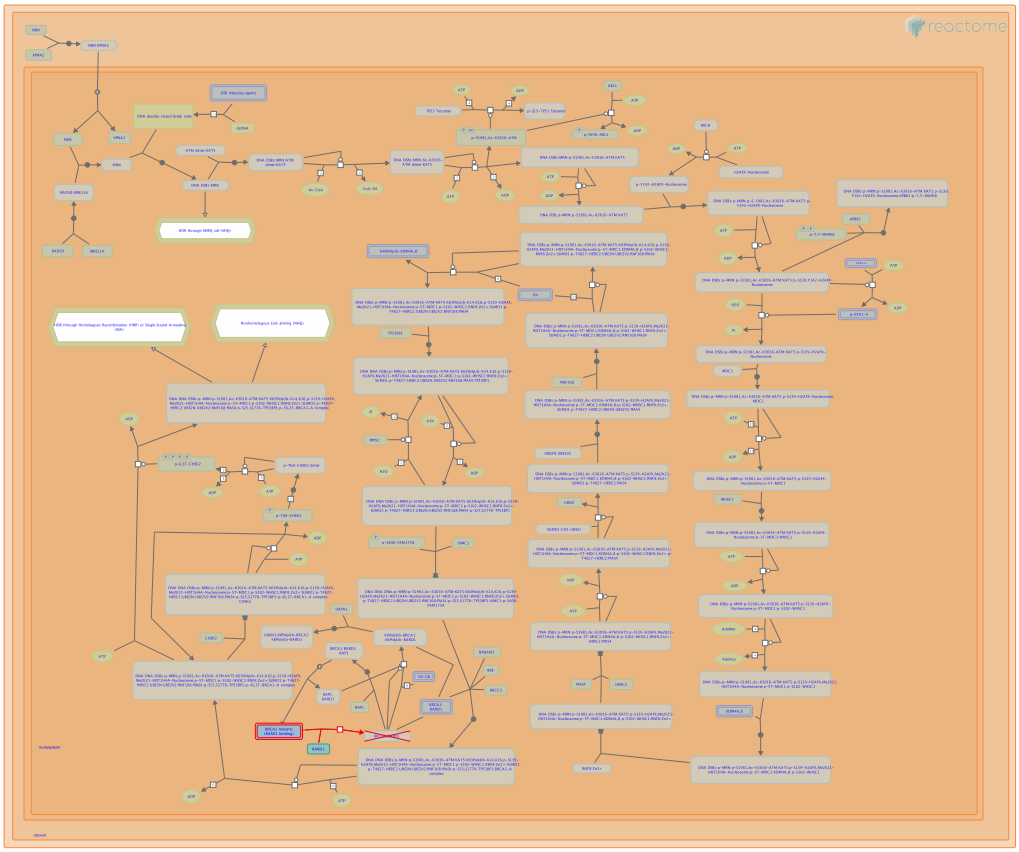
Defective DNA double strand break response due to BRCA1 loss of function



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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

