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Short Communication

Biochemical Enzyme Polymorphism and Birth Weight: Evidence of Cooperative Effect

Gloria-Bottini F*, Neri A, Magrini A, and Bottini E

Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy

***Corresponding author**

Fulvia Gloria-Bottini, Department of Biomedicine and Prevention, University of Tor Vergata, Via Montpellier, 100133 Rome, Italy, Tel: 0630889514; Email: gloria@med.uniroma2.it

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Abstract

The purpose of our study is to identify the fetal genetic factors contributing to birth weight (BW) and their possible cooperative interactions. We have reexamined our data on four genetic systems previously studied Acid Phosphatase locus 1 (ACP1), Phosphoglucomutae locus 1 (PGM1), Adenosine Deaminase (ADA1), Adenilate Kinase locus 1 (Ak1 concerning their effects on BW)

Two hundred forty five newborn infants from the White population of Rome and 343 newborns from the White population of Penne delivered by healthy nonsmoking mothers have been considered. Enzyme phenotypes were determined by starch gel electrophoresis.

Marked differences concerning BW are observed between phenotypes of Ak1 in both Rome and Penne. For other markers a BW difference between genotypes is less marked and shows variability between the two populations but are always in the same direction. In both populations, in infants from nonsmoking mothers, there is a positive correlation between the number of genetic factors and BW.A linear positive correlation is observed between the number of factors and the proportion of infants with a BW greater than the 90thpercentile.The correlation is observed in infants with gestational length > 38 weeks only. In infants from smoking mothers there is no significant correlation

The results are in line with the hypothesis that BW is influenced by a great number of genetic factors each with small effect and that there is a cooperative interaction between these factors.

INTRODUCTION

In the last decades our group has investigated the role of biochemical enzyme polymorphisms on intrauterine development [1-6]. In the present note we have reexamined our data to search for a possible cooperative interaction among the genetic systems studied concerning their effects on birth weight (BW). Four enzyme polymorphisms involved in metabolic functions have been considered: Acid Phospatase locus 1 (ACP_1), Phosphoglucomutase locus 1 (PGM_1), Adenylate Kinase locus 1 (Ak_1) and Adenosine Deaminaselocus 1 (ADA_1).

We have studied two Italian populations : Rome and Penne. The population of Rome is urban and it is a mixture of people from all regions of Italy. The population of Penne is descendant from an old Italian population called Vestini and there has been no important intermixture with other populations. Agriculture is the main activity of this population.

ACP_1 genetic polymorphism

ACP_1 is an autosomal locus which encodes for cytosolic Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP). It shows three common alleles with activity decreasing in the order ACP_1*C > ACP_1*B>ACP_1*A [7]. As flavin mononucleotide phosphatase, the enzyme regulates the concentration of flavinadenine dinucleotide, flavo enzyme activity and energy metabolism. As phosphotyrosine phosphatase cLMWPTP regulates cellular growth and glycolytic rate controlling the activity of insulin receptor and the phosphorylation of Band 3 protein (B3P) [8,9]. *A/*A and *A/*B genotypes show a low enzymatic activity and this may favor glucose metabolism through an enhancement of insulin action and through an increase of the phosphorylation of B3P.The strong differences in enzymatic activity among genotypes suggests that the enzyme has an important role in the variability of many cellular functions. This may have clinical relevance for susceptibility to diseases and to their evolution . This genetic variability may also influence intrauterine development. Indeed, we have observed an association of BW with ACP pedix genotypes [1,6].

PGM_1 genetic polymorphism

Phosphoglucomutase (PGM) catalyzes the reversible reaction glucose 1 phosphate ↔ glucose 6 phosphate. Four separate loci encode distinct sets of PGM isozymes: PGM_1, PGM_2, PGM_3 and PGM_4 (10-13). PGM_1 shows a polymorphism with two codominant alleles with activity increasing in the order: PGM_1*1 < PGM_1*2 [14]. PAK1 (p-21 activated kinase) phosphorylates

PGM_1 enhancing enzymatic activity [15]. The central role in glycide metabolism, the organ specificity of PGM isozymes, and the presence of polymorphism in all human population suggest that genetic variability of PGM is adapted to specific functions of tissues and may have an important role in diseases susceptibility and their clinical manifestations.PGM1 may also have a relevant functions during intrauterine development and we have previously shown a relationship with BW [3].

