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ORIGINAL ARTICLE

Associations of the *ANKK1* and *DRD2* gene polymorphisms with overweight, obesity and hedonic hunger among women from the Northwest of Iran

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Abstract

Background Pleasure from palatable foods can stimulate hedonic eating and, therefore, might be a major culprit for obesity. Dopamine receptor polymorphisms, especially variants in the genes regulating the D2 receptor, including ANKK1 and DRD2, are the prime candidates for assessing the individual differences in hedonic eating. This study was carried out to investigate the possible associations of the T (rs1800497) and Del (rs1799732) alleles with body mass index (BMI) and hedonic hunger among Iranian Azeri women.

Methods A total of 372 healthy overweight/obese subjects (BMI ≥ 25 kg/m^2) and 159 normal weight individuals (BMI 18.5–24.9 kg/m^2) were genotyped for the polymorphisms of ANNK1 and DRD2 genes using PCR–RFLP. BMI and hedonic hunger were also evaluated.

Results Three hundred and sixty-three (68.36%), 152 (28.63%), and 16 (3.01%) of the participants had CC, CT, and TT genotypes for ANNK1 gene, respectively. Of 515 samples genotyped for DRD2 gene, 315 (60.51%), 173 (33.59%), and 27 (5.24%) had Ins/Ins, Ins/Del, and Del/Del genotypes, respectively. The genotype and genotype frequencies were significantly different between the groups ($p = 0.04$). Significant differences were observed between the T+ genotype (TT + TC) and the T− genotype (CC) regarding the BMI and hedonic hunger scores ($p < 0.05$). In addition, Del+ group (Del/Del + Ins/Del) had higher BMI and hedonic hunger scores compared to Del− group (Ins/Ins) ($p < 0.05$).

Conclusions Our findings showed that the frequencies of T and Del alleles were greater in the overweight/obese individuals. Also, the polymorphism of ANKK1 (rs1800497) and polymorphism of the DRD2 gene (rs1799732) showed significant associations with BMI and hedonic hunger.

Level of evidence Level III, case-control study.

Keywords ANKK1 · DRD2 · Polymorphisms · Obesity · Hedonic hunger · Women

Introduction

Obesity is an important international health problem. It could be due to interactions between different environmental and genetic factors [1]. Overeating behavior in response to a food-rich environment is considered as a main cause of the high prevalence of obesity worldwide [2]. The main question that researchers face in this area is to evaluate if there are relations between overeating and food craving with addictive behavior [3]. To date, food addiction as a possible factor leading to obesity has been investigated in numerous studies [4–7]. It involves hedonic hunger, eating behavior, food choice preference and motivation [8]. Several lines of evidence show that the hedonic urges in overweight and obese individuals involve the same brain reward circuits as

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perpetuating drug abuse [7, 9, 10]. It seems that both palatable food and drugs activate the same mesolimbic dopamine reward system [11]. Several studies have shown associations among the dopamine D2 receptors (DRD2) and classical alcohol, nicotine, and opioids addictions [12–14]. There are also some other studies indicating the association between the DRD2 and the development of obesity [3, 15, 16]. Considering the crucial role of dopamine in the brain reward circuit and its involvement in food behavior, the study of genetic variants affecting the availability and secretion of dopamine has been standing out [17]. The low availability of dopamine receptor in obese subjects may be considered as the mechanism for the development of obesity by the dopamine receptor gene [18]. Some variants of dopamine receptor, especially those in the genes regulating the DRD2 and ankyrin repeats and kinase domain containing 1 (*ANKK1*), may reduce transmission of the dopaminergic signals resulting in deficiency in the dopamine-related reward system [19, 20]. Thus, they are considered as main candidates in the assessment of individual differences in dopamine signaling strength [21, 22]. *ANKK1* gene polymorphism (rs1800497), also known as *TaqIA*, is identified by the exchange of a cytosine for a thymine, which causes glutamine to lysine substitution in the 11th ankyrin repeat of *ANKK1*. This single nucleotide polymorphism (SNP) affects the dopamine receptor availability [17]. The associations between *Taq*IA polymorphism with obesity, body mass index (BMI), and food intake have been reported in some studies [3, 23, 24]. SNP located in DRD2 (rs1799732) results in the insertion (Ins) or the deletion (Del) of cytosine (C) in the promoter region of the DRD2 gene at position − 141 (− 141C Ins/Del) [25]. The − 141 C Del allele has been associated with reduced promoter activity which results in decreased DRD2 protein expression and increased ventral striatal reactivity [26].

