

## MINI-REVIEW

# Hereditary Genes and SNPs Associated with Breast Cancer

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### Abstract

Breast cancer is the most common cancer among women affecting up to one third of them during their lifespans. Increased expression of some genes due to polymorphisms increases the risk of breast cancer incidence. Since mutations that are recognized to increase breast cancer risk within families are quite rare, identification of these SNPs is very important. The most important loci which include mutations are; *BRCA1*, *BRCA2*, *PTEN*, *ATM*, *TP53*, *CHEK2*, *PPM1D*, *CDH1*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PMS1*, *PMS2*, *BRIP1*, *RAD50*, *RAD51C*, *STK11* and *BARD1*. Presence of SNPs in these genes increases the risk of breast cancer and associated diagnostic markers are among the most reliable for assessing prognosis of breast cancer. In this article we reviewed the hereditary genes of breast cancer and SNPs associated with increasing the risk of breast cancer that were recently reported from candidate gene, meta-analysis and GWAS studies. SNPs of genes associated with breast cancer can be used as a potential tool for improving cancer diagnosis and treatment planning.

**Keywords:** Breast cancer - hereditary genes - SNPs

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### Introduction

Breast cancer is a complex disease that is caused by abnormal growth and uncontrolled division of cells within the terminal duct and lobular of the breast. It mainly occurs in women and less commonly in men. The majority of breast cancers are sporadic in origin and an appreciable fraction is caused by inherited predisposition (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Breast cancer, with approximately one million new patients in each year, is the most common malignancy among women (Coley, 2008). Breast cancer is included about 10 percent of all cancers and 23 percent of women cancers in developed countries (Coley, 2008). Over 15% of healthy women have at least one first-degree relative with breast cancer and experimental data showed that the risk of breast cancer in women has been doubled in recent years (Robson et al., 2007).

Breast cancer is the second killer cancer among American women after lung cancer ([http://www.wwhf.org/hi\\_cancer\\_4.asp](http://www.wwhf.org/hi_cancer_4.asp)). Researches have shown that women with a family history of breast cancer have increased risk of developing breast cancer. The mutations responsible for increasing breast cancer risk within families are recognized. These include mutations in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS1*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *STK11* and *TP53* genes. These rare mutations are probably assigned to a small percent (2-5%) of breast cancer cases (<http://www.snpedia.com/>

[index.php/Breast\\_cancer](http://www.snpedia.com/index.php/Breast_cancer)). Germline mutations of high penetrance breast cancer susceptibility genes such as *BRCA1*, *BRCA2*, *TP53*, *CHEK2*, *ATM*, *PTEN* and *PPM1D* confer a high risk of developing hereditary breast cancer (Cybulski et al., 2011). Recently, it has also been found that mutations in *PPM1D* gene are associated with an increased risk of breast cancer and women with *PPM1D* mutations have a 20 percent chance of developing breast cancer ([http://www.icr.ac.uk/press/press\\_archive](http://www.icr.ac.uk/press/press_archive)). In most breast cancer-causing genes one copy of mutation is inherited and exists in every cell and the second copy of mutated gene exists in the tumor itself, but interestingly *PPM1D* mutations were not inherited, and rather than being in every cell, they were only found in blood cells ([http://www.icr.ac.uk/press/press\\_archive](http://www.icr.ac.uk/press/press_archive)).

As regards so far, few review articles have been published about hereditary genes and SNPs associated with breast cancer. So our studies on some genes associated with breast cancer and works that have been done by other researchers prompted us to review hereditary genes and SNPs associated with breast cancer.

### Single Nucleotide Polymorphisms (SNPs) and Their Importance in Cancer Diagnosis

The occurrence of different forms of an allele in a gene is called polymorphism. Researches have shown that genetic polymorphisms are one of the causes of individual difference in cancer incidence (Karen et al., 2006). In 2001, the complete human genome was sequenced and

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sequence analyses showed that 99% of genome sequences of different individuals were identical (Sachidanandam et al., 2001). Differences among individuals are due to the existence of 4.5 million single nucleotide polymorphisms distributed throughout the genome in both coding and non coding regions. These polymorphisms are individual different factors in having the unique traits (Chakravarti, 1999).

