Defective BARD1 does not bind BRCA1

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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. ↗

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. ↗

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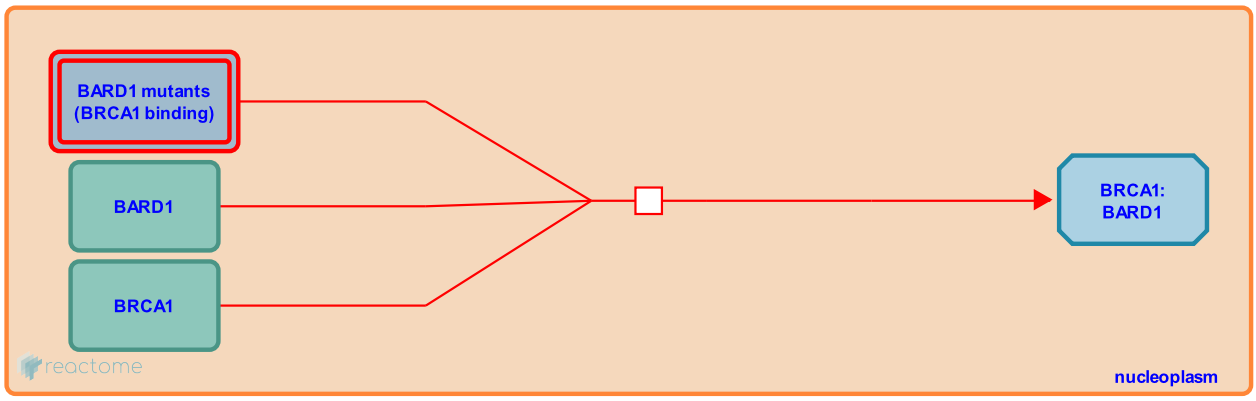
Stable identifier: R-HSA-9699163

Type: transition

Compartments: nucleoplasm

Diseases: cancer



The N-terminal RING domain and C-terminal BRCT repeats of BARD1 contribute to its binding to BRCA1 (Simons et al. 2006). While not frequently reported in cancer, missense mutations in these two regions of BARD1 affect BARD1 function in homology directed repair (HDR) by impairing its interaction with BRCA1 and may potentially contribute to hereditary breast and ovarian cancer (Lee et al. 2015).

The following BARD1 missense mutants have been reported in hereditary breast and ovarian cancer and shown to be impaired in their interaction with BRCA1 and in HDR:
BARD1 C53W (Lee et al. 2015; the C53W substitution produces an insoluble BARD1 protein)
BARD1 C71Y (Morris et al. 2002; Lee et al. 2015; the C71Y substitution produces an insoluble BARD1 protein)
BARD1 G623E (Lee et al. 2015).

The following BARD1 mutants impaired in their ability to bind to BRCA1 have been clinically reported but not in cancer samples and are annotated as candidates:

BARD1 W34R (Lee et al. 2015 - studied as a synthetic mutant, but is in ClinGen Allele Registry, Pawliczek et al. 2018)
BARD1 L44R (Morris et al. 2002, Lee et al. 2015 - studied as a synthetic mutant, but is in ClinGen Allele Registry, Pawliczek et al. 2018)
BARD1 C50G (Xia et al. 2003)
BARD1 C83G (Xia et al. 2003)

The following BARD1 mutants reported in cancer and predicted to be pathogenic have not been tested for their ability to bind to BRCA1 but share sequence similarity with functionally characterized BARD1 mutants:
BARD1 H68Y (similar to functionally characterized synthetic mutant BARD1 H68A, described in Xia et al. 2003)
BARD1 G632W (similar to functionally characterized cancer mutant BARD1 G623E, described in Lee et al. 2015).

Literature references

Clinical Genome (ClinGen) Resource, -., Wright, MW., Bizon, C., Zhen, J., Milosavljevic, A., Landrum, M. et al. (2018). ClinGen Allele Registry links information about genetic variants. *Hum. Mutat., 39*, 1690-1701. ↗

Parvinsmith, MR., Ceravolo, A., Banerjee, T., Gillespie, J., Fields, S., Parvin, JD. et al. (2015). Functional Analysis of BARD1 Missense Variants in Homology-Directed Repair of DNA Double Strand Breaks. *Hum. Mutat., 36*, 1205-14. ↗

Pao, GM., Xia, Y., Verma, IM., Chen, HW., Hunter, T. (2003). Enhancement of BRCA1 E3 ubiquitin ligase activity through direct interaction with the BARD1 protein. *J. Biol. Chem., 278*, 5255-63. ↗

Parvin, JD., Horwitz, AA., Glover, JN., Griffin, K., Williams, RS., Starita, LM. et al. (2006). BRCA1 DNA-binding activity is stimulated by BARD1. *Cancer Res., 66*, 2012-8. ↗

Editions

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