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# A comprehensive pathway of PALB2 gene that provides negative biofeedback paying regards to women breast cancer

**Dr. Partha Majumder and Debolina Chatterjee**

**Abstract**
*PALB2* has taken its place with *genuine/legitimate* breast cancer susceptibility genes. It is now well established that women who carry loss-of-function in the *PALB2* gene are in the position of similarly elevated breast cancer risks to those who carry mutations in *BRCA2*. Information about *PALB2* is now being used in breast cancer clinical genetics practice and is routinely included in breast cancer predisposition gene panel tests. However, prospective data related to the clinical outcomes of *PALB2* mutation carriers is lacking and very little information (beyond mutation penetrance) is available to guide current clinical management for carriers (affected and unaffected by cancer). In addition, clinical classification of the vast array of non-loss-of-function genetic variants identified in *PALB2* is in its infancy. These are key areas of current research efforts and are important foundations on which to move information about *PALB2* into the accuracy of public health arena.

**Keywords:** PALB2, Breast cancer, Cancer susceptibility, familial cancer, PALB2 mutation carrier

## Introduction
For the last two decades, women have been offered genetic testing of *BRCA1* and *BRCA2* in various clinical contexts. The vast majority of these women are seeking an explanation for a personal or family history of breast and/or ovarian cancer, and an accurate means of risk assessment, to facilitate risk management across the family. Indeed clinical criteria used to determine eligibility for *BRCA1* and *BRCA2* testing in many settings have been founded on the number of affected relatives and their age at diagnosis and then developed over time with increased evidence and local practice issues. Of those women who undergo testing, up to 20 % are found to carry a clinically actionable mutation in *BRCA1* or *BRCA2*. Until very recently additional genetic testing was not possible unless other clinical indicators were present (such as Li-Fraumeni syndrome that might indicate genetic testing of *TP53*). Women and their families who received uninformative genetic test results for *BRCA1* and *BRCA2* were clinically managed solely on the basis of their personal and family history. This limited the use of invasive strategies such as risk reduction surgery.
Continued research and a recent revolution in genetic technology that can be applied to this research has identified a number of additional breast cancer predisposition genes and reported a large number of additional candidate breast cancer predisposition genes that are yet to be validated. This same technology has also transitioned into molecular diagnostic laboratories and has enabled a shift from high cost single gene genetic tests to lower cost multi-gene panel tests. The uptake of gene panel tests has been rapid and included a volume of successful direct-to-the-public marketing. In some areas of clinical genetics, panel testing is now the standard of care [1]. With some important caveats and considerations discussed in this review, current data suggests that gene panel testing offers breast cancer clinical genetics practice increased opportunity to identify “actionable” genetic variants in a greater proportion of women [2, 3, 4].
However, few of the large number of genes included in many gene panel tests are *bona fide* breast cancer predisposition genes and the vast majority of genetic variation identified by these gene panel tests cannot be interpreted in terms of breast or ovarian cancer risk. This is currently a controversial area of breast cancer research and clinical genetics practice, and is discussed in detail elsewhere [5].

