Male breast cancer

Cathy B Moelans, Petra van der Groep, Paul J van Diest

Department of Pathology, University Medical Center Utrecht, Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA, Utrecht, The Netherlands / cmoelans@umcutrecht.nl, p.vandergroep@umcutrecht.nl and p.j.vandiest@umcutrecht.nl

Published in Atlas Database: December 2016

Online updated version : http://AtlasGeneticsOncology.org/Tumors/MaleBreastID6242.html
Printable original version : http://documents.revues.inist.fr/bitstream/handle/2042/68891/12-2016-MaleBreastID6242.pdf
DOI: 10.4267/2042/68891

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence. © 2018 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Review on Male breast cancer, with data on clinics, and the genes involved.

Keywords
Male breast cancer; ERBB2; FGFR1; BRCA1; PTEN; ATM; CDH1; BRCA2; PALB2; CHEK2; AR; CYP17; PIK3CA; GATA3; TP53; CCND1

Identity

Other names
Breast Neoplasms, Male
Breast Carcinoma, Male

Phylum
Female organs: Breast tumors: carcinoma

Classification

Male breast cancer (MBC) is extremely rare and accounts for less than 1% of all (Anderson et al., 2010). Only 0.2% of all cancer types in men is a breast cancer (in women, this is 31%). The annual incidence is 1/100,000 men (Ly et al., 2013). While thought traditionally to be similar to post-menopausal female breast cancer (FBC), emerging evidence suggests that MBC may be different, with unique molecular subtypes (Johansson et al., 2014). Two distinct subgroups of MBC, luminal M1 and luminal M2, have been identified which differ from the well-established intrinsic subtypes of breast cancer in women. These novel subgroups appear unique to MBC, with the luminal M2 subgroup demonstrating higher immune response and ER signaling, and luminal M1 tumors displaying more tumor invasion and metastasis, proliferation and HER2 signaling. MBCs of the luminal M1 subgroup display more aggressive features than other MBC tumors.

The frequency of histological subtypes (per WHO 2012) differs between males and females, with invasive carcinomas of no special type (ICNST) being by far the most common subtype (> 90%) (Deb et al., 2016). This is followed by and which, proportionately, are seen more frequently in males when compared to females. Conversely, in men, are less common and represent only 1% of all male breast cancers. Other less common carcinoma subtypes seen in males also include , and . The majority of MBC present as symptomatic invasive disease. The early detection of the pre-invasive form, (DCIS), is rare in the absence of effective breast screening in men (Anderson and Devesa, 2005). (LCIS) has been described mostly coexisting with invasive lobular carcinoma. MBCs more frequently express estrogen receptor (ER) and progesterone receptor (PR) than FBCs (ER > 90 versus 76%, PR > 75 versus 60% in FBC). HER2 amplification and overexpression is less frequent in males when compared to females (Deb et al., 2016). Preliminary results from 1483 MBC cases amassed by EORTC10085, TBCRC, BIG and the NABCG International Male Breast Cancer Program were reported by Cardoso et al. in 2014 (Cardoso et al., 2014). Of the tumors analysed, 92% were ER+, 35% PR+, and only 5% HER2+. Subsequently, the
most common phenotype seen in MBC is the luminal-like (ER+ and/or PR+, HER2-) subtype with only occasional HER2-driven (ER- and PR- ,HER2+) and basal-like subtypes (ER-, PR-, HER2-). Within the luminal-like subtype, there appears to be an overrepresentation of the luminal B-like category (Ki67 high) versus the luminal A-like category (Ki67 low), compared to FBC (Piscuoglio et al., 2016; Kornegoor et al., 2012a).

**Clinics and pathology**

**Disease**

MBC is usually discovered (75%) as a painless retroareolar mass. Other presenting features include nipple retraction (9%), nipple discharge (6%), ulceration (6%) and pain (5%) (Fentiman, 2009). The rarity of MBC usually results in a delay of recognition and diagnosis. Consequently, MBC is often diagnosed at older age and with a more advanced clinical stage compared to FBC (more than 40% have stage III or IV disease) (Fentiman et al., 2006). Male and female patients with breast cancer are staged similarly according to the American Joint Committee on Cancer (AJCC) or Union for International Cancer Control (UICC) guidelines.