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. ↗

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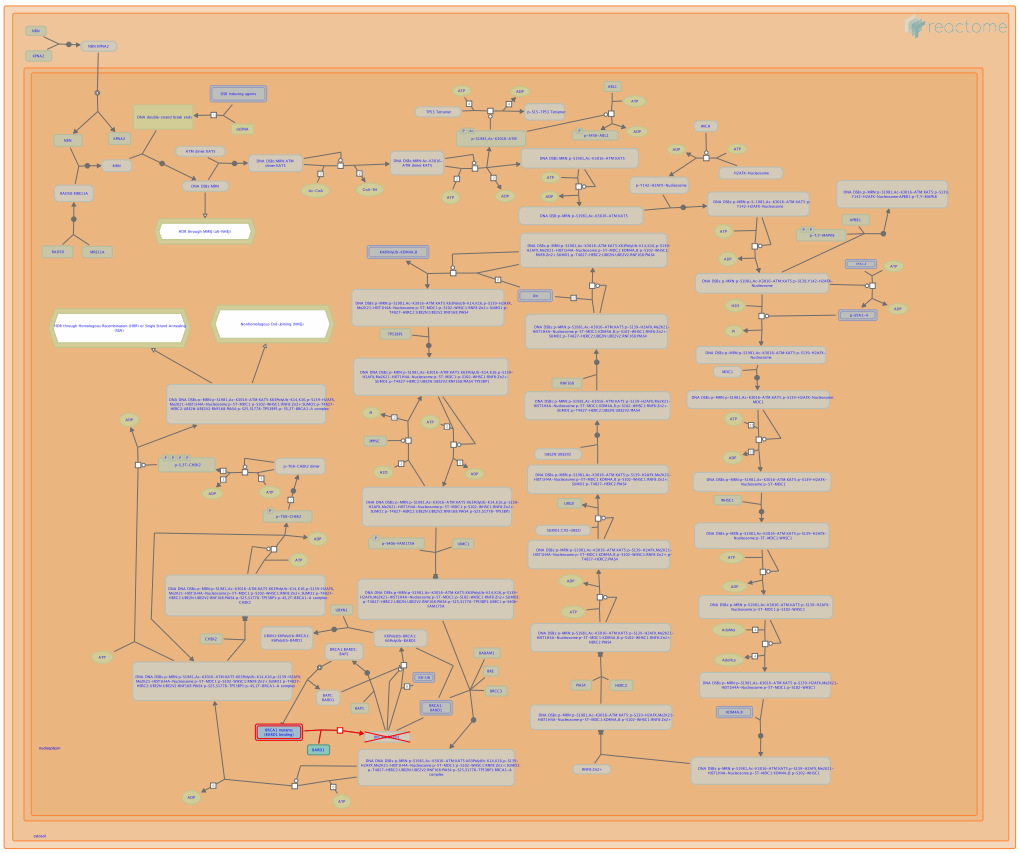
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Defective DNA double strand break response due to BRCA1 loss of function ↗

Stable identifier: R-HSA-9663199

Diseases: cancer



Germline mutations in the BRCA1 or BRCA2 tumor suppressor genes are implicated in up to 10% of breast cancers overall and 40% of familial breast cancers. Carriers of either BRCA1 or BRCA2 germline mutation are predisposed to hereditary breast and ovarian cancer (the HBOC syndrome), which is inherited in an autosomal dominant manner. Besides early onset breast and ovarian cancer, HBOC patients also have a modestly increased risk of developing other tumor types, including pancreatic, stomach, laryngeal, fallopian tube, and prostate cancer. The BRCA1 gene encodes a large protein of 1863 amino acids, which contains a RING finger domain at the N-terminus and two BRCT repeats at the C-terminus. The RING domain is responsible for heterodimerization with BARD1, which increases stability of BRCA1 and activates its E3 ubiquitin ligase activity. BRCA1 plays an important role in homology-directed repair of DNA double-strand breaks (DSBs). Brca1-null knockout mice die early during embryonic development and cells depleted of BRCA1 show genomic instability (reviewed by Roy et al. 2011). Cancer mutations that affect the RING domain of BRCA1 frequently result in the inability of BRCA1 to bind to BARD1 and participate in DNA DSB response (Wu et al. 1996, Ransburgh et al. 2010). Some mutations in the RING domain of BRCA1 were shown to affect the ubiquitin ligase activity of BRCA1 (Brzovic et al. 2001), but it is uncertain if the ubiquitin ligase activity is essential for the tumor suppressor role of BRCA1 (Shakya et al. 2011).