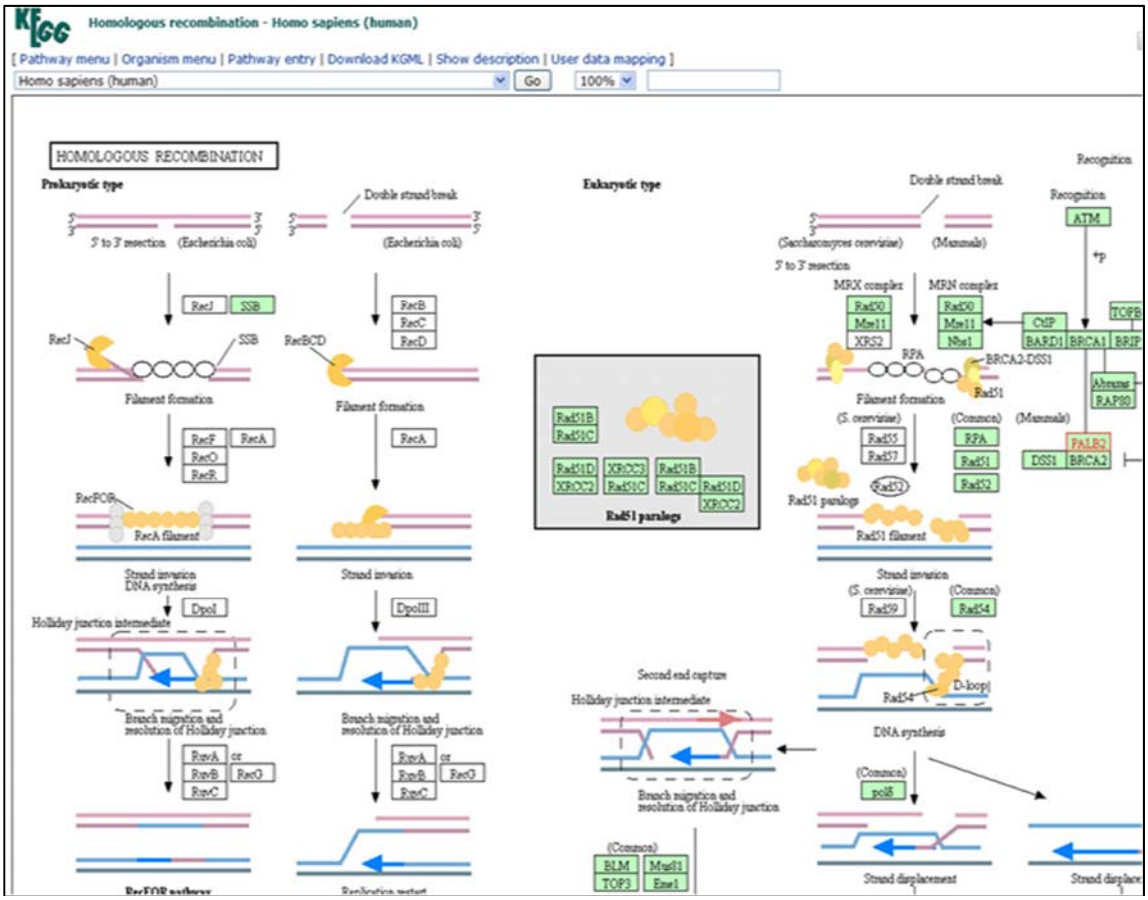



**Fig 1:** Pathways of PALB2 gene in Human (Homologous Recombination)

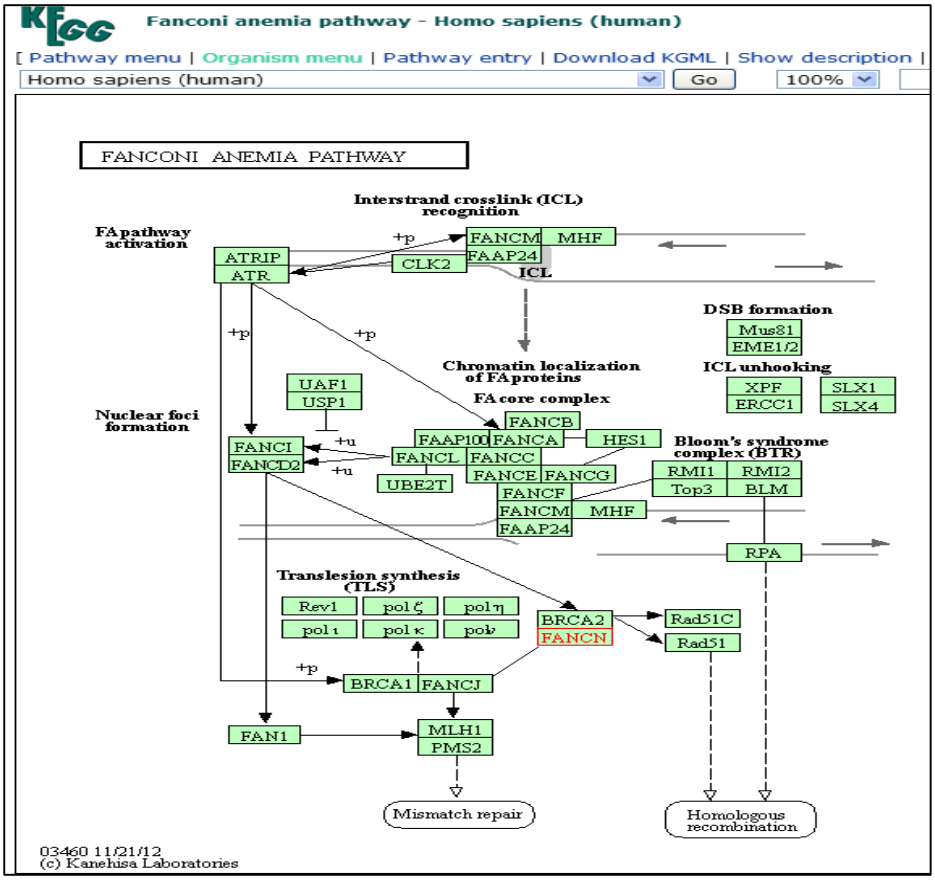



**Fig 2:** Pathway of Fanconi Anemia in Human

*PALB2* has now firmly taken its place with the small number of *genuine* breast cancer susceptibility genes. It is now well established that women who carry mutations in the *PALB2* gene are at similar breast cancer risks as those who carry mutations in *BRCA2* [6, 7]) making many rethink the appropriateness of the initial "moderate or intermediate risk gene" label [8].

*PALB2* now plays a legitimate role in breast cancer clinical genetics practice and takes a valid place on breast cancer predisposition gene panel tests. Internationally, tens of thousands of women, including those who have gone direct to the test provider, have had genetic tests for *PALB2* mutations in the context of breast cancer susceptibility. Today, many nations have (or are preparing) best practice guidelines that include recommendations for *PALB2* genetic testing and risk management [5, 9].

Currently, prospective data related to the clinical outcomes of *PALB2* mutation carriers is lacking and very little information (beyond mutation penetrance) is available to guide clinical management for carriers (affected and unaffected by breast cancer). Over the last two decades, evidence has slowly been accumulated to support recommendations around risk management and targeted treatment regimes for*BRCA1* and *BRCA2* mutation carriers. Very little of this evidence currently exists for *PALB2* mutation carriers.

Accumulating this evidence is challenging due to the very low frequency of women with *PALB2* mutations, even in affected women with a strong family history of breast and ovarian cancer. However, with new technology and international coordination there is promise that further evidence could be gathered for *PALB2* mutation carriers that will improve their clinical care within a few years.

In addition, risk estimates for *PALB2* mutations have been based on collections of loss-of-function mutations. Clinical classification of the vast array of non-loss-of-function genetic variants identified in *PALB2* is in its infancy. Informed by prior research in this area involving unclassified genetic variants in *BRCA1* and *BRCA2*, international initiatives are moving quickly to identify the best approaches to assess *PALB2* genetic variants on a variant-by-variant basis, to enable personalized use in clinical genetics practice.

*PALB2* has made it over the first hurdle and is now included in the breast cancer clinical genetics arena but to extend current utility and have an impact on improving the clinical outcomes for carriers of *PALB2* mutations and incorporate use of this genetic information into precision public health initiatives, additional data is still urgently required.

### *PALB2: A bona fide* breast cancer susceptibility gene

Mutations in *PALB2* make a small contribution to heritable breast cancer susceptibility in most populations. Germline *PALB2* mutations and carrier frequencies have been reviewed elsewhere [10]. Briefly, protein truncating mutations in *PALB2* are distributed throughout the coding region [6, 10] yet four *PALB2* mutations are of note in terms of multiple observations. As few studies have been conducted within unselected breast cancer cases, estimation of the age-specific cumulative risk (penetrance) of breast cancer associated with *PALB2* mutations has been limited.

To consider penetrance of a larger number of *PALB2* genetic variants and a larger number of families, the PALB2 interest group [19] embarked on a collaborative effort that collected data from 362 members of 154 families who had deleterious truncating, splice, or deletion mutations in *PALB2* [6]. The estimated average cumulative risk of breast cancer risk ranged from 33 % (95 % CI, 25–44 %) for a female carrier without affected relatives to 58 % (95 % CI, 50–66 %) for a female carrier with two first-degree relatives who had breast cancer diagnosed by 50 years of age. Supported by other similar observations [20], some recommend that both family history and *PALB2* genotype should be considered together for clinical breast cancer risk management.

Thus, all published estimates of penetrance of *PALB2* mutations are comparable to the breast cancer risk associated with *BRCA2* mutations: 45 % (95 % CI, 31–56 %) [7]. *PALB2* is now regarded as a *bona fide* breast cancer predisposition gene and is justifiably included on current breast cancer gene testing panels with the above evidence.

### *PALB2* mutations and risk of other cancer types

As PALB2 functions together with BRCA1 and BRCA2, in the same DNA-damage response pathway, it has been thought plausible that *PALB2* mutations, similar to *BRCA1* and *BRCA2* mutations, could predispose to other cancer types. The rarity of mutations in *PALB2* and the rarity of some of the other cancers likely to be involved (pancreatic, male breast cancer, ovarian cancer, prostate cancer) make the estimation of the risk (if any) extremely challenging. Data in this area continues to come from small (yet important) studies and case reports that accumulatively may assist this interpretation ([25] and many others). By pooling international resources, the PALB2 Interest Group estimated that the relative risk of ovarian cancer and male breast cancer for *PALB2* mutation carriers was 2.31 (95 % CI, 0.77–6.97; $P = 0.18$) and 8.30 (95 % CI, 0.77–88.56; $P = 0.08$) respectively [6].