SNPs are the most common type of genetic variation. SNPs can cause silent, harmless or harmful effects (<http://www.cancer.gov/cancertopics/understandingcancer/geneticvariation/page39>). SNPs in the genome can occur in coding and non-coding regions. More SNP occurs in non-coding regions. The researchers concluded that some of the SNPs have a useful activity. If SNP occurring with high frequency near a particular gene, it can be used as a marker for a specific gene, while SNPs occur in coding regions cause change in the produced protein of that gene and the resulting product would have effects on health(<http://www.cancer.gov/cancertopics/understandingcancer/geneticvariation/AllPages>). Whereas SNPs can act as genetic markers, SNPs profile can aid scientists to identify the complete set of genes that are involved in creating and developing complex diseases like cancer. For example scientists studied SNP profiles of many individuals including cancer patients, and comparison between different profiles made it possible to discover a small subset of SNPs that are present only in cancer patients. As a result, SNPs can be considered as markers for identification of cancer genes. Scientists also use SNPs to estimate the factors contributing to cancer risk in large populations (<http://www.cancer.gov/cancertopics/understandingcancer/geneticvariation/AllPages>).

### Hereditary Genes of Breast Cancer

About 5-10% of breast cancers are thought to be hereditary that are caused by abnormal genes (<http://www.breastcancer.org/risk/factors/genetics>). This section describes genes associated with hereditary breast cancer. Some of the most important genes associated with hereditary breast cancer and their characterizations are given in the Table 1.

#### Breast cancer susceptibility gene 1 and breast cancer susceptibility gene

Known genetic factors that are important in breast cancer include high-risk mutations in Breast Cancer susceptibility gene 1 (*BRCA1*) and Breast Cancer susceptibility gene 2 (*BRCA2*) genes (<http://www.23andme.com>). Mutations in *BRCA1* and *BRCA2* genes in germline cells cause

susceptibility to breast and ovarian cancer. *BRCA1* gene is considered as one of the breast cancer genes. The majority mutations of *BRCA1* are nonsense mutations that they are a major part of the known mutations. The high frequency of this type of mutation showed that when the gene product is defective, it will lose its performance and this process will lead to cancer (Ahn et al., 2007). Mutated *BRCA1* gene and less likely *BRCA2* gene increases ovarian cancer risk. *BRCA2* mutation in male breast cancer has been observed more than *BRCA1* mutation. Female carriers of *BRCA1* and *BRCA2* mutations are predisposed to high lifetime risk of breast cancer. Mutation in *BRCA1* and *BRCA2* gene in females also increased the risk of pancreatic cancer and other cancers, while in males it increased the risk of prostate cancer, pancreas cancer and breast cancer (Thompson et al., 2005).

There are specific mutations to particular areas of the *BRCA1* gene in breast cancer. Such mutations which can be mentioned include exon 2 mutations in Ashkenazi Jewish descent (<http://www.cancer.gov/cancertopics/understandingcancer/geneticvariation/page39>), mutation in exon 13 of African – American descent (Pal et al., 2004), mutation in exon 7 and 11 in Hindi women (Valarmathi et al., 2002) and mutation in exon 11 in region of North America (Liede et al., 2002). *BRCA1* and *BRCA2* genes play an important role in DNA repair by homologous recombination, maintain chromosome stability, activation of DNA damage control points and regulation of cell cycle (Ahn et al., 2007).

#### Checkpoint kinase 2

Checkpoint kinase 2 (*CHEK2*) encodes a G2 checkpoint kinase which is involved in DNA damage repair. Previous studies have demonstrated that mutations in *CHEK2* gene increase breast cancer risk, particularly among women with a family history of breast cancer. The risk of breast cancer may be higher for women who have both a *CHEK2* gene mutation and a family history of breast cancer (Cybulski et al., 2011). The reports indicated that faulty of *CHEK2* gene, called *CHEK2*\*1100delC, was more common in women prognosticated with breast cancer than in healthy women (The *CHEK2* Breast Cancer Case-Control Consortium, 2004). *CHEK2* 1100delC gene mutation is one of the most common genetic mutation associated with breast cancer. The risk of *CHEK2* 1100delC gene mutation is higher in women with a family history of the disease and it is estimated that women with one copy of this mutation have at least twice the risk of breast cancer (<http://www.23andme.com>). One of other *CHEK2* variants that have been associated with breast cancer risk is I157T (470T>C) variant in the FHA

