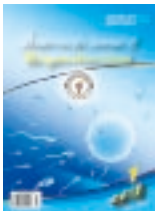

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Genetic polymorphism and natural fertility in women

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ABSTRACT

Objective: To investigate the cooperative interaction among five genetic systems (phosphoglucomutase locus 1, adenosine deaminase locus 1, acid phosphatase locus 1, adenylate kinase locus 1, and haptoglobin) concerning their effects on natural fertility in humans. Natural fertility has been evaluated by a model of age related differences between the distributions of types among pregnant women. **Methods:** A total of 137 nonsmoking consecutive puerperaes from the white population who had delivered their first born baby in the Maternity Department of S. Massimo Hospital of Penne were studied. The phenotypes of the five systems studied were determined by starch gel electrophoresis. Statistical analysis was performed using the statistical package for the social science. **Results:** There was a highly significant negative correlation between maternal age and the number of genetic factors showing a lower maternal age at the birth of the first child, which suggested a positive cooperative interaction among these factors concerning their effects on fertility. **Conclusions:** In the relationship of mother-fetus, besides nutritional factors, genetic factors involved in immunological interaction of the embryo with the mother are of paramount importance. Haptoglobin and adenosine deaminase locus 1 polymorphisms are involved in immune reactions and our data indicate that genetic variability within these systems gives a more important contribution to variation of human fertility as compared to acid phosphatase locus 1, phosphoglucomutase locus 1 and adenylate kinase locus 1 that are mainly involved in metabolic functions.

1. Introduction

Previous studies have shown an association of natural fertility with haptoglobin (Hp), phosphoglucomutase locus 1 (PGM_1) and adenosine deaminase locus 1 (ADA_1) phenotypes[1-3]. We have investigated the cooperative interaction among these systems concerning their effects on fertility. Acid phosphatase locus 1 (ACP_1) and adenylate kinase locus 1 (Ak_1) genetic polymorphisms have been also considered.

Natural fertility has been evaluated by the model of age related differences between the distribution of types among pregnant women proposed by Gimerfalb and Bottini[3]. According to this model, types that have a higher natural fertility should be over represented among pregnant women of younger age as compared to types with a lower natural fertility. In the present analysis, smoking

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women have been excluded and only women who have delivered their first live born infant have been considered. Nonsmoking women only have been included. Hp*1/*1 and ADA_1*1/*1 show a consistent reduction of maternal age as compared to carriers of Hp*2 and ADA_1*2 alleles respectively. Intermediate reduction of maternal age is observed for ACP_1 *B/*B and ACP_1 *A/*C phenotypes as compared to other ACP_1 phenotypes. The lowest difference is observed for Ak_1*1/*1 compared to carriers of Ak_1*2 allele and for carriers for PGM_1*1 allele as compared to PGM_1*2/*2 genotype.

1.1. Hp genetic polymorphism

Hp is a genetic polymorphism showing three phenotypes (Hp*1/*1, Hp*1/*2, Hp*2/*2). In consideration of its anti-inflammatory and immunomodulatory properties[4,5], it may be involved in human reproduction[6]. Hp*1/*1 is composed of small polymers that may diffuse more readily[7] explaining the greater natural fertility of Hp*1/*1 women as compared to women carrying the Hp*2 allele[2].

1.2. ADA_1 genetic polymorphism

The genetic polymorphism of ADA_1 is due to two codominant alleles (ADA_1*1 and ADA_1*2[8]. ADA_1 deaminates irreversibly adenosine to inosine. Adenosine regulates many physiological function including immune interactions. In the liver, adenosine counteracts insulin action[9] while in adipocyte it facilitates this action. Since ADA_1*1 is more active than ADA_1*2, this may influence adenosine concentration and in turn maternal-fetal immunological interactions.

1.3. ACP_1 genetic polymorphism

The genetic polymorphism of ACP_1 is due to the presence of three alleles at an autosomal locus[10]. The three alleles have an activity decreasing in the order ACP_1*C>ACP_1*B>ACP_1*A[10]. The enzyme regulates flavo-enzyme activity, energy metabolism, glycolytic rate and cellular growth[11,12]. There are strong differences in enzymatic activity among genotypes pointing to an important role in many cellular functions. *A/*A and *A/*B genotypes show a low enzymatic activity while *B/*C genotype shows a high activity, *B/*B and *A/*C show an intermediate activity.

1.4. PGM_1 genetic polymorphism

The enzyme catalyzes the reversible reaction glucose 1 phosphate glucose 6 phosphate. PGM_1 shows a polymorphism due to the presence of two codominant alleles at an autosomal locus with activity increasing in the order PGM_1*1 < PGM_1*2[13,14]. The central role in glycide metabolism, the organ specificity and the presence of the polymorphism in all human populations suggest an important role of the enzyme in tissue functions and that may have an important role in intrauterine development.

