The Effects of the *ABCC11* Gene in Breast Cancer: Universal Difference, Carcinogenesis, and Therapeutic Possibilities

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Introduction: Cancer

From as early as 3000 BC, cancer has been a prevalent health issue and has only grown serving as a disease detrimental to many societies today. Since the early nineteenth century, millions of scientists are still attempting to determine causes, biomarkers, and ultimately, cures.

Cancer is an invasive disease that causes uncontrollable growth and the spreading of cells all throughout the body. The initial cancerous cells of approximately 1 million cells (1 cm.) are known as lumps, tumors, or masses [1]. In a healthy body, human cells undergo cell division to produce new cells when old cells become damaged or die. However, in cancer patients, damaged and irregular cells begin to multiply when they should not as a result of dysregulated cell cycle. The inability of the immune cells to identify and fight off the cancer cells severely jeopardizes the patient and their ability to recover. As of 2023, there are approx. 19.3 million new cancer cases globally with an estimated 10 million deaths. Domestically, there are approximately 1.9 million new cases with around 600,000 cancer deaths in the US [3].

The initial development of a tumor can be caused by changes or mutations to the DNA in cells. DNA within cells contains individual genes that provide the cell with instructions on certain functions, growth, and division. Mutations are flaws in these instructions and may occur through genetic inheritance or outside factors such as smoking, lack of exercise, hormones, or carcinogens (cancer-causing chemicals) [2]. These mutations allow for cancerous cells to continue growing and spreading, although the growth of these cells can be stopped through surgical removal, radiation therapy, or cancer-specific medications such as chemotherapy or hormonal therapy [1].

Breast Cancer

In 2023, breast cancer was the most common cancer among women with over 250,000 deaths a year in the United States [4]. There are an estimated 2.3 million cases which make up 11.7% of cancer cases globally. Domestically, there are almost 300,000 new cases with an additional 55,700 non-invasive cases. In the US. 1 in every 8 women develop a category of breast cancer. [6]. Combined, these statistics demonstrate how prevalent breast cancer is in our society.

Breast cancer can be categorized into 4 main types: breast cancer expressing either a hormone receptor known as ER+ (estrogen receptor) or a hormone receptor known as PR+ (progesterone receptor), breast cancer expressing HER2+ (human epidermal receptor 2), and triple-negative breast cancer which lacks the presence of both hormone receptors and epidermal receptors [20]. The most prevalent type of breast cancer being the type with the presence of hormone receptors and a lack of HER2 . [5] When hormone receptors such as ER+ and PR+ are present and the spreading of cancer cells are minimal, hormone-blocking therapy is very effective [5]. HER2 is a protein that encourages cell growth. Being HER2+ means the cancer cells have high amounts of this protein, causing rapid cell growth and division. Cancers with high levels of HER2 respond better to treatments targeting the HER2 protein such as the: monoclonal antibody trastuzumab [21]. The most prevalent type of breast cancer is the

presence of hormone receptors and a lack of HER2 . Triple-negative breast cancer is when the cancer cells lack the hormone receptors ER+ and PR+, and HER2 [5][20].

Genetic mutations also play a crucial role in breast cancer risk, best exemplified by the BRCA proteins. BRCA1 and BRCA2 (BRest-CAncer susceptibility genes) are proteins that contribute to repairing DNA and are involved in the transcription regulation process in damaged DNA. Recent research suggests that these proteins are important in maintaining chromosomal stability and protects the genome from damage [19]. *BRCA1* and *BRCA2* mutations, known for their impact on DNA repair, increase the risk of developing breast cancer to 55-65% for *BRCA1* and 45-55% for *BRCA2*. The presence of *BRCA* mutations, causes women to have a lifetime risk of breast cancer development ranging from 45% to 75% [7].

The overall age-standardized rate of breast cancer among women is predicted to increase by 32.13% by 2050, with a mortality rate projected to increase by 4.69%, with the age of under 40 to be the most likely to be diagnosed [18]. Despite differences in race and ethnicity, with an increase in age, the prevalence of breast cancer is expected to increase [22]. Interestingly enough, studies indicate that African American women who are aged younger than 45 have a significant increase in breast cancer incidence, however, African American women among 45-49 have less breast cancer incidence compared to Caucasian women, who have breast cancer incidence rates higher than any other ethnicity [22]. Breast cancer is more prevalent in higher socio-demographic index (SDI) areas, most likely due to the more affordable access to harmful carcinogens such as radiation, and high levels of pollution, and higher obesity rates. Lower-SDI regions have a higher rate of mortality due to the lack of healthcare access [8]. Socioeconomic status, access to healthcare, dietary habits, and ethnicity are all aspects that affect the probability for breast cancer development.

