Livia Maccioni.

Dr.sc.hum.

Genetics of pigmentation related genes and risk of melanoma.

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)

Doktorvater: Prof. Dr. Rajiv Kumar.

The present study was aimed at determining the association of genetic variants in melanoma susceptibility genes, involved in pigmentation pathway and on chromosome locus 9p21. Agouti signaling protein (*ASIP*) locus has been implicated in phenotype variation and melanoma risk. We analyzed 21 variants informative for 495 single nucleotide polymorphisms on *ASIP* locus using Spanish cases and controls. Our data showed statistically significant association with melanoma for variants rs4911414 (intergenic), rs4911442 (intron 5 *NCOA6*), rs1015363 (intergenic), and rs910871 (intron 10 *NCOA6*). A haplotype from the variants within *NCOA6* showed an increased risk of melanoma. Our results on *ASIP* locus while confirming the association of *ASIP* locus variants with melanoma risk; surmise that associated or linked variants act as eQTL that affect other genes in the locus. Additionally, we analyzed, 25 polymorphisms on chromosome 9p21 in Spanish and German population. Ten SNPs were selected based on GWAS and an additional 15 were selected to fine map *CDKN2A*. Five variants, rs1335510 (intergenic), rs1341866 (intergenic), rs10757257 (intron 1 *MTAP*), rs10811629 (intron 5 *MTAP*) and rs1011970 (intron 9 *ANRIL*) and 1 tagging polymorphism, rs3088440 (3'UTR *CDKN2A*), showed statistically significant association with melanoma in Spanish but not in German population. Three tagging polymorphisms intronic to *CDKN2A* (rs2518719; rs2811708; rs3731239) showed the increased risk in German but not in Spanish population. The second part of study investigated the gene expression profile in metastatic melanoma cell lines using supervised and unsupervised clustering. The gene expression data from 42 cell lines showed distinct molecular subtyping of melanoma using unsupervised clustering, as classification based on *MC1R* variants or *BRAF*/*NRAS* mutation status lacked any correlation. The unsupervised clustering revealed two groups with differential gene expression patterns; one group with increased expression of immune related genes and the other group with increased expression of melanogenesis genes. The group with increased expression of immune responsive genes showed better survival than group with high expression of pigmentation genes.