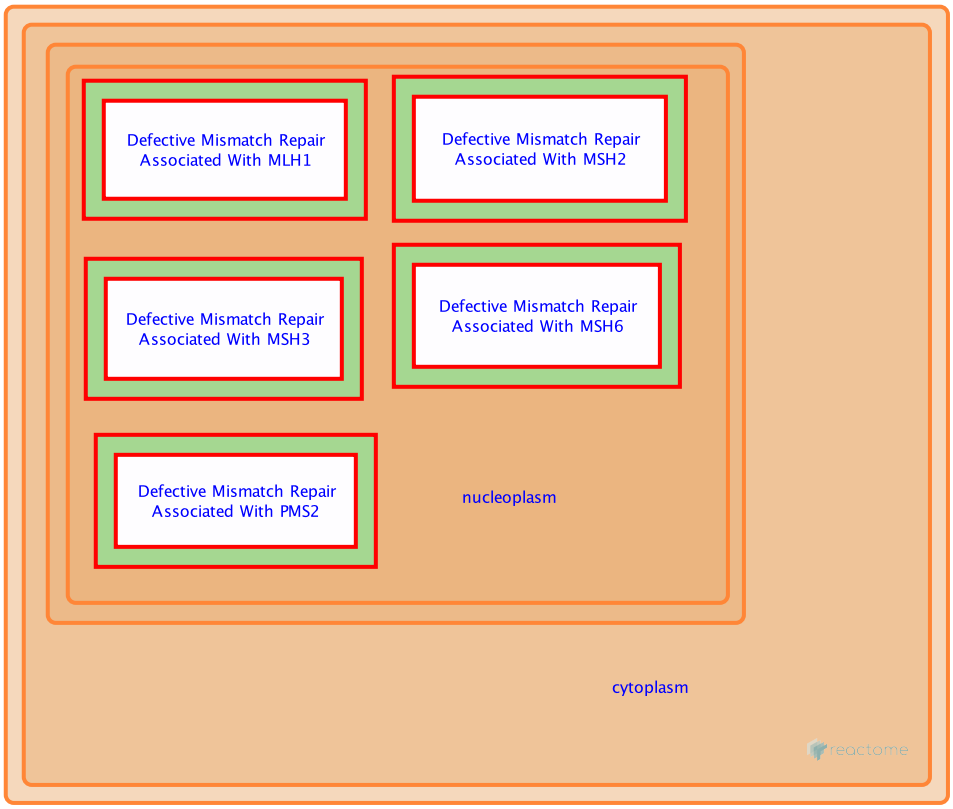
2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.
2020-11-11	Reviewed	D'Eustachio, P.
2020-11-12	Edited	Orlic-Milacic, M.

Diseases of Mismatch Repair (MMR) ↗

Location: Diseases of DNA repair

Stable identifier: R-HSA-5423599

Diseases: cancer



Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) are characterized by microsatellite instability and reduced fidelity during replication and repair steps. The MMR proteins interact with each other to execute steps within the mismatch repair pathway. Defective variants of these proteins are associated with nonpolyposis colorectal cancer. The MutS proteins are thought to directly contact double-stranded DNA, scanning along the genomic DNA for mismatches analogous to a "sliding clamp" until they encounter a base pair containing a mismatch. The MutS proteins interact with multiple proteins including other MLH and MutL, the later have significant amino acid identify and structural similarity to the MLH proteins, as well as RPA, EXO1, RFC, possibly HMGB1, and other less well-characterized proteins.

With respect to the mutator function, the MSH2/MutSaplha heterodimer is thought primarily to repair single-base substitutions and 1 bp insertiondeletion mutations, while MSH2/MutSbeta is thought primarily to repair 1-4 bp insertiondeletion mutations. The MLH and MutL heterodimer proteins interact with heterodimers of MutS proteins to help catalyze different functions. MLH1:MutLalpha is the primary complex that interacts with both MutS alpha and beta complex in mechanisms thought to be relevant to cancer prevention. Recent studies suggest that MLH1:MLH3 may also contributes to some of these processes as well, but in all mechanisms tested to a lesser degree than MLH1:PMS2.

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Editions

2014-03-03	Authored	Gillespie, ME.
2016-11-01	Reviewed	Arora, S.
2017-02-27	Edited	Gillespie, ME.

Diseases of Base Excision Repair ↗

Location: Diseases of DNA repair

Stable identifier: R-HSA-9605308

Diseases: cancer

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 other oxidative stress-related diseases. For review, please refer to Fu et al. 2012, Fletcher and Houlston 2010, Brenerman et al. 2014, Patrono et al. 2014, and D'Errico et al. 2017.

