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Association of *TNF-α* and *PTPN22* SNPs with the risk and clinical outcome of type 1 diabetes

Research Article

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Abstract: Type 1 *Diabetes mellitus* (T1DM) begins with aberrant inflammatory process followed by auto-destruction in genetically susceptible individuals. Therefore, we hypothesized that gain-of-function allelic variants *TNF*-α-238A, -308A and *PTPN22* 1858T could be associated not only with T1DM development but also with the clinical outcome in patients of Bosnia and Herzegovina. A total of 402 subjects were enrolled in the association study. SNPs were determined by PCR-RFLP. Data was analyzed by GraphPad Prism and Sigma Stat 3.5 software. Genotypes frequencies at *TNF*-α-238 and -308 loci were not statistically different between patients and controls. In contrast, distribution of genotypes at the 1858 position of PTPN22 was significantly different, due to higher frequency of gain-of-function gene variants in patients than controls. Moreover, long term glucose regulation (based on HbA1c level) was significantly worse in patients with the risk *TNF*-α-308A allele than in patients with non-risk (G) allele. However, patients with the risk allele of both genes (*TNF*-α-308A and *PTPN22* 1858T) had the worst glycemic control, suggesting that those two work synergistically. In conclusion, in a cohort from Bosnia and Herzegovina *TNF*–α-308A allele is significantly associated with the worse long-term glucose control, but *PTPN22* 1858T allele is significantly associated with diabetes development.

Keywords: *Polymorphism • Autoimmunity • Cytokine*

1. Introduction

Type 1 *Diabetes mellitus* (T1DM) is an autoimmune disease whose complex etiology is not completely understood. It is recognized to be caused by both genetic and environmental components. During T1DM pathogenesis macrophages and lymphocytes infiltrate the islets. Thereby, the intensity of the β-cell destructive process is modulated by the interaction of a large number of susceptibility genes and both known (nutritional factors and viral infection) and unknown environmental factors [1].

Activated macrophages produce proinflammmatory cytokines that can destroy pancreatic β-cells. Cytokines were therefore proposed as mediators of β-cell death *in vivo* [2], that is confirmed in NOD mice for TNF-α [3]. It was known that G-238A and G-308A SNPs in *TNF-α* promoter have a direct effect on transcriptional activity, where the A allele for both loci interprets high cytokine-producing variant. Genetically determined inter-individual variation in the production of this cytokine could predispose certain individuals with the risk genotype to develop T1DM [4].

The critical events leading to loss of T cell tolerance to pancreatic β-cells are still largely unknown. It seems that inefficient thymic negative selection increases the frequency of specific CD4+ and CD8+ T cells in the periphery, while a defective peripheral tolerance contributes to the expansion and differentiation of autoreactive Tcells [5]. Effector functions of T cells are regulated by the activation of intracellular signaling pathways in response to triggering of the T-cell receptor. Lymphoid-specific phosphatase (Lyp), encoded by the *PTPN22* gene, has direct role in setting thresholds for signaling through T-cell receptor. Thereby, the 1858T gene variant (not 1858C) is a gain-of-function form of the enzyme with significantly higher phosphatase

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