Literature references

Wu, LC., Wang, ZW., Tsan, JT., Spillman, MA., Phung, A., Xu, XL. et al. (1996). Identification of a RING protein that can interact in vivo with the BRCA1 gene product. *Nat. Genet., 14*, 430-40. ↗

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Editions

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Some pathogenic BRCA1 mutants do not bind BARD1 ↗

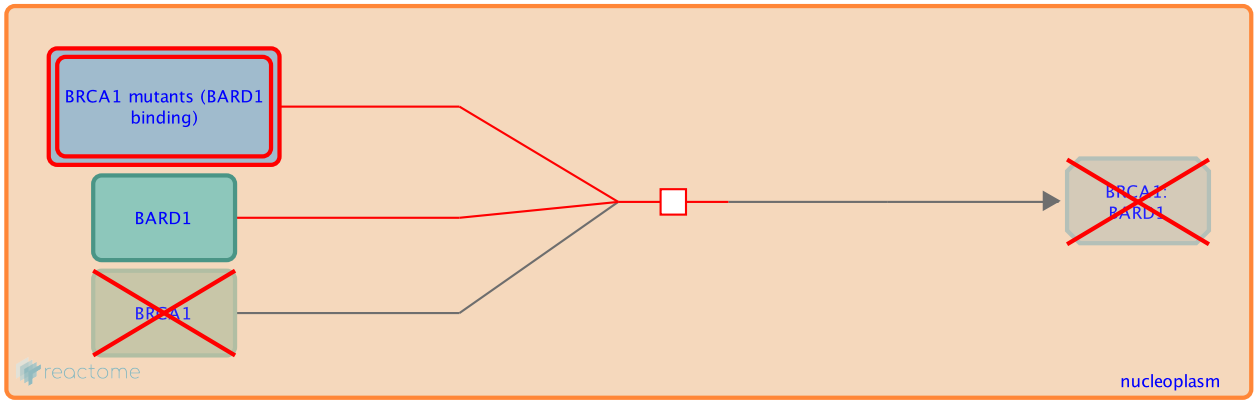
Location: Defective DNA double strand break response due to BRCA1 loss of function

Stable identifier: R-HSA-9663194

Type: transition

Compartments: nucleoplasm

Diseases: cancer



The heterodimerization of BRCA1 and BARD1 is mediated by sequences encompassing the N-terminal RING domains of both proteins (Wu et al. 1996, Brzovic, Rajagopal et al. 2001, Brzovic, Meza et al. 2001, Morris et al. 2002). Cancer-predisposing mutations in the RING domain of BRCA1 frequently disrupt the formation of the BRCA1:BARD1 complex.

The following BRCA1 mutants identified in cancer patients or in families with the hereditary breast and ovarian cancer syndrome were functionally tested and shown to be unable to bind to BARD1:

BRCA1 M18T (Ransburgh et al. 2010)

BRCA1 C24R (Ransburgh et al. 2010)

BRCA1 C27A (Ransburgh et al. 2010)

BRCA1 T37R (Ransburgh et al. 2010)

BRCA1 C39Y (Ransburgh et al. 2010)

BRCA1 H41A (Ransburgh et al. 2010)

BRCA1 H41R (Ransburgh et al. 2010)

BRCA1 C44F (Ransburgh et al. 2010)

BRCA1 C47G (Ransburgh et al. 2010)

BRCA1 C61G (Wu et al. 1996, Ransburgh et al. 2010)

BRCA1 C64G (Wu et al. 1996, Ransburgh et al. 2010)

BRCA1 C64R (Caleca et al. 2014).

The following BRCA1 mutants were identified in cancer and predicted to be pathogenic. They are annotated as candidate mutants for BARD1 binding deficiency based on sequence similarity with the functionally characterized missense mutants (the same amino acid residue affected by a missense mutation as in

a missense mutant shown to be unable to bind to BARD1) or based on the truncation of the RING domain due to frameshift mutations:

BRCA1 C24F

BRCA1 H41Q

BRCA1 C61Y

BRCA1 Q12Tfs*5

BRCA1 E23Afs*18

BRCA1 E23Rfs*18

BRCA1 E23Vfs*17

Literature references

Ransburgh, DJ., Chiba, N., Ishioka, C., Toland, AE., Parvin, JD. (2010). Identification of breast tumor mutations in BRCA1 that abolish its function in homologous DNA recombination. *Cancer Res., 70*, 988-95.

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