Mgr. Pavlína Čejková

MOLECULAR-GENETIC STUDY OF POLYGENIC DISEASES WITH A SPECIAL FOCUS ON DIABETES MELLITUS

Abstract

Polygenic diseases with complex mode of inheritance constitute an increasing public health burden. The aim of this study was to contribute to our current knowledge in genetic background of several complex diseases, namely enteropathy-type T-cell lymphoma, type 1 and type 2 diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis a psoriatic arthritis, in order to better understand the pathogenesis of the diseases with potential diagnostic, prognostic or therapeutic applications.

In the ETL, previously detected gain in chromosome band 9q was further narrowed down by microsatellite analysis to 9q34, and gDNA-based quantitative PCR confirmed amplification of both, *ABL1* and *NOTCH1*genes.

HLA genotyping of T1D manifested in childhood, adult-onset T1D and LADA showed partially different genetic predispositions. This finding points out a possible role of environmental factors that increases with age, and at least partly different immunogenetic etiology between autoimmune DM manifested in children and in adults.

Further, there is some evidence that T1D and LADA diabetes susceptibility may slightly differ as indicated by different frequencies of *HLA* and *NFKBIA* gene polymorphisms. This proposes some degree of heterogeneity among cases of autoimmune diabetes with adult onset.

Analysis of INS-VNTR (by mean of *INS* -23HphI A/T SNP) polymorphism revealed trait-based rather than disease-based association since A allele seems to be a risk factor for production of C-peptide (~ insulin) by β-cells of pancreas. Furthermore, it has been shown that IDDM1 and IDDM2 diabetic loci are independent risk factors.

It can be concluded that the progression of the three types of autoimmune diabetes (T1D in adults, T1D in children and LADA) is strongly influenced by different immunogenetic background and by impact of environmental factors modifying the ethiopathogenesis of diabetes.

The *PRL* -1149 G/T polymorphism did reveal an association with joint affliction in systemic lupus erythematosus and seems to play a role in pathogenesis of rheumatoid arthritis as documented by significantly increased heterozygote frequencies in RA patients.