ABCC11

ABCC11 is a protein, located on chromosome 16q12.1, that functions as an encoder for an ABC (ATP-binding cassette) transporter involved in cellular exporting processes and the chemical degradation of certain lipids [10]. ABCC11 is also known as MRP8 (multidrug resistance-associated protein 8), useful for the later connection between the protein and breast cancer prevalence. More specific to the transporting function of ABCC11, a variant of the protein, ABCC11 WT (Gly180), is able to carry lipophilic organic anions such as specific nucleotides, glutathione conjugates, steroid sulfates, along with certain acids like the monoanionic bile acids; glycocholate and taurocholate. [11] [12]. The transportation of these molecules are important as they are involved in cellular functions such as immune responses, maintaining cell homeostasis, and protection of the cell by pumping harmful toxins out [23].

Studies show that putative mice and rats have no orthologous gene corresponding to the human *ABCC11* gene [13]. This shows that *ABCC11* is a gene that is not highly conserved amongst vertebrates and has not undergone specification. It has a single function as it is found only in homosapiens (unless duplicated) and indicates that it was not passed through evolution and is therefore not orthologous. [13][14]. However the presence of specific single-nucleotide polymorphisms or mutations can cause this technology to be defective in function and slow down the process of recovery.

SNPs, single-nucleotide polymorphisms, are types of small mutations or modifications in the DNA that occur naturally and express different phenotypes from individual to individual [15]. These polymorphisms may cause harmful phenotypes while some may express harmless ones. In *ABCC11,* the SNP rs17822931 leads to the expression of different genotypes further causing different phenotypic expression. The SNP rs17822931 results in an amino acid shift from a glycine into an arginine within the ABCC11 protein.

With dominant expressions of glycogen and recessive expressions of arginine, different phenotypes are expressed. For example, the SNP rs17822931 538G>A– which is loathed on exon 4 with the replacement of Arg180 to Gly180– expresses the phenotype of different earwax types. Earwax, or cerumen, is a combination of secretions and skin cells that may accumulate and cause blockage in the external auditory canal. Although the accumulation of cerumen is naturally occurring and asymptomatic, too much build up can cause discomfort, tinnitus, hearing loss, dizziness or pain [17]. With the G/G and G/A genotype of SNP rs17822931 538G>A expresses a phenotype of wet earwax while the A/A genotype expresses dry earwax [24]. Studies show that this genetic polymorphism has an effect on the N-linked glycosylation of ABCC11. The variant that lacks an arginine-linked glycosylation is recognized as a misfolded protein by the endoplasmic reticulum; a structure that can detect misfolding of proteins. This also indicates that the dry earwax type is a mendelian trait with a recessive phenotype [24]. Another phenotype that is expressed differently between the different genotypes of SNP rs17822931 538G>A is the presence of axillary osmidrosis [24]. Axillary osmidrosis is the production of offensive body odor resulting from bacterial degradation. [25] The expression of the G/G and G/A variants expresses the presence of axillary osmidrosis while the A/A expression does not [24].

Interestingly enough, the allele frequency of the SNP 538G>A with either the dominant (G/G) or the receive gene (A/A) in the *ABCC11* gene varies based on ethnicity and therefore differs on an universal scale. Studies indicate that the dominant genotype is commonly found in Africans and Caucasians while the recessive gene is found more commonly within the East Asian population– primarily the Korean, Japanese, and Chinese [25]. Thus, the phenotype of wet earwax and the presence of axillary osmidrosis is predominantly high among the African and Caucasian populations whereas the Eastern Asian population indicates higher expressions of dry earwax and little to no cases of axillary osmidrosis [25] **(Fig. 1).** .

