Summary

Breast cancer (BC) is one of the most frequently occurring cancer and cancer-related deaths in women. BC become a major public health challenge. In Egypt, BC is the most frequent cancer among Egyptian females. It represents about 38% of all reported cancer cases in Egyptian females.

Wide variability in the response of individuals to drugs at the same doses may occur, not all BC patients were benefitted from treatment therapy, which may be a result of inter-individual genetic differences.

Resistance to anticancer agents is one of the most important problems in cancer treatment. Although breast cancer is one of the most sensitive solid tumors to anticancer agents, after a successful course of treatment, most patients show different degrees of drug resistance. Despite various treatment regimens used for breast cancer, the complete response to treatment is between 17–80 %.

Multidrug resistance (MDR) is a complex phenomenon which is affected by many genetic and environmental factors. It is considered a major cause for treatment failure in breast cancer. Identification of prognostic markers of treatment resistance which can be targeted effectively to reverse the resistance would represent a significant advance in treatment for breast carcinoma.
One of the mechanisms of drug resistance studied is the significant expression of human multi-drug resistance (MDR1) gene. P-glycoprotein (MDR1 gene product) is a key player in the multidrug-resistant phenotype in cancer. Genetic variations affecting function and expression of P-gp have a role in resistance to many anti-cancer drugs including anthracyclines and taxanes.

CYP2D6 is responsible for the metabolism of about 20-25% of commonly prescribed drugs. CYP2D6 is the main enzyme that catalyzes the rate-limited step in the metabolism of tamoxifen to its potent metabolite, endoxifen. Tamoxifen is heavily metabolized by several of the cytochrome P450 drug metabolizing enzymes.

According to CCR5, it was found that CCR5/CCL5 axis has an important role in tumor development, progression and invasiveness through multiple mechanisms: acting as growth factors, modulating the extracellular matrix, stimulating angiogenesis, inducing the additional stromal and inflammatory cells, and taking part in immune evasion mechanisms. CCR5 and its ligand CCL5 is also involved in drug resistance.

The aim of our study is to clarify the role of MDR1, CYP2D6 and CCR5 polymorphisms in breast cancer patients and provide a better insight into the association between these genes and prediction of response/resistance to breast cancer treatment.

Our study was performed on 40 breast cancer (BC) patients and 20 cancer-free controls. We subdivided our BC group according to treatment response into two groups, the first included responders patients (either complete response or partial response), and the other included non-responders (either static disease or progressive disease). The BC
patients were on chemotherapeutic therapy in the form FAC (5-fluorouracil + Adriamycin + cyclophosphamide) ± tamoxifen.

Blood samples (3 ml) were put on EDTA for mutation detection of MDR1, CYP2D6 and CCR5 genes based on the reverse hybridization principle using (HVD strip kit). The mutation detection assay covered 5 polymorphic loci: MDR1 3435 C>T, CYP2D6 1795delT (2D6*6), CYP2D6 1934 G>A (2D6*4), CYP2D6 2637delA (2D6*3), CCR5 32bp deletion.

The steps included: DNA isolation (using 100 µl blood sample for extraction), PCR amplification (in a multiplex reaction using biotinylated primers) and hybridization of amplified products to a test strip containing allele-specific oligonucleotide probes immobilized as an array of parallel lines, bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and color substrates and interpretation of results.

The data analysis of MDR1 C3435T gene revealed a significant increase in the frequency of mutant (T) allele and homozygous mutant (TT) genotype of in breast cancer patients and interestingly, they associated with increase response to treatment therapy.

Moreover, the results obtained for the gene CYP2D6 demonstrated that the homozygous genotype (CYP2D6 *4/*4), mutant CYP2D6 *4 allele and PM phenotype are significantly associated with the BC development and worse treatment response.

In addition, our results showed absence of relationship between CCR5 gene and breast cancer.