The − 141C Ins/Del variants are associated with other personality pathologies, such as alcoholism and schizophrenia. However, to the best of our knowledge, there is no study evaluating T (rs1800497) and Del (rs1799732) alleles in Iranian population. In addition, there are limited studies investigating the associations between these alleles and hedonic hunger. We hypothesized that T (rs1800497) and Del (rs1799732) alleles may be related to hedonic hunger and obesity. Therefore, the present study was aimed to investigate such relationships among Iranian Azeri women.

Materials and methods

Participants and study design

This cross-sectional study was conducted in Tabriz city, North-west of Iran, during December 2016–August 2017. Five hundred and thirty-one Iranian Azeri women aged 19–50 years were studied. All participants were aware of the study goals' and they provided informed consent to participation. The protocol of the study was approved by the Ethical Committee of Tabriz University of Medical Sciences [IR.TBZMED.REC.1395.1013]. The participants were selected using cluster sampling method. They recruited through posters placed at public places and health care facilities in 10 urban zones (clusters) of the city. The participants were randomly selected among those who were willing to participate in the study using a random number table. They were asked to come to our clinic and were assessed according to the inclusion and exclusion criteria. Participants who met the criteria were asked to come to the clinic on the next day within 2–3 h after breakfast. Then, the demographic and the Persian version of the power of food scale (PFS-P) questionnaires were administered to them.

According to inclusion criteria, pre-menopausal women who have lived in Tabriz for at least five consecutive years prior to their participation in the survey were studied. On the other hand, based on exclusion criteria, participants with the body mass index (BMI) of < 18.5 kg/m^2, pregnant or lactating women, those with recent weight loss or participating in weight loss programs, current smokers, those with recent history of supplement intake (within the past 3 months), women with psychotic disorders, substance abuse, alcoholism, and/or a serious medical/physical illness such as cancer, heart disease, and diabetes were excluded from the study.

Anthropometric measurements

The weight and height of the participants were measured in light clothing and bare feet after a 12-h fasting period. A calibrated electronic scale (Seca Model 770, Seca Corporation, Hanover, MD, USA) with an accuracy of 0.1 kg was used to measure weight in kilogram (kg). The participants' heights were measured using a fixed stadiometer to the nearest 0.1 cm. According to the obtained weights (kg) and heights (m), the participants' BMI was calculated in kg/m^2.

Physical activity

To estimate the physical activity of the participants, the validated short form of the Persian version of the International Physical Activity Questionnaire (IPAQ) [27] was used. According to the questionnaire, the participants were divided into low, moderate and high active groups [28]. The high active group was those with vigorous intensity activity on at least 3 days or five or more days of any combination of walking, moderate intensity or vigorous intensity activities. The moderate active group was those who engaged in 3 or more days of vigorous intensity activity and/or walking of at least 30 min per day, or 5 or more days of moderate intensity activity and/or walking of at least 30 min per day,

or 5 or more days of any combination of walking, moderate intensity or vigorous intensity activities achieving a minimum total physical activity of at least 600 MET minutes a week. The low active group was the participants who did not meet any of the criteria for either moderate or high levels of physical activity [28].

Hedonic hunger

The participants' hedonic motivation to food was assessed using the PFS-P questionnaire. The validity and reliability of the questionnaire were confirmed in our previous study [29]. The questionnaire consists of 15 items that are answered on a 5-point Likert-type scale ranging from 1 (do not agree at all) to 5 (strongly agree). The PFS consists of three factors: "food available", "food present", and "food tasted". The score of each factor was calculated by averaging the scores of all items in the factor (possible score range 1–5). The aggregate score was calculated as the mean of the factors (possible score range 1–5). The total mean score obtained from the questionnaire indicates a participant's responsiveness to the food environment. Higher scores mean greater responsiveness to the food environment [29, 30].