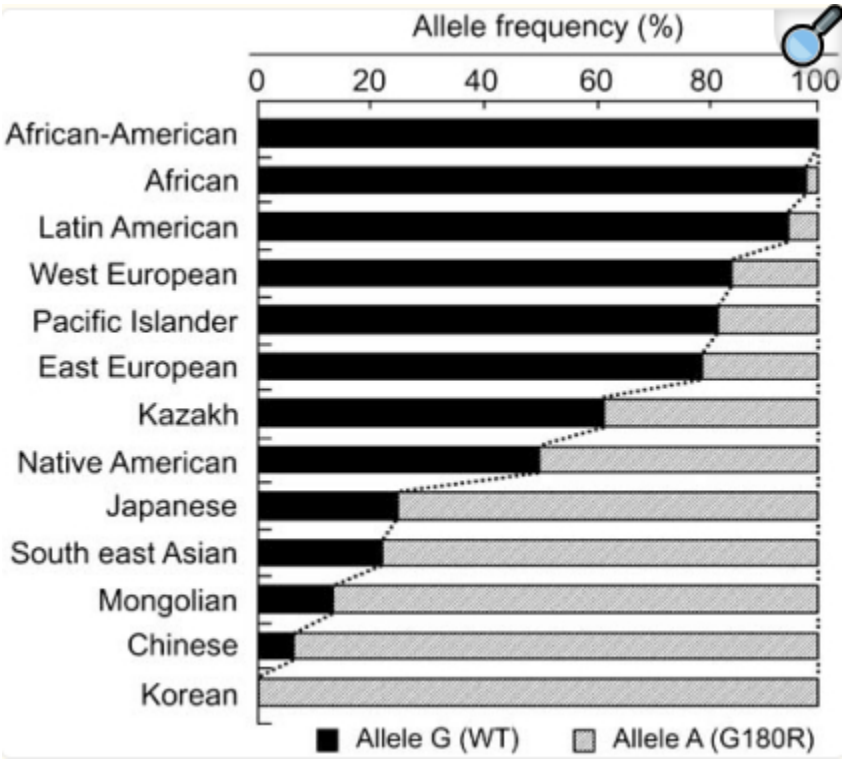

Figure 1. Infographic modeling the allele frequency of Gly180 and Arg180 across several ethnicities. The allele frequencies of the wild type (WT, Gly180) and the 538G>A (Arg180) variant of human ABCC11 among different ethnic populations. Data retrieved from Yoshiura *et al*. [25].

Research indicates that the physiological function of ABCC11 of transporting metabolites may ignite the proliferation of apocrine gland cells (sweat gland cells) which as a result increases the risk of breast cancer, indicated in Figure [A] [25]. With the addition of genetic mutations– such as the ones mentioned previously: BRCA1, BRCA2– the proliferation of the apocrine gland cells become out-of-control and unregulated [25].

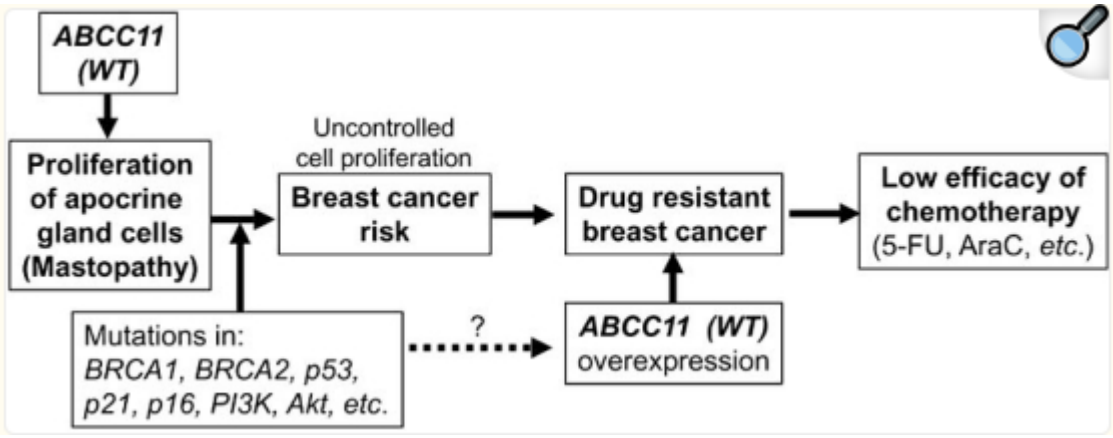

Figure 2. Infographic depicting the path to breast cancer risk by *ABCC11* (WT). The potential impact of *ABCC11* WT (538G) on the apocrine phenotype, patients' response to nucleoside-based chemotherapy, and the risk of mastopathy and breast cancer [25].

