Jian Guan
Dr. med.

Variants in Melanogenesis Genes in Melanoma Susceptibility and Survival

Promotionsfach: DKFZ (Deutschen Krebsforschungszentrum)
Doktorvater: Prof. Dr. Rajiv Kumar

The present study was mainly aimed at validating the genetic variants in susceptibility to melanoma through replication of polymorphisms selected from a dedicated pigmentation beadchip using 338 SNPs covering 65 gene regions belonging to the pigmentation pathways. Furthermore, survival analyses were performed to access the association between these variants and patients´ survival. 27 selected loci were validated via case-control analyses and survival analyses within two independent subsets from Germany comprised of 761 patients and 736 healthy ethnically matched controls, and from Spain composed of 837 cases and 1154 controls.

In the case-control study, 3 variants out of 27 loci were confirmed to have significant associations with risk of melanoma within both two populations with robust unambiguous statistical evidence. They are as follows: rs1801516 in the exon36 of ATM chr.11q22-q23 was statistical significantly associated with decreased susceptibility to melanoma; rs16891982 in the exon5 of SLC45A2 on chr.5p13.2 with decreased risk, while rs1126809 in the exon4 of the tyrosinase (TYR) on chr.11q14-q21 with increased risk. ATM is the master controller of cell cycle checkpoint signaling pathways repairing DNA double-strand breaks and stabilizing the genome. The SLC45A2 gene encodes the membrane-associated transporter protein (MATP), which is a putative membrane solute carrier as a sodium–hydrogen exchanger. TYR is the time-limiting enzyme in the melanogenesis pathway. These three polymorphisms are all missense variants located in the exon regions of genes. Our results from those 3 SNPs were in agreement with previous other reports. In addition, 9 SNPs showed significant association with melanoma risk in only one of the 2 populations.

In the survival analysis within the German population, the WNT rs199524 variant was significantly associated with decreased overall survival, metastasis free survival and survival following metastasis. Furthermore, rs16891982 in SLC45A2 showed a significantly association with decreased overall survival; the variant rs12219667 130 Kb upstream of FGFR2 was associated with increased metastasis

free survival; rs3087243 at 3`UTR of CTLA4 on chr.2q33 was significant associated with increased survival following metastasis; rs45430 at intron of MX2 on chr.21q22.3 was significant associated with decreased survival following metastasis.