

Breast cancer genes: beyond *BRCA1* and *BRCA2*

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1. ABSTRACT

Breast cancer (BC) is a heterogeneous disease. The majority of breast cancer cases (about 70 percent) are considered sporadic. Familial breast cancer (about 30 percent of patients), often seen in families with a high incidence of BC, has been associated with a number of high-, moderate-, and low-penetrance susceptibility genes. Family linkage studies have identified high-penetrance genes, *BRCA1*, *BRCA2*, *PTEN* and *TP53*, that are responsible for inherited syndromes. Moreover, a combination of family-based and population-based approaches indicated that genes involved in DNA repair, such as *CHEK2*, *ATM*, *BRIPI* (*FANCJ*), *PALB2* (*FANCN*) and *RAD51C* (*FANCO*), are associated with moderate BC risk. Genome wide association studies (GWAS) in BC revealed a number of common low penetrance alleles associated with a slightly increased or decreased risk of BC. Currently, only high penetrance genes are used in clinical practice on a wide scale. Due to the development of next generation sequencing technologies, it is envisaged that all familial breast cancer genes will be included in the genetic test. However, additional research in clinical management of moderate and low-risk variants is needed before full implementation of multi-gene panel testing into clinical work-flows. In this review, we focus on the different components of familial breast cancer risk.

2. INTRODUCTION

Breast cancer (BC) is the most common cancer in women. One in 9–12 women living in developed countries will be affected by BC in their lifetime. The idea that BC has a familial or inherited component was first proposed in 1757 when Le Dran described a 19-year old woman with BC whose grandmother and maternal uncle died of BC (1). In 1866, Paul Broca, a French surgeon, characterized a family with ten women across four generations who were affected by BC. Therefore, sufficient data was provided to create a family pedigree that clearly showed the heritable nature of the disease (2). More recent twin studies, altogether with segregation and risk analyses have markedly provided additional evidence that the development of BC has a genetic component.

Identification of genes associated with BC is complicated by the co-occurrence of sporadic and heritable BC within families. In order to identify BC susceptibility genes, large families with several affected generations and meeting stringent criteria for defining heritable BC are needed. Linkage analysis and positional cloning studies in these families began to reveal the molecular genetics underlying BC risk, with the discovery and identification of *BRCA1* (Breast CAncer gene 1) in 1994 (3, 4) and *BRCA2* (Breast CAncer gene 2) in 1995 (5, 6).

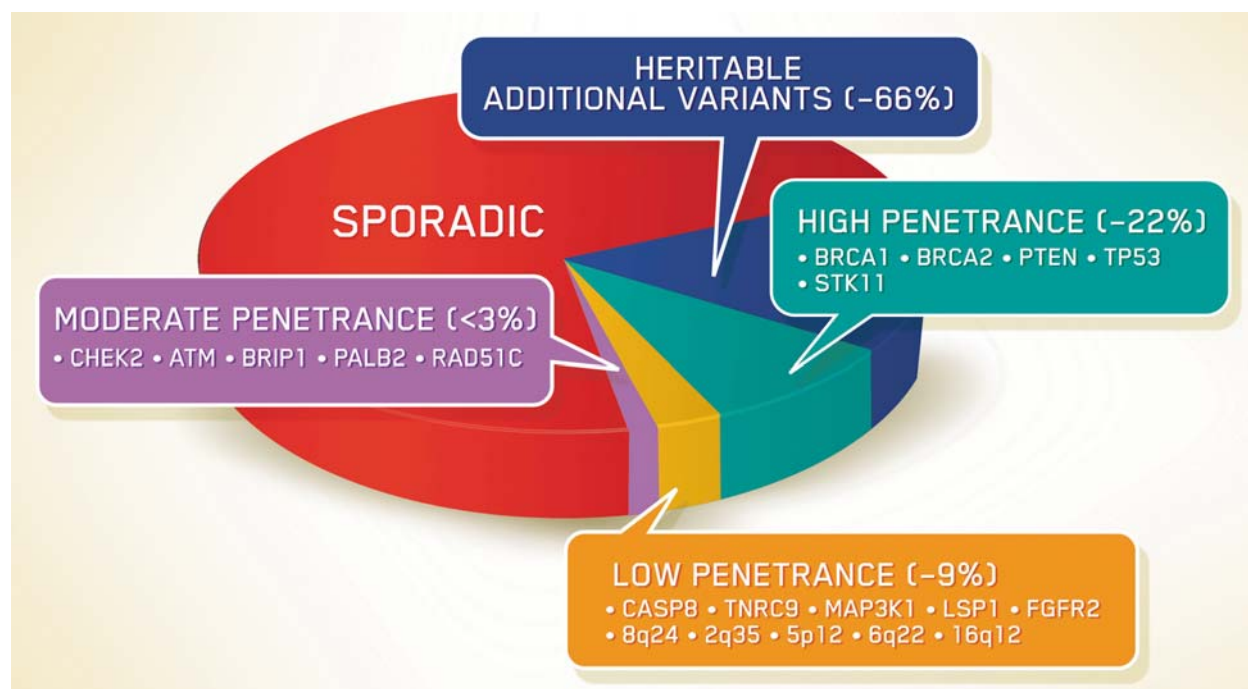


Figure 1. Molecular etiology of BC. The majority of BC cases (~70%) are considered sporadic. Familial BC (~30% of patients), often seen in families with a high incidence of BC, has been associated with a number of high-, moderate-, and low-penetrance susceptibility genes.

Following the identification of *BRCA1* and *BRCA2*, screening tests were developed to identify mutation carriers and families at risk for hereditary breast and ovarian cancer. However, many families with a high incidence of BC have no detectable mutations in *BRCA1/BRCA2* suggesting the existence of additional BC susceptibility genes.