There is still very little data and no evidence supporting an association between *PALB2* mutations and prostate cancer risk [13, 36, 37, 38, 39] although several pedigrees have been presented and a possible trend toward aggressive disease in carriers has been noted [39]. iCOGS measured *PALB2* (c.1592delT, p.Leu531Cysfs and c.3113G > A, p.Trp1038*) in 22,301 prostate cancer cases and 22,320 controls and found no evidence for association with prostate cancer risk OR 2.06, 95 % CI 0.59–7.11, $p = 0.24$ and OR 0.49, 95 % CI, 0.18–1.36, $p = 0.16$ respectively.

The *PALB2* interest group continues work to further refine breast and other cancer risks for *PALB2* mutation carriers [19].

### PALB2 mutation carriers: clinical outcomes:

As described above, recent work has increased the precision of breast cancer risk estimates for *PALB2*mutation carriers providing some new information with clinical utility. However, prospective data related to the clinical outcomes of *PALB2* mutation carriers seems to lacking and very little information (beyond mutation penetrance) which are available to guide current clinical management for carriers (affected and unaffected by breast cancer).

| Name/Gene ID | Description | Location | Aliases | MIM |
|---|---|---|---|---|
| ☑ PALB2 ID: 79728 | partner and localizer of BRCA2 [*Homo sapiens* (human)] | Chromosome 16, NC_000016.10 (23603162..23641357, complement) | FANCN, PNCA3 | 610355 |
| ☑ BRCA1 ID: 672 | BRCA1, DNA repair associated [*Homo sapiens* (human)] | Chromosome 17, NC_000017.11 (43044295..43125483, complement) | BRCAI, BRCC1, BROVCA1, FANCS, IRIS, PNCA4, PPP1R53, PSCP, RNF53 | 113705 |
| ☑ BRCA2 ID: 675 | BRCA2, DNA repair associated [*Homo sapiens* (human)] | Chromosome 13, NC_000013.11 (32315480..32399672) | BRCC2, BROVCA2, FACD, FAD, FAD1, FANCD, FANCD1, GLM3, PNCA2, XRCC11 | 600185 |
| ☐ Trp53 ID: 22059 | transformation related protein 53 [*Mus musculus* (house | Chromosome 11, NC_000077.6 (69580359..69591873) | Tp53, bbl, bfy, bhy, p44, p53 | |

**Fig 3:** PALB2 Mutation effects (Information retrieved from NCBI)

It has taken decades of research to provide the evidence base for *BRCA1* and *BRCA2* mutation carriers to make informed decision about the use of chemo-preventive agents, the use of the bilateral salpingo-oophorectomy, the use of mammography, magnetic resonance imaging (MRI) and other screening modalities, risk reducing mastectomy and targeted treatment regimes. Accumulating this evidence was challenging due in part to the very low frequency of women with *BRCA1 and BRCA2* mutations, the historically laborious and expensive process of testing for mutations in these genes and the need to follow these women prospectively.

However, in today's context where *PALB2* is being included in gene panel tests that are being conducted rapidly in large numbers at reduced costs and research can be conducted in a coordinated fashion internationally involving well established research resources (including resources founded to assess these questions for *BRCA1* and *BRCA2* mutation carriers) and in community-academic-industry partnerships- there is promise that evidence can be found for *PALB2* mutation carriers that will impact clinical practice in the short term.

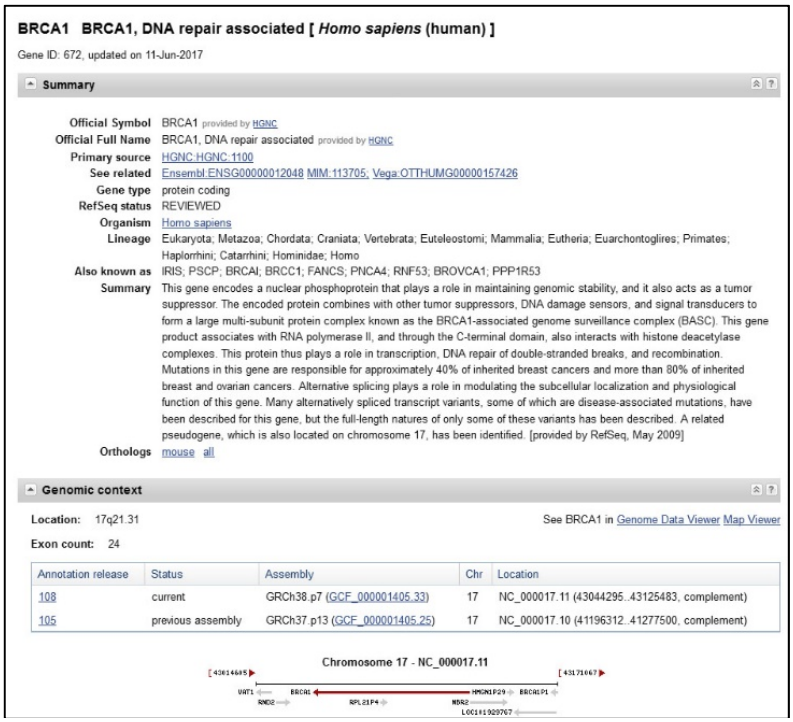
Further studies are required to test if women who carry *PALB2* mutations are at increased risk of death from breast cancer compared to non-carriers. More information is needed to understand the options for prevention and risk reduction. Intuitively, given the similar biological role of the protein, it is likely that some of the recommendations for *BRCA1* and *BRCA2* mutation carriers, including therapeutic regimes, may be relevant for *PALB2* mutation carriers – but much work is needed to resolve these questions.

To this end, a new academic-industry partnership named PROMPT– Prospective Registry of Multiplex Testing [42, 43], and many other large research initiatives are underway to address these important questions for carriers. PROMPT has scope beyond addressing these questions for *PALB2* alone and will support the rapid translation of similar information for several new breast cancer predisposition genes including *ATM*, *CDH1*, *CHEK2*, *RAD51C*, *RAD51D*, *STK11*, *TP53* in addition to *BRCA1* and *BRCA2*. PROMPT is an online research registry for people who have undergone gene panel testing and been found to have a genetic variation in one of the above genes. PROMPT is one of several initiatives that create a new paradigm for research study participation that directly involves the most relevant community. PROMPT is designed to involve those who want to share their genetic results, learn more from sharing these results and engage at a level of their choosing/comfort as a collaborator alongside physicians and researchers to learn more about how mutations in these genes (such as *PALB2*) may affect their health and cancer risks.


