Beyond Pink

Understanding Metastatic Breast Cancer (MBC) and the Genetic Connection

Types of MBC are classified according to the presence of an alteration in genes or a specific trait in the tumor cells. Gene alterations can be hereditary (passed down from a parent) or acquired (developed later in life through certain environmental risk factors). Knowing which type of gene alteration you have, which can be determined with advanced genomic testing, can help your doctor make informed treatment decisions. Genetic alterations that may be present in MBC tumors include:

Alteration Type	Inherited	Acquired
EGFR		X
ATM	X	X
BARD1	X	X
BRCA1	X	X
BRCA2	X	X
CHEK2	X	X
PALB2	X	X
STK11	X	X
PIK3CA		X
mTOR		X
TP53		X
AKT1	X	X
PTEN	X	X
CDHI	X	X
APC		X
NRAS		X
KRAS		X
CDK4		X

EGFR

The epidermal growth factor receptor (EGFR) is a protein that lives on the surface of normal cells and cancer cells. An alteration in the *EGFR* gene is acquired and can drive abnormal cell growth, which can lead to cancer. **Approximately half of all triple negative breast cancers** have cancer cells that make too much *EGFR*.

BARD1

An alteration in one copy of *BARD1* gene **increases the risk of female breast cancer**, including triple-negative breast cancer, as well as other types of cancers such as ovarian cancer.

CDK4

Cyclin Dependent Kinase 4 is a protein coding gene, mediates progression through the G1 phase when the cell prepares to initiate DNA synthesis. ***CDK4* is altered in 1.21% of breast carcinoma patients**.

PIK3CA

PIK3CA is a gene that encodes a lipid kinase involved in multiple signaling pathways. These pathways influence cellular functions such as growth, death, and proliferation. **Acquired alterations in this gene are found in 30-40% of all breast cancers**.

BRCA1 & BRCA2

Breast cancer susceptibility genes 1/2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role in maintaining the genetic stability of cells. While everyone will inherit copies of these genes, an alteration on this gene, **either hereditary or acquired, can lead to increased risk of cancer**.

BRCA gene alterations can be either hereditary (also called germline), meaning you are born with them and they were passed on from your mother or father, or acquired later in life (called somatic alterations).

APC

The *APC* gene instructs the body in making the APC protein, which acts as a tumor suppressor by keeping cells from growing and dividing too quickly. Alterations in this gene can **lead to breast cancer**.

KRAS

Another type of oncogene that instructs the body to make a protein called K-Ras, which tells cells to grow and divide. **Less than 2% of breast cancers have a *KRAS* alteration**.

ATM

Instead of activating DNA repair, the defective ATM protein allows alterations to accumulate in other genes, which may cause cells to grow and divide in an uncontrolled way. This kind of unregulated cell growth can lead to the formation of cancerous tumors. Inheriting one abnormal copy of this gene has been linked to a high rate of breast cancer. It has been suggested that women who carry an alteration in the *ATM* gene have an **estimated 20-60% increased risk for breast cancer**. Those with an *ATM* gene mutation are thought to be at increased risk for early-onset breast cancer and bilateral breast cancer.

PALB2

The *PALB2* gene is called the partner and localizer of the *BRCA2* gene. It provides instructions to make a protein that works with the BRCA2 protein to repair damaged DNA and stop tumor growth. Alterations in the *PALB2* gene are known to carry a predisposition to developing breast cancer. **The estimated lifetime risk is between 33 and 58%**.

CHEK2

CHEK2 is a tumor-suppressor gene that protects cells from becoming cancerous. People who inherit alterations in the gene are at increased risk for certain types of cancer, thus **risk of developing breast cancer can be increased by 37%**.

PTEN

The *PTEN* gene helps stop the growth of tumors. It's known as a tumor suppressor. A tumor suppressor gene is like the brakes on a car. It puts the "brakes" on cells, so they don't divide too quickly. Mutations in one copy of the *PTEN* gene can **increase the chance for developing certain types of cancer** in one's lifetime, including breast cancer.

TP53

(also known as *p53*): An alteration in this gene, which helps stop the growth of cells with damaged DNA, is a **rare cause of breast cancer**.

STK11

The *STK11* gene (also called *LKB1*) provides instructions for making an enzyme called serine/threonine kinase 11. This enzyme is a tumor suppressor, which means that it helps keep cells from growing and dividing too fast or in an uncontrolled way. People with an inherited alteration in *STK11* gene are at a **greater lifetime risk of developing many different types of cancer**, including breast, ovarian, endometrial, cervical, pancreatic, colorectal, gastric, small intestine, and lung cancer. The lifetime risk for a woman with a *STK11* mutation is about 32-54% compared to 12.5% for an average risk woman.

AKT1

This gene provides instructions for the body to make a protein called AKT1 kinase, which is found in cells throughout the body. It helps **regulate cell growth, division and survival, and also the process by which cells self-destruct when they become damaged**. The *AKT1* gene alteration is seen in cancers including breast, colon and lung.

mTOR

A protein found on various types of cells throughout the body, which is produced as a result of instructions from the *mTOR* gene. **When *mTOR* is overactivated due to a genetic alteration, cancer may result**.

NRAS

The *NRAS* gene instructs the body to make a protein called N-Ras that is involved in regulating cell division. *NRAS* belongs to a class of genes called oncogenes that, when altered, **can cause normal cells to become cancerous**.

CDHI

Women with an alteration in this gene have an **increased risk of invasive lobular breast cancer**.