As numerous genetic linkage studies had failed to identify additional genes, it became clear that no further high-penetrance genes of comparable importance to *BRCA1* and *BRCA2* exist (7). Part of these familial BC cases, without *BRCA1/2* mutations, could be attributed to shared environmental and lifestyle factors. However, studies on twins had shown that the BC risk for unaffected monozygotic twin with a co-twin diagnosed with BC is higher than that for dizygotic twins. This strongly suggests that a significant proportion of the remaining familial BC risk is likely to do with genetic factors (8) (Figure 1). At this point, it was postulated that most of this familial BC clustering might be explained by polygenic BC susceptibility. In a polygenic setting BC risk is significantly increased by simultaneous presence of several moderate- and/or low-risk BC susceptibility alleles (9). Thus, breast cancer predisposition today can be attributed to several levels of genetic susceptibility: rare high-risk alleles, conferring a risk more than five and up to 20 times as high as the risk among the general population; rare moderate-risk alleles with a relative risk greater than 1.5 and lower than 5, and common low-risk alleles conferring risks between 1.01 and 1.5 of the general population,

Whereas high-risk genes may be identified by traditional linkage analysis of genetic markers in BC families, discovering moderate and low risk BC genes requires a different approach. Over the recent years, new tools such as high-density SNP arrays became available for GWAS to decipher low-risk alleles associated with an increased BC risk in large groups of patients and controls. The aim of these studies is to identify a number of polymorphisms, each expected to impact only to a minor extent over the individual risk. Nevertheless, as most of these variants occur with high frequency in the investigated populations, they have a significant impact on the BC risk but can also be frequently found in control cohorts. However, the prevalence of moderate-risk BC alleles is too low even to be detected by SNP microarrays used for GWAS. At present, moderate-risk BC genes have been discovered through Candidate Gene Association Studies, involving evaluation of putative BC susceptibility genes in cohorts of hundreds of cases and controls.

3. BREAST CANCER GENE FAMILY

3.1. High-risk inherited syndrome genes

Hereditary breast and ovarian cancer syndrome (HBOC) is a highly penetrant autosomal dominant disorder. Mutations can be inherited either from maternal or paternal side of the family. HBOC is defined as the presence of four or more breast or ovarian cancers within the family, typically occurring at young ages or by bilaterally in the case of BC. The HBOC is characterized by an increased susceptibility to develop cancer, most often BC and/or ovarian cancer (OC). It is caused by an inherited germline

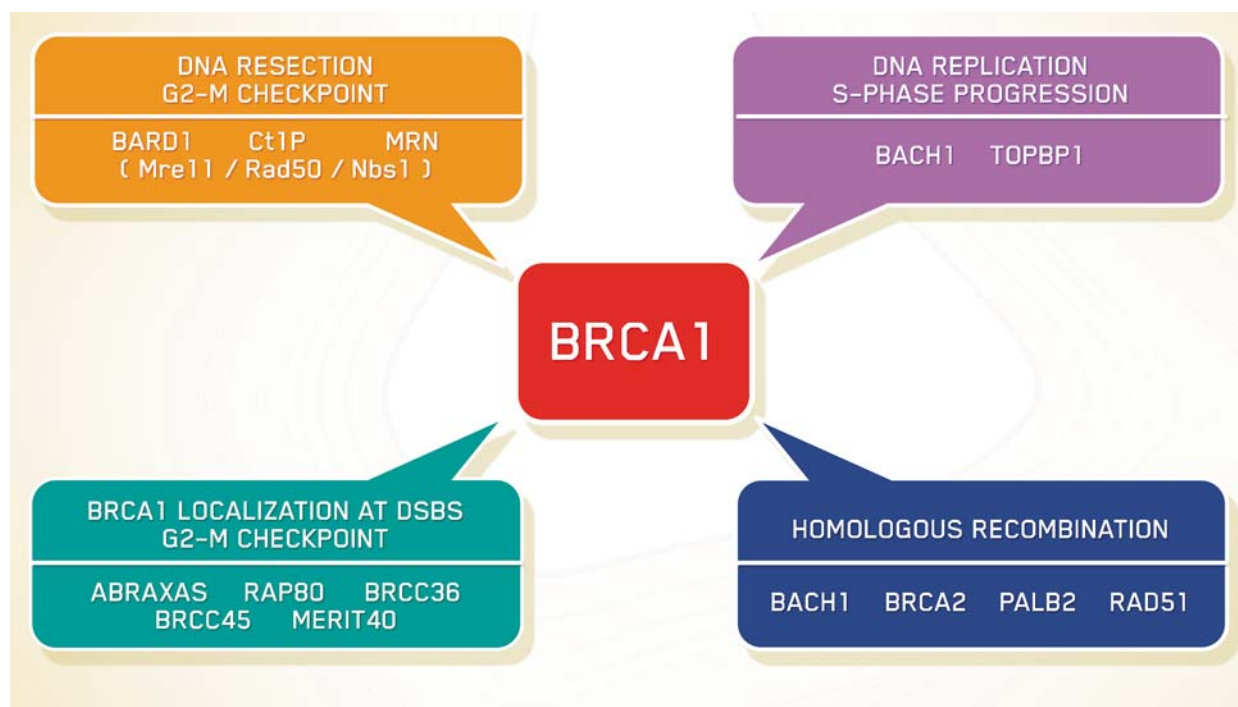


Figure 2. BRCA1 is the major subunit of various protein super complexes; most of those complexes seemed not to operate independently of each other, instead they might cooperate to promote physiological BRCA1 HR. These structures play a role in maintaining genomic stability.

mutation in cancer susceptibility genes, *BRCA1* or *BRCA2*. *BRCA1* was cloned in 1994 following a long search for the gene using linkage analysis and maps on chromosome 17q21 (4). This was closely followed by discovery of *BRCA2* on chromosome 13q12–13 in 1995 (6). They are both classic tumour suppressor genes, which are involved in the maintenance of genomic stability by facilitating DNA repair, primarily executing DNA double-strand break repair by homologous recombination (HR). Despite of *BRCA1* and *BRCA2* initially appearing to be genes with similar functions, it is now clear that these two genes are different in terms of their molecular biology, protein interactions and the cancer risks they confer (10).

