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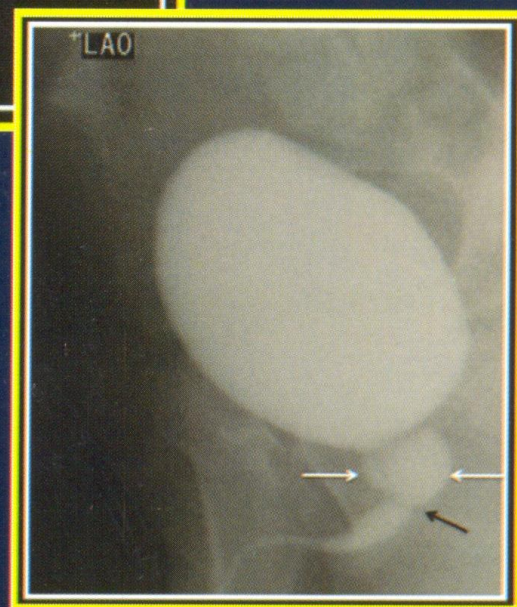
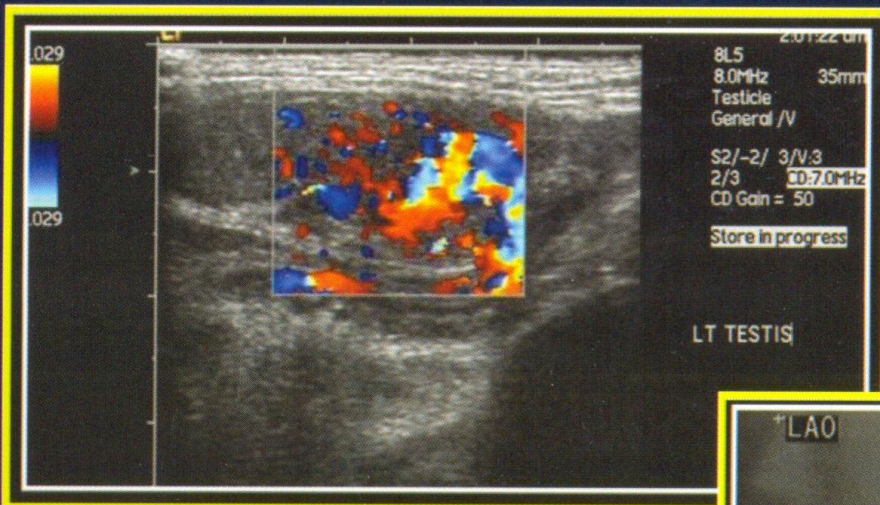
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## Genetic Markers in Breast Cancer- How Far Have We Come from BRCA1?

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### ABSTRAK

Kanser payudara adalah kanser yang paling sering ditemui pada wanita di seluruh dunia. Insiden kanser ini semakin meningkat dan merupakan penyebab kematian tertinggi. Kanser payudara diklasifikasikan sebagai sporadik atau familial –faktor risiko yang paling kuat adalah sejarah keluarga. Mutasi germline pada gen suseptibel kanser payudara penetran tinggi BRCA 1 dan BRCA 2 memberi implikasi kuat predisposisi genetik dalam lebih kurang 20% kanser familial. Walaupun BRCA 1 dan BRCA 2 tidak terlibat dalam semua kanser payudara familial, hingga kini, tiada terdapat gen-gen lain yang dikenalpasti mempunyai segregasi kuat dalam kanser payudara familial. Sungguhpun terdapat kajian untuk mengenalpasti faktor-faktor risiko berkaitan kanser payudara, varian-varian yang dikenalpasti melalui kaji asosiasi keluasan-genom (GWAS), hanya menunjukkan peningkatan sederhana risiko kanser payudara dan di masa kini tidak menunjukkan utiliti klinikal. Ulasan ini akan membincang faktor-faktor risiko genetik yang telah diketahui dalam perkembangan kanser payudara dan sejauh mana kemajuan bidang ini semenjak BRCA 1 dikenalpasti.

*Kata kunci:* kanser payudara, penanda genetik, BRCA 1

### ABSTRACT

Breast cancer is the most common malignancy that develops in women worldwide, its incidence continues to rise and it is responsible for the highest death rates. Breast cancer can be classified as sporadic or familial - the strongest risk factor today is a family history. Germline mutations in high-penetrance breast cancer susceptibility genes BRCA1 and BRCA2 have been strongly implicated in the genetic predisposition of approximately 20% of familial breast cancers. Although BRCA1 and BRCA2 do not account for all familial breast cancers, there are currently no other genes that have been identified which segregate with familial breast cancer as strongly. Despite large-scale attempts to identify genetic risk factors associated with breast cancer, the variants identified through genome-wide association studies (GWAS), only confer a modest increase in risk of breast cancer and at present lack clinical utility. This review will

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discuss the known genetic risk factors for developing breast cancer and how far the field has progressed since the identification of BRCA1.

