The Relation between Childhood Obesity and MC4R Gene and Near MC4R Polymorphisms

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ABSTRACT

Childhood obesity, especially in the developed countries including all over the world has an increasing prevalence. Regarding the major impact on public health perspective, childhood obesity should be monitored closely. Many researchers reported MC4R gene and near MC4R region polymorphisms to predispose monogenic obesity both in children and adults. In this study we investigated the relation between childhood obesity and Ser58Cys, Val50Met, Ile102Ser, Val103Ile, Asn274Ser, rs17782313 and rs17700633 polymorphisms in MC4R gene and near MC4R region in the Turkish population. It is very important to detect single gene disorders that may cause childhood obesity in order to screen children for the predisposition of obesity, as to protect them from environmental factors that may cause weight gain.

Key Words: Childhood obesity, MC4R, polymorphism, PCR, RFLP

Anahtar Sözcükler: Çocukluk çağı obezitesi, MC4R, polimorfizm, PCR, RFLP

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ÖZET

Çocukluk çağı obezitesinin, özellikle de tüm dünyada gelişmiş ülkelerde yaygın olduğu artmaktadır. Halk sağlığı perspektifi üzerindeki ana etki göz önüne alındığında, çocuklukta obezite yakından izlenmelidir. Birçoar araştırmacı, hem çocuklarda hem de yetişkinlerde monogenik obeziteyi belirlemek için MC4R genini ve MC4R bölgesi polimorfizmelerini bildirmiştir. Bu çalışmada Türk popülasyonunda MC4R geninde ve MC4R bölgesinde çocukluk çağı obezitesi ile Ser58Cys, Val50Met, Ile102Ser, Val103Ile, Asn274Ser, rs17782313 ve rs17700633 polimorfizmaları arasındaki ilişki araştırıldı. Çocukları obezite yetkinliğine karşı taramak ve onları kilo alımına neden olabilecek çevresel faktörlerden korumak için çocuklukta obeziteye neden olabilecek tek gen hastalıklarının tespit edilmesi çok önemlidir.

Anahtar Sözcükler: Çocukluk çağı obezitesi, MC4R, polimorfizm, PCR, RFLP

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INTRODUCTION

Obesity or being overweight is a major nutritional problem affecting 25% to 30% of the children and adolescents (1). Childhood obesity has an increasing prevalence especially in the developed countries (2). In addition, in many countries, childhood obesity is a powerful risk factor for type II diabetes (3).

The most common cause of monogenic obesity has been associated with the alterations in the melanocortin 4 receptor in humans (4,5). The melanocortin 4 receptor (MC4R) gene mutations was reported to be cause of autosomal dominant obesity in 1998 for the first time. The MC4R mutation prevalence in obese children and obese adults revealed 0.5 % and 6% respectively. So, it has been reported to be the most common monogenic cause of obesity(4).

Several investigators have identified various mutations in MC4R gene. Gotoda et al. reported Val103Ile mutation for the first time(6). Farooqi et al. have also found other mutations in MC4R gene(5). In a study conducted in Turkey, Mergen et al reported Asn274Ser mutation for the first time(7). Furthermore, the rs17782313 and rs17700633 polymorphisms near MC4R region were currently found to be related with monogenic obesity. Besides, these polymorphisms were reported to be associated with insulin resistance and low HDL levels (8).

In this study, the relation between childhood obesity and Ser58Cys, Val50Met, Ile102Ser, Val103Ile, Asn274Ser, rs17782313 and rs17700633 polymorphisms in MC4R gene and near MC4R region in the Turkish population have been investigated.

MATERIAL and METHODS

Patients

In this study, 80 obese children aged between 1 and 18 years old, BMI higher than the 95th percentile followed by Pediatric Endocrinology Clinic between years 2006-2009 and 50 healthy children whose BMI were above the 85th percentile were included. The total cholesterol, LDL, LDL, triglyceride (TG), glucose, insulin and HOMA-IR levels were also measured in the obese group.

