Rev. Brasil. Genet. 12, 2, 419-423 (1989)
(Brazil. J. Genetics)

DIABETES MELLITUS AND SOME GENETIC MARKERS

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ABSTRACT

The phenotypic distributions of some genetic markers [GLO, ESD, Hp, PGM, ABO, Rh] were studied in a sample of diabetes patients and in their normal relatives. A statistically significant association between the haptoglobin system and type II diabetes was detected. The relative risk of having type II diabetes was about 2.5 higher for Hp 2-2 individuals. However, since 12 tests of heterogeneity between groups were performed, it was expected that about one of them would be significant by chance alone. Therefore, the observed Hp association could be a result of a type I statistical error.

INTRODUCTION

A significant increase in the frequency of HLA-B8 and BW15 antigens in samples of type I diabetes patients as compared to normal controls was first observed by Nerup *et al.* (1974) and Cudworth and Woodwrow (1975). These findings have stimulated the search for associations between this disease and genetic markers controlled by loci on chromosome 6 linked to the HLA system, such as glyoxalase I (GLO) and properdin factor B (Bf) (Kirk *et al.*, 1979; Moens *et al.*, 1980). While a significant association between diabetes type I and the F1 phenotype of the Bf system was detected (Kirk *et al.*, 1979; Raum *et al.*, 1979), the phenotypic distribution in the GLO system considering the normal and affected groups was similar (Kirk *et al.*, 1979;

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Moens *et al.*, 1980). In the type II patients the observed GLO phenotype distribution was not in Hardy-Weinberg equilibrium (Kirk *et al.*, 1979).

The present study is concerned with the associations between diabetes mellitus and some genetic polymorphic systems [glyoxalase I (GLO), haptoglobin (Hp), esterase D (ESD), phosphoglucomutase I (PGM1), ABO and Rh] in a sample of patients living in the area of São Carlos (São Paulo, Brazil).

SUBJECTS AND METHODS

The sample studied includes 14 type I and 55 type II diabetes patients attending a private clinic (LMCK). A total of 187 normal relatives, mainly patients' sibs and offspring, were invited to participate in the study and constitutes the control group.

From each individual, a sample of venous blood was collected for the laboratory analyses. ABO and Rh typing was performed by standard procedures. Starch gel electrophoresis was used to test the following systems: Hp (Smithies, 1955), ESD (Hopkinson *et al.*, 1973), GLO (Parr *et al.*, 1977), PGM1 and PGM2 (Spencer *et al.*, 1964), and CA 2 (Hopkinson *et al.*, 1974).

The statistical method developed by Woolf (1955) was applied to investigate the association between diabetes mellitus and the genetic polymorphisms.

RESULTS AND DISCUSSION

In this sample no variation was observed in the systems Carbonic Anhydrase 2 and Phosphoglucomutase 2, all the individuals showing the phenotypes CA2 1-1 and PGM2 1-1.

In Table I the phenotype distributions in the other systems are shown. These distributions do not depart significantly from that expected by the Hardy-Weinberg law. The Table also displays the gene frequencies for the whole sample. These are very similar to those found in other Brazilian populations (e.g. Franco *et al.*, 1981; Conceição *et al.*, 1987).

No significant differences in gene frequencies were observed between type I diabetes and the control group. This result is consistent with the suggestion of Kirk *et al.* (1979) and Moens *et al.* (1980), that the Glyoxalase I polymorphism appears to be unrelated to insulin dependent diabetes.

On the other hand, a statistically significant increase in the Hp 2-2 phenotype was found among the type II diabetes patients ($\chi^2 = 7.26$, 1 d.f.). The details of the analysis of association are shown in Table II, where it can be seen that the estimated relative risk of having type II diabetes is about 2.5 for Hp 2-2 individuals.

Tentatively, these results could be explained by some different hypotheses.

Table I - Phenotypic distributions of several genetic polymorphisms in type I and type II diabetes patients and normal controls.

Phenotype	Type 1	Type II	Controls
GLO 1-1	1	6	28
GLO 2-1	6	23	53
GLO 2-2	4	15	57
Hp 1-1	2	6	16
Hp 2-1	5	12	63
Hp 2-2	4	23	41
EsD 1-1	7	27	95
EsD 2-1	4	17	51
EsD 2-2	0	0	6
PGM1 1-1	6	23	75
PGM1 2-1	3	15	49
PGM1 2-2	2	5	13
O	7	21	64
A	4	27	52
B	1	5	16
AB	2	2	9
Rh+	9	43	115
Rh-	5	12	24

Gene	Frequencies	χ^2 goodness-of-fit (Hardy-Weinberg law)		DF
GLO*1	0.39	GLO	2.34	1
Hp*1	0.37	Hp	0.004	1
EsD*1	0.80	EsD	1.17	1
PGM1*1	0.72	PGM1	3.23	1
O	0.65	ABO	1.81	1
A	0.26			
Rh+ (D)	0.56			

Table II - Woolf's method applied to the study of association between Hp 2-2 phenotype and type II diabetes mellitus.

Diabetes mellitus		Control		Relative incidence
Hp 2-2 (h)	not Hp 2-2 (k)	Hp 2-2 (H)	not Hp 2-2 (K)	x = (hK)/(Hk)
23	18	41	79	2.46
Logarithm of x y = ln x		Weight of y w = 1/h + 1/k + 1/H = 1/K		χ^2 $\chi^2 = wy^2$
0.90		7.35		5.96

The first considers that the association is real and that allele 2 of the Hp system increases the susceptibility to diabetes type II. Alternatively, the association may not reflect susceptibility and is not due to pleiotropy or linkage, but to a stratification of the population unrelated to susceptibility (Mayo, 1978).

Finally, it is worth emphazising that in this study 12 tests of heterogeneity between groups were performed, and at the 5% level, it was expected that about 1 of them should be significant by chance alone (12 x 0.05 = 0.6). For this reason we must also consider the hypothesis that these results could be taken as a type I statistical error.

ACKNOWLEDGMENTS

This research was partially supported by CNPq (40.3140/82) and FAPESP (81/0805).

RESUMO

Foram estudadas as distribuições fenotípicas de alguns marcadores genéticos (GLO, ESD, Hp, ABO, Rh) em uma amostra de diabéticos e seus parentes normais. Foi detectada associação significante entre diabetes do tipo II e fenótipo 2-2 do sistema Hp. O risco relativo de ter diabetes foi de 2,5 para os indivíduos 2-2. Todavia, dado o número de testes de heterogeneidade entre grupos efetuados, esperar-se-ia que cerca de 1 deles fosse estatisticamente significante devido ao acaso. Nesse sentido nossos resultados poderiam ser considerados como um erro estatístico do tipo I.

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(Received September 9, 1988)