**Table 1. Hereditary Genes Associated with Breast Cancer and Breast Cancer Risk**

Gene	Chromosome	Syndrome	Cancer risk	Inheritance	Reference
<i>BRCA1</i>	17q21	Hereditary Breast/Ovarian cancer	Breast: 50-90%	Autosomal Dominant	(Ford et al., 1998)
<i>BRCA2</i>	13q12	Hereditary Breast/Ovarian cancer	Breast: 41-87%	Autosomal Dominant	(Ford et al., 1998)
<i>CHEK2</i>	22q12	Hereditary Breast	Breast: 2 to 3-fold	Autosomal Dominant	(Thompson et al., 2006)
<i>PTEN</i>	10q23	Cowden	Breast: 25-50%	Autosomal Dominant	(Black et al., 2005)
<i>TP53</i>	17p13	Li-Fraumeni	Breast: >50% often by age 30	Autosomal Dominant	(Birch et al., 2001)
<i>ATM</i>	11q22-23	Ataxia Telangiectasia	Breast: 17%	Autosomal Recessive	(Thompson et al., 2005)

domain in exon 3. The IVS2+1G>A splicing mutation that is found in the US, Polish, and German patients with familial prostate cancer showed associates possibly with a 2-4 fold evaluated risk for breast cancer. Also studies have reported that mutations in this gene are associated with ovarian, lung, prostate, colon, kidney and thyroid cancers (<http://ghr.nlm.nih.gov/gene>).

#### *Phosphate and tensin homolog*

Phosphate and Tensin homolog (*PTEN*) is one of the most important tumor suppressor genes that is associated with risk of breast cancer. *PTEN* protein helps regulate the cycle of cell division and cell growth (<http://ghr.nlm.nih.gov/gene>). *PTEN* gene may function as tumor suppressors due to the ability to counteract the action of kinases. Mutation and deletions in the *PTEN* gene are reported at high frequency in breast, brain, prostate and kidney cancer (Gang et al., 2002). The effect of *PTEN* gene mutations is controversial in the beginning of breast cancer. Germline mutations of *PTEN* gene cause Cowden syndrome and hamartoma. *PTEN* c. 697C>T (R233\*) mutation causes in the introduction of premature stop codon into the *PTEN* gene and occurs in exon 7, which encodes a portion of the C2 domain and is associated with breast cancer (<http://www.mycancergenome.org/content/disease/breast-cancer/PTEN/25>).

#### *Tumor Protein 53*

Tumor Protein 53 (*TP53*) gene is one of the most important tumor suppressor genes. The risk of developing breast cancer increases with changes in the *TP53* gene. This gene has a key role in the maintenance of genome integrity and prevents the proliferation of cells with damaged DNA. Thus it plays a role in the inactivation of tumor-causing genes. About 40% of cases of breast carcinoma have mutated form of *TP53* gene (Barnes and Camplejohn, 1996). Mutations in *TP53* gene lead to unregulated cell growth and division (<http://ghr.nlm.nih.gov/gene>). One copy of the *TP53* gene is lost in some cases of breast cancer and the remaining copy which has a mutation, thus prevents the production of any tumor protein 53 in the cell and leads to a cancerous tumor. Several polymorphisms and their possible roles in breast cancer risk have been detected in the *TP53* gene (<http://ghr.nlm.nih.gov/gene>).

#### *Ataxia Telangiectasia Mutated*

Ataxia Telangiectasia Mutated (*ATM*) gene may be associated with an increased risk of breast cancer. The role of the *ATM* gene is controlling cell division. Reports have shown that having a mutation in one copy of the *ATM* gene in each cell increased the risk of developing breast cancer and *ATM* protein is half the normal amount in cells that are missing one of the *ATM* gene (<http://ghr.nlm.nih.gov/gene>). Missense mutations may be responsible for the majority of breast cancer occurring among *ATM* heterozygotes. The prevalence of *ATM* variants varies among different populations. 7271T>G and IVS10-6T>G mutations in *ATM* gene have shown that they are associated with a sufficiently high risk of breast cancer (<http://ghr.nlm.nih.gov/gene>).