*Key words:* breast cancer, genetic markers, BRCA 1

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## INTRODUCTION

Breast cancer is the most common malignancy that develops in women worldwide, its incidence continues to rise and it is responsible for the highest death rates (Kamangar et al. 2006). Breast cancer is a disease with complex aetiology with multiple predisposing factors. There is a substantial body of experimental, clinical and epidemiological evidence indicating that hormones play a major role in the development of breast cancer and this has been extensively reviewed in the literature (Clarke & Sutherland 1990; Clarkson et al. 2004; Henderson & Feigelson 2000; Pike et al. 1993; Russo & Russo 1998). Firstly, breast cancer in men is rare, suggesting an influence of the female sex steroids (Hulka & Stark 1995). Secondly, in studies conducted as early as 1896, it was reported that removal of the ovaries caused the regression of breast cancer, and subsequent studies, many years later, reported that the estrogen antagonist, Tamoxifen, had proven efficacy in the treatment of advanced breast cancer and in the reduction of breast cancer risk when used in an adjuvant setting (Cuzick et al. 2003; Jordan 2003; Russo and Russo 1998). Thirdly, it has been repeatedly demonstrated that estrogen and progesterone treatment in animal models, including rodents and monkeys, can promote mammary carcinogenesis and this is critically dependent on functional estrogen and progesterone receptors (ER and PR) (Clarke and Sutherland 1990; Clarkson et al. 2004; Russo and Russo 1998). Finally, there have been

numerous epidemiological studies which have reported increases in breast cancer risk in women with increased exposure to endogenous and exogenous hormones (Santen 2003; Writing Group for the Women's Health Initiative Investigators 2002). Endogenous and exogenous hormones can promote tumour formation by driving cell proliferation, subsequently increasing the number of cell divisions as well as the opportunity for random genetic errors (Henderson and Feigelson 2000). Alternatively, estrogen metabolites may directly generate DNA damage, thus leading to genomic instability (Liehr 2000; Yue et al. 2003). However, there is also strong evidence for a genetic component to breast cancer, the strongest risk factor today is a family history. The genetic basis for the inherited predisposition to breast cancer has been ardently investigated in the past two decades and has resulted in the discovery of several high- to low-penetrance breast cancer susceptibility genes through genome-wide linkage studies and mutational screening of candidate genes in large breast cancer case series. This review will discuss the known genetic risk factors for developing breast cancer with a particular focus on BRCA1.

## HIGHLY PENETRANT BREAST CANCER SUSCEPTIBILITY GENES

### *BRCA1/2*

Hereditary breast cancer accounts for a small but significant proportion (12.9%) of all breast cancers (Collaborative Group on Hormonal Factors in Breast

Cancer 2001). Analysis of pedigrees from high-risk breast/ovarian cancer families led to the identification and cloning of the first breast cancer susceptibility gene (BRCA1) (Hall et al. 1990; Miki et al. 1994) spanning approximately 100kb of genomic DNA and consisting of 24 exons (although exons 1 and 4 are non-coding), that encode a large multi-domain protein of 1863aa (Miki et al. 1994). The role of this protein in genetic susceptibility to breast and ovarian cancer was confirmed when germline mutations in BRCA1 were identified in individuals with a family history of breast and/or ovarian cancer (Castilla et al. 1994; Friedman et al. 1994; Miki et al. 1994). In addition to an elevated risk of breast and ovarian cancer, BRCA1 mutation carriers were also found to have an increased risk of colon, pancreatic, endometrial, cervical and prostate cancer (Brose et al. 2002; Ford et al. 1994; Struewing et al. 1997; Thompson et al. 2002b; Warner et al. 1999). However, the risk of cancer at these sites is relatively small when compared to the risk of cancer in the breast or ovary. Direct evidence that BRCA1 acted as a tumour suppressor in human breast and ovarian cancer cells came from in vitro studies where its over-expression retarded cell growth and its inhibition accelerated cell growth, while mutated forms of the protein had no effect (Holt et al. 1996; Thompson et al. 1995). A second breast cancer susceptibility gene, BRCA2 was subsequently identified in 1994 (Wooster et al. 1994).

