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Title: HLA-DPB1 and chronic sarcoidosis

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Body: Background: Beryllium disease and sarcoidosis have clinical similarities. Beryllium exposure together with the HLA-DPB1 alleles containing a glutamic acid at amino acid position 69 (Glu^{69}) is associated with beryllium sensitization and chronic beryllium disease (CBD). Aim: To determinate whether the same genetic variations of HLA-DPB1 that are found in CBD are associated with chronic sarcoidosis. Methods: HLA-DPB1 was determined in 98 Finnish patients with chronic sarcoidosis not resolved within 2 years and in 150 control subjects. The DPB1 alleles were genotyped with sequence specific primers (Olerup SSP™) and haplotypes were formed with MHC class II and class III markers. Results: 17 different DPB1 alleles were observed. The DPB1*04:02 allele was less frequent among the patients (10.2% vs.20.3%; p=0.003, OR=0.45) than controls. A haplotype with DPB1*04:01, one C4A gene and one C4B gene was increased among sarcoidosis patients (30.9% vs. 22.5%; p=0.036, OR=1.5). By studying polymorphic amino acid residues of DPB1, we did not detect an association of Glu^{69}, but a DPB1*04:02 specific amino acid variant was detected at the position 178 (Met) suggesting a protective role for chronic sarcoidosis (p=0.004, OR=0.42). Furthermore, preliminary SNP analyses of HLA class II and III region showed that the SNP associations are independent from DPB1. Conclusion: We confirm and further describe the contributory role of DPB1 with the risk associated for chronic sarcoidosis. Preliminary results suggest that both DRB1 and certain independent markers in the HLA class II and III region increase the risk for chronic sarcoidosis. However, HLA association analyses are complicated by the extensive linkage disequilibrium (LD) across the HLA region.