

## **BRIP1, a potential candidate gene in development of non-BRCA1/2 breast cancer**

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### **1. ABSTRACT**

*BRIP1* encodes a protein belonging to the RecQ DEAH helicase family. It interacts with *BRCA1*, and is involved in the repair of DNA damage and tumor suppression. Aberrations in *BRIP1* have been mainly associated with the development of breast cancer (BC), ovarian cancer, and type J Fanconi anemia. Based on recent work, we hypothesize that *BRIP1* might be the gene involved in the onset of BC in families that do not show *BRCA1/2* mutations. This review will focus on the findings supporting this hypothesis, the mechanisms linking *BRIP1* to the onset of BC, and the potential clinical relevance of its various inhibitors.

### **2. INTRODUCTION**

The FANC genes involved in the production of proteins that regulate Fanconi anemia (FA) signaling pathway, detect DNA damage, specifically inter-strand cross-links and stimulate its repair (1). Sixteen FA or FA-like genes have been identified including, *FANCA*, *FANCB*, *FANCC*, *FANCD1* (*BRCA2*), *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCJ* (*BRIP1*), *FANCL*, *FANCM*, *FANCN* (*PALB2*), *FANCP*, *RAD51C*, and *XPF* (1). The FA core complex, the main component of the FA pathway, consists of eight FANC proteins (*Fanca*, *Fancb*, *Fancc*, *Fance*, *Fancl*, *Fancf*, *Fancg*, *Fanci*, and *Fancm*) and two additional proteins called Fanconi anemia-associated proteins (Faaps) (1). Upon recognition of the DNA damage, *FANCD2* and *FANCD1* are activated by mono-ubiquitination, and bind together to form the

ID complex attracting DNA repair proteins to the site of damage, thus allowing the replication to continue (1, 2). However, *BRIP1* is not needed for *Fancd2* mono-ubiquitination, indicating that *BRIP1* acts downstream of *Fancd2* (3) in later stages of the Fanconi anemia pathway, post *Fancd2* ubiquitination (4). Thus, aberrations in any of the FANC genes abrupt the DNA repair mechanisms, resulting in Fanconi Anemia, a disorder characterized by physical abnormalities, loss of bone marrow function and elevated risk of cancer, particularly breast cancer (BC) (2). However, similar to *BRCA2*, *BRIP1*, or *PALB2*, some FANC gene mutations are specifically associated with the early onset of cancers of the breast, the ovaries and the pancreas.

*BRCA1* interacting protein C-terminal helicase1 (*BRIP1*), also known as *BACH1* or *FANCJ* was initially identified for its physical interaction with *BRCA1*. It consists of 20 exons spanning a region greater than 180 kb on chromosome 17q22 (5). The initial proof for the clinical importance of *BRIP1* was the identification of germ-line mutations within *BRIP1* in patients associated with early BC, showing normal genotypes for *BRCA1* and *BRCA2*; thus suggesting a link between *BRIP1* mutations and low penetrance breast and ovarian cancers (5-7).

Here we discuss the current knowledge of these mechanisms by various research analyses and the progress in understanding the multiple roles of *BRIP1*.

**Table 1.** *BRIP1* domains and motifs

Exon	Domains	Motifs
3	ATP Dependent RNA helicase CHL1 Ding DEXD <sub>c</sub> 2 (ABC_ATPase superfamily)	<b>Ps00197:</b> 2Fe2s_FER_1 (Iron Sulphur binding region)
4		<b>Ps01177:</b> Anaphylotoxin_1 domain
7	DEAD_2 ATP Dependent RNA helicase CHL1 Ding DEXD <sub>c</sub> 2 (ABC_ATPase superfamily)	
8	DEAD_2 ATP Dependent RNA helicase CHL1 DEXD <sub>c</sub> 2	<b>Ps00197:</b> 2Fe2s_FER_1 (Iron Sulphur binding region)
9	DEAD_2	<b>Ps00197:</b> 2Fe2s_FER_1 (Iron Sulphur binding region) <b>Ps00022:</b> EGF like domain
12		<b>Ps01208:</b> VWFC domain
13	ATP Dependent RNA helicase CHL1 Ding	
15		<b>Ps00099:</b> Thiolase
16	Helic_c2, Helicase_c2 ATP Dependent RNA helicase CHL1 Ding (ABC_ATPase superfamily)	
19		<b>Ps00197:</b> 2Fe2s_FER_1 (Iron Sulphur binding region) <b>Ps01177:</b> Anaphylotoxin_1 domain
20	Pfam13900 GVQW motif	<b>Ps00197:</b> 2Fe2s_FER_1 (Iron Sulphur binding region) <b>Ps00022:</b> EGF like domain <b>Ps00099:</b> Thiolase <b>ps00956:</b> Hydrophobin

