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Heredity as a Risk Factor for Diabetes Mellitus Type 2

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It is well known the fact that the etiopathogenesis of diabetes mellitus (DM) type 2 involves a number of risk factors. The most important of them are genetic predisposition, obesity and stress.

Purpose: The purpose of this study is to diagnose DM type 2 among subjects with certain diabetic heredity (DH) and to establish the risk of DH and kinship degree to develop DM type 2.

Methods: The study was conducted on a lot of 1458 subjects having DH, 570 males (39.09%) and 888 females (60.91%), with the mean age of 40.48± 13.58 years and BMI of 28.51±5.74 kg/m^2. The subjects have undergone an oral glucose tolerance test (OGTT) according to the WHO criteria. Most subjects had maternal (35.66%) and paternal (17.83%) DH.

Results: DM type 2 was diagnosed in 145 subjects (9.94%), impaired glucose tolerance (IGT) in 190 persons (13.03%), while 1123 persons (77.03%) had normal glucose tolerance. The risk of developing DM type 2 among subjects with DH was 3.42 times greater than in general population, while the risk of IGT was 3.37 times greater. The prevalence of DM among subjects with fraternal DH was 16.39%, in persons with maternal DH 11.15% and in subjects with paternal DH it was 8.46%. The greater the DH, the bigger the risk of developing DM. The prevalence of DM among the persons with both parents having DM was 19.05%.

Conclusions: These results confirm the role of heredity as a risk factor for developing DM. This risk is greater as the kinship degree is closer and as the DH is most important. That is why subjects with DH must perform yearly a screening for DM, at least by determining the fasting glycemia.

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A Study of Risk Factors for Type 1 Diabetes in 20 Belgian Multiplex Families

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Background and Aims: Type 1 diabetes mellitus results from selective destruction of insulin-secreting β-cells. Environmental factors (viruses, diet, maternal drug use), genetic susceptibility (HLA), and autoimmune factors (ICA, IAA) are involved in the pathogenesis. In order to detect differences in environmental, genetic and immune risk factors between diabetic and non-diabetic subjects, the members of 20 multiplex families were studied.

Subjects and Methods: A total of 48 diabetic (M/F:24/24) and 129 non-diabetic (M/F:67/62) members of 20 Belgian multiplex families were studied. The ICA and IAA status, the HLA DQ type, and the birth weight was determined in the subjects. Term and maternal age at delivery, maternal infections, diseases, alcohol and nicotin abuse, and drug use during pregnancy were recorded. Whether cow milk or breast feeding was given was also noted. Logistic regression analysis was used to determine independent risk factors for diabetes susceptibility.

Results: Diabetic subjects had a higher prevalence of ICA+ (35% vs 4%, p=0.003) and of IAA+ (88% vs 6%, p <0.0001) than non-diabetic family members. There was a negative association between the diabetic status and the HLA DQA1*0100-DQB1*0600 haplotype (p = 0.03, OR: 0.13). Birth weight, term and maternal age at delivery were similar between diabetic and non-diabetic family members. Also no differences were found between these 2 cohorts in the prevalence of maternal infections, diseases, alcohol or nicotin abuse during pregnancy. Cow milk or breast feeding did not seem to influence the later development of diabetes. We did find a negative association between the diabetic status and the use of vitamins or iron during pregnancy (p = 0.023, OR: 0.41).

Conclusion: The mode of inheritance of type 1 diabetes is complex. ICA and IAA positivity indicate the later development of diabetes, while the HLA DQA1*0100-DQB1*0600 haplotype seems protective. The use of vitamins or iron during pregnancy might play a role as well.

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Low Prevalence of IA-2 Antibody at Onset of Type 1 Diabetes in North Indian Subjects

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The prevalence of islet autoantibodies at the onset of type 1 diabetes varies widely in different racial groups. While islet antibody negative "idiopathic" type 1 diabetes forms < 10% of cases in white Caucasian patients, it may constitute a far greater proportion in other races. **Aims:** i) to determine the prevalence of antibodies to GAD (GADA), IA-2 (IA-2A) and cytoplasmic islet cell antibody (ICA) in recently diagnosed North Indian (Caucasian) subjects with type 1 diabetes ii) to compare the clinical features of islet antibody positive and "idiopathic" IDDM patients. **Materials and Methods:** Consecutive patients of type 1 diabetes of short duration were studied. GADA and IA-2A were detected by immunoprecipitation of ^{35}S-methionine labelled recombinant human antigen; ICA was detected by indirect immunofluorescence using human group O pancreas. **Results:** The prevalence of GADA, IA-2A and ICA in patients with duration <1 month and < 3 months is shown.