The histopathology of breast cancers diagnosed in BRCA1 mutation carriers differ substantially from those that occur in sporadic disease. Breast cancers that develop in BRCA1 mutation carriers are diagnosed at younger age, are of higher grade, often exhibit higher mitotic counts and have a greater proportion of tumour with continuous pushing margin (Breast Cancer Linkage Consortium 1997; Eerola et al. 2005; Eisinger et al. 1996;

Jacquemier et al. 1995; Lakhani et al. 1998; Marcus et al. 1996; Moller et al. 2002; Querzoli et al. 2001; Robson et al. 1998; Stoppa-Lyonnet et al. 2000). Breast tumours in BRCA1 mutation carriers are more likely to be negative for ER, PR and AR when compared to sporadic breast cancers (Berns et al. 2003; Eerola et al. 2005; Foulkes et al. 2004; Lakhani et al. 2002; Loman et al. 1998; Osin et al. 1998; Palacios et al. 2005; Vaziri et al. 2001; Verhoog et al. 1999). They contain less tubule formation, more nuclear polymorphism and more lymphocytic infiltrate compared with their sporadic counterparts (Breast Cancer Linkage Consortium 1997; Eisinger et al. 1996; Lakhani et al. 1998). In addition, BRCA1 mutation carriers are more likely to develop contralateral breast cancer (Robson et al. 1998; Verhoog et al. 1999). Premalignant lesions associated with increased malignancy, such as ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH), and atypical lobular carcinoma (ALH), may be more prevalent in the normal breast tissue from BRCA1 mutation carriers compared to the breast of patients without a known genetic predisposition to the disease (Hoogerbrugge et al. 2003; Kauff et al. 2003; Russo et al. 2001; Sun et al. 1996). Thus, women with an inherited predisposition to breast cancer due to a BRCA1 mutation often present clinically with breast tumours containing features associated with a highly proliferative phenotype and with a worse prognosis.

To date, more than 1600 distinct pathogenic mutations, polymorphisms and variants in the BRCA1 gene have been identified. In addition, over 1800 distinct pathogenic mutations have been identified in BRCA2 (Breast Cancer Information Core 2005). The mutations are scattered throughout the entire coding region of the genes and show no clustering or "hot spots". The frequency of these mutations varies widely among

different populations and is influenced by founder effects. For example, in the Ashkenazi Jewish community four mutations are thought to account for the majority of inherited breast and/or ovarian cancer: 185delAG, 188del11 and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene (Tonin et al. 1996). In original analyses by the Breast Cancer Linkage Consortium (BCLC), BRCA1 mutations were shown to occur in >90% of families that contained at least four breast and/or ovarian cancers; and were estimated to occur in 45% of sporadic cases (Easton et al. 1993; Narod et al. 1995). However, since the cloning of this gene (Miki et al. 1994), the prevalence estimates for BRCA1 have been much less than those estimated by initial linkage studies.

In hereditary breast cancer, mutations in BRCA1 have been shown to occur in the large proportion of cases (~30-80%) in families with both breast and ovarian cancer, whereas BRCA2 mutations account for a smaller proportion (~15-20%) (de la Hoya et al. 2002; Diez et al. 2003; Ford et al. 1998; German Consortium for Hereditary Breast and Ovarian Cancer 2002; Martin et al. 2001; Narod et al. 1995; Wagner et al. 1998). In families containing breast cancer only, BRCA1 mutations occur in around 7% of cases where there is more than one first degree relative and in 28% of cases where there are four or more affected individuals within a family (Ford et al. 1998; Malone et al. 1998). BRCA1 mutations are more prevalent in ovarian cancer only families (compared to breast cancer only families) and are detected in 31-38% of cases (Antoniou et al. 2000; Gayther et al. 1999; Reedy et al. 2002). The prevalence of BRCA1 mutations in population-based studies is considerably lower than those estimated for large multiple-case families. Perhaps the most reliable estimate to date comes from a study con-

ducted by Antoniou and colleagues, where population-based cohorts from 22 previous studies in 13 different countries were analysed. From 8139 index cases presenting with breast or ovarian cancer, 3.5% were found to carry a mutation in BRCA1 and 2.7% carried a mutation in BRCA2 (Antoniou et al. 2003). Moreover, breast cancer incidences were shown to increase with age, up to age 45-49 years in BRCA1-mutation carriers, but reached a plateau thereafter, whereas breast cancer incidence BRCA2-mutation carriers increased gradually with age (Antoniou et al. 2000; Brose et al. 2002; Scott et al. 2003).

Although BRCA1 and 2 mutations are found in a high proportion of familial breast/ovarian cancer patients, defining the penetrance (the risk that a given mutation will lead to cancer) of BRCA1 mutations remains a challenging task. Early studies of large multiple-case families suggested that the lifetime risk of disease may be as high as 85% in BRCA1 or BRCA2 mutation carriers (Easton et al. 1993; Ford et al. 1994; Ford et al. 1998; Narod et al. 1995). However, more recent analyses have shown significantly lower risks than those initially estimated, 65% for the risk of breast cancer development and 39% for the risk of ovarian cancer development up to 70 years of age for BRCA1 mutation carriers (Antoniou et al. 2000; Brose et al. 2002; Scott et al. 2003). The risk estimates for developing breast or ovarian cancer for BRCA2 mutation carriers are lower than that of BRCA1 mutation carriers at 45% (breast) and 11% (ovarian) respectively (Antoniou et al. 2000; Brose et al. 2002; Scott et al. 2003). Nevertheless, regardless of the precise penetrance estimate, BRCA1 and 2 are highly penetrant (albeit not completely) breast cancer susceptibility genes whose mutation significantly increases the risk of developing breast cancer.

