

Excess of Maternal Transmission of Type 2 Diabetes: Is there a Role of Biochemical Genetic Polymorphism?

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ABSTRACT

Objective: An excess of maternal transmission of Type 2 diabetes (T2D) has been reported in some populations but not confirmed in other studies. Mitochondrial inheritance has been proposed to explain such excess. In the present paper, we have considered the presence of T2D in the mother and/or in the father in relation to the risk of T2D and to age at onset of the disease in the offspring. The distribution of two genetic polymorphisms involved in glucose metabolism in relation to the presence of T2D in the mother has been also considered. **Materials and Methods:** Two hundred and seventy-nine participants with T2D were studied in the population of Penne, a small rural town in the eastern side of central Italy. Adenosine deaminase locus 1 (ADA₁) and phosphoglucomutase locus 1 (PGM₁) phenotypes were determined by starch gel electrophoresis. Statistical analyses were carried out using commercial software (SPSS). **Results:** The proportion of patients from T2D mothers is much greater as compared to the proportion of the patients from T2D fathers ($P < 0.0001$). Age at onset of the disease in patients in whom one or both parents are T2D is lower as compared to other patients. The distribution of ADA₁ and PGM₁ phenotypes in participants with T2D depends on the presence of diabetes in the mother. **Conclusions:** About the transmission of T2D, our data confirm the high proportion of maternal T2D and show the role of two common biochemical polymorphisms involved in glucose metabolism.

Key words: Adenosine deaminase, fetal imprinting, maternal transmission, phosphoglucomutase, type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) is a heritable condition in which maternal and paternal diabetes confer risk to the offspring. Several studies suggest that the offspring of a mother with T2D is more likely to develop diabetes as compared to offspring of a father with T2D. Some studies, however, have not confirmed these results.^[1-6]

Mitochondrial heredity has been suggested as a possible factor explaining this maternal effect, but contrasting results have been obtained.^[7,8] The role of genetic factors acting during intrauterine life with possible effects on offspring metabolism has been scarcely investigated.

In the present paper, we have considered the presence of T2D in the mother and/or in the father in relation to the risk of T2D and to age at onset of the disease. Moreover, we have studied the distribution of two genetic factors involved in glucose metabolism: Phosphoglucomutase locus 1 (PGM₁) and adenosine deaminase locus 1 (ADA₁) in relation to the presence/absence of a mother with T2D.

Genetic polymorphism of adenosine deaminase locus₁ (ADA₁)

ADA is a polymorphic enzyme present in all mammalian tissue.^[9] It is encoded by a locus with two codominant alleles ADA₁*1 and ADA₁*2 located on the long arm of chromosome 20 that is associated with increase enzymatic activity in the

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order: ADA₁*1 > ADA₁*2. ADA catalyzes the irreversible deamination of adenosine to inosine exerting an important role in the regulation of adenosine concentration in body fluids.

Adenosine, a purine nucleoside present in plasma and in other extracellular fluids, is an important local hormone. Current interest is focused on a wide variety of effects produced by adenosine through activation of cell surface adenosine receptors. Adenosine counteracts the action of insulin in the liver by activation of A2D receptors. On adipocyte, adenosine seems to facilitate insulin's action.^[10-13]

Genetic polymorphism of PGM

PGM is a widely distributed enzyme that catalyzes the reversible reaction glucose 1 phosphate ↔ glucose 6 phosphate. Four separate loci determine distinct sets of PGM isozymes: PGM₁, PGM₂, PGM₃, and PGM₄.^[14-17] About 85–95% of total PGM activity is determined by the PGM₁ locus which shows an electrophoretic polymorphism determined by the occurrence of two codominant alleles: PGM₁*1 and PGM₁*2 at a locus on the short arm of chromosome 1. The activity associated with PGM₁*2 is higher than with PGM₁*1. Pak1 (P-21 activated kinase) binds to phosphorylates and enhances the enzymatic activity of PGM₁.^[18]

MATERIALS AND METHODS

We have reexamined the clinical records of 279 participants with T2D from the population of Penne considered in a previous study.^[19] These patients are a random sample from a population of about 2000 participants with T2D under care at the Center of Diabetology of the local Hospital. Penne is a small rural town located in Easter side of Central Italy. The people are the descendants of an old Italic population called “Vestini.”

ADA₁*1 and PGM₁*1 phenotypes were determined by starch gel electrophoresis according to Spencer *et al.*^[9,13] There are three PGM₁ phenotypes: PGM₁*1, PGM₁*2/*1, and PGM₁*2 and three ADA₁ phenotypes: ADA₁*1, ADA₁*2/*1, and ADA₁*2.

Chi-square test of independence, variance analysis, and discriminant analysis were carried out by SPSS programs.^[20] The number of participants is not the same in all tables due to random missing values of the variables considered.