DNA extraction and genotyping

Fasting venous blood samples were collected for genotyping process. The genomic DNA extraction from peripheral blood cell was carried out using standard techniques. The genotyping was carried out by the Restriction Fragment Length Polymorphism (RFLP)-PCR. DNA amplification of the 237 base pair (bp) of ANKK1 gene was done using primers: Forward: 5′CCTTCCTGAGTGTCA TCAAC3′ and Reverse: 5′ACGGCTCCTTGCCCTCTA G3′. In addition, the following primers were designed to amplify a 156-bp fragment of the DRD2 gene: forward common primer 5′GACCCAGCCTGCAATCAC3′ and reverse primer 5′AGGAGCTGTACCTCCTCGG3′. The PCR was performed in a DNA thermocycler, and samples were denatured at 94 C for 5 min followed by 30 cycles under the following conditions for ANKK1: denaturing at 95 °C for 30 s, annealing at 59 °C for 30 s, and extension at 72 °C for 30 s. The final extension step was lengthened to 5 min. The same procedure was used for DRD2 except that the annealing step was at 65 °C for 30 s. ANKK1- and DRD2-amplified PCR fragments were digested with Thermo Scientific Taq1 and MvaI (BstNI) restriction enzymes, respectively. The primers, annealing temperature, restriction enzyme and fragment size are described in Table 1.

Digested fragments were visualized via acrylamide gel electrophoresis. In the presence of T allele of ANKK1 gene, PCR product was left uncut. However, in the presence of C allele, the fragment was cut into 124 and 113 bp. For DRD2 gene, Ins allele was left uncut and Del allele was cut into 124,32 bp [31, 32].

Statistical analysis

Data were analyzed using version 23.0 of SPSS software. The normality of the distribution of the variables was assessed by Kolmogorov–Smirnov goodness of-fit test. Hardy–Weinberg equilibrium was evaluated. Descriptive data are presented as the mean ± standard deviation (SD). Chi-square or Fisher's exact test was applied to compare categorical variables where applicable. The independent *t* test was used to compare quantitative variables between the groups. Analysis of covariance (ANCOVA) was used to compare quantitative variables between the groups, adjusting for given covariates. In all statistical tests, a *P* value of less than 0.5 was considered significant.

Table 1 Genotype profiles obtained for ANKK1 and DRD2 polymorphisms

SNPs	Primers	Annealing temperature	Restriction enzyme	Cut sequences	Fragment size (bp)
ANKK1(rs1800497)	Forward: 5′CCTTCC TGAGTGTCATCA AC3′ Reverse: 5′ACGGCT CCTTGCCCTCTA G3′	59 °C	TaqI	5′…T^ C G A …3	*C* = 124,113 *T* = 237
DRD2 (rs1799732)	Forward: 5′GACCCA GCCTGCAAT CAC3′ Reverse: 5′AGGAGC TGTACCTCCTCG G3′	65 °C	Bst NI (MVaI)	′ CC^WGG	Ins *C* = 124,32 Del *C* = 156

Results

Table 2 indicates the demographic characteristics of the participants. Three hundred and seventy-two (70%) of the participants were overweight/obese. The mean age and BMI were 35.52 ± 8.86 years and 30.38 ± 6.84 kg/m^2, respectively. Less than one percent of the participants were highly active, about 7.30% were minimally active and about 92% were inactive. The mean of PFS scores of the participants were 2.99 ± 0.87. Three hundred and sixty-three (68.36%), 152 (28.63%), and 16 (3.01%) of the participants had CC, CT, and TT genotypes, respectively. While all samples were analyzed for ANKK1 genotyping, 19 out of 531 DNA samples were not enough for DRD2 genotyping. Of 512 samples 312 (60.93%), 173(33.79%), and 27 (5.28%) had Ins/Ins, Ins/Del, and Del/Del genotypes, respectively. These frequencies were in Hardy–Weinberg equilibrium ($p > 0.05$).

Table 3 shows the comparison of genotype frequencies in the normal weight and overweight/obese participants. There were significant differences in the genotype frequencies of ANKK1 between the groups ($p = 0.007$). Compared to the normal weight women, higher frequencies of the CT (31.99%) and TT (4.28%) genotypes and a lower distribution of the CC (64.25%) genotype were observed in the overweight/obese group. In addition, significant differences were observed in the DRD2 genotype frequencies between the groups. Overweight/obese women had higher frequencies of Ins/Del (38.29%) and Del/Del (6.34%) genotypes and a lower frequency of the Ins/Ins (55.37%) genotype than the normal weight women.

Table 4 shows the frequencies of haplotype in the participants. Statistically significant differences were observed between the frequencies of the haplotypes among the groups. Eight haplotypes were found and all of them had a frequency of more than 1% except TI/TD and TD/TD, which were observed only in one of the normal weight and one of the overweight/obese participants, respectively. The most frequent haplotypes in the studied groups were CI/CI, CI/CD, and CI/TI, respectively. Since the number of participants with TT genotype was very small, we combined those with TT or CT genotypes as group T+ and those with CC genotype as group T−. Similarly, participants with Ins/Del or Del/Del genotypes were considered as group Del+ and those with Ins/Ins genotype as Del− group.