## Some Genes Act as Modifiers of Breast Cancer Risk

#### *ER- $\alpha$ and ER- $\beta$ genes*

Estrogen has been shown to contribute to the development and progression of breast cancer risk through its metabolites and have been reported that polymorphisms in estrogen receptor gene Estrogen receptor- $\alpha$  (*ER- $\alpha$* ) and Estrogen receptor- $\beta$  (*ER- $\beta$* ) act as modifiers of breast cancer risk and are associated with the increased risk of breast cancer in women (Schiff et al., 2004). *ER- $\alpha$*  and *ER- $\beta$*  are located on chromosomes 6q25.1 and 14q22-24 in human respectively (Hosseini, 2011). Some of the studies suggested that alterations in *ER- $\alpha$*  and *ER- $\beta$*  occur during breast cancer development. The human *ER- $\alpha$*  gene has been shown to have a low mutational frequency in breast cancer tissue (Roodi et al., 1995).

#### *PR-A and PR-B genes*

Progesterone hormone regulates ovulation and is responsible for pregnancy associated proliferation and differentiation of breast and endometrium. The progesterone receptor gene (*PR*) is located on 11q22-23 and encoded receptor protein. The *PR* gene is transcribed from two alternative promoters and translated into different zinc-finger protein Progesteron receptor-A (*PR-A*) and Progesteron receptor-B (*PR-B*). There are variants that alter function and or expression of the *PR* gene (Karen et al., 2006).

#### *SNPs associated with breast cancer*

Several recent studies reported genes involved in DNA repair and SNPs associated with increased risk of breast cancer. Access to candidate genes indicated that the average risk of breast cancer for rare mutations in genes involved in DNA repair (*PALB2*, *BRIP1*, *CHEK2*, *ATM* and *RAD50*) has increased. Genome Wide Association Study (GWAS) has identified SNPs as low-percent breast cancer susceptibility polymorphisms within genes as well as in chromosomal loci with no known gene (*LSP1*, *TOX3*, *FGFR2*, *TGFBI*, *MAP3K1*, *2q35* and *8q*) (Ahmed et al., 2007). Specific hereditary breast cancer-associated mutations are found in people with Ashkenazi Jewish ancestry. These mutations account for 80-90% of hereditary breast cancer and ovarian cancer cases in this ethnic group. These SNPs include 185delAG and 5382insC in the the *BRCA1* gene and 6174delT in the *BRCA2* gene (Nechushtan et al., 2009). A recent meta-analysis estimated that women with either the 185delAG or 5382insC *BRCA1* mutation have approximately 60% risk of developing breast cancer by age 70 and for women with the 6174delT *BRCA2* mutation estimated risk of breast cancer is about 50% by age 70. These mutations increased the risk of breast cancer in men. Risk of breast cancer estimated at 6.9% at the age 80 for males with a *BRCA2* mutation (Mendel, 2012). Fiuji (2011) studied the frequency of the 5382insC (rs76171189) mutation of the *BRCA1* gene by ARMS-PCR in 100 Iranian breast cancer patients in Mashhad. Control samples were selected from 30 healthy women. They reported a significant correlation between 5382insC (rs76171189) mutation and



breast cancer and reported that there is a high frequency of 5382insC mutation among Iranian people who are suffering from breast cancer (Fiuji, 2011). Also Fiuji et al. (2011) investigated the frequency of the 18delAG mutation of the *BRCA1* gene by ARMS-PCR in 100 Iranian breast cancer patients in Mashhad. Results showed a high frequency of 18delAG mutation among Iranian people who are suffering from breast cancer (Fiuji et al., 2011). Fiuji et al. (2011) designed and produced kits for identification of mutations 5382insC and 185delAG of *BRCA1* gene by ARMS-PCR method (Fiuji et al., 2011a; 2011b)