**Fig 4:** PALB2 Mutants in human Classification of rare variants

In contrast to several other breast cancer predisposition genes, there is no evidence that missense variants in *PALB2* (as a combined group) are associated with increased risk for breast cancer [44, 45]. We and others have reported that the breast cancer risk fraction contributed by missense variants in *BRCA1*, *BRCA2*, *ATM* and *CHEK2* is as high, if not higher, than protein-truncating variants in these genes [46, 47, 48]. However, interpretation of the rare genetic variation observed in *PALB2* on a variant-by-variant basis, especially the rare missense variants, remains challenging [44]. That is, on a variant-by-variant basis it is difficult provide any information that can be used to guide clinical management of carriers of rare missense mutations.

In some practices, the previous approach of breast cancer clinical genetics to generalize risk within groups of similar mutations (e.g., protein truncating mutations in *BRCA1*) has not been automatically applied in the context of *PALB2* due to i) a perception that the *PALB2* risk estimates currently include data from a disproportionate number of the founder *PALB2* mutations (and thus may not represent the average risk associated with all loss-of-function mutations) and ii) the more recent characterisation of variants in *BRCA1*(e.g., R1699Q [49, 50]) and *BRCA2* (e.g., K3326* [51, 52]) with more moderate or low risk of breast cancer that is also a plausible scenario for variants in other genes, including *PALB2*.



**BRCA1 BRCA1, DNA repair associated [ *Homo sapiens* (human) ]**

Gene ID: 672, updated on 11-Jun-2017

**Summary**

| | |
|---|---|
| **Official Symbol** | BRCA1 provided by HGNC |
| **Official Full Name** | BRCA1, DNA repair associated provided by HGNC |
| **Primary source** | HGNC:HGNC:1100 |
| **See related** | Ensembl:ENSG00000012048 MIM:113705; Vega:OTTHUMG00000157426 |
| **Gene type** | protein coding |
| **RefSeq status** | REVIEWED |
| **Organism** | Homo sapiens |
| **Lineage** | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo |
| **Also known as** | IRIS; PSCP; BRCAI; BRCC1; FANCS; PNCA4; RNF53; BROVCA1; PPP1R53 |
| **Summary** | This gene encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor. The encoded protein combines with other tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). This gene product associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complexes. This protein thus plays a role in transcription, DNA repair of double-stranded breaks, and recombination. Mutations in this gene are responsible for approximately 40% of inherited breast cancers and more than 80% of inherited breast and ovarian cancers. Alternative splicing plays a role in modulating the subcellular localization and physiological function of this gene. Many alternatively spliced transcript variants, some of which are disease-associated mutations, have been described for this gene, but the full-length natures of only some of these variants has been described. A related pseudogene, which is also located on chromosome 17, has been identified. [provided by RefSeq, May 2009] |
| **Orthologs** | mouse all |

**Genomic context**

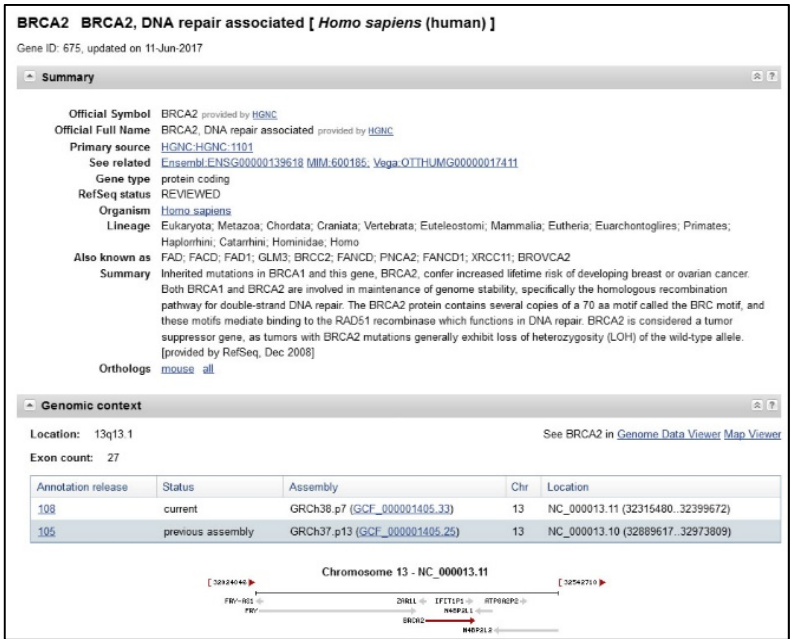
**Location:** 17q21.31 — See BRCA1 in Genome Data Viewer Map Viewer

**Exon count:** 24

| Annotation release | Status | Assembly | Chr | Location |
|---|---|---|---|---|
| 108 | current | GRCh38.p7 (GCF_000001405.33) | 17 | NC_000017.11 (43044295..43125483, complement) |
| 105 | previous assembly | GRCh37.p13 (GCF_000001405.25) | 17 | NC_000017.10 (41196312..41277500, complement) |

Chromosome 17 - NC_000017.11

**Fig 5:** Complete information of mutation in BRCA1



**BRCA2 BRCA2, DNA repair associated [ *Homo sapiens* (human) ]**

Gene ID: 675, updated on 11-Jun-2017

**Summary**

| | |
|---|---|
| **Official Symbol** | BRCA2 provided by HGNC |
| **Official Full Name** | BRCA2, DNA repair associated provided by HGNC |
| **Primary source** | HGNC:HGNC:1101 |
| **See related** | Ensembl:ENSG00000139618 MIM:600185; Vega:OTTHUMG00000017411 |
| **Gene type** | protein coding |
| **RefSeq status** | REVIEWED |
| **Organism** | Homo sapiens |
| **Lineage** | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo |
| **Also known as** | FAD; FACD; FAD1; GLM3; BRCC2; FANCD; PNCA2; FANCD1; XRCC11; BROVCA2 |
| **Summary** | Inherited mutations in BRCA1 and this gene, BRCA2, confer increased lifetime risk of developing breast or ovarian cancer. Both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The BRCA2 protein contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair. BRCA2 is considered a tumor suppressor gene, as tumors with BRCA2 mutations generally exhibit loss of heterozygosity (LOH) of the wild-type allele. [provided by RefSeq, Dec 2008] |
| **Orthologs** | mouse all |