Duration	IA-2A	GADA	ICA	Any antibody
< 1 month	3/16 (19%)	9/16 (56%)	9/24 (37%)	9/16 (56%)
< 3 months	6/28 (21%)	16/28 (57%)	16/36 (44%)	18/28 (64%)

The prevalence of each of the 3 autoantibodies, and especially of IA-2A, was lower than that reported in white Caucasian patients with IDDM. Subjects with one or more autoantibody did not differ in their clinical features (age, age at onset of diabetes, body mass index, ketosis at onset, hemoglobin A1c) or prevalence of thyroid microsomal and parietal cell antibody, when compared with antibody negative patients. **Conclusions:** The prevalence of patients with IA-2A was far lower, while that of patients with "idiopathic" type 1 diabetes considerably greater, than that reported in white Caucasian IDDM subjects.

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Mutations of the Cystic Fibrosis Transmembrane Regulator Gene in Patients of Fibrocalculous Pancreatic Diabetes

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Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, which is unique to developing countries. It results from chronic pancreatitis unlinked to alcohol consumption. Its etiology is currently unclear but genetic susceptibility may be important. Mutations in the cystic fibrosis transmembrane regulator (CFTR) gene have been shown to predispose to idiopathic chronic pancreatitis (ICP) in white Caucasian patients. **Aim:** To study the role of mutations of the CFTR gene in patients with FCPD and tropical calcific pancreatitis (TCP). **Materials and Methods:** 18 patients (9 with FCPD, 9 with TCP) were studied. The CFTR gene mutations (promoter region, all 27 exons with flanking intron sequences, including the 5-thymidine variant (5T) of the polythymidine tract of intron 8) were detected by multiplex heteroduplex analysis and

direct sequencing. **Results:** Mutations were identified in 2 (11%) patients (both females, 1 with FCPD). The overall mutation frequency was 0.083, far lower than in ICP (0.24); among females it was 0.25, similar as in white subjects with ICP (0.20). One affected patient (onset of pain 8 years, diabetes at 25 years) was homozygous for the 5T variant (common in congenital bilateral absence of the vas deferens); the second patient (onset of pain 8 years) was heterozygous for the missense mutation R1070Q in exon 17b. Neither of the patients had evidence of sino-pulmonary dysfunction and except for an earlier age of onset of pain (8 years vs. 18.5 years) they had similar clinical features to other patients. **Conclusions:** Mutations of the CFTR gene may play a role in the etiology of some patients with FCPD.

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Serum Paraoxonase Enzyme Activities and Genetic Polymorphisms in Patients with Type 2 Diabetes

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Human serum paraoxonase (PON1) is associated with high-density lipoprotein (HDL) and inhibits the oxidation of low-density lipoprotein (LDL), suggesting that PON1 protects against atherosclerosis. We detected three polymorphisms of the PON1 gene, -108C/T (-108bp upstream ATG start codon), 55L/M and 192Q/R. We also investigated PON1 enzyme activities as paraoxonase (PON), arylesterase (ARYL) and diazoxonase (DIAZ), and serum PON1 concentration in 106 patients with type 2 diabetes and 161 control subjects.

All three enzyme activities and specific activities of PON1 in diabetic patients were significantly lower than those in controls, while there was no difference in serum PON1 concentration between the patient and control groups. The specific activities of PON, ARYL and DIAZ in patients were 6.82 ± 3.14 nmol/min/U (mean ± SD, U; unit for serum PON1 concentration), 4.77 ± 0.17 μmol/min/U and 193 ± 92 nmol/min/U, respectively, whereas those in controls were 9.33 ± 3.92 nmol/min/U, 5.36 ± 0.14 μmol/min/U and 242 ± 103 nmol/min/U, respectively. There was no significant difference in the allelic frequencies of -108C/T, 55L/M or 192Q/R between the patient and control groups. When each enzyme activity was compared between the patient and control groups in each genotype subgroup, all activities were lower in the patient group. The PON and ARYL activities were lower in patients with retinopathy or nephropathy than in those without such complications, and the ARYL activity was also lower in patients with neuropathy.