Johnson et al. (2007) studied 1,037 potentially functional SNPs in 437 women with two primary breast cancer and 2,463 controls. Their results showed that twenty five of these SNPs in the *BRCA1*, *BRCA2*, *ATM*, *TP53* and *CHEK2* genes were associated with breast cancer. SNPs that had risk allele for breast cancer included SNPs of the *BRCA1* gene (rs1799950, rs4986850, rs22279945, rs16942, and rs1799966), SNPs of the *BRCA2* gene (rs766173, rs144848, rs4987117, rs1799954, rs11571746, rs11571747, rs4987047, rs11571833 and rs1801426), SNPs of the *ATM* gene (rs3218707, rs4987945, rs4986761, rs3218695, rs1800056, rs1800057, rs3092856, rs1800058 and rs1801673), SNPs of the *CHEK2* gene (rs1787991) and SNPs of the *TP53* gene (rs1042522) (Johnson et al., 2007). Cox et al. (2007) genotyped nine SNPs that based on prior evidence had reported association with breast cancer. They used datasets that include 11391-18290 patient cases and 14753-22670 controls from 9-15 studies and found evidence from an association with breast cancer for *CASP8* D302H (rs1045485) with odds ratios of 0.89 and 0.74 for heterozygotes and rare homozygotes, respectively, and weaker for *TGFB1* L10P (rs1982073) with odds ratios of 1.07 and 1.16 for heterozygotes and rare homozygotes, respectively (Cox et al., 2007). Stacey et al. (2007) genotyped approximately 300,000 SNPs in 1,600 Icelandic individuals with breast cancer and 11,563 controls. They reported rs13387042 on chromosome 2q35 and rs3803662 on chromosome 16q12 associated with breast cancer (Stacey et al., 2007). Antonis et al. (2007) studied SNP in the 5' UTR of the gene *RAD51* (135 G→C) that based on prior evidence was reported as a possible modifier of breast cancer risk in *BRCA1* and *BRCA2* mutation carriers and observed evidence of an increased breast cancer risk in CC homozygotes. They analyzed *BRCA1* and *BRCA2* mutation carriers separately and reported cancer risk statistically significant only for *BRCA2* mutation carriers. They concluded that 135 G→C may modify the risk of breast cancer in *BRCA2* mutation carriers by altering the expression of *RAD51* (Antonis et al., 2007). Ahmed et al. (2009) carried out a Genome Wide Association Study for breast cancer susceptibility loci in two stages involving 37,012 cases and 40,069 controls from 33 studies in the CGEMS Collaboration and Breast Cancer Association Consortium and reported strong evidence for susceptibility loci on 3p (rs4973768) and 17q (rs6504950) that are associated with breast cancer (Ahmed et al., 2009). Zheng et al. (2009) carried out a Genome Wide Association Study in order to identify risk variants for breast cancer among Chinese women and analyzed

607728 SNPs in 1505 cases and 1522 controls. They reported that SNP rs2046210 at 6q25.1 located upstream of the gene encoding estrogen receptor  $\alpha$ , showed strong association with breast cancer (Zheng et al., 2009). Nechushtan et al. (2009) investigated a germline single nucleotide polymorphism in the first intron of the gene encoding MDM2 at position 309, an important modular of P53. Then they studied 453 Ashkenazi breast cancer patients of which 180 patients were positive for *BRCA1/2* mutations. They reported that MDM2SNP309G/C main effect on *BRCA1/2* mutation carriers is linked to its effect on patient survival Nechushtan et al., 2009). Thomas et al. (2010) carried out a three-stage Genome Wide Association Study of breast cancer in 9,770 cases and 10,799 controls and two new SNPs were identified. The first SNP was on chromosome 1p11.2 (rs11249433) and the second one was on chromosome 14q24.1 (rs999737). They also reported associations with loci on chromosome 5p12, 2q35, 8q24, 10q26, 5q11.2 and 16q12.1 (Thomas et al., 2010). Fu et al. (2010) investigated SNP rs11249433 in the 1p11.2 region that was previously identified as a novel genetic risk factor for breast cancer and the association was in patients with estrogen receptor (ER+) versus ER- cancer. They reported association between SNP rs11249433 and expression of the *NOTCH2* gene in the 1p11.2 region and showed that the expression of *NOTCH2* differed in subgroups of breast tumors and by genotypes of the breast cancer associated SNP rs11249433 (Fu et al., 2010).

