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Enterovirus infection and low Treg function: two possible biomarkers of progression to autoimmune T1D

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Background and aims: Diabetes-related autoAbs, high-risk HLA-II haplotypes, and low first-phase insulin response are the main risk markers of progression to disease in siblings of T1D patients. Environmental factors may also play a critical role. T regulatory cells (Tregs) activity is commonly reduced in autoimmune disease.

Materials and methods: HLA typing, T1D-related autoAbs (IAA, GADA, IA-2A), enteroviruses (EV) in blood were determined in: one T1D patient with 14-years disease duration, his younger brother with long-standing T1D-related autoAbs, and 10 healthy controls. The two brothers shared the same high-risk HLA-II haplotypes. In all individuals the numbers and functionality of Tregs were determined. During a 3-years follow-up, the autoAb-positive brother showed a normal first-phase insulin response (90th percentile). $CD4^+$ CD25highCD127low Tregs in all subjects were evaluated by FACS, sorted, and cultured in vitro for functional analysis. RT-PCR assays targeting ≥100 EV types (5'UTR, 5'UTR-VP2, and 3D genome regions) were used for EV detection in blood.

Results: The diabetic child and his asymptomatic parents were carrying an EV of the B species in blood. The autoAb-positive brother and all healthy controls were EV-negative. Treg functionality was significantly reduced in the diabetic patient as compared to the autoAb-positive brother and the healthy controls.

Conclusions: These limited observations indicate that overt diabetes is associated with T1D-related autoAbs and, possibly, chronic EV infection. The diabetic child also showed reduced Treg functionality. Glucose homeostasis appeared to be conserved in the sibling showing T1D-related autoAbs but not carrying virus in blood. Normal Treg functionality seems associated with normal glucose homeostasis. Thus, serial determinations of EV biomarkers and Treg functions may be of value in predicting the progression to overt disease in siblings of children with T1D.

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Type 1 diabetes and juvenile idiophatic arthritis: a case report

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T1DM is an autoimmune disease initiated by the interaction between environmental and genetic factors, that cause loss of immunologic tolerance to self antigens. T1DM is a polygenic, common, complex disease with major susceptibility lying in the Major Histocompatibility Complex (MHC) on chromosome 6 with other smaller effects seen in loci non HLA-related. Autoimmune diseases cluster within families and individuals, but the aggregation with some type of disease is quite rare. Our case report consists of a girl affected by T1DM who developed juvenile idiophatic arthritis. Born at term (birth weight 2.9 kg) from the mother's third pregnancy, she came to our observation at age 22 months old. Mother was from Philippines. Family history was negative for autoimmune diseases. She was admitted to hospital with a severe DKA, (glycemia 29 mmol/l, pH 6.9, BE -28.6) and immediately put on insulin therapy. GAD antibody titer was elevated. After 2 months she reported pain at right knee with swelling and intra-articular inflammation and limited movement. The C reactive protein and C3 complement were normal. The erythrocyte sedimentation rate was slightly elevated. Serology for antinuclear factor was positive. Juvenile rheumatoid arthtritis was diagnosed and she started non steroid anti-inflammatory agents (ibuprofene) and then methotrexate administration with remission of the disease. HLA was: DRB1 08, 15. This complex is not usually associated with DM1 and Arthrtis, in Caucasian population. Other genetic association studies, using genome-wide scanning strategy, have not been investigated yet.

Conclusion: The clinical phenotype of an unusual association of autoimmune diseases (T1DM and JIA), with an unusual HLA class II genes may suggest that our knowledge about HLA genes and autoimmunity needs to be improved in the Asian population (mother was from Philippines). Unknown genetic factors might have some role in the clinical phenotype.

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ERBB3 associates with metabolic control after disease onset in children with type 1 diabetes

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Objectives: Genetic studies have identified more than 50 chromosomal regions that associate with type 1 diabetes (T1D). Whether the same regions also affect disease progression and metabolic control remains to be clarified. SNPs in genes with a presumed function in the β-cells are of particular interest. The aim was to investigate if specific SNPs associated with T1D could explain differences in metabolic control after disease onset in children diagnosed during childhood.

Methods: Blood samples were collected from 1074 children diagnosed with T1D before 11 years of age. DNA was extracted from whole blood on filter paper cards. Genotyping of *MHC*/rs2187668, *MHC*/rs7454108, *INS*/rs689, *PTPN22*/rs2476601, *IFIH1*/rs1990760, *ERBB3*/rs2292239 and *TNFAIP3*/rs2327832 was performed using TaqMan assays (ABI) on CFX384 real-time PCR system (BioRad). Genotypes were called using the SNPman software. The subjects were characterized for gender, age at diagnosis, diabetes duration, HbA1c, insulin dose and IDAA1c (calculated as HbA1c + 4 * insulin dose/kg/24 hours). Linear regression was used to test the association between metabolic control (HbA1c, insulin dose and IDAA1c) as dependent variables and SNP genotypes as descriptive variables.

Results: : rs2292239 was significantly associated with a lower IDAA1c ($P = 0.0067$) and a lower HbA1c ($P = 0.019$) in a recessive model corrected for gender, age at diagnosis and diabetes duration. None of the other SNPs had any effect on the metabolic control.

Conclusions: We have identified a risk SNP for T1D that associates with better metabolic control in children with childhood onset of disease. The candidate gene *ERBB3* has been shown to be down-regulated in human islets after cytokine stimulation, which indicates a functional role in the β-cells. Identification of SNPs that affect metabolic control could aid the