In conclusion, all specific enzyme activities of PON1 were lower in patients with type 2 diabetes independent of the -108C/T, 55L/M or 192Q/R polymorphism, and this impaired PON1 function may be involved in development of diabetic complications.

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Tumor Necrosis Factor-Alpha (TNFα)-308 (G to A) Gene Polymorphism in Chinese Subjects with Type 2 Diabetes

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TNFα provides an important link between obesity and insulin resistance. A polymorphism in the promoter region of the TNFα at the -308 (G to A) position has been shown to be associated with increased TNFα gene expression. We studied the TNFα-308 (G to A) gene polymorphism in 339 Hong Kong Chinese Type 2 diabetic patients and 202 age- and sex-matched normal subjects. The prevalence of the wild type (GG), heterozygous (AG) & homozygous genotypes (AA) in the diabetic patients were, respectively, 83.8%, 14.7% & 1.5%. These were similar to that in the normal subjects (84.7%, 15.3% & 0 respectively, all NS). With logistic regression analysis, no relationship was found between the -308A polymorphism and diabetic state. However, among the diabetic patients, body mass index was inversely correlated while glycated hemoglobin was positively correlated with the -308A homozygous genotype. When the newly diagnosed diabetic patients (duration of disease ¢G1 year) were compared with those who had been diagnosed for >1 year, the -308A homozygous genotype was all confined to the former group (2.8% Vs 0, $p<0.05$). Taken these findings together, we hypothesize that subjects with TNF-308 AA genotype may have increased lipolytic activity which aggravates insulin resistance that is already present in diabetic subjects, accompanied by weight loss and increased glycemia.

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Identification of a New Mutation in the Hepatocyte Nuclear Factor-1 α Gene in a Polish Family with Early Onset Type 2 Diabetes Mellitus

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Aims: Recently, several genes associated with early onset, autosomal dominant type 2 diabetes (MODY) have been described. Mutations in the HNF-1α gene seem to account for a substantial proportion of this type of diabetes in the U.K. population. However, the frequency of diabetes due to mutations in this gene in other populations is unknown. **Materials and Methods:** We identified 14 families with early onset, autosomal dominant type 2 diabetes to determine the frequency of mutations in the HNF-1α gene and their contribution to the development of diabetes in a Polish population. The 10 exons and promoter region of the gene were screened for sequence differences by direct sequencing of DNA from the probands of these families and from 96 unrelated non-diabetic individuals. **Results:** We detected several previously described polymorphisms that were also present in the non-diabetic controls. However, one sequence difference, a deletion of a cytosine in codon 225 in exon 3 (designated S225fdelC), was a new mutation resulting in a frame shift and synthesis of a nonsense peptide from amino acids 225 to 232 followed by stop codon. Thus, the mutation S225fdelC effectively caused the loss of a part of the DNA binding domain and the entire transactivation domain. This mutation was present in four affected members of the family. They developed diabetes at an early age (mean age at diagnosis 23y) and were characterized by severely impaired insulin secretion. One of the carriers developed psoriasis, which was probably not related to the HNF-1α mutation. We did not find other phenotypic abnormalities in the carriers. In addition, there was a diabetic family member who was not a S225fdelC carrier. He developed diabetes later in life and had a higher C-peptide level. **Conclusion:** We have identified a new HNF-1α mutation that represents the first MODY mutation identified in a Polish population. MODY3 mutations, including those in the exon 4 "hot spot", do not appear to be a very common cause of early onset autosomal dominant type 2 diabetes in the Polish population.

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Lack of Association between Genetic Variation in the Uncoupling Protein-1 Gene and Gestational Diabetes Mellitus

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Uncoupling protein-1 (UCP-1) is a specific protein uncouples proton trans-