Annika Brendle geb. Vaclavicek
Dr. sc. hum.

Genes in prolactin pathway and mitotic checkpoint as low penetrant risk factors for familial breast cancer

Geboren am 14.08.1980 in Ludwigsburg
Diplom der Fachrichtung Agrarbiologie mit Biotechnologie am 13.01.2005 an der Universität Hohenheim, Stuttgart

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Kari Hemminki, MD, PhD

According to the polygenic model of inherited breast cancer predisposition, combinations of genetic variants in different candidate genes are supposed to account for a large portion of the excess familial risk for breast cancer. The presented case-control studies were performed on a German study population and focused on the effects of putative functional and regulatory relevant SNPs in candidate genes with a strong probability to be involved in breast cancer development.

Taken together, we have investigated SNPs, haplotypes and their interaction in the PRL and PRLR gene, respectively, in genes of the JAK/STAT pathway, as well as in six major mitotic checkpoint genes and their risk contribution to breast cancer susceptibility.

PRL is involved in the development of the mammary gland, in cellular growth and differentiation, as well as in the initiation and maintenance of lactation. It is expressed in both the normal and malignant breast. In addition, most breast cancers express the PRLR and a higher PRLR expression in the malignant than the adjacent histologically normal tissue has been reported. Our results indicate a role of PRL and the PRLR in the development of breast cancer. In the PRL gene we identified two promoter polymorphisms which where associated with an increased risk. Moreover, we observed an increase in breast cancer risk for carriers of the haplotype containing these two SNPs. In the PRLR gene we identified the TCC haplotype, which contained the C allele of the SNP rs9292573, which was individually associated with a significantly decreased breast cancer risk. As a further evidence, individuals´ increasing number of the PRL and PRLR risk haplotypes increased the breast cancer risk significantly ($\chi^2 = 12.15$, $P = 0.007$).

Furthmore, we investigated SNPs in the genes of the JAK/STAT pathway (JAK2, STAT3, STAT5A, STAT5B) which is activated amongst others by PRL binding to its receptor. The proteins of the JAK/STAT pathway participate in a series of normal cellular processes such as differentiation, proliferation, cell growth, survival and apoptosis. In the JAK2 gene we identified two SNPs with a protective effect and one SNP which increased the risk. Since no haplotypes with a significant association with breast cancer risk were identified, we do not consider these SNPs as true risk factors. In the STAT gene region we identified a two SNP haplotype which explained best the observed increased risk in this region. Furthermore, consideration of the diplotypes revealed that the carriers of a diplotype with at least one risk haplotype AC, were at a significantly increased risk, while the AT/GT diplotype consisting of the protective AT and the wild type GT haplotype, respectively, showed a protective effect of borderline significance.

As a result, polymorphisms and haplotypes in the PRL and PRLR genes, as well as in the genes of the JAK/STAT pathway have an influence on breast cancer risk, and the accumulation of variants may thus enhance the development of breast cancer. However, it needs to be tested if the polymorphisms have an impact on gene expression and protein characteristics.

Moreover, we investigated six genes of the mitotic checkpoint, which mediates and controls the accurate chromosome segregation between two daughter cells during mitosis as well as the loss of telomere capping function. Neither the individual SNPs, nor the haplotypes showed an effect on breast cancer risk. The appliance of the multifactor dimensionality reduction method revealed no gene-gene interactions. Therefore our results strongly indicate that combinations among the investigated SNPs in the selected mitotic checkpoint genes do not affect the risk of breast cancer.

In conclusion, polymorphisms may contribute to the inter-individual variability in susceptibility to breast cancer, and accumulation of variant alleles may have a high impact on breast cancer at the individual level. The identification of susceptibility genes and gene variants associated with disease risk is essential for the understanding of the pathogenesis of the disease and the development of medical diagnostics, prevention and therapeutic strategies.