BRCA1 associates with multiple repair proteins and cell cycle regulators, being capable of forming multiple protein complexes which contribute to its role in maintaining chromosome stability and tumour suppression. BRCA1 is a substrate of the central DNA damage response kinases ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related protein) that control the DNA damage response. BRCA1 is required for homology directed repair, a pathway that facilitates error-free repair of double-strand breaks (DSBs) and resolution of stalled DNA replication forks through HR, as well as post-replicative repair in response to UV damage. Recently, it has been discovered the BRCA1 role of maintaining heterochromatin integrity via H2A ubiquitination. The BRCT domain of BRCA1 has been indicated important for cell cycle checkpoint, HR and tumour suppression. BRCT associated complexes give additional roles to BRCA1 in a number of diverse cellular processes maintaining genome

stability and tumour suppression (11). BRCA1 also regulates the transcription of several genes in cancer including *ATM*, (12) and homeostasis of itself so that levels remain capable of maintaining genome integrity in response to genotoxic insult (13) (Figure 2).

BRCA2 primary function is in HR and it is based upon its ability to bind to the strand invasion recombinase RAD51. BRCA2 contains eight BRCT repeats, each of which can bind and recruit RAD51 to sites of DNA damage. BRCA2 also interacts with PALB2, through which it localizes to DSBs together with BRCA1 (14).

BRCA1 and BRCA2 are involved in maintaining genome integrity, at least in part, by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps. Thus, the complete loss of function of either protein leads to a dramatic increase in genomic instability.

BRCA1 and *BRCA2* gene mutation screening is widely available for at-risk families in developed countries. Thousands of different disease-associated mutations have been identified (Breast Cancer Information Core, BIC). Most deleterious mutations introduce premature termination codons through small frameshift deletions or insertions, nonsense or splice junction alterations, or large deletions or duplications. Deleterious missense mutations are typically confined within specific residues of functional motifs. However, the risk contribution of numerous other sequence variants, such as missense changes, small in-frame deletions and insertions, synonymous variants,

Beyond BRCA1 and BRCA2

alterations in non-coding sequences or in untranslated exonic regions, remains unclear.

The estimated *BRCA1* and *BRCA2* mutation carrier frequencies in the general population are between 1 in 300 and 1 in 800. This frequency is higher in the Ashkenazi Jewish population in which 1 in 40 people carries one of three main disease-causing mutations (15). Founder mutations exist in other ethnic and geographic populations too, such as the Norwegian, Dutch, and Icelandic.

Several studies have estimated the penetrance associated with *BRCA1* and *BRCA2* mutations. Female carriers of deleterious *BRCA1* and *BRCA2* mutations are predisposed to high lifetime risks of breast and ovarian cancer and increase risk of pancreatic and possibly other type of cancers. The risk of breast cancer for *BRCA1* mutation carriers by the age 70 years old has been estimated in the range of 40–87% and for ovarian cancer of 16–68%. The corresponding risks for *BRCA2* mutation carriers were estimated to be 40–84% for breast cancer and 11–27% for ovarian cancer (16). Male *BRCA2* mutation carriers are at increased risk of pancreas, prostate and breast cancer (17). In addition to this, it has been reported that penetrance estimates vary among, and within mutation carrier families, by age at onset of the index case and by the types of cancer in the index case (16). This could be partly explained by the influence of environmental factors such as breast feeding, child-bearing and hormonal factors, as well as low-penetrance genetic variants. GWAS have identified common alleles, which have been associated with increased BC risk. Further work has demonstrated that some of these act multiplicatively to alter BC risk in *BRCA2* carriers (18). Recent data suggest that genomic variation at multiple *loci* that encode proteins biologically interacting with *BRCA1* are associated with modified BC and OC risk in women who carry *BRCA1* mutations (19).

There are other inherited cancer syndromes with BC as a clinical manifestation in which mutations in associated genes confer a similar BC risk as *BRCA1/BRCA2*. These include Cowden syndrome associated with *PTEN*, Peutz-Jeghers syndrome with *STK11* and Li-Fraumeni syndrome with *TP53* mutations. Mutations in these genes are even less common than in *BRCA1* and *BRCA2*.

TP53 was first identified in 1979 and it is now the most common altered gene in solid tumours. *P53* is essential in cell-cycle control, resulting in either a delay in cell-cycle progression or apoptosis. Inherited germline mutations are rare. However, they are known to result in Li-Fraumeni syndrome (LFS). LFS causes childhood tumours: soft tissue, osteosarcomas, gliomas, adrenocortical carcinoma, and very early onset BC. Over 70% of classical LFS families inherited *TP53* mutations. LFS only accounts for less than 0.1% of BC, but mutations in *TP53* confer an 18- to 60-fold increased risk of BC under the age of 45 years old compared to the general population. In recent years, some researchers have investigated the contribution of *TP53* mutations to HBOC (20) and have

suggested the need to analyze *TP53* in all early-onset BC women (younger than 36 years old) lacking mutations at the *BRCA1* and *BRCA2* genes. Blanco *et al.* (21) proposed to offer *TP53* germline testing to early-onset BC women (<36) with other LFS core cancer in the family.

