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Search for breast cancer susceptibility genes in the growth hormone/insulin-like growth factor-1 axis

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The work in this dissertation summarizes the investigation of polymorphisms in the GH1/IGF-1 axis in relation to breast cancer risk by means of the planning and conducting case-control studies. Many findings were novel and they reflected the complexity of the gene regulation along the GH1/IGF-1 pathway. The statistical significance of individual polymorphisms was not overwhelming, but the consistency of the findings added to their credibility. Additionally, the use of familial cases instead of consecutive cases, and the confirmation of the positive findings in an independent population, increased the power of our study. We studied “functional polymorphisms” with a potential or reported function as well as “haplotype polymorphisms” that do not have an influence on the gene product but are useful for haplotype analyses. Our work was based on examining individual polymorphisms, haplotypes and gene-gene interactions.

In particular, we showed a significant protective effect for the *GHRHR* C-261T promoter single nucleotide polymorphism (SNP), while further SNPs in the *GHRH* and *GHRHR* genes were not associated with the risk of breast cancer. Our results indicate that polymorphisms in the *SST* and *SSTR2* gene may contribute to a decreased breast cancer risk. Furthermore, our results point out that polymorphisms in the *GHRL* and its receptor genes do not contribute to breast cancer risk.

In the *GH1* gene, two of the SNPs (A-137G and G-93delG) lead to a decreased risk of breast cancer. The G-93delG variant allele was also involved in the only haplotype protecting against breast cancer. We detected no associations between the four *GHR* polymorphisms (GHRd3, Gly186Gly, Cys440Phe and Ile544Leu) and breast cancer

risk. However, in a haplotype analysis with these SNPs, the rare haplotype dGGC showed a protective effect. The *IGF-1* CA repeat polymorphism and the *IGFBP3* A-202C SNP were associated with familial breast cancer risk, which was stronger in individuals homozygous for both of these polymorphisms. A small effect was detected in consecutive cases diagnosed below the age of 50. In postmenopausal breast cancer cases no effect was observed.

In the study on variants in the *IRS1, IRS2* and *SHC1* genes we detected a significantly decreased risk for breast cancer in carriers of the variant Val allele at codon 300 in the *SHC1* gene. The IRS1 and IRS2 polymorphisms did not show any influence on breast cancer risk, nor did haplotypes or genotype combinations. Additionally, we identified a novel 22bp duplication polymorphism in the *CRKII* promoter which results in *in silico* multiplication of various putative transcription factor binding sites. In combination with the Arg17 A allele, a protective effect was observed. No effect on breast cancer risk was observed for five SNPs in the *IRS4* gene.

In summary, the studied SNPs were mainly associated with a decreased breast cancer risk (8 out of 36). Only two polymorphisms of the 36 studied ones showed an increased breast cancer risk. This lead to the suggestion that genetic variants in the GH1/ IGF-1 axis do not increase the mitogenic and antiproliferative features of the pathway, but rather protect the cells from proliferation. Our study contributes to the world-wide effort of identification of low-penetrance genetic variants, which may be useful tools for prevention, prognosis and planning of individual therapy. However, more work is needed to characterize the effect of the polymorphisms on signalling through the GH1/IGF-1 axis and further on susceptibility to breast cancer and prognostic characteristics of the tumours. It should now be tested if the variants associated with breast cancer risk influence GH1 and IGF-1 bioavailability and the signalling properties