The study was approved by the Sanitary Direction of the Hospital, and informed consent was obtained from all patients.

RESULTS

Table 1 shows the proportion of patients with T2D in relation to the presence of this disease in the mother or in the father.

The proportion of patients with only the mother affected by T2D is greater as compared to the proportion of patients with only the father affected by T2D ($P < 0.0001$).

Table 2 shows the age at the onset of diabetes in relation to parental presence of diabetes. The age at onset of diabetes in the offspring whose the parents are not affected by T2D is greater than that of offspring whose the mother only is affected ($P = 0.000$) or whose mother and father are affected ($P = 0.008$).

Table 3 shows the distribution of ADA₁ and PGM₁ phenotypes in T2D patients in relation to the presence of T2D in the mother. In patients with a mother affected by T2D, the proportion of carriers of ADA₁*2 allele is lower as compared to other patients (11.2% vs. 20.0%). This difference is very marked among females (3.6% vs. 19.5%; $P = 0.04$) while is absent in males (19.2% vs. 20.6%; data not shown). In patients with a mother affected by T2D, the proportion of carriers of PGM₁*2 allele is lower compared to other patients (33.3% vs. 50.2%; $P = 0.035$). The pattern is similar in males and in females (data not shown).

We have also considered a possible effect of maternal diabetes on other variables. No effect was detected on sex ratio and on body mass index of the offspring. A tendency to a lower frequency of dyslipidemia and a tendency to higher values of glycemia and glycosylated Hgb were observed in patients with a mother affected by T2D.

DISCUSSION

The present study suggests a strong maternal effect on susceptibility to T2D in the population of Penne. Early onset of T2D in the offspring has been observed in the presence of T2D in one parent. In the offspring affected by T2D, the presence of T2D in the mother is associated with significant effects in the distribution of two genetic polymorphisms ADA₁ and PGM₁ involved in glucose metabolism.

Table 1: Percent proportion of participants with T2D with and without parental familiarity

Patients with T2D	Number of participants	Proportion (%)
Only mother with T2D	48	17.2
Only father with T2D	11	3.9
Mother and father with T2D	7	2.5
Mother and father without T2D	213	76.3
All participants	279	

Test of hypothesis that maternal familiarity=Paternal familiarity. $\chi^2=23.2$, $df=1$, $P<0.0001$. T2D: Type 2 diabetes

Table 2: The relationship between age at onset of T2D and parental familiarity

Patients with T2D	Mean (years)	SE	Number of participants
Only mother with T2D (a)	49.58	1.08	48
Only father with T2D (b)	49.27	3.34	11
Mother and father with T2D (c)	43.43	1.76	7
Mother and father without T2D (d)	56.25	0.77	208
All patients with T2D	54.47	0.66	274

Variance analysis $P=0.000$. Tukey test - (a vs. b) $P=1.000$, (a vs. c) $P=0.461$, (a vs. d) $P=0.000$, (b vs. c) $P=0.651$, (b vs. d) $P=0.135$, (c vs. d) $P=0.008$. T2D: Type 2 diabetes

Table 3: Distribution of ADA₁ and PGM₁ phenotypes in T2D patients according to the presence of T2D in the mother. Percent proportion in parenthesis

Patients with T2D		
ADA ₁	ADA ₁ ,1	ADA ₁ ,21
Mother with T2D	48	6 (11.1%)
Other	176	44 (20.0%)
Independence between the two groups $P=0.140$		
PGM ₁	PGM ₁ ,1	Carriers of PGM ₁ *2
Mother with T2D	34	17 (33.3%)
Other	103	104 (50.2%)
Independence between the two groups $P=0.035$		
Discriminant analysis		
Independent	ADA ₁ and PGM ₁ phenotypes	
Dependent	Mother with T2D versus mother without T2D	

Chi-square - $\chi^2=7.794$, $df=2$, $P=0.020$. Coefficients of discriminant function - PGM₁=0.843, ADA₁=0.527

An effect of parent T2D on the age at onset of disease has also been observed in other populations also.^[21]

Until recently, in Italian rural populations, avoiding undernourishment of newborns and children was the priority, and excess weight was considered as a sign of well-being. In the 1st year of life, nourishment is under maternal control resulting in a possible maternal cultural heredity for excess weight and a tendency to glucose intolerance due to excessive caloric intake.

A new aspect emerging from our study is the association with genetic factors involved in glucose metabolism. During intrauterine life, maternal genetic factors involved in glucose metabolism may give an imprinting upon the metabolism of offspring with relevant effects on susceptibility to T2D. This aspect has not yet received much attention; and further studies in this direction are warranted.

CONCLUSIONS

A high proportion of maternal transmission of T2D is confirmed in the population of Penne. The data suggest a role of adenosine deaminase and phosphoglucomutase in maternal transmission of T2D.

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