Table 5 shows the comparisons of age, BMI, and hedonic hunger scores between T+ and T− and between Del+ and Del− groups. There was no significant difference in the mean age between the T− and T+ and between Del+ and Del− groups. The T+ group had significantly higher BMI and hedonic hunger than T− group. Similarly, the Del+

Table 2 Demographic and anthropometric characteristics of the studied participants ($n = 531$)

Variables	Mean ± SD
Age (year)	35.52 ± 8.86
BMI (kg/m^2)	30.38 ± 6.84
PFS total score	2.99 ± 0.87

PFS Power of Food Scale, *BMI* body mass index

Table 4 Haplotype distribution in normal weight, overweight/obese participants ($n = 462$)

Haplotype	Normal weight ($n = 129$)	Overweight/obese ($n = 333$)	*P* value*
CI/CI**	88 (68.21)	117 (35.13)	< 0.001
CI/CD**	21 (16.28)	105 (31.53)	
CI/TI**	16 (12.40)	75 (22.52)	
CD/CD	3 (2.32)	11 (3.30)	
CD/TD**	0	11 (3.30)	
TI/TI	0	7 (2.10)	
TI/TD	1 (0.77)	6 (1.80)	
TD/TD	0	1 (0.3)	

*Fisher's exact test; **significantly different between the groups

Table 3 Genotype Distribution in normal weight, overweight/obese participants

Genotype	Normal weight ($n = 159$) *N* (%)	Overweight/obese ($n = 372$) *N* (%)	*P* value*
CC**	124 (77.99)	239 (64.25)	0.007
CT**	33 (20.75)	119 (31.99)	
TT	2 (1.25)	14 (4.28)	
Genotype	Normal weight ($n = 149$)	Overweight ($n = 363$)	*P* value
InsIns**	111 (74.5)	201 (55.37)	< 0.001
InsDel**	34 (22.82)	139 (38.29)	
DelDel	4 (2.68)	23 (6.34)	

*Fisher's exact test; **significantly different between the groups

Table 5 Subject's characteristics by carrier status

Variables	T− (CC)	T+ (CT/TT)	*P* value	Del− (Ins/Ins)	Del+ (Ins/Del, Del/Del)	*P* value*
Age (year)	35.62 ± 9.08	35.48 ± 8.84	0.869[a]	35.66 ± 8.69	35.30 ± 9.13	0.659[a]
BMI (kg/m^2)	30.05 ± 6.70	31.13 ± 6.81	0.047[a]	29.73 ± 6.36	31.35 ± 6.94	0.003[a]
PFS mean scores	2.88 ± 0.81	3.21 ± 0.93	0.004[b]	2.90 ± 13.64	3.22 ± 14.26	0.014[b]

PFS Power of Food Scale, *BMI* body mass index

[a]Independent *t* test

[b]ANCOVA test adjusted for age, BMI and physical activity

group had significantly higher BMI and hedonic hunger scores as compared with Del− group.

Discussion

In the present study, for the first time, the variants of ANKK1 and DRD2 genes and their associations with hedonic hunger were assessed among Iranian Azeri women. Five hundred and thirty-one women were studied and their BMI, physical activity, hedonic hunger, genotypes, and haplotypes were investigated.

Eating behavior, food choice preference, motivation, and hedonic hunger are involved in food addiction, which is considered as the main cause of obesity [8]. Most of the hedonic mechanisms are related to the brain reward system [33]. Dopamine is the central brain signaling molecule that controls food reward [3]. The dopaminergic regulation in the brain reward system that is involved in the development of obesity is carried out through dopamine receptors [34]. Therefore, the genes' polymorphisms related to dopamine receptors are considered as one of the predisposing factors for obesity [34].

In the present study, the frequencies of T allele in the normal weight and overweight/obese groups were 11.64 and 28.16%, respectively, which were significantly different between the groups. This finding was in accordance with other studies [35–39]. In addition, we found significant differences in the allele frequencies of DRD2 polymorphism (rs1799732) between the overweight/obese and normal weight controls. The frequencies of Del allele in the normal weight and overweight/obese groups were 14.09 and 25.48%, respectively. Most studies examine the polymorphism of -141C Ins/Del (rs1799732) in individuals with drug addiction or psychological disorders and there are limited studies in healthy and/or obese individuals [40]. Davis et al. (2008) reported the frequencies of 17.8, 13.4, and 16.3% for Del allele in healthy normal controls (BMI 22.38 kg/m^2), subjects with overeating disorders, and obese (BMI 39.60 kg/m^2) individuals, respectively [41].

