Breast cancer is the most common cancer among women worldwide. Both genetic and non-genetic factors contribute to the etiology of breast cancer. The Fanconi/BRCA pathway is involved in Fanconi Anemia and hereditary breast cancer. In the first part of the thesis examines the role of novel genes and mutations in de ‘missing heritability’ of breast cancer. The second part of the thesis, focuses on the identification of targeted therapy for hereditary and non-hereditary breast cancer. In chapter 2, the role of SLX4, a novel Fanconi Anemia gene was examined in 729 BRCA1/BRCA2-negative familial breast cancer cases and one truncating splice site mutation and four possible pathogenic missense mutations were identified. In chapter 3, a novel mutation in the splice donor site of intron 1, close to non-coding exon 1 of BRCA2 was found in a Fanconi Anemia patient. Although we did not observe breast cancer cases with such splice site mutations, an increased breast/ovarian cancer risk as a consequence of such mutations cannot be excluded. We therefore recommend including these splice sites of non-coding exons in the screening of BRCA1 and BRCA2 in familial breast cancer. Chapter 4, investigated the cellular role of the breast cancer gene CHEK2 and showed a resistance to alkylating agents in cell lines derived from women with a homozygote CHEK2*1100delC mutation. When cross-linker sensitivity was analysed in breast cancer cell lines (a hallmark of BRCA1/BRCA2 mutated tumors), an amplification of the helicase RECQL5 appeared to be responsible for cross-linker sensitivity in one of the cell lines (chapter 5). In chapter 6, a kinome siRNA screen in combination with an anthracycline identified some interesting candidates possibly involved in the viability of this BRCA1-deficient triple negative breast cancer cell line. In the last chapter of this thesis (chapter 7), the systemic treatment regime and outcome for patients with metastatic breast cancer is being evaluated in clinical practice. In conclusion, this thesis provides new insights in the missing heritability of breast cancer and discovered an amplification of the helicase RECL5 responsible for sensitivity to chemotherapy. Further research is needed to determine the value of these finding for patient care.