**Etiology**

The current literature suggests that genetic factors including BRCA2 mutations, family history, age, androgen/estrogen imbalance, and environmental exposures may predispose to male breast cancer (Ferzoco and Ruddy, 2016). Like many cancers, MBC is an age-related malignancy, with incidence peaking in the mid-60s. Men diagnosed with breast cancer tend to be 5-10 years older than women diagnosed with breast cancer. Those with a family history of breast cancer have two to three times the risk of developing breast cancer themselves. This risk increases when multiple family members are affected. About 20% of men with breast cancer have at least one first-degree female relative with breast cancer. BRCA1/2 mutations, and specifically BRCA2 mutations, are a clear causal factor for MBC. Multiple population-based studies have shown that 4-15% of men with breast cancer carry deleterious BRCA2 mutations and less than 5% carry a BRCA1 mutation (Ferzoco and Ruddy, 2016). Mutations in CHEK2 may confer an increased risk of MBC too, although the relative risk of these mutations, particularly CHEK2*1100delC, are uncertain (Neuhausen et al., 2004). Mutations within the DNA binding domain of androgen receptor have been described in MBC patients and there is a link between the cytochrome p540c17α enzyme (CYP17A1) and MBC. See section Genetics for more gene aberration specific information. Hormonal imbalance, in particularly the excess of estrogen and a deficiency of testosterone, can confer heightened risk for the development of MBC. This imbalance can be caused by testicular abnormalities, liver diseases/cirrhosis and obesity. Furthermore, having Klinefelter’s syndrome (characterized by one or more additional X chromosomes, testicular dysgenesis, gynecomastia, low testosterone concentrations and increased gonadotrophins) is strongly associated with MBC, with a 20-50 times higher risk compared to the general male population (Hultborn et al., 1997). Gynecomastia on the other hand, caused by an imbalance in estrogen and androgen levels, is not a risk factor for MBC (Ewertz et al., 2001; Krause, 2004). Interfering with estrogen or androgen levels by administration of estrogen or anti-androgens to trans-sexuals and for treatment of prostate cancer have been implicated as causative factors in MBC (Ganly and Taylor, 1995; Karamanakos et al., 2004; Gooren et al., 2013).

Radiation exposure increases risk of breast cancer in both women and men. Small numbers of chest X-rays do not, but prolonged exposure to radiographs or radiotherapy may be harmful (Fentiman, 2009). Environmental exposures including electromagnetic radiation, heat, polycyclic aromatic hydrocarbons, alcohol, and red meat have been studied in relation to male breast cancer, but none have convincingly found to be associated with incidence across studies (Ottini et al., 2010).

**Epidemiology**

In Western countries MBC comprises less than 1% of all cancers in men. Worldwide variation of MBC resembles that of FBC with higher incidences in North America and Europe and lower incidences in Asia (Ottini et al., 2010). A substantial higher rate of MBC cases has been reported in Africa. The incidence rates of MBC in Uganda and Zambia for example are 5% and 15%, respectively (Bhagwandeen, 1972; Ojara, 1978). Similar to FBC, MBC incidence in Japan is significantly lower than the average (IARC, 1976). Recent epidemiological studies indicate that MBC incidence is rising (Giordano et al., 2004; Stang and Thomssen, 2008; Speirs and Shaaban, 2009). The incidence and mortality of MBC increase with age. The bimodal age distribution seen in FBC patients is absent in MBC patients. Median age at diagnosis is 68.5 years with 5% of patients diagnosed with distant metastases (M1). Of patients presenting without distant metastases (M0), 60% are lymph node negative and 51% have T1 tumors at diagnosis (tumor size 2 centimeters or less) (Cardoso et al., 2014). Breast cancer mortality and survival rates have improved significantly over time for both MBC and FBC, but progress for men has lagged behind that for women (Anderson et al., 2010). Overall survival, especially 5-year overall survival, is lower compared to female patients because of the older age at diagnosis and more advanced stage at...
Male breast cancer

presentation (Giordano et al., 2004). Disease specific survival rates are higher than overall survival rates due to older average age and deaths from other comorbid diseases (Giordano, 2005).

