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FULL LENGTH ARTICLE

Obesity phenotype in relation to gene polymorphism among samples of Egyptian children and their mothers

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Abstract Obesity is complex heterogeneous disease controlled by genes, environmental factors, and their interaction. Genetic factors account for 40–90% of the body mass index variations. Body mass index (BMI) of children correlates more closely with maternal than paternal BMI. So, this studu was aimed to investigate the role of leptin receptor LEPR Gln223Arg, the uncoupling protein 2 (UCP2 G 866 A) and insulin receptor gene (INSR exon 17) polymorphisms in the pathogenesis of obesity. A cross-sectional study executed on 130 children and their obese mothers; classified into 2 groups according to their BMI. The 2 groups were evaluated regarding the anthropometry. Restriction fragment length analysis for LEPR Gln223Arg, UCP2 -866 G/A and INSR exon 17 polymorphisms were applied. It was reported that increased risk of obesity was found in LEPR AG + AA genotype and the A allele. Significant statistical difference was detected only in female children. Concerning UCP2, the AG followed by the GG genotype was the most frequent in all groups and the G allele was the mostly present in obese mothers and obese male children but with no statistical significance. There was difference in the INSR genotype and alleles between groups, but this difference was not statistically significant. This study concluded that the LEPR Gln223Arg, UCP2 G 866 A and INSR exon 17 polymorphisms are related to obesity in Egyptian population. Further researches on larger population are recommended to ascertain the implications of LEPR, UCP2 and INSR polymorphisms in obesity.

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Introduction

Obesity prevalence has increased all over the world as a pandemic.[1] Obesity is a multifactorial disease, controlled by genetic and environmental factors as well as the complex interactions among them. Approximately 118 candidate genes are associated with obesity.[2] Some of them are genes encoding leptin (LEP), leptin receptor (LEPR), uncoupling proteins (UCP) and insulin receptor (INSR) gene.

Body weight regulation and stability depends upon an axis with three interrelated components: food intake, energy expenditure and adiposeness.[3] The most important factor leptin; an endogenous hormone; decreases appetite and increases energetic consumption and insulin, with its peripheral regulating role.[4] Leptin controls lipid homeostasis effect by binding to leptin receptor (LEPR), belongs to class I cytokine receptor family. The long isoform LEPRb plays a key role in body weight regulation expressed in the hypothalamus.[5] It was reported that allele frequencies in the Gln223Arg variant of the LEPR gene are characterized by a significant population of origin effect.[6] Hence, LEPR Gln223Arg polymorphism may be expected to have more impact on risk of obesity in the developing countries with a much higher percentage of obese women as in Egypt.

Uncoupling proteins (UCP) is associated with energy and maintain fatty acid homeostasis. Uncoupling protein UCP2 is considered as candidate genes for obesity. This is due to reduce energy expenditure by increasing coupling of oxidative phosphorylation, thereby contributing to the development of obesity.[7] The most interesting polymorphisms in UCP2 gene is 866G/A (rs659366) in the promoter region. Development and progression of diabetes and obesity phenotypes are related by UCP2 $-866\ G > A$.[8]

Insulin resistance and obesity are interrelated.[9] Moreover, insulin resistance may occur secondary to resistance at the insulin receptor. Insulin receptors expressed in the brain were found to reduce food intake. The most important polymorphism for INSR gene is at exon 17 which is necessary for insulin signal transduction as it has been shown mutation in exon 17 of the INSR causes severe insulin resistance and hyperinsulinemia.[10]

The aim of the present study was to explore the role of leptin receptor LEPR Gln223Arg, uncoupling proteins UCP2 866G/A and insulin receptor INSR axon 17 polymorphisms; at genetic level; in the pathogenesis of obesity. Since a large proportion of adult obesity starts during childhood, the differences in genotype and allele frequencies in obese mothers and in juvenile obesity were examined.

Subjects and methods

Subjects

This study was derived from a cross-sectional survey through a project funded by National Research Centre (NRC) Egypt: entitled "Familiar Overweight and Obesity in Children and Adolescents: Diagnostic Clinical, Behavioral, Genetic and Biochemical Markers and Intervention" (10th Research Plan of the NRC); after taking approval from Ethical Committee of NRC (Registration Number is 13/168). It was carried in the "Medical Excellence Research Center (MERC)" through the period 2013–2016.

It included 130 children of both sexes (74 males and 56 females) and their mothers. All the mothers were obese; their BMI above 30 kg/m^2. While the children were classified into 2 groups according to their BMI: 32 obese children with BMI above 95th percentile (12 males and 20 females) and 98 normal weight children with BMI ranged between 15th and 85th percentiles (62 males and 36 females) according to the Egyptian Standard Growth Curves[11] for corresponding age and sex. According to the child BMI, the mothers were reclassified into 2 groups: group I included obese mothers and their children are obese (32 mothers), and group II included obese mothers and their children were of normal healthy weight (98 mothers).

The mothers were chosen randomly from all categories of the employee (at the National Research Centre (NRC)) and their relatives and neighbors. They participated in the study after signing a written informed consent form of the Medical Ethical Committee of NRC. The age range of the children was 5–18 years with a mean age $10.83 + 3.82$. All participants were informed about the purpose of the study and their permission in the form of written consent was obtained.

Methods

Anthropometric measurements including weight, height, and body mass index (BMI) of all the children and their mothers were conducted; in addition to the genetic analysis.

Anthropometric measurements

Weight was measured using a commercial scale (Seca Scale, Germany) with accuracy up to nearest 100 g. The subjects were asked to remove their footwear and wear minimal clothes before weighing them. Standing body height was measured, to the nearest 0.1 cm by using Holtain Stadiometer with the shoulder in a relaxed position and arms hanging freely and without shoes. The scales were recalibrated after each measurement following the recommendations of the International Biological Program.[12] Body Mass Index (BMI) was calculated as body weight in kilograms/height in meter^2. Children BMI percentile was calculated according to their age and sex based on the Egyptian Growth Reference Charts.[11] A child with BMI below 85th percentile was considered healthy weight, with BMI between 85th and 95th percentile overweight and those with BMI $\geq$95th percentile obese. While mothers with BMI below 25 kg/m^2 were considered healthy weight, with $25 \leq$ BMI ≤ 29.9 kg/m^2 overweight and with BMI $\geq$30 kg/m^2 were considered obese.

Genetic analysis

DNA extraction and genotyping. Genomic DNA was extracted from peripheral blood by using DNA extraction and purification kit (Qiagen) according to the manufacturer's protocol. The concentration of genomic DNA was determined by the quantitative method based on the

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