Zhang et al. (2008) genotyped polymorphisms in the regulatory regions of *ER- $\alpha$*  gene (rs3798577) among 300 breast cancer cases and 390 controls in a Chinese population and they identified that the TT allele frequency of *ER- $\alpha$*  was significantly higher in cases than controls (Zhang et al., 2008). Abbasi et al. (2012) scanned variants of the *ER- $\alpha$*  and *ER- $\beta$*  genes in 150 Iranian patients and control individuals by SSCP method and reported three SNPs in codon 10 (TCT→TCC), codon 325 (CCG→CCC) and codon 594 (ACG→ACA) in *ER- $\alpha$*  gene and one SNP in codon 392 (CTC→CTG) of *ER- $\beta$*  gene that have additive effects in developing breast cancer. They also revealed that SNP in codon 392 of *ER- $\beta$*  is more effective than SNPs in codons 10, 325 and 594 of *ER- $\alpha$*  gene in developing LN metastases in breast cancer patients (Abbasi et al., 2012). Also Hosseini, (2010) investigated expression of *ER $\alpha$*  and *ER $\beta$*  gene in cancer tissues and reported that higher expression of *ER $\alpha$*  gene and lower expression of *ER $\beta$*  gene in cancer tissues can be important factors in the breast cancer development (Hosseini, 2010).

There are variants that alter function and/or expression of PR. De Vivo et al. (2002) showed a G to A exchange at position +331 in the promoter region and revealed that this SNP enhances the transcription of PR-B and increases the ratio PR-B to PR-A and has been postulated to predispose women to breast cancer through increasing PR-B – dependent stimulation of mammary cell proliferation (De Vivo et al., 2002). Zabetian et al. (2010) reported that PR-A and PR-B genes can be used as references for identification and screening of cancer patients from healthy persons, even in the first stages of the disease (Zabetian et al., 2010). Cai et al. (2011) conducted a genome wide association study among more than 31,000

women of East-Asian, European, and African ancestry in order to investigate a single nucleotide polymorphism (rs2046210 A/G allele) with breast cancer risk at 6q25.1 position. Their result showed a significant association for rs2046210 and breast cancer risk in Chinese, Japanese and European-ancestry American women for the AG and AA genotypes (Cai et al., 2011). Long et al. (2012) performed a four-stage Genome Wide Association Study to identify novel genetic susceptibility loci for breast cancer in 19,091 cases and 20,606 controls in East-Asian descents including Chinese, Korean, and Japanese women and reported SNP rs9485372, near the TGF- $\beta$  activated Kinase (*TAB2*) gene in chromosome 6q25.1 associated with breast cancer risk in the combined analysis of the samples. They also

reported SNP rs9383951 located in intron 5 of the *ESR1* gene and that SNP rs7107217 located at 11q24.3 were associated with breast cancer risk (Long et al., 2012).

Recently, researches have been focused on SNPs that have statistically significant association with breast cancer risk in the general population such as modifiers of risk in *BRCA1* and *BRCA2* mutation carriers. These genetic modifiers for carriers of mutations in *BRCA1* and *BRCA2* have been identified through studies of single nucleotide polymorphism (SNPs) in candidate genes and genome wide association study (GWAS) includes: D302H of *CASP8* (Engel et al., 2010), rs2981522 of *FGFR2*, rs3803662 of *TOX3/TNRC9*, rs889312 of *MAP3K1* (Antonioni et al., 2010), rs3817198 of *LSP1*, rs13387042 of 2q35 and rs13281615 of 8q24 (Garcia-Closas., 2008). Also several loci have been indicated in which the occurrence of SNPs is associated with breast cancer risk in the general population. Some of these loci identified in the general population are shown in Table 2