The genetic syndromes that can cause obesity, numerical and structural chromosomal disorder, endocrine disease which can cause obesity, and drug usage related with obesity were not included in this study. This study had been accepted by Local Ethical Committee of Gazi University Faculty of Medicine with a number of 412 in December 22, 2008. Five ml of blood samples were taken from all of the participants. DNA isolation was performed with high salt concentration method. PCR-RFLP technique was used for the Ser58Cys(A172T), Val50Met(G148A), Ile102Ser (T305G), Val103Ile (G307A), Asn274Ser (A821G), rs17782313 (T>C), and rs17700633 (G>A) polymorphisms analyses. In order to genotype the amplified PCR products Alu I was used for Ser58Cys; Bsu 36I was used for Val50Met; Bst I was used for Ile102Ser polymorphisms(9). Also, we used Hinc II for Val103Ile; P1e for Asn274Ser; Pvu II for rs17782313 and finally Ssp I for rs17700633 polymorphisms.

Data analysis was performed using SPSS (Statistical Package for Social Science) for Windows 11.5 program. Descriptive statistics for continuous variables were given as mean ± standard deviation or median (minimum-maximum) in the form of categorical variables, the number of cases were displayed as (%). Significant difference between the groups in terms of averages, and the median values are evaluated in terms of Student’s t test and Mann-Whitney U test respectively. The categorical variables, were examined with Pearson’s chi-square or Fisher’s exact tests. The genotypes were calculated with Hardy Weinberg equilibrium. A p value lower than 0.05 was considered to be statistically significant.

RESULTS

The demographic features of the subjects are shown in Table 1. There was no statistically significance between the obese and control group in terms of gender or age distribution (p> 0.05). The average body weight and height of obese patients and controls were 67.6 ± 22.8 kg, 150.5 ± 18.1 cm and 36.9 ± 16.3 kg, 143.9 ± 29.1 cm respectively (Table 1).

DISCUSSION

Metabolic diseases such as obesity, is the result of the interaction of a limited number of common genetic variants. Under certain environmental conditions, showing variable penetrance of the genes can contribute to obesity. In this respect, MC4R mutations, has been reported to have a potential role in the development of obesity(10).

Dubern et al. reported the Val50Met polymorphism to be the cause of monogenic obesity(9). Our study revealed that GA genotype of Val50Met, was higher in the control group than obese group (p<0.05). Also, the frequency of A allele was also found to be lower in the obese group (p<0.05).

Regarding Ser58Cys polymorphism, no significance relation was found between clinical and laboratory findings between the obese and control groups(9,11). We also did not find a relation between this polymorphism and total cholesterol, LDL, glucose, insulin and HOMA-IR levels in the obese group (p>0.05). However, the TT genotype of Ser58Cys polymorphism in the obese group was correlated with low TG and HDL levels (p<0.05).

However, there was also no significant relation had been reported between clinical and laboratory findings between the obese and control groups, regarding Ile102Ser polymorphism(9,13). We also did not find a relation between this polymorphism with the laboratory findings (p>0.05).

Gotada et al. reported Val103Ile polymorphism for the first time(6). Other studies did not find a relation between the obese and control groups regarding this polymorphism(12,13). We also did not determine this polymorphism in our study. Mergen et al. reported Asn274Ser polymorphism for the first time(7). Reinehr et al. did not find a relation between the obese and control groups regarding this polymorphism(14). In our study, this polymorphism had not been detected in obese and control groups. Q et al. reported the TC and CC genotypes of rs17782313 polymorphism to be associated with BMI and increased insulin resistance(8). Kring et al. have shown the relation between the A-allele of rs17700633 and C-allele of rs17782313 with increased body fat, increased BMI, lower HDL cholesterol levels and increased insulin levels(15).
The frequency of C-allele in rs17782313 polymorphism has been demonstrated to be increased in the children and adolescents with severe obesity (16). Our study was also consistent with literature, revealing the higher C-allele frequency of rs17782313 polymorphism in the obese group with respect to the control group (p<0.05). Also, the AA genotype of rs17700633 polymorphism in the obese group was correlated with high insulin and HOMA-IR levels (p<0.05).

