Protective and predisposing HLA class I and class II haplotypes in diabetic families from Eastern Croatia: a pilot study

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Human leukocyte antigen (HLA) genes are major genetic determinants of type I diabetes (T1D) susceptibility, with variable predispositional effects across populations. In order to examine the extent of haplotypic risk and the patterns of HLA associations with T1D in the population of East Croatia, A, B, DRB1 and DQB1 loci were typed at low resolution using sequence-specific primer PCR methodology. Single and multipoint genetic associations were assessed through transmission disequilibrium testing of multilocus haplotypes in 13 nuclear families (55 subjects), estimated according to the expectation-maximization algorithm. Empirical P-values and pairwise linkage disequilibrium measures were obtained. No Mendelian errors were detected. Generally, DQB1\*02, DQ8 and DQ7 were commonly inherited in cis with DRB1\*03, DRB1\*04 and DRB1\*11, respectively. The most frequent (10%) ancestral haplotype (A1-B8-DR3-DQ2) was not associated with risk of T1D. DQ8 allele and two-locus (permuted P=0.047) DRB1\*04-DQB1\*DQ8 haplotype (85.7% transmission, p=0.0049, RR=6.0) were preferentially transmitted to affected probands, indicating the robust diabetogenic effect of these alleles. Conversely, DQ7 allele (14.3% transmission, p=0.047, RR=0.17) and B\*18-DRB1\*11-DQ7 haplotype (no transmissions, p=0.0018) were nominally highly protective, being significantly less transmitted to diabetic children. These findings confirm DRB1\*04-DQ8 and DRB1\*11-DQ7 as major HLA determinants of T1D susceptibility in Eastern Croatia. Sample size enlargement, DQA1 loci typing and high resolution testing are required for in-depth information on hierarchyof risk effects at the DR-DQ haplotype levels.