### 3. STRUCTURE OF *BRIP1*

*BRIP1*, member of FANC (Fanconi anemia, complementation groups) family, is located on the long arm of chromosome 17 (17q22; from base pair 61,679,185 to base pair 61,863,558), encompassing 180.7.7 kb of DNA including 19 introns and 20 exons (8). While, it is normally confined within the cytoplasm, nuclear envelope and the nucleus, post DNA damage translocates BRIP1/RPA1 complex to the nucleus (5).

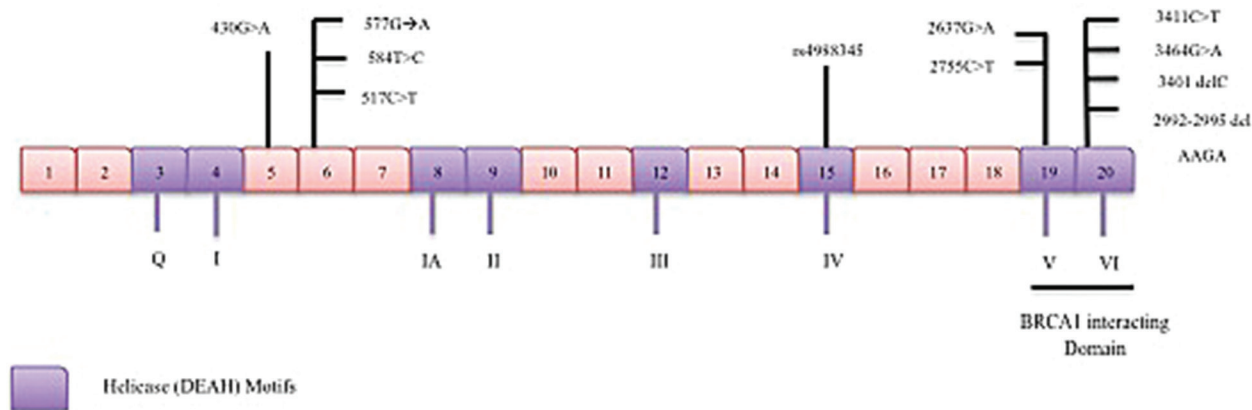
*BRIP1* protein consists of 1249 amino acids involved in DNA damage repair as well as a conserved helicase ATP-core binding domain, comprised of eight motifs (Q(0), I, Ia, II, III, IV, V, VI) (9) (Table 1). The principal motif is the iron-sulfur (Fe-S) cluster, characterized by four conserved cysteine residues; 4Fe-4S iron-sulfur-binding is essential for helicase activity to occur (10, 11). The other conserved motif, Q (DEAH box DNA helicase type), crucial for coordinating ATP binding, *BRIP1* catalytic activity and DNA repair function (12, 13), contributes to the onset of Fanconi anemia and BC. The C-terminal of *BRIP1* interacts with *BRCA1* through BRCT repeats (14) (Figure 1).

### 4. FUNCTIONS OF *BRIP1*

Physiologically, *BRIP1* is expressed in both malignant and normal cells. The following sections will discuss the role of *BRIP1* in both normal and malignant cells.

