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Genetic variants in susceptibility to childhood acute lymphoblastic leukemia

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The present study was aimed at identifying genetic variants in susceptibility to childhood acute lymphoblastic leukemia (ALL) through replication and validation of polymorphisms selected from two genome wide association studies. The first part of the study was based on the replication of polymorphisms selected from a previously conducted genome wide scan using 50K DNA-SNP microarrays. 47 selected polymorphisms representing 36 distinctive genetic loci were screened in a case-control study consisting of 425 cases from the BFM study trials and 552 ethnically matched controls. No significant association with risk of ALL could be confirmed from this study.

The second part of the study consisted of validation of 40 polymorphisms selected from a previously conducted genome wide association study on DNA microarrays with 370K polymorphisms. The association of polymorphisms (1) rs4132601 in the 3'UTR of *IKZF1* on 7p12.2, (2) rs7089424 in the intron of *ARID5B* on 10q21.2, (3) rs2239633 in the intron of *CEBPE* on 14q11.2 and (4) rs3731217 the intron of *CDKN2A* on 9p21.3 with risk of ALL was discovered through the initial genome wide scans. The present study validated these associations in an independent large population comprising 1500 cases from the BFM study trials and 1516 ethnically matched controls with robust statistical significance. Furthermore, it was shown that the association of polymorphisms rs4132601, rs7089424 and rs2239633 was confined to risk of B-cell ALL. However, the effect of the polymorphism rs3731217 on chromosome 9p21.3 was confirmed for risk of overall ALL, B-cell and T-cell ALL separately. There were no interactions between any of the pairs of loci tested. The effect of the susceptibility variants for the four polymorphisms was dose dependent, with risk of ALL increasing with increasing number of risk alleles. Estimation of proportion of ALL susceptibility attributable to the risk variants of the four

SNPs was > 80%. *IKZF1* has crucial roles in hematopoiesis. *ARID5B* plays important roles in embryogenesis and growth regulation. *CEBPE* has been shown to interact with cell cycle regulators. *CDKN2A* is an important regulator of the cell cycle. In addition to the ALL risk variant, at least 29 polymorphisms at the *CDKN2A* locus were shown to be associated with risk of various disorders including cancers in previously conducted genome wide association studies. Linkage disequilibrium mapping analysis of these polymorphisms showed (1) disease-specific sequestering at distinctive regions and (2) absence of LD between the disease-associated SNPs. This was suggestive of the importance of the 9p21.3 locus in various biological processes and independent molecular mechanisms of function for each region.