Pathology

The Pathologist assesses resection margins, lymph node status, tumor size, tumor grade, mitotic activity, histological subtype, lymphovascular invasion, hormonal receptor status (by immunohistochemistry) and HER2 status. As already mentioned in the section "Classification", the majority of MBC are invasive ductal carcinomas (of no special type) (> 90%) (Deb et al., 2016). Lobular carcinomas are less common and represent only 1-2% of all MBCs. MBCs more frequently express ER and PR than FBC (ER > 90% versus 76%, PR > 75% versus 60% in FBC). HER2 amplification and overexpression is less frequent in males (5%) compared to females (10-15%) (Cardoso et al., 2014; Deb et al., 2016). Subsequently, the most common phenotype seen in MBC is the luminal-like (>95%; ER+ and/or PR+, HER2-) subtype with only occasional HER2-driven-like (ER- and PR-, HER2+) and basal-like (triple negative) subtypes [ER-, PR-, HER2-]. Within the luminal-like subtype, MBC are more frequently luminal B-like (Ki67 high) compared to FBC (Piscuoglio et al., 2016; Kornegoor et al., 2012a). Fibrotic focus is seen in 25% of MBC and correlated to hypoxia-inducible factor-1a overexpression (Kornegoor et al., 2012b). Although rare, DCIS and LCIS are recognised precursor lesions, as in the female breast. In contrast to females, columnar cell lesions, recognized precursor lesions of low grade lesions in the female breast, seem to be very rare in the male breast (Verschuur-Maes et al., 2014).

Invasive micropapillary male breast cancer, a common histotype in the male breast.
Solid pattern of invasive ductal male breast cancer, a common histotype in the male breast.

Invasive lobular male breast cancer, a rare histotype in the male breast.
Adenoid cystic male breast cancer, a rare histotype in the male breast.

**Treatment**

As MBC is rare, there are few clinical trials specifically focused on gender-orientated treatment; many clinical recommendations in MBC are therefore derived from studies performed in female breast cancer. Surgery is the first choice of treatment and most men undergo modified radical mastectomy with axillary lymph node dissection or sentinel node biopsy (Giordano, 2005). This is primarily due to a paucity of breast tissue in men as well as the fact that male BC usually occurs in central locations. Postsurgical radiation criteria are extrapolated from female breast cancer studies. Although postoperative radiation is often routinely utilized in all stages of male breast cancer to help decrease the risk of local recurrence, this risk is believed to be small, especially in early stage disease (3% in stage 1/2). Men with tumors ≥ 5 cm, T4 and lymph node positive disease are therefore more likely to receive post-surgery radiation (Chakravarthy and Kim, 2002).

Adjuvant endocrine therapy is standard treatment in MBC patients because the majority is hormone receptor positive. Many retrospective series have evaluated the effectiveness of tamoxifen (Nolvadex®; AstraZeneca Pharmaceuticals, http://www.astrazeneca-us.com) in MBC, showing a reduced risk of breast cancer recurrence and death in the metastatic and adjuvant setting. The role of aromatase inhibitors in the adjuvant setting for male patients is limited (Giordano, 2005) and their use as monotherapy or in combination with gonadotropin-releasing hormone (GnRH) analogues is largely restricted to the metastatic stage of the disease (Zagouri et al., 2015).

Given the established benefit of chemotherapy in women and the limited suggestive evidence in men, most clinicians use similar guidelines for adjuvant chemotherapy in male and female patients (Giordano, 2005).

**Prognosis**

The 5-year and 10-year relative survival rate for men with breast cancer is 84 and 72 percent, respectively (Howlader et al., 2016). Tumor stage is determined using the American Joint Committee on Cancer classification system, which considers tumor size, nodal involvement, and distant metastases. More than 40% of men with breast cancer present with stage 3/4 disease and therefore men have a worse overall survival but similar disease specific survival compared to women (Giordano, 2005). When MBC is diagnosed early, preferable when only DCIS is present, the tumors are mostly low to intermediate grade and the occurrence of distant metastasis is very unlikely (Ruddy and Winer, 2013).