#### 4.1. Physiological functions of *BRIP1* in normal cells

The principal function of *BRIP1* is in the maintenance of genome integrity by regulating replication stress responses and, homologous recombination and cross-link repair (15). Upon its binding with RPA, *BRIP1* removes DNA-bound proteins in order to stabilize the replication fork and unwind the substitutive DNA structures that can obstruct normal DNA functions, thus providing genomic stability (16, 17). Also, *BRIP1* interacts with MLH1, a mismatch repair protein and along with FANCA, they localize to the sites of DNA crosslinks to unwind DNA and restore stalled replication forks (18). Interestingly, a study showed that the effect of *BRIP1* catalytic activity on Bloom syndrome (BLM) protein stability, is one of the factors required for maintaining genome stability and preventing replication stress (19).



**Figure 1.** Schematic representation of *BRIP1* structure and its mutations.

More interestingly, *BRIP1* contains the information needed for the production of a protein regulating the repair of DNA damage. It is a DNA dependent ATPase and DNA helicase, which interacts with *BRCA1* to repair DNA double-strand breaks by homologous recombination ultimately leading to chromosome stability. The *BRIP1* protein acts as a helicase and interacts with the BRCT domain of *BRCA1* during DNA damage; *BRIP1* unwinds the two strands of DNA double helix and *BRIP1*-*BRCA1* complex repairs DNA damage. Thus, *BRIP1* protein interacts with the *BRCA1* gene protein, within the cell nucleus, to repair broken strands of DNA during G2-M phase of the cell cycle; thus *BRIP1* and *BRCA1* proteins appear as tumor suppressors (20). However, in certain conditions, when *BRIP1* fails to bind to *BRCA1*, it facilitates poleta-dependent bypass (21). With the marked association between *BRCA1* and *BRIP1*; cells lacking *BRIP1* are sensitive to both DNA cross-linking agents and ionizing radiation and, are deficient in homologous recombination repair of double strand breaks (3). A recent study demonstrated that while, *FANCD2* was required for *BRIP1* chromatin localization; *BRIP1* in turn was required for regulating *FANCD2* localization onto chromatins in response to mitomycin C-induced DNA damage (22).

A few *BRIP1* phosphorylation sites have been identified that promote interactions to regulate DNA repair and checkpoint responses. The first phosphorylation site identified was Ser-990, where *BRIP1* binds to the BRCT repeats, indicating BRCT domain as a phosphor-protein binding domain (23); lack of this site inhibits homologous recombination (21). Interestingly, this site also overlaps with the binding to BLM protein, suggesting this interaction is influenced by phosphorSer-990 (19). *BRIP1*, while known to disrupt a RAD51-single-stranded DNA and impede RAD51 strand exchange, a major process in regulating DNA repair through homologous recombination (16); it interacts with TOPBP1 at Thr-133 for ATR-dependent phosphorylation as a consequence of stalled replication fork (24). Furthermore, in normal cells,

following DNA damage, acetylation of *BRIP1* at lysine 1249 enhances DNA damage repair and checkpoint signaling (25).

#### 4.2. Physiological functions of *BRIP1* in Fanconi anemia type J (FA-J)

A number of germline mutations have been found in the genes of the FA signaling pathway linked to Fanconi anemia, characterized by hypersensitivity to DNA-damaging agents, increased chromosome breakage and impaired DNA repair process. Individuals affected with FA are at a higher risk of developing solid tumors of the head and neck, and of gynecological systems (26).