A number of other rare syndromes have been associated with an increment of 40–60% BC risk. For instance, mutations in E-Cadherin gene *CDH1* cause hereditary diffuse gastric cancer, and have been associated with BC higher risk (22). In Lynch syndrome mutations in *MLH1*, *MSH2*, *MSH6* and *PMS2* are responsible for cumulative OC and BC risk (23).

3.2. Moderate breast cancer risk alleles

Familial linkage analysis, the methodology used to discover *BRCA1* and *BRCA2*, depends on high-penetrance alleles that ensure a clear segregation of the gene among cases. Whereas, detecting lower-risk (less penetrant) genes requires other genetic strategies such as large case-control association studies and family-based studies, through sequencing candidate genes. Good candidate cancer genes to be likely to play a role in hereditary BC and OC are those coding for proteins interacting with *BRCA1* or *BRCA2* in complexes that are part of the cellular DNA repair machinery (24).

After intensive research examining many candidates, a few, relatively uncommon (population frequency less than 1%), genes associated with moderate risk of BC were identified. These include *CHEK2*, *ATM*, *BRIP1*, *PALB2*, and *RAD51C*, which were largely identified through a combination of family and population based approaches. These genes are associated with relative risk of ≥ 1.5 and < 5 . It has been estimated that mutations in them are responsible for less than 3% of familial BC (25).

3.2.1. *CHEK2* and *ATM*

Germline *CHEK2* (checkpoint kinase 2) sequence variants have been reported in families with LFS that do not carry *TP53* mutations (26). *CHEK2* encodes a cell cycle checkpoint kinase implicated in DNA repair. *CHEK2* emerged from the sequencing of plausible candidate genes in families with multiple cases of BC families without *BRCA1/2* mutations (27). Its association with increased BC risk has been explored in many studies since 2002, and nowadays, its significance has been demonstrated with a high statistical degree.

A particular germline mutation *CHEK2* 1100delC, has been associated with a two-fold to three-fold increase in BC risk. Many large studies have reported this finding, including the *CHEK2* Breast Cancer Case-Control Consortium, which examined more than 10,000 breast cancer cases and more than 9,000 controls from 10 case-control studies in five countries (28). *CHEK2* 1100delC was found in 201 cases (1.9%) and 64 controls (0.7%) (OR 2.34; 95% CI 1.72–3.20; $P = 10^{-7}$).

In 2008, a meta-analysis of studies assessing *CHEK2* risk in populations of northern and eastern European descent, calculated odds ratios for BC in unselected populations, early-onset BC, and familial BC.

For early-onset BC, the study estimated an OR of 2.6 (95% CI 1.3–5.5) and also found that for patients selected from a population with familial BC, *CHEK2* 1100delC heterozygotes had a much higher OR 4.8 (95% CI 3.3–7.2). *CHEK2* mutation carriers either with a strong family history of BC or a history of bilateral disease was found to be at comparable risk to *BRCA* carriers with an estimated lifetime risk of 37% and 59% respectively (29).

These results suggest that *CHEK2* 1100delC screening should be considered in patients with a strong family history of BC (30). There does not appear to be an increased risk of other malignancies with heterozygous *CHEK2* mutations. A recent publication has described families with homozygous *CHEK2* 1100delC mutations in which the BC risk was estimated more than twice the risk of heterozygous (31). Other *CHEK2* mutations have also been associated with BC susceptibility (32). *CHEK2* mutations are much more often associated with incomplete cosegregation. This clearly implies that there must be another significant factor present in the family that confers BC risk.

Biallelic mutations in Ataxia telangiectasia-mutated (*ATM*) gene cause the autosomal recessive disease Ataxia-telangiectasia (AT). This is a neurodegenerative disorder that is characterized by cerebellar ataxia, telangiectases, immunodeficiency, hypersensitivity to ionizing radiation and approximately 100 times increased risk of cancer (33). *ATM* is a protein kinase involved in the response to DSBs in a pathway that includes TP53, *BRCA1* and *CHEK2*. DSBs activate *ATM*, which in turns, activates the full DNA damage response (34). Heterozygous *ATM* mutation carriers, found in approximately 0.5–1.4% of the general population, do not display the symptoms observed in patients. However, several studies have shown an increased risk of cancer in them: tumours of breast, pancreas, stomach, bladder, ovary, and chronic lymphocytic leukaemia (35).

Extensive research has been carried out into the association of *ATM* mutations and BC, showing that up to 13% of BC may be due to heterozygous *ATM* mutations (36). The relative risk of BC in heterozygous *ATM* female carriers has been estimated in 2.37 (95% CI, 1.51–3.78) that of the general population (37). Moreover, it has been described that *ATM* mutations are more frequent in BC patients selected on the basis of a family history of BC than from those compared to unselected patients (38).

3.2.2. The MRN (MRE11–RAD50–NBS1) complex

The MRN complex is composed of three proteins, *MRE11*, *RAD50* and *NBS1*. It binds to damaged DNA and undergoes a series of conformational changes to activate and increase *ATM* affinity for its substrates and retain active *ATM* at sites of DSBs. MRN complex plays a key role in DNA damage detection and activation of the *ATM* kinase (39). Its role in maintaining genome integrity is underscored by chromosome instability and cell-cycle checkpoint defects common to all patients with complete loss of any one of these components.