Ak_1 genetic polymorphism

Ak_1 catalyzes the reversible reaction ATP+AMP↔ADP and has an important role in the synthesis of nucleotides as well as of DNA and RNA [16]. Ak_1 locus is polymorphic and shows two common alleles with activity decreasing in the order Ak_1*1 > Ak_1*2 [17]. Ecto-Ak_1 modulates mucociliary clearance of respiratory mucosa through interaction with G-protein coupled P2Y receptors [18,19]. The enzyme has been also found in the endothelial cells of umbilical vein. The involvement of this enzyme in DNA and RNA synthesis suggests an important role in intrauterine development, indeed we have found a significant relationship between Ak_1 genotype and neonatal parameters [4].

ADA_1 genetic polymorphism

ADA_1 is a polymorphic enzyme present in all mammalian tissue [20]. The enzyme is encoded by an autosomal locus in the chromosome 20 with two codominant alleles with activity decreasing in the order ADA_1*1 > ADA_1*2. ADA catalyzes the deamination of adenosine to inosine contributing to the control of adenosine concentration in body fluids. Adenosine is an important local hormone that regulates many physiological functions. In the liver adenosine counteracts insulin action [21] while in adipocyte facilitates insulin action. Genetic variation of adenosine concentration may have an important role in intrauterine development through the regulation of glucose metabolism and maternal fetal immunological interactions. Recently it has been suggested that some aspects of ADA_1 action are similar to those of growth factors [22].We have observed a significant relationship between ADA polymorphism and neonatal parameters [5].

The aim of the present study is to identify the fetal genetic factors contributing to BW and their possible cooperative interactions

MATERIAL AND METHODS

Two hundred forty five consecutive newborn infants from the White population of Rome and 343 newborns from the White population of Penne delivered by healthy nonsmoking mothers have been studied. Birth weight (BW) was registered in the delivering room. BW percentile was evaluated for each class of gestational age according to tables for Italian population. Gestational age was estimated from the date of the last menstrual period and checked with the Dubowitz score.

The data were collected a few years ago before the establishment of Ethical Committee. Informed Consent was obtained by the mothers of newborns to participate in the study that was approved by the Council of Department.

ACP_1, PGM_1, Ak_1 and ADA_1 phenotypes were determined by starch gel electrophoresis according to the methods reported by Harris group [7,10,17,20].

Statistical analyses were performed according to SPSS programs [23].

Because of random missing in the determination of phenotypes the number of subjects is not the same for all genetic polymorphisms.

No statistically significant deviation from Hardy-Weinberg expectation have been observed.

RESULTS

Table (1) shows mean BW in relation to the phenotype of the four genetic systems examined. Marked differences are observed between phenotypes of Ak_1in both Rome and Penne. For other

Table 1: Birth weight in relation to Ak_1, ACP_1, ADA_1 and PGM_1 genetic polymorphisms of the newborn. Nonsmoking mothers.

	Rome			Penne		
Ak_1						
	Mean BW (grams)	**S.E.**	**N°**	**Mean BW (grams)**	**S.E.**	**N°**
*1/*1	3376.6	34.8	204	3360.5	24.9	324
*1/*2	3555.7	55.9	14	3490.0	93.4	19
	P=0.007			P=0.160		
ACP_1						
*A/*A + A/*B	3394.5	50.5	96	3384.6	40.6	151
Other genotypes	3321.2	52.4	129	3353.1	31.9	173
	P=0.200			P=0.550		
ADA_1						
*1/*1	3398.2	34.8	188	3382.3	26.7	288
*1/*2	3339.7	111.2	37	3297.2	57.3	54
	P=0.650			P0.190		
PGM_1						
*1/*1	3390.6	52.1	111	3435.4	38.5	167
*1/*2 +*2/*2	3346.7	48.3	121	3298.9	32.6	146
	P=0.420			P=0.007		

markers BW differences between genotypes shows a variability between the two populations but are always in the same direction.

Table (2) shows the relationship of BW with the number of genetic factors that favor intrauterine growth. In both populations there is a positive correlation that is more marked in Penne than in Rome.