Initially, *BRIP1* was identified by positional cloning as a gene mutated in Fanconi anemia type J (FA-J) (8), a rare disorder resulting in bone marrow failure, anemia, leukopenia and thrombopenia, hematologic and developmental abnormalities (cardiac, renal, skeletal and limb malformations), abnormal pigmentation, as well as high risk for the development of cancer (2, 26). A recurrent nonsense mutation (2392C→T), R798X (exon 17; deletion of helicase motif IV and *BRCA1*-interacting region) was identified in 5 alleles from 4 different ethnic background individuals, thus indicating to either be a hot-spot or a primeval mutation (8). Furthermore, three splice mutations in the intervening sequence (IVS) were identified; IVS3+5G→T (deletion of exon 3 encoding helicase motif I), IVS17+2insT (deficiency of exons 17 or 18; partial deletion of helicase motif VI) and, IVS11-498A→T (intronic nucleotide substitution; affected helix motifs between II and III) (8). From the remaining mutations, three were missense (1941G→C (exon 14; between motifs III and IV), 2119C→T (exon 15; motif IV) and, 765G→T (exon 7; helicase motif IA) and one was a frameshift mutation (2255-2256delAA) resulting in a premature stop codon (exon 15; inside motif V) (8). These mutations linked *BRIP1* with the onset and development of FA-J.

Any mutation or loss of the following members of the RecQ DEAH helicase family including *BLM*, *WRN* and *RECQL4* results in chromosomal instability syndromes which can confer a high risk of developing cancer (8, 27). Similar to these homologs is *BRIP1* whose loss or deficiency can be associated with DNA repair defect and predispose to breast, ovarian and pancreatic cancers (26).

#### **4.3. Physiological functions of *BRIP1* in cancer**

As mentioned above, *BRIP1* binds directly to the BRCT domains of *BRCA1* and functions as a tumor suppressor. Mutations in *BRIP1* increase the risk for development of BC and Fanconi anemia (5, 8). The following sections will highlight the various findings linking *BRIP1* to the development of BC.

##### **4.3.1. Physiological functions of *BRIP1* in breast cancer**

*BRIP1* has been considered as a low-penetrance BC predisposing gene (28). Although, several studies have been carried out to investigate the role of *BRIP1* in the onset of BC, the underlying mechanisms remain nascent. Several studies have laid the platform to explain the role of *BRIP1* in DNA repair mechanisms and genetic stability. Familial cases of BC lacking *BRCA* mutations can possibly be explained by the identification of low/moderate penetrance genes like *BRIP1* (29). Rahman and colleagues were the first to provide evidence of *BRIP1* gene as a BC susceptibility gene by carrying out mutational screening of the whole *BRIP1* gene sequence in a British group of familial BC cases and controls (30). Alterations in low penetrance genes such as *BRIP1* result in defects in DNA damage repair mechanisms, causing sporadic BC. Interestingly, haplo-insufficiency of *BRIP1* results in a short non-functional BRIP1 protein which fails to interact with BRCA1 protein to repair DNA damage, and stimulate cell growth and proliferation, leading to the onset of BC.

Previous studies have revealed potential associations between *BRIP1* variants and the onset of BC, and have identified truncating mutations in *BRIP1*, indicating the high-risk of non-BRCA1/BRCA2 families to BC (7). Mutation analysis or genotyping of *BRIP1* have identified SNPs and two alternatively spliced human isoforms for *BRIP1* are involved in various molecular and biological functions including ATP-dependent DNA helicase activity, protein binding, DNA binding, double-strand break repair, DNA damage checkpoint, DNA duplex unwinding (5, 7). Furthermore, BRIP 2392C>T mutation was found to be rare in the Irish population (31) as compared to its frequency in other populations (7), thus indicating *BRIP1* as a low-penetrance gene. A recent study among Korean patients identified one novel truncating mutation (1018C > T) in one patient, while 8 missense mutations were observed in 15 individuals (32). Among the missense mutations, 5 (787C > T, 1421T > C,

1442G > A, 2543G > A, and 2854A > G) were novel and 3 (430G > A, 587A > G, and 2830C > G) were known to be previously described (32).

