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Effects of energy expenditure gene polymorphisms on obesity-related traits in obese children

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Summary
Objective: To assess the frequencies of common polymorphisms of genes associated with energy expenditure among Hungarian obese children and investigate their influences on obesity-related traits and metabolic complications of common childhood obesity.
Research methods and procedures: In a total of 528 obese children (age 13.2 ± 2.6 years) an oral glucose tolerance test and determination of fasting serum lipid levels were carried out, blood pressure and resting energy expenditure were measured and the children were genotyped for the following gene polymorphisms: Trp64Arg of β_3-adrenoreceptor (*ADRB3*), −3826 A/G of uncoupling protein (*UCP*)-*1*, exon 8 45 bp del/ins and −866 G/A of *UCP-2*, −55 C/T of *UCP-3*, and Pro12Ala of peroxisome-proliferator activated receptor gamma-2.
Results: Carriers of the *ADRB3* Arg64 allele had a significantly higher relative body weight and relative body mass index compared with non-carriers. The *UCP-2* exon 8 del/ins polymorphism was associated with higher degree of obesity, insulin resistance, dyslipideamia and lower adjusted metabolic rate. Children with *UCP-3* −55 T/T genotype had a significantly lower adjusted metabolic rate than the C allele carriers.

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Conclusion: We found evidence for associations between common polymorphisms of the *ADRB3*, the *UCP-2* and *UCP-3* genes and basic metabolic rate as well as level and metabolic consequences of common obesity among Hungarian school-aged children.

Introduction

Genes concerned with energy utilisation constitute one of the major groups of genes implicated in the polygenic background of common obesity and its metabolic complications. Replicated associations between genetic variants of the β_3-adrenoreceptor (*ADRB3*), the mitochondrial uncoupling proteins (*UCPs*) 1, 2 and 3, and the peroxisome proliferator-activated receptor-γ2 (*PPARG*) genes and obesity-related traits have been reported [1]. Functional variants of these important candidate obesity genes include the Trp64Arg polymorphism of *ADRB3* (rs4994), which was associated with decreased lipolytic sensitivity [2] and is one of the most firmly established obesity susceptibility gene polymorphisms. The G variant of the *UCP-1* −3826 A/G polymorphism (rs1800592) was related with reduced mRNA expression [3], and higher capacity of weight gain [4], while the A variant of the *UCP-2* −866 G/A polymorphism (rs659366) and the T variant of *UCP-3* −55 C/T polymorphism (rs1800849) were associated with enhanced transcriptional activity and lower BMI and risk of obesity [5—7]. The insertion variant of the *UCP-2* 45 bp exon 8 deletion/insertion (del/ins) polymorphism was proposed to result in reduced mRNA stability [5] and greater risk of developing obesity [8], and the Pro12Ala mutation of *PPARG* (rs1805192) was associated with reduced DNA binding and altered receptor activity [9].

The aim of our study was to assess the frequency of the above common polymorphisms of energy expenditure genes previously implicated in the development and metabolic complications of obesity among Hungarian obese school-aged children, and to investigate the influences of these genetic variants on obesity related traits and metabolic complications of obesity.

Patients and methods

Overweight or obese children ($n = 528$) aged 6—18 years, referred to the Obesity Center of the Department of Pediatrics, Medical Faculty, University of Pécs were included in the study. All participants underwent a detailed clinical examination aimed at determining the etiology and consequences of their obese state. Those with features to suggest rare metabolic or genetic conditions, endocrinological disorders, or growth problems were excluded. Children were classified as overweight or obese according to international cut-off BMI values for overweight or obesity by sex and age [10]. Written informed consent was obtained from all parents of the children before enrollment and the study was approved by the ethic review committee of the University of Pécs.

Examinations

Anthropometric measurements were carried out by the same investigator. Relative body weight and relative body mass index (BMI), calculated as the percent ratio between actual weight or BMI, respectively, and the ideal weight or BMI for age, gender and height were determined on the basis of Hungarian national standards [11]. Skinfold thicknesses were measured with a Holtain caliper and body fat was estimated using Slaughter et al. equations [12].

Fasting blood samples were collected, and a 2-h oral glucose tolerance test (OGTT) was performed with administration of the standard 1.75 g/kg (maximum 75 g) glucose. Definitions used for the obesity-related metabolic conditions were as follows: hyperinsulinaemia — fasting serum insulin >20 μU/mL (mean + 2SD value of 100 control Hungarian children) and/or postload peak serum insulin during OGTT >150 μU/mL [13]; impaired glucose regulation (IGR) — fasting blood glucose ≥5.6 mmol/L or 2-h blood glucose during OGTT ≥7.8 mmol/L (American Diabetes Association criteria); dyslipidaemia — high fasting triglyceride (>1.1 mmol/L [<10 years]; >1.5 mmol/L [>10 years]) or low fasting HDL-cholesterol (<0.9 mmol/L) concentration (criteria of the Hungarian Lipid Consensus Conference [14]); hypercholesterolaemia — total fasting cholesterol concentration >5.2 mmol/L [14]. Insulin resistance/sensitivity was estimated with the homeostasis model assessment (HOMA) index and the OGTT-derived whole body insulin