We have also examined the effect of sex, maternal age and gestational age on the correlation of BW with the number of genetic factors. In infants from smoking mothers there is no significant correlation. In infants from nonsmoking mothers the correlation has the same behavior in males and females: in females, however, the correlation with BW is stronger as compared to males. The correlation with BW in mother aging ≥ 28 years is similar to that observed in younger mothers. The correlation is observed in infants with gestational length > 38 weeks only (data not shown).

The relationship between the number of genetic factors and percentile class of birth weight is depicted in figure (1). A linear positive correlation is observed between the number of factors and the proportion of infants with a BW greater than 90th percentile.

DISCUSSION

The present analysis suggests a cooperative interaction among metabolic enzymes polymorphisms concerning their effects on BW. No association has been found in newborns from smoking moders.

The effect of each factor is small and shows a variability between the two populations but it is always in the same direction for all phenotypes considered. Moreover, the factors show an additive effect in both populations. Therefore, the hypothesis that the association reported could be the effect of a mere sampling chance artifact appears unlikely.

Previous studies have evaluated the proportion of BW variance due to fetal and maternal genetic factors and that due to environmental factors. The purpose of our study was to attempt to identify the fetal factors contributing to BW. Our observations are in line with the hypothesis that BW is influenced by a great number of genetic factors each with a small effect and suggest a cooperative effect between these factors.

An interesting aspect emerging from the study is represented by the fact that the effect of the factors examined upon BW is evident in the last period of gestation only and not before 38 weeks.

The variability of the effect of phenotype on BW is more marked for ACP_1, ADA_1 and PGM_1 than for Ak_1. Since Ak_1 is involved in DNA and RNA synthesis while the other polymorphism are involved in glucose metabolism, the greater variability observed

Table 2: Additive effect of newborn Ak_1, ACP1, ADA_1 and PGM_1 genetic polymorphisms on birth weight in nonsmoking mothers.

Number of genetic factors	Rome			Penne		
	Mean BW (grams)	S.E.	N°	Mean BW (grams)	S.E.	N°
≤ 1	3330.8	48.0	85	3304.5	32.8	107
2	3409.6	50.5	91	3390.3	36.1	123
≥ 3	3436.9	78.1	42	3544.7	67.8	61
Linear correlation	P=0.110			P=0.000		

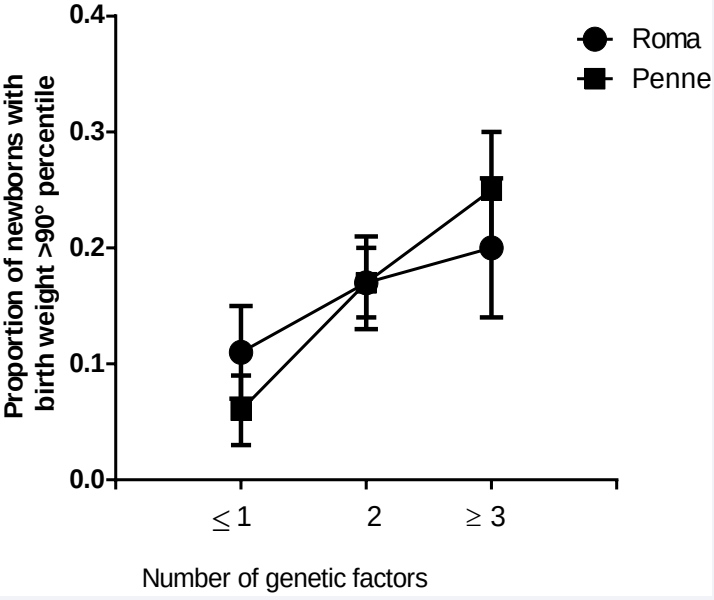

Figure 1 The rtealtionship between the number of genetic factors favouring intrauterine growth and the proporation of new borns with a BW>90° percentile. Linear correaltion: p=0.001.

for ACP_1, ADA_1 and PGM_1 phenotypes may be due to difference in alimentary factors between the two populations. This could be connected with the fact that the population of Penne is rural while the population of Rome lives in an urban environment.

The limitation of the study is represented by the relatively small number of the subjects examined.

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