### *Does BRCA1 mutation position alter disease phenotype?*

A critical question in mutation screening of BRCA1 is whether the position of the mutation correlates with the cancer phenotype (i.e. breast or ovarian cancer). Knowing the biological consequence of a particular mutation could provide valuable information to patients seeking counselling on which type of preventative and management measures to undertake, if a mutation is found. The first formal evidence linking risk to mutation position came from Gayther et al., (1995) who found that for 22 different mutations in 32 families, the ratio of breast to ovarian cancer was significantly lower after a "change point". This change point was codon 1435 in exon 13, where a BRCA1 mutation 5' of this codon conferred a significantly higher risk of developing ovarian cancer (Gayther et al. 1995). This has been confirmed by a study conducted in the UK (The Scottish/Northern Irish BRCA1/BRCA2 Consortium 2003), however, other studies have failed to confirm a relationship between mutation position and cancer phenotype (Frank et al. 1998; Serova et al. 1996).

In a population-based study of women with BRCA1-related ovarian cancer, the risk of breast cancer in first degree relatives was found to increase proportionally as the mutation position approached the carboxyl terminus of the gene (Risch et al. 2001). In contrast to previous reports, a study conducted by the Breast Cancer Linage Consortium of 356 BRCA1-related families found that mutations in the central portion of the gene (nucleotides 2401-4190) had a significantly higher ovarian: breast cancer ratio when compared to mutations between nucleotides 1-2400 or nucleotides 4191-end (Thompson et al. 2002a). This was supported by an Australian study which, although subjects with ovarian cancer were not included, found that mutations within

the central portion of the gene (2356-4592) were associated with a decreased risk of breast cancer, compared to mutations at the N- and C-terminus (Scott et al. 2003). Furthermore, the same genotype-phenotype relationship was also observed in a meta-analysis of 22 previous studies, although statistical significance was not achieved (Antonioni et al. 2003).

Although it is possible that the position of the mutation within BRCA1 will affect the prevalence of breast or ovarian cancer, there is no solid evidence as yet, to suggest that this is the case. The available research is limited and has produced conflicting results as to which mutated regions present greater risk for breast or ovarian cancer.

### *Other high penetrance breast cancer susceptibility genes*

High penetrance breast cancer susceptibility genes, other than BRCA1/2, have been identified as a result of their association with other inherited cancer syndromes and include TP53, PTEN and STK11.

The p53 tumour suppressor protein is essential for the response to DNA damage and is classed as a "guardian of the genome" (Rozan & El-Deiry 2007; Vousden & Lu 2002). The involvement of the p53 protein, encoded by TP53, in multiple cellular pathways involved in tumour suppression has long been established, and somatic mutations in the gene are frequently observed in many types of solid tumours (Olivier et al. 2009). Germline mutations in TP53 cause Li-Fraumeni syndrome, an inherited disorder that greatly increases susceptibility to breast and other cancers. Although if present they are highly penetrant, conferring up to a 10 fold increase in the risk of developing breast cancer, these mutations are very rare and account for a much lower familial risk than

BRCA1 and BRCA2 (Laloo et al. 2006). Moreover, they are uncommon in non-Li-Fraumeni breast cancer families (Borresen 1992; Laloo et al. 2006).

Germline mutations in PTEN and STK11 are known to lead to Cowden and Peutz-Jeghers syndrome respectively (Hearle et al. 2006b; Nelen et al. 1996). Individuals with Cowden syndrome have an estimated 30-50% risk of developing breast cancer by the age of 70 years (Nelen et al. 1996), while the risk of developing breast cancer is approximately 45% in individuals with Peutz-Jeghers syndrome (Hearle et al. 2006a; Lim et al. 2004). However, PTEN and STK11 mutations are rare in high risk breast/ovarian cancer individuals that do not carry BRCA1/2 mutations (Guenard et al. 2007; Guenard et al. 2010). Interestingly, gross aberrations in PTEN were found in BRCA1 heterozygous mutation carriers and loss of PTEN expression was associated with basal-like sporadic breast cancer cases, indicating that its loss may be tightly linked with deficiencies in the double-strand break DNA repair pathway (Saal et al. 2008).

Together, mutations in BRCA1/2, TP53, PTEN and STK11, although highly penetrant, only account for around 20-25% of the familial risk of breast cancer. Moreover, mutations in TP53, PTEN and STK11 are rare in patients who do not have the cancer syndromes associated with these genes and they are unlikely to contribute to a substantial fraction of breast cancer susceptibility in high-risk breast cancer families who do not harbour inactivating mutations in the BRCA1/2 tumour suppressor genes.