Prognostic factors that have been evaluated include the size of the lesion, mitotic index, tumor grade, lymph node status and molecular type, all of which correlate well with prognosis (Giordano et al., 2004; Ruddy and Winer, 2013; Kornegoor et al., 2012a). Based on numbers from 2009, node negative MBC have a five-year survival rate of 90%, compared with
Male breast cancer

65% five-year survival rate for node positive MBC (Fentiman, 2009). Also, grade 1 patients have a five-year survival of 76%, dropping to 65% for those with grade 2 tumours and 43% for grade 3 MBC (Fentiman, 2009). In more recent studies, ER negativity (Ruddy and Winer, 2013; Abreu et al., 2016), fibrotic focus >8 mm, hypoxia-inducible factor-1α overexpression and nuclear area (Kornegoor et al., 2012a; Veta et al., 2012) appear to be prognostic factors in MBC too. There is no or little evidence of a correlation between HER2, Ki67, PR or lymphovascular invasion and prognosis (Ruddy and Winer, 2013).

Prognostic models that have been developed for FBC like the Multivariate Prognostic Index (consisting of mitotic index, tumour size and lymph node status), Nottingham Prognostic Index (consisting of grade, tumour size and lymph node status), Adjuvant! and Predict seem to perform quite well for MBC patients too (van der Pol et al., 2016). The combination of Bcl2 expression and mitotic index on the other hand, as opposed to FBC does not predict survival in MBC (Lacle et al., 2013).

Interestingly, a multicenter international study that pooled data from 13 cancer registries found that 12.5% of 3409 MBC survivors went on to develop a different (non-breast) cancer, and that risk of new primary cancers was elevated in the small intestine, rectum, pancreas, skin (non-melanoma), prostate, and lymphatics/blood. Other more recent studies have confirmed an elevated risk for other cancers in MBC survivors (Ruddy and Winer, 2013).

Genetics

Note

The majority of MBC cases are sporadic, with many different oncogenes and tumor suppressor genes involved, while 10% are estimated to be due to an inherited predisposition (Rizzolo et al., 2013). In comparison with FBC there is a larger proportion of BRCA2 germline mutation carriers, (occurring in 10% of MBC), and underrepresentation of BRCA1 germline mutation carriers (found in only 1%). PALB2 and CHEK2 mutations have been reported in families with MBC. The contribution of BRIP1 and RAD51C mutations to breast cancer predisposition in males seems to moderate compared with CHEK2 and PALB2. The androgen receptor (AR) gene and the cytochrome p540c17α gene (CYP17) have been suggested to play a role in MBC predisposition but these results were not supported by additional studies. Lastly, besides in Klinefelter syndrome patients, MBC have been reported rarely in Li-Fraumeni, Cowden and Lynch syndrome patients (Deb et al., 2016).

HYPERMETHYLATION

Promoter hypermethylation is common in MBC and high methylation status correlates with aggressive phenotype and poor survival. ESR1 and GSTP1 promoter hypermethylation seem to be involved in development and/or progression of high-grade MBC. Although FBC and MBC share a set of commonly methylated genes, many of the studied genes are less frequently methylated in male breast cancer, pointing towards possible differences between male and female breast carcinogenesis (Kornegoor et al., 2012d). Unsupervised clustering of the most variable CpGs among MBC revealed two stable epitypes, designated ME1 and ME2, closely associated with the transcriptional subgroups luminal M1 and M2 (see “Classification”). Tumors in the ME1 group were more proliferative and aggressive than ME2 tumors, and showed a tendency toward inferior survival. ME1 tumors also displayed hypermethylation of PRC2 (polycomb) target genes and high expression of EZH2, one of the core components of PRC2. Differential methylation patterns were not only seen between the MBC epitypes, but also between MBCs and FBCs that cluster together (Johansson et al., 2015).

