Defective D-loop formation mediated by PALB2, BRCA2 and RAD51 due to loss-of-function of PALB2 in BRCA1 binding

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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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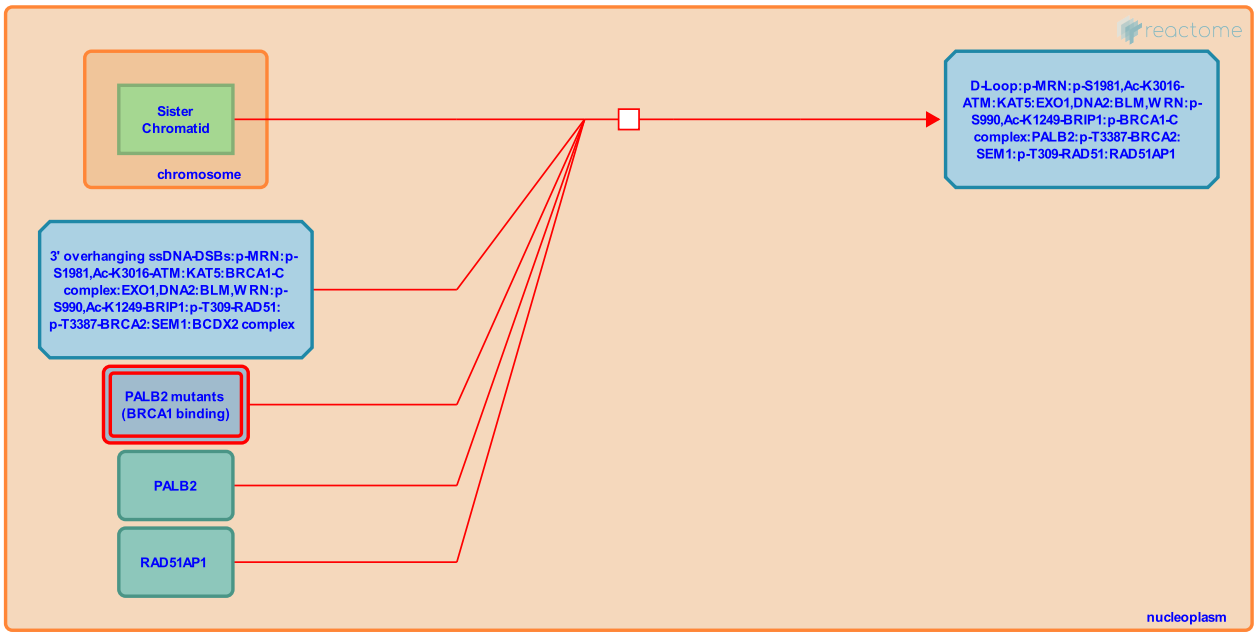
Stable identifier: R-HSA-9704330

Type: transition

Compartments: nucleoplasm

Diseases: cancer



The coiled-coil domain at the N-terminus of PALB2 represents a hotspot for mutations in *PALB2*. Several *PALB2* missense mutants have been characterized either in targeted studies (Sy et al. 2009, Foo et al. 2017, Song et al. 2018) or as part of high throughput approaches to characterize clinical variants of uncertain significance (reviewed in Boonen et al. 2020).

The following PALB2 missense mutants have been shown to be at least partially defective in their ability to bind to BRCA1 (some of these mutants were also shown to be defective in their ability to homodimerize and to promote homologous recombination repair (HRR); in addition, some have been shown to confer sensitivity to DNA damaging agents or to PARP inhibitors):
PALB2 L21A (originally studied as a synthetic mutant with an amino acid substitution at one of the coiled-coil domain residues of PALB2 that are critical for BRCA1 binding and homodimerization (Sy et al. 2009, Song et al. 2018); this mutant has also been reported clinically, in Clingen Allele Registry (Pawliczek et al. 2018), as a consequence of an in-frame indel in *PALB2*)
PALB2 L24S (Boonen et al. 2019; Wiltshire et al. 2020; also shown to be defective in HRR (Boonen et al. 2019, Wiltshire et al. 2020), confer sensitivity to cisplatin (Wiltshire et al. 2020) and PARP inhibitor olaparib (Wiltshire et al. 2020))
PALB2 Y28C (partially impaired in BRCA1 binding, Foo et al. 2017; significantly impaired BRCA1 binding, Rodrigue et al. 2019; does not disrupt PALB2 self-interaction (Foo et al. 2017); not significantly defective in HRR and does not confer sensitivity to DNA damaging agents and PARP inhibitors (Foo et al. 2017); partially defective in HRR (Rodrigue et al. 2019, Wiltshire et al. 2020) and significantly sensitive to cisplatin and PARP inhibition (Boonen et al. 2019))
PALB2 L35P (Foo et al. 2017, Rodrigue et al. 2019, Boonen et al. 2019, Wiltshire et al. 2020; does not disrupt PALB2 self-interaction (Foo et al. 2017); also shown to be defective in HRR (Foo et al. 2017, Rodrigue et al. 2019, Boonen et al. 2019, Wiltshire et al. 2020), confer sensitivity to platinum salts (Foo et al. 2017, Boonen et al. 2019, Wiltshire et al. 2020), and confer sensitivity to PARP inhibitors (Foo et al. 2017, Boonen et al. 2019, Wiltshire et al. 2020))
PALB2 R37H (not significantly affected in BRCA1 binding, Foo et al. 2017; partially impaired in BRCA1 binding, Boonen et al. 2019; partially defective in HRR (Foo et al. 2017, Rodrigue et al. 2019, Boonen et al. 2019, Wiltshire et al. 2020))

Interestingly, some of the PALB2 variants that show a defective interaction with BRCA1, such as PALB2 L24S, PALB2 Y28C, and PALB2 L35P, seem to have slightly elevated protein levels (Foo et al. 2017, Boonen et al. 2019,

Wiltshire et al. 2020).

Synthetic PALB2 mutants generated by directed mutagenesis, PALB2 L21P (Zhang et al. 2009), PALB2 L24P (Zhang et al. 2009), PALB2 Y28A (Sy et al. 2009) and PALB2 L35A (Sy et al. 2009) are also unable to bind BRCA1 and show impaired homologous recombination function.

The following PALB2 mutants, reported in cancer and predicted to be pathogenic, have not been functionally studied and are annotated as candidate loss-of-function mutants for BRCA1 binding based on their sequence similarity with functionally studied PALB2 mutants:
PALB2 L21F (similar to PALB2 L21A)
PALB2 L35F (similar to the synthetic mutant PALB2 L35A, described by Sy et al. 2009 and to the functionally characterized cancer-associated mutant PALB2 L35P)
PALB2 R37C (similar to PALB2 R37H)
PALB2 E12* (truncation mutants that lacks the coiled coil domain involved in BRCA1 binding, which maps to residues 9-42, as described by Sy et al. 2009; this truncation mutant may be a null mutant as the protein is predicted to have only the first 11 amino acids).

A comprehensive list of variants in the *PALB2* gene is provided at the Leiden Open Variation Database (LOVD) (https://databases.lovd.nl/shared/genes/PALB2) (Fokkema et al. 2011).

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