The Type 1 Diabetes - HLA Susceptibility Interactome - Identification of HLA Genotype-Specific Disease Genes for Type 1 Diabetes - DTU Orbit (10/08/2019)

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Background: The individual contribution of genes in the HLA region to the risk of developing type 1 diabetes (T1D) is confounded by the high linkage disequilibrium (LD) in this region. Using a novel approach we have combined genetic association data with information on functional protein-protein interactions to elucidate risk independent of LD and to place the genetic association into a functional context. Methodology/Principal Findings: Genetic association data from 2300 single nucleotide polymorphisms (SNPs) in the HLA region was analysed in 2200 T1D family trios divided into six risk groups based on HLA-DRB1 genotypes. The best SNP signal in each gene was mapped to proteins in a human protein interaction network and their significance of clustering in functional network modules was evaluated. The significant network modules identified through this approach differed between the six HLA risk groups, which could be divided into two groups based on carrying the DRB1*0301 or the DRB1*0401 allele. Proteins identified in networks specific for DRB1*0301 carriers were involved in stress response and inflammation whereas in DRB1*0401 carriers the proteins were involved in antigen processing and presentation. Conclusions/Significance: In this study we were able to hypothesise functional differences between individuals with T1D carrying specific DRB1 alleles. The results point at candidate proteins involved in distinct cellular processes that could not only help the understanding of the pathogenesis of T1D, but also the distinction between individuals at different genetic risk for developing T1D.

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