This study is an original study as this is the first time to study 7 different polymorphisms in MC4R gene and near MC4R region in childhood obesity in Turkey. We found a relation between Ser58Cys, Ile102Ser, Asn274Ser and Val103Ile polymorphisms with childhood obesity in Turkey. However, we did not find a relation between Ser58Cys, Ile102Ser, Asn274Ser and Val103Ile polymorphisms with childhood obesity. Also the Val50Met was found to be lower in the obese group.

As a conclusion, MC4R gene and near MC4R polymorphisms lead to changes in energy intake and spending. So, it is very important to detect single gene disorders that may cause childhood obesity in order to screen children for the predisposition of obesity, as to protect them from environmental factors that may cause weight gain, also keeping away them from sedentary lifestyle.

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Conflict of interest
No conflict of interest was declared by the authors.

REFERENCES
1-Keller C, Stevens KR. Assessment, etiology, and intervention in obesity in children. Nurse Pract. 1996; 21: 31-36, 38, 41-42.
2-Martorell R, Kettle K, Hughes ML, Grummer-Stawn ML. Overweight and obesity in preschool children from developing countries. International Journal of Obesity 2000; 24:959-67.
3-Young TK, Dean HJ, Flett B, Wood-Steiman P. Childhood obesity in a population at high risk for type 2 diabetes. J. Pediatr. 2000;136:365-9.
4-List JF, Haberner JF. Defective melanocortin 4 receptors in hyperphagia and morbid obesity. N. Engl. J. Med. 2003;348:1160-3.
5-Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham, T, O’Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N. Engl. J. Med. 2003; 348: 1085–95.
6-Gotoda T, Scott J, Altman TJ. Molecular screening of the human melanocortin-4 receptor gene: Identification of a missense variant showing no association with obesity, plasma Glucose, or insulin Diabetologia 1997; 40:976-979.
7-Mergen M, Mergen H, Ozata M, Oner R, Oner C. A novel melanocortin 4 receptor (MC4R) gene mutation associated with morbid obesity. J. Clin. Endocrin. Met. 2001;86: 3448-51.
8-Qi L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. Human Molecular Genetics 2008;17:3502-8.
9-Dubern B, Clement K, Pellioux V, Froguel P, Girardet JP, Guy-grand B. Mutational analysis of melanocortin-4 receptor, agouti-related protein, and alpha-melanocyte-stimulating hormone genes in severely obese children. J. Ped. 2001;139:204-9.
10-Vasse C, Clement K, Durand E, Hercberg S, Guybrand B, Froguel P. Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity J. Clin. Invest. 2000; 105:253-62.
11-Yurtcu E, Yilmaz A, Ozkurt Z, Koluksa E, Yilmaz M, Keles H, et al. Melanocortin-4 receptor gene polymorphisms in obese patients. Biochem. Genet. 2009;47:295-300.
12-Farooqi IS, Yeo GSH, Keogh JM, Aminian S, Jebb SA, Butler G. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency J. Clin. Invest. 2000;106:271-9.
13- Hinney A, Schmidt A, Nottebom K, Heibült O, Becker I, Ziegler A et al. Several mutations in the melanocortin-4 receptor gene including a frameshift mutation associated with dominantly inherited obesity in humans. J. Clin. Endocrinol. Metab. 1999; 84:1483–6.
14-Reinehr T, Hebebrand J, Friedel S, Toschke MA, Brumm H, Biebermann H. Lifestyle Intervention in Obese Children With Variations in the Melanocortin 4 Receptor Gene. Obesity 2009:17;282-9.
15-Kring SI, Holst C, Toubro S, Astrup A, Hansen T, Pedersen O. Common variants near MC4R in relation to body fat, body fat distribution, metabolic traits and energy expenditure. International Journal of Obesity 2010;34:182-9.
16-Loos RIF, Lindgren CML, Li S, Wheeler F, Zhao JH, Prokopenko I. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nature Genetics 2008; 40:768-75.