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Identification of true risk alleles for lymphoid neoplasms

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Lymphoid neoplasms comprise a broad variety of sub-entities characterised by different histological, molecular and cytogenetic features. They can be classified into two main subgroups; Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), the latter can be further divided into B-cell lymphoma (B-NHL) and T-cell lymphoma. Inherited or acquired immunodeficiencies are strong risk factors for lymphoma, but due to their low population frequency they cannot explain the majority of cases. The observation that individuals with a family history of haematopoietic cancers are at increased risk of lymphoma suggests that disease susceptibility has a genetic component. The number of publications reporting an association between genetic variants and lymphoma risk has increased substantially during the last years. However, most studies examining genetic predisposition to lymphoma were based on small sample sizes, and so far only a few identified associations could be replicated. Therefore, the aims of this thesis were the replication of identified associations and the detection of new genetic factors associated with lymphomagenesis.

The Illumina GoldenGate™ Assay was utilized to genotype 1536 SNPs in nearly 1500 samples of the EpiLymph study, a multi-centre case-control study carried out in six European countries. The association between polymorphisms and risk of HL, T-NHL and B-NHL as well as the most frequent B-NHL subtypes was estimated by calculating odds ratios (ORs), and 95 % confidence intervals (CI) using unconditional logistic regression, adjusted for age (continuous), sex and study centre, with the statistical software SAS.

Members of the STAT family are essential in various signaling cascades and their impact on lymphomagenesis was reported previously. The subsequent analysis of 210 SNPs in 23 JAK-STAT signaling related genes revealed polymorphisms in nine genes (*BMF*, *IFNG*, *IL12A*, *SOCS1*, *STAT1*, *STAT3*, *STAT5A*, *STAT6*, *TP63*) to be significantly associated with lymphoma risk. At a pathway significance level, we estimated a risk reduction of 28 % among carriers of the heterozygous genotype of the *STAT3* variant (rs1053023) for B-NHL. Reduced risk for HL was seen for the heterozygous genotype of the functional *STAT6* SNP (rs324011). Support for the observed relevance of JAK-STAT pathway related polymorphisms was achieved by haplotype-based and gene-gene interaction analyses. These findings contribute to the understanding of the prominent role of this signalling cascade in immune responses and diseases characterized by immune dysfunction.

DNA double strand breaks may occur in the course of lymphocyte development consequent to processes that target the increase of immune diversity, or as a result of

exogenous factors, e.g. ionizing radiation or chemical exposure. Efficient DNA repair is essential for chromosomal stability and requires the activation of repair mechanisms, homologous recombination and non-homologous end-joining. Significant association with an altered HL risk was observed for five SNPs in the *MRE11A*, *RAD51C* and *RAD52* genes, with pathway-level significance for two *RAD52* variants. B-NHL risk was modified by SNPs of the *MRE11A* and *RAD54B* genes. The results demonstrate the importance of genetic variability in the DNA repair machinery as etiological factors for lymphomas. In addition, we observed a strong increase of the *RAD52* effect on HL risk among ever smokers compared to never smokers. The observed joint effect of smoking habit and genotype on HL risk highlights the necessity of gene-environment (GxE) interaction analyses to elucidate biological mechanism relevant in tumourigenesis.

Xenobiotics such as solvents have been associated with lymphoma risk. ABC transporters are essential for the membrane transport of xenobiotics and crucial cellular compounds and were therefore studied in the context of the current thesis. Carriers of the SNP rs6857600 minor allele in *ABCG2* were at a decreased risk of B-NHL overall. Furthermore, a decreased risk of CLL was associated with the *ABCG2* rs2231142 variant - a finding which was replicated in an independent population.

To keep the possibility of false positive findings at a low level we controlled for multiple comparison. However, to strengthen our results, the observed associations require replication in an independent study sample. Despite the large sample size available for the thesis, statistical power for subtype analyses was limited. Therefore, pooled analyses in the context of the InterLymph Consortium, an international consortium of epidemiological lymphoma studies, are warranted to validate subtype-specific risk estimates. In addition, further GxE analyses will be conducted in the distinct InterLymph studies to gain further insights in the mechanisms of lymphoma development.

Validated SNPs that are relevant in the etiology of lymphomas may also have a prognostic implication and further research in that direction is warranted. Overall, the identification of risk loci for lymphomas pave the road for a better risk assessment and may benefit strategies for individualized therapies.