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

Çocukluk Çağı Obezitesi ile MC4R Geni ve Yakın MC4R Polimorfizmleri Arasındaki İlişki

Ozgur Erkal[1, 2], Mehmet Ali Ergun[1], Mehmet Boyraz[3], Aysun Bideci[3], Peyami Cinaz[3]

[1]Gazi University Faculty of Medicine Department of Medical Genetics, Ankara, Turkey,
[2]Ministry of Health Antalya Education and Research Hospital, Department of Genetics, Antalya, Turkey,
[3]Gazi University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Turkey

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

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ÖZET

Çocukluk çağı obezitesinin, özellikle de tüm dünyada gelişmiş ülkelerde yaygınlığı artmaktadır. Halk sağlığı perspektifi üzerindeki ana etki göz önüne alındığında, çocuklukta obezite yakından izlenmelidir. Birçok araştırmacı, hem çocuklarda hem de yetişkinlerde monogenik obeziteyi belirlemek için MC4R genini ve MC4R bölgesi polimorfizmlerini bildirmiştir. Bu çalışmada Türk popülasyonunda MC4R geninde ve MC4R bölgesinde çocukluk çağı obezitesi ile Ser58Cys, Val50Met, Ile102Ser, Val103Ile, Asn274Ser, rs17782313 ve rs17700633 polimorfizmleri arasındaki ilişki araştırıldı. Çocukları obezite yatkınlığına 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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ORCID IDs: O.E. 0000-0003-1059-8774, M.A.E. 0000-0001-9696-0433, M.B. 0000-0002-4289-9128, A.B. 0000-0003-0302-414X, P.C.0000-0001-5942-1852

Address for Correspondence / Yazışma Adresi: Mehmet Ali Ergun, MD, PhD Department of Medical Genetics Gazi University Faculty of Medicine Besevler Ankara Turkey
E-Mail: aliergun@gazi.edu.tr

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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, HDL, 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; Bsr I was used for Ile102Ser polmorphisms(9). Also, we used Hinc II for Val103Ile; Ple I for Asn274Ser; PvuI for rs17782313 and finally SspI for rs17700633 polymorphisms.

Data analysis was perfomed 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).

Table 1. The demographic fetaures of obese and control groups.

Variables	Control group	Obese group	P
Age (years)	10.9±4.6	12.1±3.2	0.117
Sex M/F	29 (%58.0) / 21 (%42.0)	40 (%50.0) / 40 (%50.0)	0.374
Weight (kg)	36.9±16.3	67.6±22.8	-
Height (cm)	143.9±29.1	150.5±18.1	-
BMI	16.7±2.5	28.9±4.9	-

M: Male F:Female

Regarding Ser58Cys, Val50Met, Ile102Ser, Val103Ile, Asn274Ser, rs17782313 and rs17700633 polymorphisms; we found statistical significance only in Val50Met and rs17782313 in allele frequencies between obese and control groups. The Val50Met GA genotype was found to be higher in the control group than obese group (p□0.05). Regarding these polymorphisms and total cholesterol, HDL, LDL, TG, glucose, insulin ve HOMA-IR levels our positive findings are below:

The TT genotype of Ser58Cys polymorphism in the obese group was correlated with low TG and HDL levels (p□0.05). The AA genotype of Val50Met polymorphism in the obese group was correlated with low HDL level (p□0.05). The C allele frequency in rs17782313 polymorphism was higher in the obese group with respect to the control group. The AA genotype of rs17700633 polymorphism in the obese group was correlated with high insulin and HOMA-IR levels (p□0.05). We also found that 40.4% of the obese group was carrying both rs17782313 and rs17700633 polymorphisms (p<0.05).

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).

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 polymoprhism 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. Qi *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 in 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 in 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 rs17700633 and rs17782313 plymorphisms 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.

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