**Genomic context**

**Location:** 13q13.1 — See BRCA2 in Genome Data Viewer Map Viewer

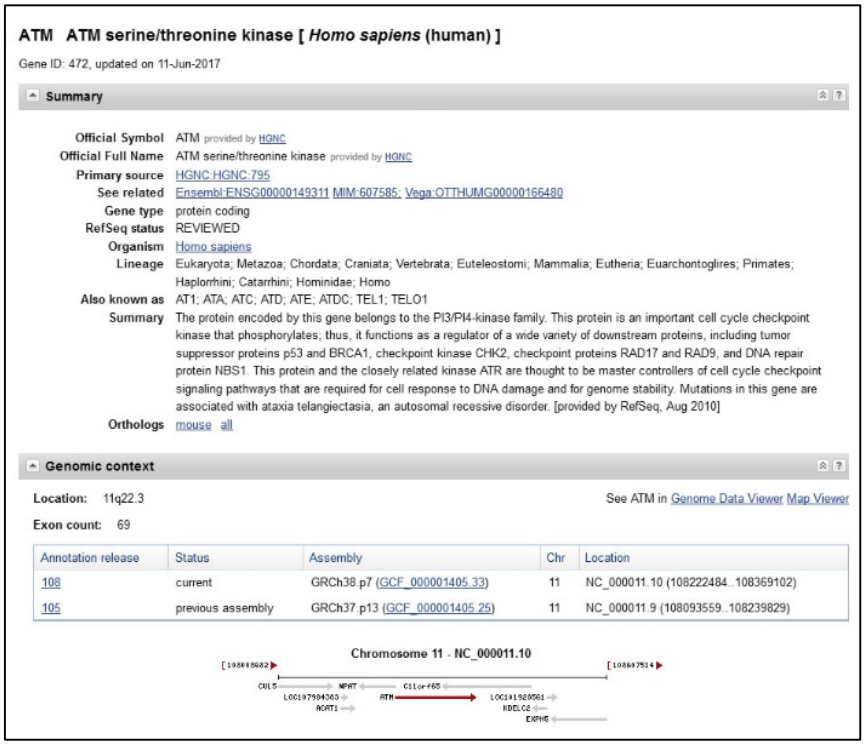
**Exon count:** 27

| Annotation release | Status | Assembly | Chr | Location |
|---|---|---|---|---|
| 108 | current | GRCh38.p7 (GCF_000001405.33) | 13 | NC_000013.11 (32315480..32399672) |
| 105 | previous assembly | GRCh37.p13 (GCF_000001405.25) | 13 | NC_000013.10 (32889617..32973809) |

Chromosome 13 - NC_000013.11

**Fig 6:** Complete information of BRCA2 Mutant in human

There is therefore a need to extend international efforts that are currently trying to classify rare variants identified in *BRCA1* and *BRCA2* for clinical use to include rare variants identified in *PALB2* (and other genes) to assist the clinical management of the individuals who carry them. Several activities are well underway.



**ATM ATM serine/threonine kinase [ *Homo sapiens* (human) ]**

Gene ID: 472, updated on 11-Jun-2017

**Summary**

| | |
|---|---|
| **Official Symbol** | ATM provided by HGNC |
| **Official Full Name** | ATM serine/threonine kinase provided by HGNC |
| **Primary source** | HGNC:HGNC:795 |
| **See related** | Ensembl:ENSG00000149311 MIM:607585; Vega:OTTHUMG00000166480 |
| **Gene type** | protein coding |
| **RefSeq status** | REVIEWED |
| **Organism** | Homo sapiens |
| **Lineage** | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo |
| **Also known as** | AT1; ATA; ATC; ATD; ATE; ATDC; TEL1; TELO1 |
| **Summary** | The protein encoded by this gene belongs to the PI3/PI4-kinase family. This protein is an important cell cycle checkpoint kinase that phosphorylates; thus, it functions as a regulator of a wide variety of downstream proteins, including tumor suppressor proteins p53 and BRCA1, checkpoint kinase CHK2, checkpoint proteins RAD17 and RAD9, and DNA repair protein NBS1. This protein and the closely related kinase ATR are thought to be master controllers of cell cycle checkpoint signaling pathways that are required for cell response to DNA damage and for genome stability. Mutations in this gene are associated with ataxia telangiectasia, an autosomal recessive disorder. [provided by RefSeq, Aug 2010] |
| **Orthologs** | mouse all |

**Genomic context**

**Location:** 11q22.3 — See ATM in Genome Data Viewer Map Viewer

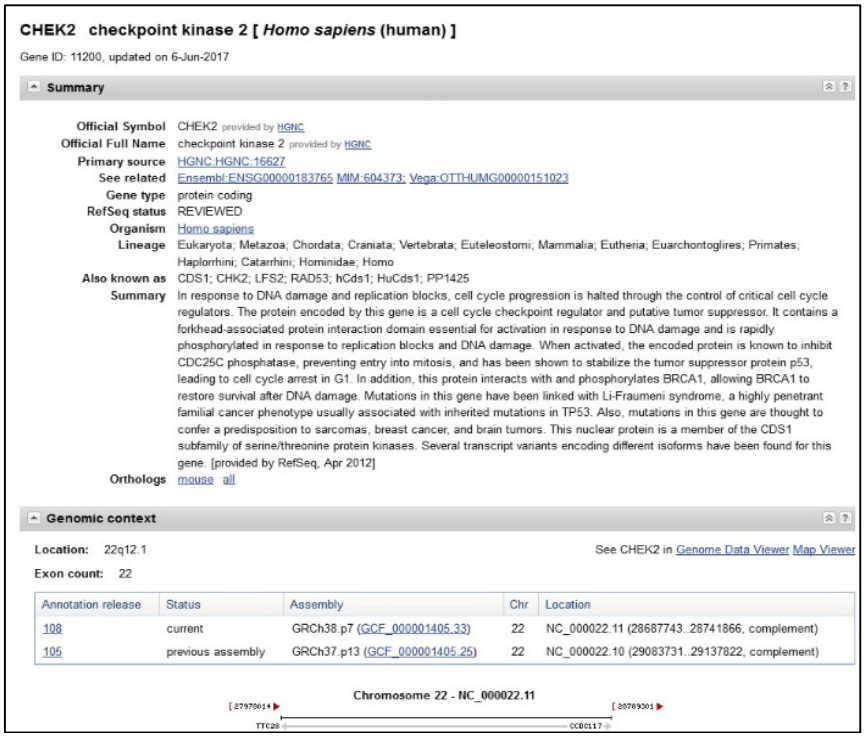
**Exon count:** 69

| Annotation release | Status | Assembly | Chr | Location |
|---|---|---|---|---|
| 108 | current | GRCh38.p7 (GCF_000001405.33) | 11 | NC_000011.10 (108222484..108369102) |
| 105 | previous assembly | GRCh37.p13 (GCF_000001405.25) | 11 | NC_000011.9 (108093559..108239829) |

Chromosome 11 - NC_000011.10

**Fig 7:** Complete informations of ATM Serine/Threonine Kinase in human

The most extensive and internationally set groups working in this area include The PALB2 Interest Group [6, 19] and The Evidence-based Network for the Interpretation of Germline Mutation Alleles (ENIGMA) [53, 54, 55] whose members are providing a range of data to accumulate new evidence on a variant-by-variant basis to be assessed in multifactorial risk models. These groups are also providing expert opinion to global databases and classification initiatives and working to communicate new information to clinical genetics practices urgently in need of individualized information.



