

# Genetic factors involved in breast cancer

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## ABSTRACT

According to the World Health Organization, as of 2021, breast cancer is the most common malignancy in women worldwide, accounting for up to 12% of all new cancer cases diagnosed each year. Moreover, breast cancer is the second leading cause of cancer-related death in women.

In Romania, over 7.000 new breast cancer cases are diagnosed every year, with 80% of them being diagnosed in an advanced stage where treatment does not lead to curing the disease but only to prolonging life.

The genetic factors identified to be involved in breast cancer risk comprise numerous biomarkers including the highly penetrant breast cancer susceptibility genes (BRCA1, BRCA2, PTEN, TP53, CDH1 and STK11), a number of genes with more moderate penetrance (CHEK2, BRIP1, ATM, PALB2) and low penetrance alleles. Prediction models suggest that, for now, there is a low probability to discover new high-penetrance genes.

**Keywords:** BRCA 1, BRCA 2, PTEN, TP53, CDH1

## INTRODUCTION

Once the screening tests have been widely implemented, the number of cases diagnosed with breast cancer significantly increased, transforming this malignancy into the most commonly encountered gynecologic neoplasia [1,2]. In this respect, the concept of personalized medicine has been widely applied in such cases in order to maximize the chances to achieve long term survival. Meanwhile, this concept provided support for the fact that breast cancer also has a significant genetic component, the most frequently incriminated pathogenic variants being represented by BRCA1, BRCA2 and PALB2 mutations [3,4]. The aim of the current paper is to discuss about the influence of genetic mutations on the risk of breast cancer development.

## HIGHLY PENETRANT BREAST CANCER SUSCEPTIBILITY GENES

The first major gene associated with hereditary breast cancer was discovered in 1990. This gene is

BRCA1 (BRCA1 DNA repair-associated protein, OMIM #113705) and is located on chromosome 17 (cytogenetic location 17q21.31). BRCA1 was discovered using linkage analysis in families with suggestive pedigrees [5]. Next, in 1994, the BRCA2 (BRCA2 DNA repair-associated protein, OMIM #600185) gene was discovered on chromosome 13 (cytogenetic location 13q13.1) [6].

A mutation in either BRCA1 or BRCA2 triggers an increased risk for breast and other types of cancers. Tumors caused by variations in BRCA1 have a tendency to be of the basal-like phenotype, have a high histologic grade and to be triple-negative tumors (do not generally express the estrogen receptor, ER, progesterone receptor, PR and Her2/neu. Tumors caused by mutations in BRCA2 resemble more closely to sporadic tumors [7]. Mutations in BRCA1 and BRCA2 genes are inherited in an autosomal dominant way but behave recessively on the cellular level as tumor suppressor genes involved in DNA break repair [8]. Women who carry mutations in BRCA1 or BRCA2 present a lifetime risk of breast cancer of 50%–85% [9]. Men who carry mutations

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in BRCA1 have a higher risk of breast cancer, though to a lesser degree than carriers of BRCA2 mutations who have an estimated 5%–10% risk of cancer during their lifetime [10]. There is an well-known increased risk for ovarian cancer that has an appraised lifetime risk of 10–40% in BRCA1 carriers and 10%–20% for BRCA2 carriers [11, 12]. Biallelic BRCA2 mutations manifest clinically with Fanconi anemia complementation group D1 and present an increased risk for cancers during childhood [9]. Biallelic BRCA1 mutations have been infrequently described and are considered to be lethal for embryos, in most cases [8].

Nonetheless, mutations in BRCA1 and BRCA2 are considered to explain only a small percentage of familial breast cancers, approximately 15%. Although rare, but highly penetrant genes include PTEN (phosphatase and tensin homolog, OMIM #601728, cytogenetic location 10q23.31), TP53 (tumor protein p53, OMIM #191170, cytogenetic location 17q13.1), CDH1 (cadherin 1, OMIM# 192090, cytogenetic location 16q22.1) and STK11 (serine/theronine protein kinase 11, OMIM #602216, cytogenetic location 19q13.3) each conferring a distinct clinical syndrome. It is predicted that the known high-penetrance genes are responsible for more than 25% of breast cancer cases.