#### **VARIANTS IN BREAST CANCER SUSCEPTIBILITY GENES WITH INTERMEDIATE PENETRANCE**

Four intermediate-penetrance breast cancer susceptibility genes, CHEK2, ATM, PALB2, and BRIP1, were identified

through direct re-sequencing of candidate genes in familial association studies. Disease-causing mutations in these genes are predominantly ones that cause premature protein truncation, but are rare and confer a relative risk of breast cancer of 2- to 4-fold. All four genes are involved in the BRCA1 DNA repair pathway.

#### *ATM and CHEK2*

BRCA1 is a target for phosphorylation by several checkpoint kinases in response to DNA damage. The kinases that participate in this signalling cascade upstream of BRCA1 include ATM and the checkpoint protein CHEK2. ATM is a protein kinase that is structurally related to the phosphoinositide-3 kinase (PI3K)-related kinase family and is a central component of the DNA damage response (Yang et al. 2003; Zhou & Elledge 2000). CHEK2 is activated by ATM and the phosphorylation of BRCA1 by CHEK2 has been shown to govern which pathway DNA damage will be repaired by: phosphorylation of BRCA1 at Ser-988 promotes the repair of damaged DNA by homologous recombination (error-free), while suppressing repair by non-homologous recombination (error prone) (Zhang et al. 2004). It was demonstrated by Renwick and colleagues that monoallelic ATM mutations were present in 2.04% of familial breast cancer cases and were associated with a 2.37 fold increased breast cancer risk (Renwick et al. 2006). The CHEK2\*1100delC was found to have a frequency of 1.1% in healthy individuals and 5.1% in individuals with breast cancer from 718 BRCA1 or BRCA2 mutation negative families (Meijers-Heijboer et al. 2002). In the largest study to date, involving over 26,000 cases and 27,000 controls, heterozygosity for the CHEK2\*1100delC was associated with a 3-5 fold increase in the risk of developing breast cancer. Furthermore, in familial

breast cancer cases the CHEK2\*1100delC was associated with a 37% lifetime risk of breast cancer, which was almost as high as the lifetime risks conferred by mutations in BRCA1 or 2 in this study (Weischer et al. 2008).

#### *BRIP1 and PALB2*

BRIP1 and PALB2 encode for proteins that co-localize with BRCA1 and BRCA2 to mediate the repair of DNA double-strand breaks (De Nicolo et al. 2008; Rahman et al. 2007; Seal et al. 2006; Xia et al. 2006). Truncating mutations arising in these genes are rare, exhibited in approximately 0.1% of the United Kingdom breast cancer cohort, and confer an approximately two-fold increase in the risk of breast cancer compared to population risks (Rahman et al. 2007; Seal et al. 2006). Founder mutations have been observed in French-Canadian, Finnish and Polish populations, allowing for the identification of a gene-disease association (Dansonka-Mieszkowska et al. 2010; Erko et al. 2007; Foulkes et al. 2007). However, mutations in BRIP1 and PALB2 show incomplete segregation with disease in relatives of probands who have breast cancer (Rahman et al. 2007; Xia et al. 2007), making it difficult to use this information in predictive screening to estimate individual breast cancer risk. There is no evidence to date that monoallelic mutations in BRIP1 and PALB2 confer a phenotype beyond predisposition to breast cancer, although biallelic mutations in these genes are implicated in Fanconi anemia (Reid et al. 2007).

Inactivating mutations in the intermediate penetrance genes ATM, CHEK2, BRIP1 and PALB2 are rare, with fewer than 1% of the population being heterozygote for these variants. Collectively, mutations in these genes account for approximately 2.3% of the familial breast cancer risk (Rahman et al. 2007).

## **THE IDENTIFICATION OF NEW LOW RISK VARIANTS**

### *Genetic modifiers of risk in the general population*

Since the identification of BRCA1 twenty years ago (Hall et al. 1990; Miki et al. 1994), numerous studies have used candidate gene approaches to identify other breast cancer susceptibility genes (BRCAx) whose mutations may lead to an increased risk of breast cancer, with limited success- BRCAx still remains elusive. Mutations in the high and moderate penetrance breast cancer susceptibility genes described above account for approximately 25% of breast cancers; are rarely found in sporadic cases and thus, much of the genetic component of breast cancer risk remains to be characterised. The majority of breast cancers do not arise through typical patterns of familial inheritance, they occur sporadically. Sporadic breast cancers differ markedly from familial breast cancers; with respect to their age of onset (post-menopause versus pre-menopause), their phenotype (receptor positive versus receptor negative in BRCA1 mutation carriers) and their clinical behaviour (familial breast cancers tend to be more aggressive). Thus, candidate gene approaches in large familial pedigree studies are likely to miss common genetic variation that confers a risk of breast cancer in the majority of the population. Genome-wide association studies (GWAS) in very large study populations of breast cancer cases and unaffected controls have gained momentum in recent years, enabling an unbiased investigation of genetic variation across the whole genome, as opposed to examination of selected variants in a few key genes, in an effort to discover new breast cancer susceptibility loci. To date, 13 breast cancer susceptibility loci have been discovered by these



approaches (Table 1). None of the identified variants are in the coding regions of genes, although some of the regions contain or are nearby known genes (e.g. FGFR2, MAP3K1, RAD51L) and five of the variants are located in non-genic regions (1p11.2, 2q35, 3p24, 5p12, 8q24) (Ahmed et al. 2009; Cox et al. 2007; Easton et al. 2007; Hunter et al. 2007; Milne et al. 2009; Stacey et al. 2008; Thomas et al. 2009). The individual variants confer only a modest increase in the risk of breast cancer, of up to approximately 1.65 fold.