1.5. Ak_1 genetic polymorphism

The enzyme catalyzes the reversible reaction ATP+AMP$\longleftrightarrow$ADP with an important role in the synthesis of DNA and RNA[15]. AK_1 shows a polymorphism due to the presence of two common alleles at an autosomal locus with enzymatic activity decreasing in the order AK_1*1>Ak_1*2 [16].

2. Materials and methods

A total of 137 nonsmoking consecutive puerperaes from the White population who had delivered their first born baby in the Maternity Department of S. Massimo Hospital of Penne were studied. Verbal informed consent was obtained from these women to participate to the study that was approved by the Sanitary Direction of the Hospital. The data were collected a few years ago before the institution of an Ethical Committee. Nonsmoking women only have been included. The phenotypes of the five genetic systems were determined by starch gel electrophoresis[2,8,10,13,16].

Correlation analysis and eta (η) statistics were performed using the Statistical Package for the Social Science (SPSS). Eta statistics is a measure of the strength of association: η^2 measures the proportion of variance of dependent variable explained by the independent variable.

3. Results

Table 1 showed maternal age at delivery of the first child in relation to the phenotype of Hp, ADA_1, Ak_1, PGM_1 and ACP_1 genetic polymorphisms. Hp*1/*1 and ADA_1*1/*1 showed a consistent reduction of maternal age as compared to carriers of Hp*2 and ADA_1*2 alleles respectively. Intermediate reduction of maternal age was observed for ACP_1 *B/*B and ACP_1 *A/*C genotypes as compared to other ACP_1 phenotypes. The lowest difference was observed for Ak_1*1/*1 compared to carriers of Ak_1*2 allele and for carriers for PGM_1*1 allele as compared to PGM_1*2/*2 genotype.

Table 1
Maternal age at delivery of the first child in relation to phenotype of Hp, ADA_1, Ak_1, PGM_1, ACP_1 genetic polymorphisms.

Polymorphism	Phenotype	Maternal age	Number of women
Hp	*1/*1	23.6±1.0	18
	*1/*2 and *2/*2	26.2±0.5	119
ADA_1	*1/*1	25.5±0.4	118
	*2/*1	28.2±1.2	19
Ak_1	*1/*1	25.8±0.4	125
	*2/*1	26.6±1.1	12
PGM_1	*1/*1 and *1/*2	25.8±0.5	114
	*2/*2	26.6±0.9	23
ACP_1	*B/*B and *A/*C	24.9±0.6	57
	*A/*A,*A/*B and *C/*B	26.4±0.6	80

Non smoking mothers are included.

We have examined the relationship between the number of genetic factors associated with early reproduction and maternal age at first delivery considering only Hp and ADA_1. There was a highly significant negative correlation between the number of genetic factors associated with early reproduction and maternal age (correlation coefficient=-0.23, P=0.007; η^2=0.05) suggesting a positive cooperative interaction between the two genetic factors concerning their effects on fertility.

Considering all the five genetic factors studied, there was also a high significant negative correlation between the number of factors and maternal age at delivery of the first child. Compared to the analysis with two factors, the correlation coefficient was higher (-0.28 *vs*. -0.23) and the proportion of the variance of age explained by the number of factors was higher (0.08 *vs*. 0.05).

4. Discussion

As stated by Gimelfarb and Bottini[3] considering for example women with type A and women with type B, in absence of limiting factors except natural selection if type A is more fertile than type B, type A will produce more children and faster than type B. Assuming that there is a limit to this number and both types have the same limit, type A will reach such limit faster than type B. Therefore, the difference in the distribution of types among puerperae of different ages could represent an index of maternal selection at reproductive level.

Our analysis suggests an additive action of the genetic factors examined in female natural fertility suggesting that natural fertility depends on many genetic factors, each one with a relatively small effect. It is likely that environmental factors also play an important role

In the mother-fetus relationship, besides nutritional factors, genetic factors involved in immunological interaction of the embryo with the mother are of paramount importance since the first steps of zygote implantation. Hp and ADA_1 polymorphisms are involved in immune reaction and our data indicate that genetic variability within these systems gives the most important contribution to variation of human fertility. ACP_1, PGM_1 and Ak_1 are mainly involved in metabolic functions and our data suggest a less important contribution to variation of human fertility.

The relatively low number of women examined represents a limitation of this study. If confirmed in other clinical settings, the results could have practical importance in the prediction of success in assisted reproduction.

Conflict of interest statement

The authors declare that there was no conflict of interest.

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