Mutations in all three members of the MRN complex have been noted in human cancers. Mutations of *MRE11*, *NBS1* and *RAD50* manifest as ataxia-telangiectasia-like disorder (ATL), Nijmegen breakage syndrome (NBS) and NBS-like disorder, respectively. Unsurprisingly, carriers of *MRE11*, *NBS1* and *RAD50* mutations have been implicated in BC. Rare germline mutations in *MRE11* have been proposed to be BC risk alleles, however this remains to be verified in case-control studies. A small number of hereditary OC, a single base mutation in exon 10 of *MRE11* (913 C>T) has been reported (40).

Screening for mutations in all the three MRN genes in Finnish population discovered a founder mutation in *RAD50* associated with a 4.3-fold increase in BC predisposition (OR 4.3, 95% CI 1.5–12.5) (41). However, this mutation has not yet been found in any other populations, including other Nordic states, making difficult the confirmation of this association.

Mutations in the *NBS1* gene cause NBS, which is characterized by increased chromosome instability, immunodeficiency, sensitivity to radiation and predisposition to cancer. Over 90% of NBS patients are homozygous for the founder mutation 657del5 (42). Heterozygous carriers of the 657del5 allele have a 3.1-fold increase risk of BC (OR 3.1; 95% CI 1.4–6.6) (43). Polish population studies reported the founder *NBS1* 657del5 mutation in 3.7% of familial BC compared to 0.6% of controls from the general population (44). Other *NBS1* mutations have also been reported in hereditary BC. *NBS1* can be added to the growing list of genes involved in DNA double strand break repair which if mutated confer a 2–4-fold increased risk for BC (43).

3.2.3. The FANC family

Fanconi anaemia (FA) is a genetic disease characterized by progressive aplastic anemia, multiple congenital defects, and susceptibility to both hematologic and solid malignancies. A defect in any of the proteins along the FA pathway prevents cells from repairing interstrand crosslinks and predisposes them to chromosomal breakage and cell death.

The relationship between FA and BC susceptibility did not become fully apparent until it was discovered that *BRCA2* and *FANCD1* were two different names for the same gene (45). *BRCA1* does not belong to the FA gene family, even though it is a key component of the FA pathway. The FA-*BRCA* pathway coordinate a complex mechanism that enlists elements of three classic DNA repair pathways, namely homologous recombination (HR), nucleotide excision repair (NER) and mutagenic translesion synthesis, in response to genotoxic insults. FA causative mutations occur in 13 genes that have been cloned: *FANCA*, *B*, *C*, *D1* (*BRCA2*), *D2*, *E*, *F*, *G*, *I*, *J* (*BRIP1*), *L* (*PHF9*), *M* (*Hef*) and *N* (*PALB2*). Many of FANC proteins form a nuclear complex, the integrity of which is essential for the monoubiquitination of *FANCD2*. Following DNA damage the monoubiquitinated *FANCD2* colocalises with *BRCA2*, *FANCN*, *FANCI* and *RAD51* in

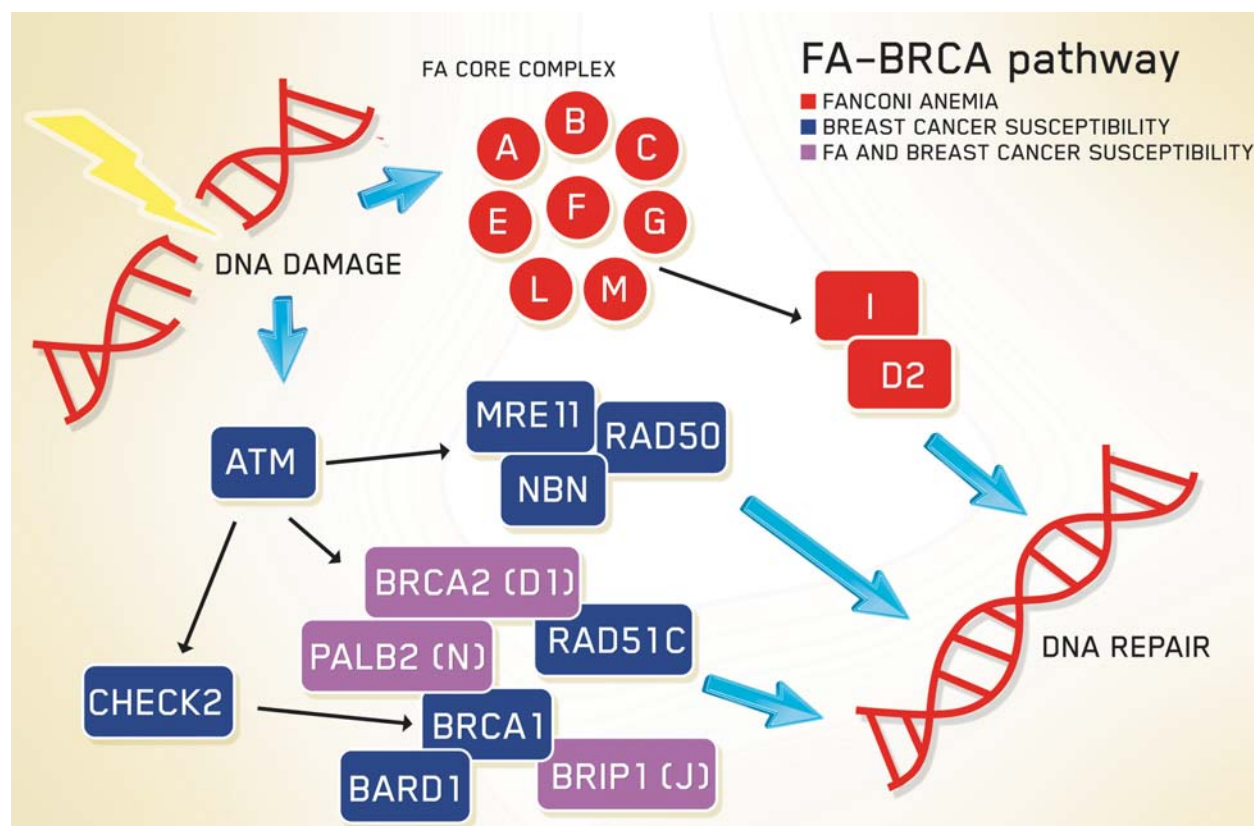


Figure 3. FA-BRCA pathway

nuclear repair *foci* at sites of double strand breaks (46) (Figure 3).