Cytogenetics

Cytogenetics Molecular

Cytogenetic data in MBC are largely based on comparative genomic hybridization (CGH) studies preceded by a handful of small-scale karyotyping and microsatellite marker studies (Mitchell, 1990; Gudmundsson et al., 1995; Wingren et al., 1997; Rudas et al., 2000). Genomic gains are more common in MBC than in FBC and often involve whole chromosome arms, while losses of genomic material are less frequent (Tommasi et al., 2010; Johansson et al., 2011). The most common aberrations are similar between the genders, but high-level amplifications are more common in FBC (Johansson et al., 2011). Chromosomal gains are most frequent at 1q (~50%), 8q (~50%), 11q (~40%), 16p (~40%), 17q (~40%), 20q (~30%), 7q (~20%) and Xp (~20%). Losses are most commonly observed at 8p (~40%), 11q (~40%), 13q (~30%), 16q (~30%), 17p (~30%), 1p (~20%) and 22q (20%) (Rudlowski et al., 2006; Tommasi et al., 2010; Johansson et al., 2011; Piscuoglio et al., 2016). Gains at 16p, 20q and Xq and losses at 13q correlate significantly with a higher degree of cytogenetic complexity (Rudlowski et al., 2006). In MBC chromosome 17 shows less complex rearrangements and fewer copy number changes compared to FBC. Frequent gains of 17q, encompassing two distinct amplicons, and losses of 17p were observed, but no whole chromosome 17 polyplodies (Lacle et al., 2015). Copy number loss on 1q4 was less frequent in MBC than FBC and, in combination with 16p gain, identifies a group of MBC with low propensity to develop lymph node metastases (Lacle et al., 2013). Using fluorescence in situ hybridization (FISH) and...
Male breast cancer

among genetic alterations in (male) breast cancer is immense and it is therefore not possible to elaborate on all of them. A selection was made based on the aberration frequency and the amount of evidence/literature present. Several of the genes/proteins involved in MBC have already been described in female breast cancer (secretory type), a recurrent chromosomal translocation t(12;15)(p13;q25) leading to the formation of the ETV6 / NTRK3 fusion gene has been described in secretory MBC as well (Arce et al., 2005). To our knowledge, only nine previous articles deal with adenoid cystic carcinoma (ACC) in the male breast but none of these studies have reported on the well-known recurrent translocation t(6;9)(q22-23:p23-24) in FBC, resulting in a fusion of the two transcription factor genes MYB and NFIB (Persson et al., 2009; Tang et al., 2015).

Genes involved and proteins

Note
The number of genetic alterations in (male) breast cancer is immense and it is therefore not possible to elaborate on all of them. A selection was made based on the aberration frequency and the amount of evidence/literature present. Several of the genes/proteins involved in MBC have already been described in female "Breast: Ductal carcinoma". These will not be repeated here (HER2/ERBB2, FGFR1, BRCA1, PTEN, ATM and CDH1).

BRCA2 (breast cancer 2, early onset)

Location
13q13.1

DNA / RNA
The BRCA2 gene is composed of 27 exons. The structure and function of BRCA2 have extensively been described elsewhere (http://atlasgeneoncology.org/Genes/BRCA2ID164ch13q13.html) and will therefore not be repeated here.

Protein
Multiple population-based studies have shown that 4-15 % of men with breast cancer carry deleterious BRCA2 mutations (Ferzoco and Ruddy, 2016). By the age of 80 years, the cumulative risk of breast cancer in male BRCA2 germline mutation carriers has been estimated at 7% (Thompson et al., 2001). Among men with a family history of breast and/or ovarian cancer, reported mutation frequencies are generally higher. In the largest study so far comprising 642 families with MBC (these families had at least one additional case of FBC or ovarian cancer), BRCA1/2 mutation prevalence was 35.8% (95% CI: 32.2% to 39.6%) for MBC with at least one FBC or ovarian cancer in the family. BRCA2 mutations were found more frequently (13-65%) than BRCA1 mutations (3-9%) in families without occurrence of ovarian carcinoma. In cases where additional ovarian carcinoma cases were present in the family, a similar prevalence of mutations was found in BRCA1 (23-27%) and BRCA2 (27-30%) (Kast et al., 2016). In addition, there are populations who carry founder mutations that are significantly more common. For example, the BRCA2 999del5 founder mutation is implicated in over 40 % of Icelandic MBC cases (Thorlacius et al., 1996). This mutation, a 5 bp deletion in exon 9 starting at nucleotide 999, leads to a stop codon at nucleotide 1047 and to premature truncation of protein translation. Among BRCA2 MBCs, grade significantly decreases with increasing age at diagnosis. Compared with BRCA2 FBCs, BRCA2 MBCs are of significantly higher stage and higher grade (Silvestri et al., 2016).