**Table 2. SNPs Associated with Breast Cancer in the General Population**

Locus-SNP	Gene	Frequency (White Europeans)	Reference
<b>SNPs identified through candidate gene studies</b>			
10p14-rs1045485	<i>CASP8</i>	0.13	Cox et al., 2007
<b>SNPs identified by GWAS</b>			
10q26-rs2981582	<i>FGFR2</i>	0.38	Garcia-Closas et al., 2008
16q12-rs3803662	<i>TOX3/TNRC9</i>	0.25	Garcia-Closas et al., 2008
5q11-rs889312	<i>MAP3K1</i>	0.28	Garcia-Closas et al., 2008
8q24-rs13281615	intergenic	0.4	Garcia-Closas et al., 2008
11p15-rs3717198	<i>LSP1</i> , LOC643714	0.3	Garcia-Closas et al., 2008
3p24-rs4973768	<i>NEK10</i> , <i>SLC4A7</i>	0.46	Ahn et al., 2007
17q23-rs6504950	<i>COX11</i>	0.27	Ahn et al., 2007
6q25-rs2046210	<i>ESR1</i>	0.34	Zheng et al., 2009
9p21-rs1011970	<i>CDKN2A</i> , <i>CDKN2B</i>	0.17	Thussbas et al., 2006
10p15-rs2380205	<i>ANKRD16</i> , <i>FBXO18</i>	0.43	Thussbas et al., 2006
10q21-rs10995190	<i>ZNF365</i>	0.15	Thussbas et al., 2006
10q22-rs704010	<i>ZMIZ1</i>	0.39	Thussbas et al., 2006
11q13-rs614367	intergenic	0.15	Thussbas et al., 2006
2q35-rs13387042	intergenic	0.52	Milne & Antoniou., 2011
<b>SNPs carried in mutation carriers through GWAS</b>			
19p13-rs8170	C19orf62	0.19	Antonis et al., 2007
19p13-rs2363956	C19orf62	0.5	Antonis et al., 2007

## Electronic Databases That Study SNPs in Breast Cancer

There are databases that study SNPs in breast cancer. Some of the databases are shown in Table 3

## Conclusions

Occurrence of SNPs in *BRCA1*, *BRCA2*, *ATM*, *TP53*, *PTEN*, *BARD1*, *BRIP1*, *CDH1*, *CHK2*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *PMS1*, *PMS2*, *RAD50*, *RAD51C*, *STK11*, *PPM1D*, *ER- $\alpha$*  and *ER- $\beta$*  genes increases the risk of breast cancer. Thus SNPs, identification is of major importance in population. Of course SNPs with genetic association with breast cancer are suitable for screening breast cancer in high risk population and

**Table 3. Large Web Databases for SNP Associated with Breast Cancer**

Site	Description	URL
DbSNP	The Single Nucleotide Polymorphism Database is a free public archive for genetic variation, dbSNP database applied research in pharmacogenomics and the association of genetic variation with phenotypic traits	<a href="http://www.ncbi.nlm.nih.gov/projects/SNP">http://www.ncbi.nlm.nih.gov/projects/SNP</a>
23 and Me	Database that is provided allows online access to more than 200 reports and traits, including carrier status, response to drugs and the risk of disease and it is located as part of the new genetic discoveries that can benefit us all	<a href="https://www.23andme.com/">https://www.23andme.com/</a>
SNPshot	SNPshot make available summarized information linking genes, SNPs, drug efficacy, adverse drug reactions, populations, diseases, and literature references and SNPshot contain information on phenotypic effects of genetic variants, focusing on effects on drug response. Drug responses in individual patients are mostly influenced by variants in drug-metabolizing enzymes, drug transporters, drug receptors	<a href="http://bioai4core.fulton.asu.edu/snpshot/">http://bioai4core.fulton.asu.edu/snpshot/</a>
SNPedia	SNPedia: is a database of human single-nucleotide polymorphisms (SNPs) and genotypes	<a href="http://www.SNPedia.com">http://www.SNPedia.com</a>
SNPdbe	SNPdbe database of effects, with predictions of computationally annotated functional impacts of SNPs. Database entries represent nsSNPs in dbSNP and 1000 Genomes collection	<a href="http://www.rostlab.org/services/snpdbe">http://www.rostlab.org/services/snpdbe</a>
HapMap	Database which will describe the common patterns of human genetic variation. HapMap is a key resource for researchers to find genetic variants affecting health, disease and responses to drugs and environmental factors	<a href="http://hapmap.ncbi.nlm.nih.gov/">http://hapmap.ncbi.nlm.nih.gov/</a>

progeny. Therefore, SNPs of genes associated with breast cancer are used as a potential tool for improving cancer diagnosis and treatment planning. Recently, the cost and time of sequencing are reduced and it provides to screen all genes associated with breast cancer risk and suggests that developing a screening test for known mutations. Therefore, in the near future low cost of next-generation whole genome sequencing and high throughput technologies allow to discovery SNPs that associated with breast cancer and can do screening programs on the basis of genetic information in order to reduce mortality associated with breast cancer. Also, developing knowledge of the mutations, role in breast cancer susceptibility allows the explanation of breast cancer risk in individual family members and risk level appropriate screening and risk management confirmations.

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