Constitutional inactivating mutations in genes responsible for FA have been clearly associated with an increased susceptibility to both BC and OC (47) and include the genes *BRCA2* (*FANCD1*), *FANCN* (*PALB2*) and *FANCI* (*BRIP1*).

One third of patients homozygous for a FA gene mutation will develop cancer by the age of 40 years old. From those patients followed in the International Fanconi Anaemia Registry, 10% developed solid tumours. These included squamous cancer of the head and neck, medulloblastomas, oesophageal and skin cancers, gynecological cancers, as well as liver and kidney tumours (48). Strong associations exist between heterozygous mutations of *BRCA2/FANCD1* and breast and/or ovarian cancer development, as described in *BRCA1/BRCA2* families. However, heterozygous mutations in other FA genes have also been shown to be associated with an increased risk of BC. Evidence that other FA pathway-related proteins were also BC susceptibility genes did not unfold until *BRIP1* was identified in *FANCI* patients (49). *FANCI*, also known as *BACH1* or *BRIP1*, is a *BRCA1*-associated DEAH helicase involved in translesion synthesis helping the polymerase bypass the interstrand crosslink, placing its role distal to the monoubiquitinated *FANCD2* of the FA pathway. *BRCA1-FANCI* interaction is essential

for promoting error-free repair, checkpoint control and for limiting DNA damage tolerance (50). The most common germline *FANCI/BRIP1* mutant allele is found both in BC and FA patients. In 2006, truncating mutations in *BRIP1* were identified in BC families. Segregation analysis assessed a Relative Risk (RR) of BC of 2.0 (95% CI 1.2–3.2), that increased to 3.5 (95% CI 1.9–5.7) for carriers younger than 50 years old (51).

The discovery of another BC predisposition gene in the FA pathway *PALB2* or *FANCN* (52), suggests that proteins acting downstream of monoubiquitinated *FANCD2* and *FANCI* increase the risk of BC, while those acting upstream do not (53). The role of *PALB2* in homologous repair is to behave as a protein that functionally bridges *BRCA1* and *BRCA2* and also cooperates with *RAD51* to stimulate recombination (54). Biallelic *PALB2* mutations have been described as responsible for FA subtype *FANCN*. Research on BC families without *BRCA1/2* mutations resulted in identifying *PALB2* mutations. However the *PALB2* mutations rarity makes accurate estimation of its penetrance more difficult. A familial-based case-control association study of *PALB2* showed that a monoallelic mutation confers an OR of 2.3 (95% CI 1.4–3.9) for BC (53). Higher BC risk has been estimated for the c.1592delT Finnish founder mutation (OR 3.94, 95% CI 1.5–12.1) (55). As with *BRCA2* heterozygotes, *PALB2* mutations have been associated with an increased risk of pancreatic cancer (56).

Interestingly, another FA related gene *SLX4* or *FANCP* has been identified (57). *SLX4* encodes a protein acting downstream of *FANCD2* and involved in assembling several endonucleases. Recent studies, analysing *SLX4/FANCP* in patients with familial BC did not support a major role for *SLX4* coding variants in familial BC risk. Although, it suggests that rare mutations might make a minor contribution (58, 59). More studies on *SLX4/FANCP* in BC families are required in order to quantify the risk originate by these rare variants.

Similar results were found in the case of exome sequencing in 438 BC families, where two families were shown to carry independent heterozygous truncating mutations in *FANCC* (60).

The FA pathway remains intricately related to BC susceptibility and further investigation will help to identify potential cancer genes in wild-type *BRCA1/BRCA2* breast-ovarian cancer families.

3.2.4. The RAD51 family

The RAD51 family consists of several proteins, which preferentially bind to single-stranded DNA, and form complexes with each other. RAD51 unwinds duplex DNA and forms helical nucleoprotein filaments at the site of a DNA break (61). BRCA2 stimulates RAD51-dependent strand exchange (62). *RAD51C* was discovered to be the cause of a Fanconi-like disorder (63) and is a new cancer susceptibility gene (64). Six clearly pathogenic mutations were found among 1,100 breast/ovarian cancer families. The mutations were found exclusively within 480 pedigrees with the occurrence of both breast and ovarian tumors and not in 620 pedigrees with breast cancer only or in 2,912 healthy controls. This is distinctive behaviour from the situation observed with monoallelic mutations in the FA-related genes *PALB2* and *BRIP1*, which are rarely present with OC. What it is even more striking, is that apparently there was complete segregation of the mutations to affected individuals, suggesting a penetrance level similar to *BRCA1/2*. Recently, a mutational screening of the *RAD51C* gene in a large series of 785 Spanish breast and/or ovarian cancer families identified 1.3% of mutations, and suggested the inclusion of the genetic testing of *RAD51C* into the clinical setting (65).