**CHEK2 checkpoint kinase 2 [ *Homo sapiens* (human) ]**

Gene ID: 11200, updated on 6-Jun-2017

**Summary**

| | |
|---|---|
| **Official Symbol** | CHEK2 provided by HGNC |
| **Official Full Name** | checkpoint kinase 2 provided by HGNC |
| **Primary source** | HGNC:HGNC:16627 |
| **See related** | Ensembl:ENSG00000183765 MIM:604373; Vega:OTTHUMG00000151023 |
| **Gene type** | protein coding |
| **RefSeq status** | REVIEWED |
| **Organism** | Homo sapiens |
| **Lineage** | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo |
| **Also known as** | CDS1; CHK2; LFS2; RAD53; hCds1; HuCds1; PP1425 |
| **Summary** | In response to DNA damage and replication blocks, cell cycle progression is halted through the control of critical cell cycle regulators. The protein encoded by this gene is a cell cycle checkpoint regulator and putative tumor suppressor. It contains a forkhead-associated protein interaction domain essential for activation in response to DNA damage and is rapidly phosphorylated in response to replication blocks and DNA damage. When activated, the encoded protein is known to inhibit CDC25C phosphatase, preventing entry into mitosis, and has been shown to stabilize the tumor suppressor protein p53, leading to cell cycle arrest in G1. In addition, this protein interacts with and phosphorylates BRCA1, allowing BRCA1 to restore survival after DNA damage. Mutations in this gene have been linked with Li-Fraumeni syndrome, a highly penetrant familial cancer phenotype usually associated with inherited mutations in TP53. Also, mutations in this gene are thought to confer a predisposition to sarcomas, breast cancer, and brain tumors. This nuclear protein is a member of the CDS1 subfamily of serine/threonine protein kinases. Several transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Apr 2012] |
| **Orthologs** | mouse all |

**Genomic context**

**Location:** 22q12.1 — See CHEK2 in Genome Data Viewer Map Viewer

**Exon count:** 22

| Annotation release | Status | Assembly | Chr | Location |
|---|---|---|---|---|
| 108 | current | GRCh38.p7 (GCF_000001405.33) | 22 | NC_000022.11 (28687743..28741866, complement) |
| 105 | previous assembly | GRCh37.p13 (GCF_000001405.25) | 22 | NC_000022.10 (29083731..29137822, complement) |

Chromosome 22 - NC_000022.11

**Fig 8:** Complete informations of CHEK2 Variant in human

The assessment and clinical classification of rare missense variants in *PALB2* are likely to require incorporation of many pieces of evidence to enable clinical utility. Some of this evidence is likely to come from so-called functional assays. Fortunately, several functional domains of PALB2 are recognized including a coiled-coil structure, an ETGE-type KEAP1 binding motif, a chromatin-association motif (ChAM) at the N-terminus and a WD repeat motif in the C-terminus (reviewed elsewhere [10]). These domains, coupled with PALB2's role in DNA repair and Fanconi anemia, are facilitating work that is pitched at assessing the functional differences between wildtype PALB2 and PALB2 carrying rare missense mutations in key functional domains. Park *et al*., characterized effects of missense mutations of the PALB2 WD40 domain and demonstrated that PALB2 L939W (c.2816 T > G) and PALB2 L1143P (c.3428 T > A) display a decreased capacity for DNA double-strand break-induced homologous recombination and an increased cellular sensitivity to ionizing radiation [56]. This data offers much potentially useful information for rare variant classification.

Calibrated assays for functional assessment of variants in *BRCA1* and *BRCA2* have been developed and reported [57, 58]. Recently, a publically available resource for functional analysis of missense variants in*BRCA1* (*BRCA1* Circos) has been made available to facilitate meta-analysis of functional data and improve classification of variants in that gene [59]. It is anticipated that groups such as the Functional Working Group of ENIGMA [60] will be able to develop similar resources for PALB2 once assays are further developed and data is available.

## Conclusions

This gene encodes a protein that functions in genome maintenance (double strand break repair). This protein binds to and colocalizes with the breast cancer 2 early onset protein (BRCA2) in nuclear foci and likely permits the stable intranuclear localization and accumulation of BRCA2. PALB2 binds the single strand DNA and directly interacts with the recombinase RAD51 to stimulate strand invasion, a vital step of homologous recombination. PALB2 can function synergistically with a BRCA2 chimera (termed piccolo, or piBRCA2) to further promote strand invasion. Variants in the *PALB2* gene are associated with an increased risk of developing breast cancer of magnitude similar to that associated with BRCA2 mutations and *PALB2*-deficient cells are sensitive to PARP inhibitors.

## Author's Contribution

Author, Debolina Chatterjee has extended in depth research and exclusive study regarding the present spectrum of PALB2 gene that has been manifested to write her this review in favour of mankind and well being of health science and cultivation.

In this paper, the author achieved extreme guidance favoring the in depth cultivation with a positive output from Dr. Partha Majumder, Human Physiologist and Systems Biologist, Former Principal Scientist of Helixinfosystems and Former Head & Coordinator of Sikkim Manipal University (CC:1637), Kolkata, India. Dr. Partha Majumder contributed a pioneer role to the design of the study, data analysis, and revision of the manuscript.