PALB2 (partner and localizer of BRCA2)

Location
16p12.2

Protein
PALB2 (partner and localizer of BRCA2) plays a critical role in homologous recombination repair (HRR) through its ability to recruit BRCA2 and RAD51 to DNA breaks. The 1,186-amino acid protein has a calculated molecular mass of about 130 kD, contains an N-terminal coiled coil domain and a C-terminal WD40 repeat domain that interacts with BRCA2 and RAD51. Inherited heterozygosity for this gene has been associated with an increased risk of breast cancer. Additionally, biallelic mutations of PALB2 have been linked to Fanconi anemia, which also has an increased risk of developing malignant disease.

PALB2 mutations have been found in families with both FBC and MBC, suggesting that this gene may be involved in MBC risk (Rahman et al., 2007; Gàrcèa et al., 2009). Moreover, PALB2 heterozygotes are 4-fold more likely to have a male relative with breast cancer (Casadei et al., 2011). Based on a handful of studies, PALB2 may have a role as moderate-penetrance gene in MBC at a comparable extent as for female breast cancer (Rizzolo et al., 2013). A recent study added strength to this evidence by performing whole exome sequencing in germline DNA of 1 male and 2 female...
BRCA1/2 mutation-negative breast cancer cases from a pedigree showing a first-degree family history of MBC and targeted PALB2 sequencing in 48 high-risk, BRCA1/2 mutation-negative MBC cases (Silvestri et al., 2016). According to this largest study so far, the frequency of PALB2 pathogenic mutations in high-risk MBC cases is higher than that observed in high-risk FBC cases (ie, 4% vs 1%).

**CHEK2 (CHK2 checkpoint homolog (S. pombe))**

**Location**
22q12.1

**Protein**
The protein encoded by checkpoint kinase 2 (CHEK2) is a cell cycle checkpoint regulator and putative tumor suppressor. It contains a forhead-associated protein interaction domain essential for activation in response to DNA damage and is rapidly phosphorylated in response to replication blocks and DNA damage. When activated, the encoded protein is known to inhibit CDC25C phosphatase, preventing entry into mitosis, and has been shown to stabilize the tumor suppressor protein TP53, leading to cell cycle arrest in G1. In addition, this protein interacts with and phosphorylates BRCA1, allowing BRCA1 to restore survival after DNA damage. Mutations in this gene have been linked with Li-Fraumeni syndrome, a highly penetrant familial cancer phenotype usually associated with inherited mutations in TP53. Also, mutations in CHEK2 are thought to confer a predisposition to sarcomas, breast cancer, and brain tumors. This nuclear protein is a member of the CDS1 subfamily of serine/threonine protein kinases. Several transcript variants encoding different isoforms have been found for this gene.

It has been estimated that the CHEK2 1100delC mutation accounts for 9% of MBC cases and confers about 10-fold increase of breast cancer risk in men lacking BRCA1 and BRCA2 mutations (Meijers-Heijboer et al., 2002). Other studies have reported lower CHEK2 mutation frequencies in MBC, ranging from 2% to 4% (Sodha et al., 2004; Syrjakoski et al., 2004; Wasielewski et al., 2009).