Germline mutations affecting either the domain activity or the expression of messenger RNA (mRNA) of *BRIP1* were associated with the early onset and susceptibility to BC (5, 10). The first meta-analysis study on the polymorphisms identified that while, C47G (rs4988351) was heterogeneous and associated with an increased risk to BC; polymorphisms, Pro919Ser and G64AA had no association with BC (33). A germline mutation in exon 20 of *BRIP1*, c.2992–2995delAAGA, disrupted its BRCA1 binding domain leading to a premature codon interfering with the stability of the protein and its function (5, 28). Interestingly, in another study involving high-risk Jewish cases who were negative for mutations in both *BRCA* genes, seven germline mutations were identified in *BRIP1*; three missense (p.Ala745Thr (novel), p.Val193Ile and p.Ser919Pro), two silent (Glu879Glu and Tyr1137Tyr) and two intronic (c.346+21A>G and c.508-31C>G) mutations (34). Furthermore, two independent germline (missense) mutations P47A and M299I targeting the helicase domain of *BRIP1* were associated with the early onset of familial BC as it disrupts the ATPase and helicase activities of the protein, thus causing a decrease in the BRIP1 enzyme activity (5). Mutational analysis of tumors from Chinese BC patients identified sixteen germline mutations, with no protein truncated mutations; intronic variants (IVS7+15T>A and, IVS15+19A>C) and one localized in the 3'-UTR region (4049C>T) were found (35). Furthermore, 3 previously identified silent mutations (E879E, S919P and, Y1137Y) (5, 36, 37) along with 10 amino acid sequence substitutions (571G>A, 653G>T, 728A>G, 2564G>C, 2971C>G, 3418C>G, 3715G>C, 3736G>A, 3798C>A, and 3829G>C) were detected. Among these mutations, a novel heterozygous missense-type variant (Q944E; 2971C>G; exon 19) was also identified and linked with the risk of developing BC. However, the variants (4049C>T and, S919P) were observed in controls as well and hence were indicated not to be significantly associated with BC (35).

Surprisingly, *in silico* mutational analysis of *BRIP1* in a breast tumors of Italian men patients (BRCA1/2-, CHEK2-, and, PALB2-) identified R264W as a pathogenic mutation, however, LoH analysis did not show association of this variant and BC risk (38). Furthermore, in the same study, a synonymous variant E879E (38) and three previously reported variants (P919S, IVS4-28G>A and, 3'UTR 4049C>T) among females (7, 10) were also described; however, the study demonstrated no association between *BRIP1* variants and BC risk in males (38).

In another study performed on Swedish BC patients, one novel (517C-T) and three previously reported (2637G-A, 2755C-T and, 3411C-T) (5)



polymorphisms were identified (37). The rare, c.517C(T) variant resulted in Arg173Cys substitution, leading to abnormal protein localization to the nucleus, thus indicating its role in the susceptibility of BC (5, 37). Interestingly, BRIP P919S mutation was classified as a low penetrance BC allele (39); a mutation not detected among US individuals affected with BC (40). In a Finnish study, a novel heterozygous c.3101C>T (Pro1034Leu) variant was identified in both, a BC case as well as a control with an unknown cancer status, thus suggesting this variant to be a rare disease-related allele (36).

Recently, an evaluation of BRIP1 polymorphisms as risk factors for BC was performed in a Chinese population; complete analysis of possible SNPs (rs2048718, rs4988344, rs8077088, rs6504074, rs4986764, rs4986763, rs11079454, rs7213430, rs34289250, rs4988345, and rs12937080) was performed using MassARRAY system; this study established a link between the rs7213430 allele and BC risk (41). As mentioned above, the BRIP1 missense mutation, rs4986764 (Pro919Ser; exon 18); linked to increased risk of BC (33, 39), showed a high frequency in BC patients in this study, however, association between the rs4986764 C allele (exon18) and BC was not observed (41). Also, Arg173Cys (rs4988345) mutation predisposing to BC, (42), was not associated with BC in this study (41). Similar to another published findings (43), this study also revealed no association between rs4988344 and the onset of BC (41). In this study, the previously identified polymorphisms, rs2048718 (5'-UTR) (37), did not find a genetic association to BC (41). Since this study did not include some of the crucial SNPs (rs2048718, rs4986764, rs4986763, rs11079454, and rs7213430), further investigation are required to establish a link between these SNPs and the risk of developing BC (41).