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## References

1. Zentner D, Thompson TN, James PA, Trainer A, Ades LC, Macciocca I *et al*. The cardiac genetics clinic: a model for multidisciplinary genomic medicine. Med J Aust. 2015; 203(6):261:e1-6.
2. Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS *et al*. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol. 2014; 32(19):2001-9. doi:10.1200/JCO.2013.53.6607
3. Desmond A, Kurian AW, Gabree M, Mills MA, Anderson MJ, Kobayashi Y *et al*. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol. 2015; 1(7):943-51. doi:10.1001/jamaoncol.2015.2690
4. Thompson ER, Rowley SM, Li N, McInerny S, Devereux L, Wong-Brown MW *et al*. Panel Testing for Familial Breast Cancer: Calibrating the Tension between Research and Clinical Care. J Clin Oncol. 2016. doi:10.1200/JCO.2015.63.7454
5. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL *et al*. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015; 372(23):2243-57. doi:10.1056/NEJMsr1501341
6. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkas K, Roberts J *et al*. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014; 371(6):497-506. doi:10.1056/NEJMoa1400382
7. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL *et al*. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003; 72(5):1117-30.
8. Rahman N, Seal S, Thompson D, Kelly P, Renwick A, Elliott A *et al*. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. 2007; 39(2):165-7.
9. Evi Q. Cancer Treatment Online. https://www.eviq.org.au
10. Southey MC, Teo ZL, Winship I. PALB2 and breast cancer: ready for clinical translation! Appl Clin Genet. 2013; 6:43-52. doi:10.2147/TACG.S34116
11. Dansonka-Mieszkowska A, Kluska A, Moes J, Dabrowska M, Nowakowska D, Niwinska A *et al*. A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. BMC Med Genet. 2010; 11:20. doi:10.1186/1471-2350-11-20
12. Foulkes WD, Ghadirian P, Akbari MR, Hamel N, Giroux S, Sabbaghian N *et al*. Identification of a novel truncating PALB2 mutation and analysis of its contribution to early-onset breast cancer in French-

Canadian women. Breast Cancer Res. 2007; 9(6):R83. doi:10.1186/bcr1828
13. Erkko H, Xia B, Nikkila J, Schleutker J, Syrjakoski K, Mannermaa A *et al*. A recurrent mutation in PALB2 in Finnish cancer families. Nature. 2007; 446(7133):316-9. doi:10.1038/nature05609
14. Casadei S, Norquist BM, Walsh T, Stray S, Mandell JB, Lee MK *et al*. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011; 71(6):2222-9. doi:10.1158/0008-5472.CAN-10-3958
15. Teo ZL, Sawyer SD, James PA, Mitchell G, Trainer AH, Lindeman GJ *et al*. The incidence of PALB2 c.3113G > A in women with a strong family history of breast and ovarian cancer attending familial cancer centres in Australia. Fam Cancer. 2013; 12(4):587-95. doi:10.1007/s10689-013-9620-4
16. Teo ZL, Park DJ, Provenzano E, Chatfield CA, Odefrey FA, Nguyen-Dumont T *et al*. Prevalence of PALB2 mutations in Australasian multiple-case breast cancer families. Breast Cancer Res. 2013; 15(1):R17. doi:10.1186/bcr3392
17. Southey MC, Teo ZL, Dowty JG, Odefrey FA, Park DJ, Tischkowitz M *et al*. A PALB2 mutation associated with high risk of breast cancer. Breast Cancer Res. 2010; 12(6):R109. doi:10.1186/bcr2796
18. Erkko H, Dowty JG, Nikkila J, Syrjakoski K, Mannermaa A, Pylkas K *et al*. Penetrance analysis of the PALB2 c.1592delT founder mutation. Clin Cancer Res. 2008; 14(14):4667-71. doi:10.1158/1078-0432.CCR-08-0210
19. PALB2 Interest Group. http://www.palb2.org
20. Heikkinen T, Karkkainen H, Aaltonen K, Milne RL, Heikkila P, Aittomaki K *et al*. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. 2009; 15(9):3214-22. doi:10.1158/1078-0432.CCR-08-3128
21. Keogh LA, Southey MC, Maskiell J, Young MA, Gaff CL, Kirk J *et al*. Uptake of offer to receive genetic information about BRCA1 and BRCA2 mutations in an Australian population-based study. Cancer Epidemiol Biomarkers Prev. 2004; 13(12):2258-63.
22. Peterlongo P, Catucci I, Colombo M, Caleca L, Mucaki E, Bogliolo M *et al*. FANCM c.5791C > T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor. Hum Mol Genet. 2015; 24(18):5345-55. doi:10.1093/hmg/ddv251
23. Cybulski C, Carrot-Zhang J, Kluzniak W, Rivera B, Kashyap A, Wokolorczyk D *et al*. Germline RECQL mutations are associated with breast cancer susceptibility. Nat Genet. 2015; 47(6):643-6. doi:10.1038/ng.3284
24. Southey MC, Park DJ, Nguyen-Dumont T, Campbell I, Thompson E, Trainer AH *et al*. COMPLEXO: identifying the missing heritability of breast cancer via next generation collaboration. Breast Cancer Res. 2013; 15(3):402. doi:10.1186/bcr3434.
25. Vietri MT, Caliendo G, Casamassimi A, Cioffi M, De Paola ML, Napoli C *et al*. A novel PALB2 truncating mutation in an Italian family with male breast cancer. Oncol Rep. 2015; 33(3):1243-7. doi:10.3892/or.2014.3685
26. Peterlongo P, Catucci I, Pasquini G, Verderio P, Peissel B, Barile M *et al*. PALB2 germline mutations in familial breast cancer cases with personal and family history of pancreatic cancer. Breast Cancer Res Treat. 2011; 126(3):825-8. doi:10.1007/s10549-010-1305-1
27. Tischkowitz MD, Sabbaghian N, Hamel N, Borgida A, Rosner C, Taherian N *et al*. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. Gastroenterology. 2009; 137(3):1183-6. doi:10.1053/j.gastro.2009.06.055
28. Hofstatter EW, Domchek SM, Miron A, Garber J, Wang M, Componeschi K *et al*. PALB2 mutations in familial breast and pancreatic cancer. Fam Cancer. 2011; 10(2):225-31. doi:10.1007/s10689-011-9426-1
29. Slater EP, Langer P, Niemczyk E, Strauch K, Butler J, Habbe N *et al*. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010; 78(5):490-4. doi:10.1111/j.1399-0004.2010.01425.x
30. Ghiorzo P, Pensotti V, Fornarini G, Sciallero S, Battistuzzi L, Belli F *et al*. Contribution of germline mutations in the BRCA and PALB2 genes to pancreatic cancer in Italy. Fam Cancer. 2012; 11(1):41-7. doi:10.1007/s10689-011-9483-5
31. Harinck F, Kluijt I, van Mil SE, Waisfisz Q, van Os TA, Aalfs CM *et al*. Routine testing for PALB2 mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated. Eur J Hum Genet. 2012; 20(5):577-9. doi:10.1038/ejhg.2011.226
32. Salo-Mullen EE, O'Reilly EM, Kelsen DP, Ashraf AM, Lowery MA, Yu KH *et al*. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015; 121(24):4382-8. doi:10.1002/cncr.29664
33. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P *et al*. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015; 518(7540):495-501. doi:10.1038/nature14169
34. Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP *et al*. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women with Ovarian Cancer. J Natl Cancer Inst. 2015; 107:11. doi:10.1093/jnci/djv214.
35. Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S *et al*. Inherited Mutations in Women with Ovarian Carcinoma. JAMA Oncol. 2015; 1-9. doi:10.1001/jamaoncol.2015.5495
36. Tischkowitz M, Easton DF, Ball J, Hodgson SV, Mathew CG. Cancer incidence in relatives of British Fanconi Anaemia patients. BMC Cancer. 2008; 8:257. doi:10.1186/1471-2407-8-257
37. Tischkowitz M, Sabbaghian N, Ray AM, Lange EM, Foulkes WD, Cooney KA. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in hereditary prostate cancer. Prostate. 2008; 68(6):675-8. doi:10.1002/pros.20729
38. Mantere T, Haanpaa M, Hanenberg H, Schleutker J, Kallioniemi A, Kahkonen M *et al*. Finnish Fanconi anemia mutations and hereditary predisposition to breast and prostate cancer. Clin Genet. 2015; 88(1):68-73. doi:10.1111/cge.12447
39. Pakkanen S, Wahlfors T, Siltanen S, Patrikainen M, Matikainen MP, Tammela TL *et al*. PALB2 variants in hereditary and unselected Finnish prostate cancer cases.