Importantly, candidate gene approaches and the recent GWA studies have found no evidence that common variants in high risk breast cancer susceptibility genes such as BRCA1/2, TP53, ATM and CHEK2 are associated with increased breast cancer risk (Baynes et al. 2007; Lu et al. 2010). In fact, few of the genes in the regions identified by GWAS had previously been reported to be associated with breast cancer. The strongest association with breast cancer risk was found for a SNP located in intron 2 of FGFR2 (rs2981582), where women carrying two copies of the high risk allele were observed to have a 1.63 fold increased risk when compared to women who carried two copies of the low risk allele (Easton et al. 2007). The FGF signalling pathway has previously been shown to induce mammary tumours in mouse models (Dickson et al. 2000) and in particular, amplification of FGFR2 has been shown to occur in 5-10% of human breast cancers (Adnane et al. 1991; Heiskanen et al. 2001). Recent studies by Meyer et al., have demonstrated that homozygotes for the high risk FGFR2 allele have increased expression of FGFR2 and functional studies have indicated that this is due to altered binding affinity of FGFR2 for the transcription factors Oct-1 and C/EBP $\beta$  (Meyer et al. 2008). This was the first study to determine a biological

consequence caused by variants identified through GWA studies and clearly demonstrates a mechanism that may lead to increased breast cancer risk in individuals who are homozygous for the high risk FGFR2 allele. However, a functional consequence for many of the variants still remains at large and the biological mechanisms underlying the observed increase in breast cancer risk are unknown.

It is apparent that each individual variant identified through GWA studies only accounts for a modest increase in the risk of developing breast cancer, suggesting that most of the unexplained breast cancer risk could be accounted for by a polygenic model, where risk alleles act multiplicatively (Pharoah et al. 2008). A recent study by Reeves et al., (2010) comparing 13 risk alleles (Table 1 and ATM: rs1800054) in 10 306 women with breast cancer and 10 393 women without breast cancer; has investigated the combined effect 7 SNPs that were most strongly and significantly associated with breast cancer risk individually (Reeves et al. 2010). Odds ratios (ORs) were shown to increase from 0.75 to 1.45 for cases in the bottom fifth quintile compared to cases in the top fifth quintile, however, ORs in the top fifth quintile did not differ greatly from the OR of the individual FGFR2 allele (1.20), which showed the strongest association with breast cancer risk. The cumulative risk of developing breast cancer was 8.8% for cases in the top fifth quintile compared to 4.4% for cases in the bottom fifth quintile. Thus, although a polygenic risk model for the variants has been demonstrated, the cumulative lifetime risk (8.8%) of developing breast cancer in women in the top fifth quintile was shown to be similar to that of women with one affected first-degree relative (9.1%) and far less than that of women with two affected first-degree relatives (15.4%) (Reeves et al. 2010). In addition, it has been demonstrated that

12 of the identified variants show no interactions with other risk factors for breast cancer including HRT, age at menopause, age at menarche, BMI and parity (Travis et al. 2010); and variants identified from GWA studies conducted by Hunter et al., (Hunter et al. 2007) and Thomas et al. (Thomas et al. 2009) were found to have no association with breast cancer survival (Azzato et al. 2010). Thus at this stage, polygenic risk scores are not a useful tool to inform women of their risk of developing breast cancer and appear to have limited utility in breast cancer prognostication.

#### *Genetic modifiers of risk in BRCA mutation carriers*

Given the substantial heterogeneity in penetrance estimates for BRCA1 mutation carriers between studies of different populations, in addition to the variation in penetrance estimates observed between individuals, it is reasonable to postulate the existence of other factors which may modulate the risk of cancer in BRCA1 mutation carriers. In this way, "modifiers" may act in conjunction with the mutated BRCA1 allele to bring about an earlier diagnosis in an individual, thus affecting the penetrance of this gene.