Investigators have recently sequenced *RAD51D* in 911 wild-type *BRCA1/2* breast-ovarian cancer families as well as 1,060 population controls (66). Inactivating mutations were identified in 8 in 911 breast and ovarian cancer families (0.9%), 0 in 737 BC families, and 1 in 1060 controls (0.09%). There was a higher prevalence of mutations present in families with more cases of OC. The RR of OC for carriers of deleterious *RAD51D* mutations was estimated at 6.3 (95% CI 2.86–13.85) whereas RR of BC was non-significantly increased. New data support the previous observation that loss-of-function mutations in *RAD51D* predispose to OC but do not to BC.

The XRCC2 and XRCC3, members of RAD51 family, maintain chromosomal stability during HR (67). *XRCC2* and *XRCC3* have been found to modulate sporadic

BC (68) and OC (69). A coding-region variant in *XRCC3* was associated with sporadic melanoma giving an OR 2.36 (1.44 –3.86); (70) and found to be twice as common in differentiated thyroid cancer as compared to cancer free control subjects ($P=0.006$) (71). Combined risk genotype analysis revealed that *RAD51* SNPs enhance BC risk in patients with *BRCA2* mutations, whereas *XRCC3* SNPs significantly enhance BC risk in carriers of *BRCA1* mutations and in patients with hereditary BC (72).

A homozygous frameshift mutation in *XRCC2* being associated with a previously unrecognized form of FA was recently reported (73). *XRCC2* binds directly to the C-terminal portion of the product of the BC susceptibility pathway gene *RAD51*, which is central to HR. *XRCC2* also complexes *in vivo* with RAD51B (*RAD51L1*), the product of the breast and ovarian cancer susceptibility gene *RAD51C9* and with the product of the OC risk gene *RAD51D*, and localizes together on sites of DNA damage (74). An exome-sequencing study of families with multiple BC individuals identified two families with *XRCC2* mutations. One of them with a protein-truncating mutation and the other one with a probably deleterious missense mutation (75). From other *XRCC* genes investigated, *XRCC1* 399Gln allele acts as a recessive allele in association with BC risk (76).

3.2.5. Bloom syndrome and BLM

Bloom syndrome (BS) is an inherited disorder characterized by short stature, sun-sensitive skin changes, and an increased risk of cancer. Affected individuals can develop any of the cancers found in general population, but they arise unusually early in life and develop more than one type. BS is a very rare disorder in most populations and its overall frequency is unknown. It is more common in people of Central and Eastern European with Ashkenazi Jewish ancestry with a frequency of 1 in 50,000. Mutations in *BLM* cause BS and its pathway play important roles in HR based repair of DSBs (77). Heterozygous mutation carrier rate in Caucasians for *BLM* mutations is unknown since BS is exceedingly rare. Two recurrent truncating mutations in *BLM* were shown in a case control study to be associated with increased BC risk in Russia (78). An elevated risk of colorectal cancer in Ashkenazi Jews carrying the common *BLM* (*Ash*) mutation and a non-significant excess of BC were reported (79), even though, a later study failed to confirm them (80). Through a whole exome sequencing approach intended to underlay familial BC predisposition in multiple multigenerational wild-type *BRCA1/2* breast-ovarian cancer families, two heterozygous mutations in *BLM* were detected which were known pathogenic (60).

3.2.6. RAP80, Abraxas and other possible breast cancer genes

The BRCA1 A complex, a deubiquitinating system, contains at least five different components: RAP80, Abraxas, MERIT40, BRE/BRCC45 and BRCC36 (81–83). RAP80 and Abraxas have the critical function of localizing BRCA1 to DNA-damage foci. Binding partners of BRCA1 including PALB2 and BRIP1 have been shown to be moderately associated with BC. Although, strong evidence has not yet been found for mutations in *RAP80* and

Abraxas (84), one report found a mutation that could be a possible candidate, *RAP80* delE81, in a conserved region of the ubiquitin interacting motif of *RAP80* (85). Functional studies show that it abolishes binding to ubiquitin side chains and impaired its localization and recruitment of BRCA1 to DSBs. Further analysis in case-control studies will be needed to confirm this association. *MERIT40* is a BRCA1 and *RAP80* interacting protein essential for protein-protein interactions of a BRCA1 complex also containing *Abraxas*, *BRCC36* and *BRCC45*. It is a mediator of checkpoint functions and DNA damage signaling through a deubiquitination cascade. Based on its interaction with BRCA1 and its role in genome integrity maintenance, *MERIT40* is a candidate gene for hereditary susceptibility to BC. Data suggest that mutations predisposing to BC are either very rare or absent in the coding region of *MERIT40*. It would be interesting to know whether large genomic rearrangements, or mutations in transcriptional regulatory regions, could represent alternative and more typical ways of deregulating *MERIT40* function. It might also be that mutations in *MERIT40* are poorly tolerated, pointing *MERIT40* essentiality in DNA damage response and other functions, maintaining genomic integrity (86).

RNF8, *UBC13* and *MMS2* are involved in the DNA damage response pathway, play important roles in BRCA1-mediated DNA damage recognition, maintenance of genomic integrity and cell-cycle checkpoint control (87). Based on the evidence that several players in the ubiquitin-mediated BRCA1 dependent DNA damage recognition seem to contribute to BC predisposition, *RNF8*, *UBC13* and *MMS2* were considered plausible candidate susceptibility genes. A recent study examined the role of *RNF8*, *UBC13* and *MMS2* in familial BC by performing a mutation screening of these genes in 123 Northern Finnish BC families. Data suggested that mutations in *RNF8*, *UBC13* and *MMS2* unlikely make any sizeable contribution to BC predisposition in this population (88). Previous studies suggested that *RNF8* could be a novel tumour suppressor (89) but it seems that germline mutations predisposing to BC in this gene are very rare or not found. It is of interest that another E3 ligase, *RNF168* which acts together with *UBC13* to amplify the *RNF8*-dependent histone ubiquitylation, showed to be defected in Riddle syndrome, an immunodeficiency and radiosensitivity disorder. However, it is still unclear whether Riddle is associated with genome instability or increased tumour incidence (90).