J Negat Results Biomed. 2009; 8:12. doi:10.1186/1477-5751-8-12
40. Cybulski C, Kluzniak W, Huzarski T, Wokolorczyk D, Kashyap A, Jakubowska A *et al*. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. 2015; 16(6):638-44. doi:10.1016/S1470-2045(15)70142-7
41. Teo ZL, Provenzano E, Dite GS, Park DJ, Apicella C, Sawyer SD *et al*. Tumour morphology predicts PALB2 germline mutation status. Br J Cancer. 2013; 109(1):154-63. doi:10.1038/bjc.2013.295
42. PROMPT. https://promptinfo.squarespace.com/about-us/
43. Memorial Sloan Kettering Cancer Center. New Academic-Industry Partnership creates online registry for patients tested for inherited cancer risk. 2014. https://www.mskcc.org/press-releases/new-academic-industry-partnership-creates-online-registry-patients-tested-inherited-risk
44. Tavtigian SV, Chenevix-Trench G. Growing recognition of the role for rare missense substitutions in breast cancer susceptibility. Biomark Med. 2014; 8(4):589-603. doi:10.2217/bmm.13.143
45. Tischkowitz M, Capanu M, Sabbaghian N, Li L, Liang X, Vallee MP *et al*. Rare germline mutations in PALB2 and breast cancer risk: a population-based study. Hum Mutat. 2012; 33(4):674-80. doi:10.1002/humu.22022
46. Scott CL, Jenkins MA, Southey MC, Davis TA, Leary JA, Easton DF *et al*. Average age-specific cumulative risk of breast cancer according to type and site of germline mutations in BRCA1 and BRCA2 estimated from multiple-case breast cancer families attending Australian family cancer clinics. Hum Genet. 2003; 112(5-6):542-51. doi:10.1007/s00439-003-0908-6
47. Tavtigian SV, Oefner PJ, Babikyan D, Hartmann A, Healey S, Le Calvez-Kelm F *et al*. Rare, evolutionarily unlikely missense substitutions in ATM confer increased risk of breast cancer. Am J Hum Genet. 2009; 85(4):427-46
48. Le Calvez-Kelm F, Lesueur F, Damiola F, Vallee M, Voegele C, Babikyan D *et al*. Rare, evolutionarily unlikely missense substitutions in CHEK2 contribute to breast cancer susceptibility: results from a breast cancer family registry case-control mutation-screening study. Breast Cancer Res. 2011; 13(1):R6. doi:10.1186/bcr2810
49. Lovelock PK, Spurdle AB, Mok MT, Farrugia DJ, Lakhani SR, Healey S *et al*. Identification of BRCA1 missense substitutions that confer partial functional activity: potential moderate risk variants? Breast Cancer Res. 2007; 9(6):R82. doi:10.1186/bcr1826
50. Spurdle AB, Whiley PJ, Thompson B, Feng B, Healey S, Brown MA *et al*. BRCA1 R1699Q variant displaying ambiguous functional abrogation confers intermediate breast and ovarian cancer risk. J Med Genet. 2012; 49(8):525-32. doi:10.1136/jmedgenet-2012-101037
51. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL *et al*. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet. 2013; 45(4):353-61. doi:10.1038/ng.2563. 61e1-2
52. Meeks HD, Song H, Michailidou K, Bolla MK, Dennis J, Wang Q *et al*. BRCA2 Polymorphic Stop Codon K3326X and the Risk of Breast, Prostate, and Ovarian Cancers. J Natl Cancer Inst. 2016; 108(2). doi:10.1093/jnci/djv315
53. ENIGMA Consortium. http://enigmaconsortium.org
54. Spurdle AB, Healey S, Devereau A, Hogervorst FB, Monteiro AN, Nathanson KL *et al*. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Hum Mutat. 2012; 33(1):2-7. doi:10.1002/humu.21628
55. Nguyen-Dumont T, Stewart J, Winship I, Southey MC. Rare genetic variants: making the connection with breast cancer susceptibility. AIMS Genet. 2015; 2(4):281-92. doi:10.3934/genet.2015.4.281
56. Park JY, Singh TR, Nassar N, Zhang F, Freund M, Hanenberg H *et al*. Breast cancer-associated missense mutants of the PALB2 WD40 domain, which directly binds RAD51C, RAD51 and BRCA2, disrupt DNA repair. Oncogene. 2014; 33(40):4803-12. doi:10.1038/onc.2013.421
57. Guidugli L, Pankratz VS, Singh N, Thompson J, Erding CA, Engel C *et al*. A classification model for BRCA2 DNA binding domain missense variants based on homology-directed repair activity. Cancer Res. 2013; 73(1):265-75. doi:10.1158/0008-5472.CAN-12-2081
58. Quiles F, Fernandez-Rodriguez J, Mosca R, Feliubadalo L, Tornero E, Brunet J *et al*. Functional and structural analysis of C-terminal BRCA1 missense variants. PLoS ONE. 2013; 8(4):e61302. doi:10.1371/journal.pone.0061302
59. Jhuraney A, Velkova A, Johnson RC, Kessing B, Carvalho RS, Whiley P *et al*. BRCA1 Circos: a visualisation resource for functional analysis of missense variants. J Med Genet. 2015; 52(4):224-30. doi:10.1136/jmedgenet-2014-102766
60. Millot GA, Carvalho MA, Caputo SM, Vreeswijk MP, Brown MA, Webb M *et al*. A guide for functional analysis of BRCA1 variants of uncertain significance. Hum Mutat. 2012; 33(11):1526-37. doi:10.1002/humu.22150