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**MYBL2 related Genes as Prognostic Markers for Breast Cancer**

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The aim of the presented thesis was to investigate the contribution of polymorphisms in candidate genes to the risk and clinical outcome of breast cancer. The inherited genetic variation is a known risk factor for breast cancer, and survival in breast cancer also has an inherited component. Further knowledge about breast cancer susceptibility variants may provide new insights into the genetic background and biological progression of breast cancer.

In this thesis, twenty SNPs were selected from 20q13 amplicon genes for its impact on breast cancer susceptibility and clinical outcome. In addition to the SNPs in 20q13 amplicon genes, twenty-eight SNPs were selected in MYBL2 related genes, which associated with MYBL2 via a DNA binding manner. The presented studies were performed on a Swedish population-based cohort of 783 breast cancer cases and in 506 Polish familial/early onset cohort of breast cancer cases.

As a novel finding, four polymorphisms in STK4 and AURKA associated with steroid hormone receptor status in both populations. In the joint analysis, the minor allele carriers of rs6017452 had more often hormone receptor-positive tumours, while homozygotes for the minor alleles of rs7271519, rs2273535 and rs8173 had more often hormone receptor-negative tumours than homozygotes for the common allele. BC-specific survival analysis of AURKA

suggested that the Swedish carriers of the minor allele of rs16979877, rs2273535 and rs8173 might have a worse survival rate compared with the major homozygotes. The survival probabilities associated with the AURKA genotypes depended on the tumour phenotype. In the Swedish case-control study, associations with breast cancer susceptibility were observed for three MYBL2 promoter polymorphisms in a dominant model (rs619289, p=0.02, rs826943, p=0.03 and rs826944, p=0.02), two AURKA promoter polymorphisms (rs6064389, p=0.04 and rs16979877, p=0.02) and one 3'UTR polymorphism in ZNF217 (rs1056948, p=0.01).

Moreover, 28 SNPs were selected from 12 MYBL2 related genes. BC-specific survival analysis of BIRC5 suggested that the Swedish carriers of the minor allele of rs8073069 and rs1042489 have a worse survival compared with the major homozygotes. The survival probabilities might be caused by altered BIRC5 gene expression. Furthermore, the results suggested that polymorphisms in BCL2 and CLU may be associated with tumours characteristics in breast cancer. In BCL2, minor allele carriers of rs1564483 had more often hormone receptor-positive tumours than major homozygotes carriers. Another SNP in BCL2, rs4987852, was associated with tumours in stage II-IV and histologic grade 3. In CLU, the minor allele carriers of rs9331888 were more likely to have tumours with region lymph node metastasis and tumours in stage II-IV than major homozygotes carriers.

In conclusion, this study confirmed the impact of the previously identified susceptibility locus and provided preliminary evidence for novel susceptibility variants in breast cancer. Notably, the study also provided evidence for the first time that genetic variants at 20q13 may affect hormone receptor status in breast tumours and influence tumour aggressiveness and survival of the patients. In addition to the genetic variation at the 20q13 locus, the common variants in MYBL2 related genes were investigated. Two polymorphisms in BIRC5 had prognostic value in breast cancer.

Breast cancer is a complex disease associated with both genetic and environmental factors**.** Therefore, the identification of environmental factors in combination with genetic factors contributing to breast cancer prognosis will provide useful tools for prevention, prognosis and guidelines for breast cancer therapy.