3.3. Breast cancer low-risk alleles

Part of the unexplained fraction of familial relative risk is likely to be explained by a polygenic model involving a combination of many individual variants with weak associations to risk, the so called low-penetrance polymorphisms. For above mentioned purpose large GWAS were conducted, intended to identify common variants SNPs associated with increased BC risk based upon patterns of linkage disequilibrium LD in human genome. The frequency of these alleles may range from 5% to 50% and could possibly be higher in families with BC. Individually they only have a small effect on BC risk (relative risk ≥ 1.01 and < 1.5). Nevertheless, they may

collectively account for a large component of BC heritability.

GWAS became a powerful tool in the identification of further low-penetrance BC susceptibility genes. Over the last four years, GWAS have identified more than 25 BC susceptibility variants that account for ~9% of the heritability of the disease (91). GWAS are hypothesis-free approaches and none of the genes identified had been previously linked to BC risk, with the exception of *FGFR2*, a gene encoding for a transmembrane tyrosine kinase known to be involved in mammary gland development and breast carcinogenesis (92).

Other GWAS identified *loci* associated with BC in large studies involving thousands of subjects are, *MAP3K1* (mitogen-activated kinase 1), *LSP1* (lymphocyte-specific protein), and *TNRC9* (trinucleotide repeat-containing 9), along with a 110 kb region of chromosome 8q24 (93 and references therein). Associations with other chromosomal regions, 2q35, 5p12, 6q22, and 16q12, also have been reported (94, 95, 96). Further analysis showed that allelic variation at *FGFR2*, *TNRC9*, 8q24, 2q35, and 5p12 are associated with physiological characteristics of breast tumours, such as ER status (97). Moreover, it has been shown that specific *FGFR2*, *MAP3K1*, and *TNRC9* variants may interact with *BRCA1* and *BRCA2* mutations to increase BC risk (18).

4. PERSPECTIVE

Although *BRCA1* and *BRCA2* genetic testing is rapidly evolving in the clinical setting, much work is yet to be done. Mutations in these genes are successful at explaining only around half of the dominant multi-case BC families and their contribution to the heritable risk of BC has been estimated to be no more than around 20% of the total. Furthermore, the identification and management of individuals with high risk BC predisposition by these gene mutations are now well accepted in clinical practice. Although evidence-based risk management is only possible in a relatively small group of families, as it is limited by the identification of an underlying genetic mutation, the benefits for those abovementioned individuals are well established (98). Through a candidate gene approach, mutations in other high and moderate penetrance cancer-susceptibility genes have been identified in a further small proportion of families. However, the underlying etiology of the increased susceptibility to BC in the majority of multi-case BC families remains unknown.

Lack of segregation within familial cases due to the modest increase in risk compared to the general population makes difficult to advocate for screening of moderate penetrance alleles. Current models suggest that these genes act multiplicatively in yet unknown alleles (99). A significantly elevated overall risk given a strong familial background would be expected, as was seen for *CHEK2* 1100delC (29). Additionally, some mutations may confer a risk that may be as high as that of *BRCA*. Therefore testing for moderate penetrant alleles, given an appropriate clinical background of ethnic origin and family

history, may provide clinically relevant information that stratifies patients allowing segmentation of high-risk group where intensified surveillance or chemoprevention might be appropriate.

With the advent of targeted capture and massively parallel sequencing, it is now feasible to sequence many genes simultaneously with high coverage, as well as improving mutation detection sensitivity. An example of the use of this technique is the BROCA test, a breast/ovarian cancer panel of 21 tumour suppressor genes that included *BRCA1*, *BRCA2*, *PALB2*, *NBN*, *BRIP1*, *RAD50*, *RAD51C*, *CHEK2*, *ATM*, *MRE11A*, *BARD1*, *TP53*, *PTEN*, *CDH1*, *STK11*, *MUTYH*, *MSH2*, *MLH1*, *MSH6*, *PMS2*, and *PMS* (100). The major advantages of next-generation sequencing techniques are not only higher throughput and lower cost, but also the potential for deeper coverage, which refers to an increased number of reads at each sequenced base. It would seem that this genomic sequencing strategy, or similar ones, should facilitate such studies.

The emerging technology of massively parallel DNA sequencing has a major impact on progress in genomics and personalized medicine. The knowledge that genetic susceptibility to BC is attributed to germline mutations in genes that encode DNA repair proteins has revolutionized the way that affected patients are treated. Additional research priorities include the implementation of emerging multi-gene panel testing into clinical work-flows. It also includes the downstream impact on treatment decisions, as well as cost and resource utilization, and also long-term outcomes including survival expectancy. Clinical guidelines for next-generation sequencing and other novel genetic diagnostics are not yet available and additional research is required to guide their rational use.

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Abbreviations: BC: breast cancer; BS: Bloom syndrome; DSBs: double-strand breaks; FA: Fanconi anemia; GWAS: Genome-Wide Association Studies; HBOC: hereditary breast ovarian cancer syndrome; HR: homologous recombination; LFS: Li-Fraumeni Syndrome; NBS: Nijmegen breakage syndrome; OC: ovarian cancer; RR: relative risk.

Key Words: Hereditary Breast Ovarian Cancer Syndrome, *BRCA1*, *BRCA2*, Fanconi Anemia genes, breast cancer genes, genetic diagnosis, Review

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