**AR (Androgen Receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease))**

**Location**
Xq12

**Protein**
The androgen receptor (AR) gene is more than 90 kb long and encodes a protein that has 3 major functional domains: the N-terminal domain, DNA-binding domain, and androgen-binding domain. The protein functions as a steroid-hormone activated transcription factor. Upon binding the hormone ligand, the receptor dissociates from accessory proteins, translocates to the nucleus, dimerizes, and then stimulates transcription of androgen responsive genes. This gene contains 2 polymorphic trinucleotide repeat segments that encode polyglutamine and polyglycine tracts in the N-terminal transactivation domain of its protein. Two alternatively spliced variants encoding distinct isoforms have been described. Androgen hyposensitivity caused by either AR mutations or long CAG repeats might be a causal factor for MBC (Di Lauro et al., 2015). Mutations in the AR gene have been described in MBC and were shown to be associated with complete androgen insensitivity (CAIS) (Wooster et al., 1992; Lobaccaro et al., 1993). Also, variations of the polyglutamine (CAG) repeat within exon 1 of AR were demonstrated in MBC, with shorter CAG tracts associated with increased AR transcriptional activity, and longer CAG tracts resulting in a suboptimal ligand-mediated stimulation of AR (Young et al., 2000; Song et al., 2012). Immunohistochemistry studies of MBC samples reported AR expression in a range of 34-95% (Di Lauro et al., 2015). In addition to this striking variability, controversy exists, and conflicting data were reported, on the association between AR expression and disease stage and/or survival outcomes.

**CYP17A1 (cytochrome P450 family 17 subfamily A member 1)**

**Location**
10q24.32

**Protein**
This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum. It has both 17alpha-hydroxylase and 17,20-lyase activities and is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens. Mutations in this gene are associated with isolated steroid-17 alpha-hydroxylase deficiency, 17-alpha-hydroxylase/17,20-lyase deficiency, pseudohemaphroditism, and adrenal hyperplasia. A polymorphic T to C substitution has been described that creates an additional CCACC type promoter site 34 bp upstream from the site of initiation of translation (Carey et al., 1994). It is thought that the additional promoter site may increase the rate of transcription of the gene and thereby increase enzyme activity. Serum oestradiol
levels are higher in women hetero- and homozygous for the C allele of the CYP17 gene (Feigelson et al., 1998). A germline T to C variant in CYP17 has been associated with an increased male breast cancer risk (Young et al., 1999) with an odds ratio (OR) of 2.10 (95% confidence interval 1.04–4.27). A subsequent study, however, did not observe a significant association between MBC risk and CYP17 genotype, but the frequency of the CC genotype was higher among carriers of the BRCa2 999del5 Icelandic founder mutation (33.3%) than non-carriers (16.7%; Gudmundsdottir et al., 2003).

**PIK3CA (phosphoinositide-3-kinase, catalytic, alpha polypeptide)**

**Location**
3q26.32

**Protein**
The PIK3CA gene is composed of 21 exons, 20 of them coding exons, and encodes a cytoplasmic protein of 1,068 amino acid residues. The PIK3CA gene encodes the p110alpha protein which is a catalytic subunit of the class I PI 3-kinases (PI3K). Class I PI3K are heterodimeric molecules composed of a p110 catalytic subunit and a regulatory subunit. PI 3-Kinasen (phosphoinositide 3-kinases, PI3Ks) coordinate a diverse range of cell functions including proliferation, cell survival, degranulation, vesicular trafficking and cell migration. PIK3CA activating mutations show a high prevalence in female breast cancer (40.1% coding mutations in METABRIC) (Pereira et al., 2016) and are associated with higher age at diagnosis, hormone receptor positivity, HER2 negativity, lower tumor grade and stage, and lymph node negativity. PIK3CA mutations have been associated with significantly longer metastasis-free survival, especially in the PR-positive and HER2-positive subgroups (Cizkova et al., 2012), may have independent driver properties in a HER2-positive context, and have been implicated in resistance to anti-HER2 therapies (Nahta and Esteva, 2006). The majority of mutations occur at three hotspots (E542, E545, or H1047), making these ideal targets for therapeutic development. MBC less frequently harbor PIK3CA mutations (20%) than ER-positive/HER2-negative FBC but nevertheless it is the most frequently mutated gene in MBC. Almost all reported PIK3CA mutations in MBC affected the hotspots (Piscuoglio et al., 2016).