As discussed previously, the ABCC11 protein is also known as MRP8 (multidrug resistance-associated protein 8). This protein has earned its name due to its inherent drug transporting function, including chemotherapeutics. Interestingly, the SNP rs17822931 (WT 538G), induces conformational changes in the structure of the protein that reduces its ability to transport common chemotherapeutics used to treat breast cancer thus inducing chemotherapy resistance in these patients and causing breast cancer incidence to increase while efficacy of therapy decreases [25].

Due to the different ethnic variations in allele frequencies and their corresponding phenotypes– such as wet or dry earwax and the presence or absence of axillary osmidrosis– the ethnic variations in allele frequencies can also be attributed to breast cancer risk and efficacy of chemotherapy treatment [25]. Further research on the implications of the direct correlation between WT(538G) and its physiological role of drug resistance, scientists may be more equipped with knowledge to develop possible *ABCC11* 538G (WT; Gly180) targeted therapies.

Therapeutic Possibilities

Advancements in sequencing technologies have enabled detailed analysis of ABCC11 variants and their functional impacts. High-throughput sequencing allows for comprehensive genotype-phenotype associations, contributing to a better understanding of ABCC11's role in breast cancer. Additionally, although no specific drugs currently target ABCC11, research into the ABC transporter family could lead to new therapeutic options.

Early screening and detection for cancer, can significantly reduce the mortality rates for cancer. This has led to advancements in technologies that focus on identifying biomarkers– biological molecules found in tissues, fluids, and blood that indicate abnormal conditions, diseases, or conditions– that can aid in early detection of cancer [27]. ABCC11 is not expressed ubiquitously throughout the body but is instead expressed in higher levels throughout certain organs and tissues, particularly the mammary tissues and apocrine glands [28]. Although it may be costly and timely to have mammary tissue testing on each patient for signs of early detection, through the testing of apocrine glands scientists and medical professionals may be able to utilize results for early indications of breast cancer. ABCC11 is not expressed all throughout the human body, however, through the testing of a human's sweat glands and possibly through the type of earwax the patient possesses, breast cancer may be detected during its earlier stages. The identification of the SNP rs17822931 can also allow for patient stratification by stratas of patients expressing the WT (538G), or the variant form Arg538 (as noted earlier, the WT (538G) expresses phenotypes of wet earwax, the presence of axillary osmidrosis, and increased breast cancer incidence). By doing so, medical professionals would be able to screen patients exhibiting the WT (538G) allele more frequently for breast cancer development. With the expectation of an increased chance of breast cancer development, early screening would allow for the treatment of earlier stages of breast cancer.

Along with early screening of breast cancer development, due to the involvement in drug resistance in ABCC11, this underscores its potential as a therapeutic target. Further research into the gene and its direct relationship with drug resistance in chemotherapy can offer ideas on modifying or targeting ABCC11, possibly improving chemotherapy outcomes. Research into how different ABCC11 genotypes affect drug efficacy is crucial for developing effective treatment strategies.

Due to the fact that *ABCC11* genetic variants exhibit variability across ethnic groups, future research should focus on the ethnic and geographical variations in ABCC11-related breast cancer risk which is crucial to the knowledge of breast cancer risk and treatment responses. Understanding these differences may ultimately aid in personalized prevention and treatment strategies

Conclusion

Cancer and –more specifically– breast cancer, serves as a detrimental cause of death not only in America, but globally. Breast cancer takes millions of lives every year, therefore, research and new therapeutic possibilities are crucial to fostering a more knowledgeable foundation for new cancer treatments. Here we discuss the role of SNP rs17822931 538G>A in the *ABCC11* gene, which carries phenotypes such as wet earwax, axillary osmidrosis, and an increased rate of breast cancer prevalence. Furthermore, due to the physiological nature of ABCC11, increased expression may also lead to a decrease in the efficiency of chemotherapy. Studies indicating the global differences in expression between Eastern and Western individuals also correlates with global differences in breast cancer incidence, suggesting that identification of novel treatments targeting this SNP may be critical in treating this ethically vulnerable group.

Although breast cancer research is continuing to evolve, with further studies of the ABCC11 protein and the SNP rs17822931 538G>A, the scientific world will grow with potential to develop new technologies serving as potential biomarkers and therapies globally.

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