Candidate gene approaches have identified several genetic variants that may alter the risk of breast cancer in BRCA1 mutation carriers. There are several reports that allelic variants of the Androgen Receptor (AR) and the Amplified In Breast Cancer 1 (AIB1) gene, can modify the risk of breast cancer in BRCA1 mutation carriers (Kadouri et al. 2004; Rebbeck et al. 1999; Rebbeck et al. 2001). However, other studies have found no excess breast cancer risk in BRCA1 mutation carriers according to their AR allele or AIB1 polymorphism status (Hughes et al. 2005; Kadouri et al. 2001; Menin et al. 2001; Montgomery et al. 2005; Spurdle et al. 2005). TP53 may

also play a role in BRCA1-related tumorigenesis. TP53 has been found to be mutated in 53-77% of BRCA1-related breast cancers, but only in 30-35% of sporadic breast tumours (Crook et al. 1997; Crook et al. 1998; Greenblatt et al. 2001; Phillips et al. 1999; Sensi et al. 2003). Likewise, TP53 mutations are found in 50-83% of ovarian cancers linked to BRCA1 compared to 30-49% of sporadic ovarian tumours (Buller et al. 2001; Ramus et al. 1999; Reedy et al. 2001; Rhei et al. 1998). Thus, the high rate of TP53 mutations found in cancers of BRCA1 mutation carriers indicates that inactivation of p53 function may act as a modifier of cancer risk in these women. However, subsequent studies have found no association between polymorphisms in TP53 (Arg72Pro) or MDM (309G>T) (either singly or in combination) and breast cancer risk in BRCA1 or BRCA2 mutation carriers, suggesting that the inactivation of TP53 and its signalling pathway may occur as a result of tumour progression rather than being a risk modifier (Sinilnikova et al. 2009). The RAD51 135G>C polymorphism has been shown to increase breast cancer risk in BRCA2 mutation carriers by approximately 3 fold, but does not increase breast cancer risk in BRCA1 mutation carriers or the general population (Antoniou et al. 2007; Zhou et al. 2010). Instead, the RAD51 135G>C polymorphism may protect against the risk of breast cancer in BRCA1 mutation carriers (Jakubowska et al. 2007c). There is also evidence that the 677C>T polymorphism in Methylenetetrahydrofolate reductase (MTHFR) and the C to T transition in the 3' untranslated region of the Prohibitin (PHB) may increase breast cancer risk in BRCA1 mutation carriers (Jakubowska et al. 2007a; Jakubowska et al. 2007b). Allele variants of the Insulin-like Growth Factor-1 (IGF1) and the Progesterone Receptor (PR) are known to alter hormonal sensitivity and have

**Table 1:** Classes and key features of known breast cancer susceptibility genes (Ahmed, et al. 2009; Cox, et al. 2007; Easton, et al. 2007; Hunter, et al. 2007; Milne, et al. 2009; Stacey, et al. 2008; Thomas, et al. 2009)

Class of Breast Cancer Susceptibility Genes	Key Features			Risk variants
	Genes/Alleles	Frequency	Risk of breast cancer	
<b>High-penetrance breast cancer susceptibility genes</b>	<i>BRCA1, BRCA2, TP53</i>	Rare (population carrier frequency $\leq 0.1\%$ )	10 to 20 fold relative risk	Multiple, different mutations that predominantly cause protein truncation
<b>Intermediate-penetrance breast cancer susceptibility genes</b>	<i>ATM, CHEK2, BRIP1, PALB2</i>	Rare (population carrier frequency $\leq 0.6\%$ )	2 to 4 fold relative risk	Multiple, different mutations that predominantly cause protein truncation
<b>Low-penetrance breast cancer susceptibility alleles</b>	rs2981552 ( <i>FGFR2</i> , 10q), rs3803662 ( <i>TOX3</i> , 16q), rs889312 ( <i>MAP3K1</i> , 5q), rs3817198 ( <i>LSP1</i> , 11p), rs1045485 ( <i>CASP8</i> , 2q), rs13281615 (8q), rs13387042 (2q), rs10941579 (5p), rs2046210 (6q), rs4973788 ( <i>SLC44A7</i> , 3p), rs6504950 ( <i>COX11</i> , 17q), rs8009944 ( <i>RAD51L1</i> , 14q), rs11249433 (1p)	Common (population frequency 5-50%)	up to ~1.25 fold (heterozygous) or 1.65 fold (homozygous) relative risk	Single nucleotide polymorphisms (SNPs) that are causal or in linkage disequilibrium with the causal variant

been shown to modify the risk of breast and ovarian cancer respectively, in BRCA1 mutation carriers (Jernstrom et al. 2005; Runnebaum et al. 2001). Polymorphisms in the Harvey Rat Sarcoma 1 (HRAS1) proto-oncogene as well as common variants of the BRCA1 wild-type allele itself have been shown to increase the risk of ovarian cancers in BRCA1 mutation carriers (Ginolhac et al. 2003; Phelan et al. 1996). Other groups have reported low expression of the pro-apoptotic protein B-cell Lymphoma Protein 2 (Bcl-2) and amplification of the Myelocytomatosis (MYC) oncogene, in BRCA1-associated breast tumours compared to sporadic cases (Freneaux et al. 2000; Grushko et al. 2004), but whether these genes act as risk modifiers in BRCA-related tumourigenesis is unknown.