**GATA3 (GATA binding protein 3)**

**Location**
10p14

**Protein**
The GATA3 gene contains 6 exons. The full length GATA3 protein contains either 443 amino acids (isoform a) or 444 amino acids (isoform b), corresponding to molecular weights of 47.9 kDa and 48.0 kDa respectively. The GATA3 protein contains two zinc finger motifs as well as two transactivation domains. The N-terminal zinc finger is known to stabilize DNA binding and interact with other zinc finger proteins, whereas the C-terminal zinc finger binds DNA. As such, GATA3 is a member of the GATA family of zinc-finger binding transcription factors that regulates the specification and differentiation of many tissue types including the breast.

In the context of FBC, GATA3 is intimately associated with luminal cell identity and function, and mutated in 11% of patients (Pereira et al., 2016). A truncating splice variant at position 308 is by far the most prevalent hotspot (23% of GATA3 mutations). In MBC, GATA3 is mutated in 15% of patients, and restricted to the luminal B-like breast cancer subtype. These mutations are associated with worse disease-free survival and interestingly, the pattern of mutations found in males does not resemble that of female breast cancers. In fact, the majority of GATA3 mutations found in MBC are frameshift mutations and do not affect the aforementioned hotspot (Piscuoglio et al., 2016).

**TP53 (Tumour protein p53 (Li-Fraumeni syndrome))**

**Location**
17p13.1

**Protein**
The structure and function of the TP53 transcription factor have extensively been described elsewhere (http://atlasgeneticsoncology.org/Genes/GC_TP53.html) and will therefore not be repeated here. Mutations in the TP53 gene can be found in 50% of human cancers. More than 80% of TP53 mutations are missense mutations that lead to the synthesis of a stable oncoprotein that accumulates in the nucleus of tumor cells. In The Cancer Genome Atlas (TCGA) project, six MBC were included, of which none had TP53 mutations (Cancer Genome Atlas Network, 2012). A massively parallel sequencing study based on 59 MBC detected a lower frequency of TP53 mutations in ER-positive/HER2-negative MBC compared with ER-positive/HER2-negative FBC (7% vs. 22%) (Piscuoglio et al., 2016).

**CCND1 (B-cell leukemia/lymphoma 1)**

**Location**
11q13.3

**Protein**
he CCND1 gene contains 5 coding exons. The structure and function of CCND1 (Cyclin D1) have extensively been described elsewhere (http://atlasgeneticsoncology.org/Genes/BCL1ID36.html) and will therefore not be repeated here. The CCND1 gene is amplified in 12-18% of MBC (Bärlund et al., 2004; Kornegoor et al., 2012; Rizzolo et al., 2016) and amplification is associated
Male breast cancer

with poor prognosis (Kornegoor et al., 2012). Cyclin D1 was shown to be a selective repressor of androgen-dependent signaling and androgen receptor function (Comstock et al., 2011) and a driver of androgen-dependent DNA damage repair, thereby contributing to radioresistance (Casimiro et al., 2016).

References


Anderson WF, Devesa SS. In situ male breast carcinoma in the Surveillance, Epidemiology, and End Results database of the National Cancer Institute. Cancer. 2005 Oct 15;104(8):1733-41


Male breast cancer


Krause W. Male breast cancer--an andrological disease: risk factors and diagnosis Androlologia 2004 Dec;36(6):346-54


Ojara EA. Carcinoma of the male breast in Mulago Hospital, Kampala East Afr Med J 1978 Oct;55(10):489-91


Persson M, Andrén Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NF1B transcription factor genes in carcinomas of the breast and head and neck Proc Natl Acad Sci U S A 2009 Nov 3;106(44):18740-4


Rudas M, Schmidinger M, Wenzel C, Okamoto I, Budinsky A, Fazeny B, Marosi C. Karyotypic findings in two cases of male breast cancer Cancer Genet Cytogeten 2000 Sep;121(2):190-3


Male breast cancer


Speirs V, Shaaban AM. The rising incidence of male breast cancer Breast Cancer Res Treat 2009 May;115(2):429-30


Syrljokski K, Kuukasjärvi T, Avunin A, Kallioniemi OP. CHEK2 1100delC is not a risk factor for male breast cancer population Int J Cancer 2004 Jan 20;108(3):475-8


This article should be referenced as such: