Coding variants at hexa-allelic amino acid 13 of HLA-DRB1 explain independent SNP associations with follicular lymphoma risk.

Non-Hodgkin lymphoma represents a diverse group of blood malignancies, of which follicular lymphoma (FL) is a common subtype. Previous genome-wide association studies (GWASs) have identified in the human leukocyte antigen (HLA) class II region multiple independent SNPs that are significantly associated with FL risk. To dissect these signals and determine whether coding variants in HLA genes are responsible for the associations, we conducted imputation, HLA typing, and sequencing in three independent populations for a total of 689 cases and 2,446 controls. We identified a hexa-allelic amino acid polymorphism at position 13 of the HLA-DR beta chain that showed the strongest association with FL within the major histocompatibility complex (MHC) region (multiallelic p = 2.3 × 10⁻¹⁵). Out of six possible amino acids that occurred at that position within the population, we classified two as high risk (Tyr and Phe), two as low risk (Ser and Arg), and two as moderate risk (His and Gly). There was a 4.2-fold difference in risk (95% confidence interval = 2.9-6.1) between subjects carrying two alleles encoding high-risk amino acids and those carrying two alleles encoding low-risk amino acids (p = 1.01 × 10⁻¹⁴). This coding variant might explain the complex SNP...
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