Numerous other candidate genes have been investigated as modifiers of BRCA1/2 penetrance, however, they have been met with limited success. Given the lack of targets found to positively correlate with breast cancer risk by candidate gene approaches in BRCA1/2 mutation carriers, GWAS studies are now being applied to BRCA1/2 mutation carriers. Initial studies have focussed on determining whether variants that increase breast cancer risk in population based-studies confer a similar risk of breast cancer development in BRCA1/2 mutation carriers. To this end, five of the variants identified by GWAS (Table 1) have been genotyped in women who are BRCA1 and 2 mutation carriers. While variants in FGFR2, TNCR9, LSP1, MAP3K1 and the 2q35 region were associated with breast cancer risk in BRCA2 mutation carriers, only the TNCR9 variant and the 2q35 region was associated with breast cancer risk in BRCA1 mutation carriers (Antoniou et al. 2008; Antoniou et al. 2009). More recently, GWA studies have been carried out in BRCA1/2 mutation carriers to

identify new modifiers of disease risk in these individuals. Interestingly, FGFR2 was the only locus to reach GWAS statistical significance and showed a similar magnitude of risk (approximately 1.3 fold increased risk) as reported for breast cancer risk in population-based studies (Gaudet et al. 2010). Thus, variants that modify breast cancer risk in the general population also appear to modify breast cancer risk in BRCA2 mutation carriers. However, this does not appear to be the case in BRCA1 mutation carriers where one locus (19p13) containing 5 variants has been reported to be associated with breast cancer risk in these individuals and a similar association was also reported for ER-negative and triple negative cases (Antoniou et al. 2010). These results seem to reflect the distinct biology of BRCA1-related breast cancers, which are predominantly hormone receptor negative, compared to BRCA2-related and sporadic breast cancers, and further highlights the genetically divergent pathways that lead to tumourigenesis in these women.

## SUMMARY AND CONCLUSIONS

Following the identification of BRCA1 and BRCA2 as high penetrance breast cancer susceptibility genes, significant effort has been aimed at identifying further susceptibility genes that may account for the missing heritability to breast cancer. The advances made have been small and the elusive BRCAx has still not been found. This has led to the conclusion that there are in fact no other high penetrance breast cancer susceptibility genes and that the remainder of the genetic risk to breast cancer can be accounted for by a polygenic model, where many variants of low penetrance act multiplicatively to increase the relative risk of developing breast cancer. In the last 3 years, with considerable advances in technology, a multitude of data has

been generated by GWAS leading to the identification of 13 new low penetrance variants that individually account for a modest increase in breast cancer risk. However, the results have been somewhat disappointing, when combined these variants still only lead to a small increase in breast cancer risk and the information generated thus far, will not be informative in a clinical setting in determining an individuals' risk of developing breast cancer and therefore, will not be useful in preventative strategies.

How far have we come from BRCA1 in predicting breast cancer risk? To date, most of the GWAS on breast cancer have been carried out in populations unselected for ER status, grade, age, ethnicity, etc. But breast cancer is an extremely heterogeneous disease where gene-environment interactions, especially those influencing estrogen exposure, play a major role in determining disease onset and expression and this has been repeatedly demonstrated. In this regard, it has been shown that the relative risks for each of the 13 low penetrance variants are significantly influenced by ER status (FGRR2, TNCR9), grade (FGRR2, TNCR9), bilateral disease (2q35) and lobular versus ductal carcinoma (2q35) (Reeves et al. 2010). Genetically, sporadic breast cancer can be subdivided into 5 distinct sub-groups and hormone receptor status plays a major role in discriminating these sub-groups (Sorlie et al. 2003). BRCA1-related tumours consistently group with sporadic tumours that are negative for ER, PR and HER2, "triple negative" (Sorlie et al. 2003). The most recent GWAS on BRCA1 carriers highlights the genetic heterogeneity of breast cancer, where only one locus was shown to influence breast cancer risk and this locus had not previously been associated with sporadic disease. This locus was associated with the risk of developing ER-negative breast cancer and triple-nega-

tive breast cancer, but not ER-positive breast cancer (Antoniou et al. 2010). Other studies have also shown significantly stronger associations of many of the 13 identified variants with ER-positive disease compared to ER-negative disease and this is especially true of the polygenic model (Reeves et al. 2010). The most recent GWAS on ER-negative breast cancer found that there were no significant associations with any of the variants examined and found no evidence to suggest that ER-negative breast cancer has a polygenic basis for disease development, unlike ER-positive breast cancer (Li et al. 2010). Thus, recent GWAS on breast cancer have reiterated that importance of viewing breast cancer sub-types as distinct entities and underpin the genetically diverse pathways by which these tumour sub-groups develop.

In conclusion, although the variants identified by GWAS have little clinical applicability at present, it is likely that more refined GWA studies of tumour sub-groups with defined pathological characteristics will shed more light on risk prediction in the future.

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