#### **4.3.2. Physiological functions of BRIP1 in other cancers**

Several lines of evidence from the literature indicate that *BRIP1* is also involved in other cancers. In fact, whole genome sequencing identified one rare mutation in *BRIP1* (c.2040\_2041insTT), which was associated with increased susceptibility to develop ovarian cancer by 36% as well as a reduced lifespan by 3.6. years (6). Furthermore, parallel sequencing of *BRIP1* in tumors collected from patients with ovarian, fallopian tube and peritoneal carcinomas identified germline loss-of-function mutation (44). On the other hand, in a more recent study, *BRIP1* was involved in arresting DNA synthesis and preventing mutations in melanoma cells exposed to UV irradiation, thus suggesting that skin tumors could be sensitive to inter-strand cross linking agents, one of the characteristic features of FA-J (45).

Interestingly, genotyping of Caucasian patients affected with prostate cancer, revealed a truncating mutation, R798X in *BRIP1* (46). In the same study, further

analysis of *BRIP1* revealed the presence of the SNPs; rs6504074 and rs8076727, which were associated with the onset of prostate cancer (46). Moreover, a recent study, identified a stop-gain c.2392 C>T (p.(Arg798°)) mutation in *BRIP1* which was first identified in FA (47).

### **5. POTENTIAL THERAPEUTIC STRATEGIES TARGETING BRIP1**

Several studies have been carried out to develop suitable inhibitors targeting *BRIP1* in order to guide the design of appropriate therapeutic strategies against cancer. Some of these studies have led to the development of small molecules targeting *BRIP1* signaling pathways targeting; such as Werner syndrome (WRN) helicase inhibitor (48-50). In a recent study, 5-fluorouracil (5-FU), a known chemotherapeutic agent reduced *BRIP1* expression, while it increased sensitivity to oxaliplatin in gastric tumors (51). However, in MLH1-induced colorectal cells, *BRIP1* expression was upregulated, suggesting tumor cells were resistant to 5-FU (52), thus indicating differential expression of *BRIP1* in different tumors. Furthermore, based on *BRIP1*'s interaction with BLM, BLM helicase inhibitors could promote sister chromatid exchange (19).

Other strategies include use of PARP1 inhibitors involved in repairing single strand breaks and sensitizing *BRIP1* induced tumors (53). Interestingly, cells deficient in *BRIP1* are sensitive to treatment with cisplatin (54). While *BRIP1* is known to be involved in repairing DNA inter-strand crosslinks, it also plays a role in G4-DNA, thus suggesting that *BRIP1* induced tumors is sensitive to telomestatin, a G4-DNA ligand regulating the stabilization of G4-DNA structures (53). All these attempts emphasize the importance of understanding the underlying mechanisms of *BRIP1* in cancer in order to establish appropriate and efficient therapeutic strategies. As a matter of fact, enzymes (S990A) targeting *BRIP1* signaling pathways particularly involved in over-reactivity of helicases such as Fe-S domain can pave the way towards the design of useful strategies for cancer treatment (53).

### **6. SUMMARY AND PERSPECTIVE**

*BRCA1/2* are the major susceptibility genes for the onset BC. Based on various mutations (truncated, germ-line and missense) identified in breast tumors from patients in different populations studied, *BRIP1* appears to play a major role in the development of BC. However, the pathogenicity of *BRIP1* mutations requires further investigation. In a polygenic setting, several moderate-risk and/or low-risk BC susceptibility alleles contribute, together, to increased risk of BC. The majority of familial BC clustering could be explained by polygenic BC susceptibility (55). *BRIP1* interacts with several proteins involved in regulating DNA damage responses and

checkpoint signaling, which are crucial for maintaining chromosomal and genomic stability. Therefore, further investigations targeting non-BRCA1/2 mutation cases, will ultimately lead to a better understanding of BRIP1-signaling mechanism involved in BC tumor suppression function. Validating BRIP1 as breast tumor suppressor will pave the way to the design of specific therapeutic strategies against BC.

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