Literature references

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Editions

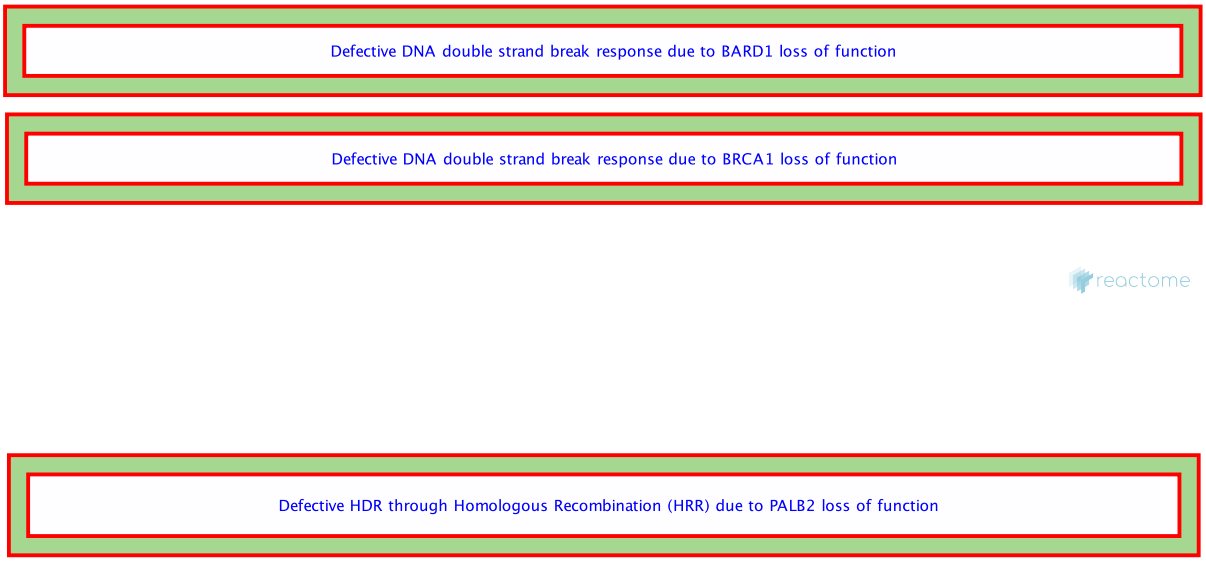
2018-05-12	Authored	Orlic-Milacic, M.
2018-08-09	Edited	Orlic-Milacic, M.

Diseases of DNA Double-Strand Break Repair ↗

Location: Diseases of DNA repair

Stable identifier: R-HSA-9675136

Diseases: cancer



Diseases of DNA double-strand break repair (DSBR) are caused by mutations in genes involved in repair of double strand breaks (DSBs), one of the most cytotoxic types of DNA damage. Unrepaired DSBs can lead to cell death, cellular senescence, or malignant transformation.

Germline mutations in DSBR genes are responsible for several developmental disorders associated with increased predisposition to cancer:

Ataxia telangiectasia, characterized by cerebellar neurodegeneration, hematologic malignancies and immunodeficiency, is usually caused by germline mutations in the ATM gene;

Nijmegen breakage syndrome 1, characterized by microcephaly, short stature and recurrent infections, is caused by germline mutations in the NBN (NBS1) gene;

Seckel syndrome, characterized by short stature, skeletal deformities and microcephaly, is caused by germline mutations in the ATR or RBBP8 (CtIP) genes.

Heterozygous germline mutations in BRCA1, BRCA2 or PALB2 cause the hereditary breast and ovarian cancer syndrome (HBOC), while homozygous germline mutations in BRCA2 and PALB2 cause Fanconi anemia, a developmental disorder characterized by short stature, microcephaly, skeletal defects, bone marrow failure, and predisposition to cancer.

Somatic mutations in DSBR genes are also frequently found in sporadic cancers.

We have so far annotated defects in DSB response caused by loss-of-function mutations in BRCA1 and its heterodimerization partner BARD1, which prevent the formation of the BRCA1:BARD1 complex.

For review, please refer to McKinnon and Caldecott 2007, Keijzers et al. 2017, and Jachimowicz et al. 2019.

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Keijzers, G., Bakula, D., Scheibye-Knudsen, M. (2017). Monogenic Diseases of DNA Repair. *N Engl J Med, 377*, 1868-1876. ↗

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