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Genetic variants in cell adhesion and immune related genes in human melanoma

Promotionsfach: Molecular Genetic Epidemiology
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The present study was aimed at identifying genetic variants in different integrin and in interferon genes for association with melanoma susceptibility, survival and therapy in melanoma patients recruited in Germany. The first part of the study was based on the analysis of 19 non-synonymous variants in the coding region of the human integrin genes representing 3 beta subunits and 13 alpha subunits. The variants in *ITGA10* and *ITGA6* genes showed association with decreased risk, and variants in *ITGA2*, *ITGAE*, and *ITGAM* were associated with increased risk of melanoma. The haplotype analysis revealed association of CA haplotype of *ITGAE*, and TAC haplotype of *ITGAX* with the risk modulation. A prediction analysis of functional effect, homology modeling and multiple sequence alignments supported our data for linkage of variants in the *ITGA2* and *ITGAE* genes with susceptibility. Our experimental data indicated a possible role for some of the variant alleles and/or haplotypes of the integrin genes in melanoma susceptibility, which is augmented by the theoretical analysis performed.

In the second part of this study we investigated the association of 44 SNPs, which encompassed 15 interferon genes and represented 299 SNPs located on chromosome 9p22, with metastasis free progression, overall survival and time from metastasis to death in melanoma patients from Germany. The polymorphisms, which showed statistically significant association with those parameters were located in two main regions. One region of 26 Kb, which encompassed the *IFNW1* and *INFA21* genes, and another region of 91kb, which encompassed the *IFNA6*, *IFNA13*, *IFNA2*, *IFNA8* and *IFNA1* genes. In the 26 Kb region, five SNPs were found to be statistically significantly associated with survival. However, the strongest effects were observed for the carriers of the variant alleles of the rs10964859 (C>G), rs10964862 (C>A) and rs10081742 (A>G) polymorphisms. The rs10964859 was located at 3'UTR of the *IFNW1* gene. Our results

showed that patients, who were carriers of the variant alleles for rs10964859 and rs10964862 polymorphisms, had an increased risk of developing metastasis. These findings could be validated in an independent group of patients from Spain and confirmed as well in the combined analysis. Furthermore, patients carriers of the homozygous variant genotypes for the rs10964859 and rs10964862 polymorphisms, were at a higher risk of death. Haplotype analysis showed three frequent haplotypes associated with increased metastasis in accordance with individual SNP data. In the 91 Kb region the variant alleles of three SNPs, rs597408 (A>G), rs7043990 (T>C) and rs632941 (G>A) were associated with melanoma outcome. The strongest effect was observed on the metastasis free progression and on the overall survival analysis for the carriers of homozygous genotype for the rs597408 polymorphism in the patients from Germany. We found that the genotypes of the patients from Germany and from Spain for rs10964859, rs10964862 and rs10081742 polymorphisms showed adverse effects in different groups after stratification according to the therapy. In this study, we identified genetic variants in interferon genes associated to melanoma progression and survival, which also showed to have an influence on the efficacy of the therapy in patients with this disease.