## MODERATE PENETRANTE GENES

Because linkage studies have failed to prove additional high penetrant breast cancer susceptibility genes, new studies have focused on genes that are supposed to increase the risk of breast cancer depending on their known cellular functions in families with a predisposition to breast cancer. Thus, studies have identified a number of additional DNA repair genes that interact with BRCA1, BRCA2 and/or the BRCA pathways, and confer an increase in the breast cancer risk. These genes include: CHEK2 (checkpoint kinase 2, OMIM #604373, cytogenetic location 22q12.1), BRIP1 (BRCA1-interacting protein 1, OMIM #605882, cytogenetic location 17q23.2), ATM (ATM serine/theronine kinase, OMIM #607585, cytogenetic location 11q22.3) and PALB2 (partner and localizer of BRCA2, cytogenetic location 16p12.2).

CHEK2\*1100delC/NM\_007194.4(CHEK2):c.1100del / NP\_009125.1:p.Thr367fs is the most frequent mutation, found in up to 2% of the population. This variant is detected in higher numbers in breast cancer patients with a family record or those who had negative BRCA1 and BRCA2 testing. In this cases the prevalence may be as high as 5% [2]. CHEK2 is a protein kinase involved in the cell cycle regulation in G2-phase that is rapidly phosphorylated as a response to the damaged DNA. Activated CHEK2 stabilizes p53 and interacts with BRCA1. The CHEK2 \*1100delC var-

iant determines a twofold increase in female breast cancer and 10-fold increase in male breast cancer [2]. Considering their overlapping effect on DNA repair, no risk increase was reported in patients carrying both CHEK2 and BRCA1 or BRCA2 mutations. Assuming that homozygous CHEK2 mutations are lethal in utero, there is no known associated biallelic phenotype for this gene. [8].

The BRIP1 protein interacts with the BRCA1 C-Terminus (BRCT) domain of BRCA1. BRIP1 mutations are known to be involved in less than 1% of breast cancer cases. ATM is a protein kinase with a role in DNA repair and the regulation of BRCA1 and CHEK2. Homozygous ATM mutations are associated with the autosomal recessive ataxia-telangiectasia. The projected prevalence of monoallelic ATM mutation is 1%. The PALB2 protein associates with BRCA2 and is involved in nuclear localization and stability. PALB2 has an estimated incidence of 1%–2%. Biallelic PALB2 mutations cause Fanconi anemia complementation group N (which is clinically similar to complementation group D1 caused by biallelic BRCA2 mutations) and results in a higher incidence of childhood cancers. Increased frequencies of PALB2 mutations have been described in correlation with male breast cancer, though this likely only contributes to a minority of familial cases.

Additional genes involved in DNA damage repair, such as RAD51C and genes belonging to the MRN DNA repair pathway (MRE11, RAD50, NBN) have also been investigated. However, no mutations were clearly associated with increased cancer risk in screened high-risk families were screened.

UK studies [5,8] have estimated that these moderately penetrant genes account for less than 3% of familial breast cancer, looking at BRCA mutation-negative women with a personal or family history for the disease.

## LOW-PENETRANCE ALLELES

Following the development and advancement of laboratory techniques and sequencing capabilities have advanced, Genome-Wide Association Studies (GWAS) have been carried out in order to identify additional genetic variants that that may contribute to the breast cancer risk in a polygenic fashion. Since it is currently impractical to perform large whole-genome studies, instead sampling of Single-Nucleotide Variants (SNVs) distributed over the genome is often used to evaluate the genetic variability. SNVs are found both in genes and intergenic regions; mutations in the non-coding DNA might be markers for variation in gene regulatory elements. These studies involve thousands of cases and controls to confer them enough precision in appreciating a change in risk of cancer [8].

A recent meta-analysis assessed the studied variants to date, excluding those in highly penetrant genes [13]. Clear associations were seen in 10 variants spanning over six genes (ATM, CASP8, CHEK2, CTLA4, NBN and TP53) and a mild association was noted in an additional four variants across four genes (ATM, CYP19A1, TERT and XRCC3).

Evaluation for low-penetrance alleles is not presently part of normal clinical evaluation for breast cancer. Management of persons found to carry these modifications, as with moderate-penetrance genes, should rely on their estimated risk as determined by the previously described validated risk assessment types [2].

## CONCLUSION

Despite decades of medical research, less than 30% of cases with a expressive personal and/or family record of hereditary breast cancer have a clear causative gene mutation. Majority of cases are caused by a mutation in one of the highly penetrant breast cancer susceptibility genes (BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11) and there are current guidelines that provide appropriate measures towards the management of these patients. A minority of cases are caused by variants in moderate penetrant genes (CHEK2, ATM, BRIP1, and PALB2). A number of low-penetrance alleles have been identified using advanced genetic testing methods.

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