In the present study, eight haplotypes were observed and their frequencies were significantly different between the groups (Table 4). CI/CI was the most abundant haplotype and TD/TD haplotype was only observed in one participant in the overweight/obese group. No CD/TD, TI/TI, or TD/TD haplotype was observed in the normal weight group. The TI/TD haplotypes with three risk alleles were seen in 0.77% of the normal weight and 1.8% of obese/overweight participants. In addition, the frequency of the CD/TD haplotype with three risk alleles was 0 and 3.30% in the normal weight and overweight/obese participants, respectively. Statistical significant differences were noted in the frequency of CI/CI, CI/CD, CI,TI and CD/TD between the groups. The T and Del allele may lead to a reduction in the density of dopamine receptors, which may be a reason for differences in individual's desire for delicious foods and, consequently, weight gain [40].

In the present study, the means of BMI and hedonic hunger were significantly higher in the participants with T+ than those with T− and in Del+ than those with Del− genotypes. In line with these findings, some studies reported higher BMI in individuals with T allele [21, 22, 36]. In contrast, some other studies found no significant differences in BMI between subjects with T or C allele [8, 20, 41]. Roth et al. (2013) found that only individuals homozygote for T allele were at the risk of weight gain and failure to respond to weight loss interventions [42, 43].

Some studies showed that T allele carriers tend to eat more in comparison with T− individuals [1, 16, 44]. Significant relationship between the presence of T allele and hedonic hunger has been reported among Asian-American students [8]. Stice et al. (2008) reported that T allele carriers experienced changes in dopamine-related performance in the striatum area of the brain [45]. In fact, dopamine is called "pleasure molecule" or "anti-stress molecule" and when dopamine is released into synapses, the activation of dopamine receptors makes the sensation of pleasure in the individuals [46]. Evidence support the response of the brain's DA system to rewards. However, the role of DA is poorly understood [47]. Previous studies reported that blocking D2 receptors increases food intake [34, 48].

Brain imaging studies have shown that individuals who have one or two copies of the T allele in the *ANNK1* gene have 30–40% lower D2 receptors and have modified brain dopamine

signaling [49]. However, it is not clear how low availability of D2 receptor increases the risk of overeating. This higher risk of overeating in these subjects may be driven by DA's regulation of dorsolateral prefrontal cortex (DLPFC) and medial prefrontal regions, which participate in the inhibition of inappropriate behavioral response tendencies [34, 49].

The hypothesis in this regard is that reducing the D2 receptor reduces the sensitivity of the reward system, so the individuals subsequently overeat to compensate for this reward deficiency [50, 51]. People tend to eat highly palatable energy-rich food which usually has high levels of fat, sugar, or both [3, 11]. Consuming large quantities of these nutrients resulted in excessive DA release and a sense of reward and pleasure. It was observed that such compensatory overeating was a predictor for obesity [11].

There are very few studies investigated the association of DRD2 polymorphism with BMI and hedonic hunger [40]. Lencz et al. reported that deletion allele in patients with schizophrenia who are treated with D2 receptor antagonists predicts weight gain [52]. D2 receptor antagonists decrease the limbic dopaminergic activity and are likely to increase reward-seeking behaviors such as hedonic eating [53]. Furthermore, there is disagreement about the functional effect of DRD2 Ins/Del variation on D2 receptor expression in the brain [54, 55]. Methodological differences in the quantification of D2 receptors may explain the conflicting results, but further research in this area is needed [56, 57].

The present study has some strengths. We assessed, for the first time, the associations between T (rs1800497) and Del (rs1799732) alleles and hedonic hunger in an Iranian population. In addition, there are very few studies investigating such relationships worldwide and the present one provide further evidence in the support of the relationship between these alleles and hedonic hunger.

Limitations

There are some limitations with this study. First, the study was carried out in only one city of Iran, Tabriz. Although Tabriz is one of the major cities in the northwest of Iran, there are other cities with different cultures. Second, only women were studied and there is no information on hedonic hunger among Iranian men. Therefore, further studies with larger sample sizes (both men and women) in different areas of Iran are recommended to further assess hedonic hunger in Iranian populations.

What is already known on this subject?

ANKK1 gene polymorphism is associated with obesity, BMI and food intake. The -141C Ins/Del variants are associated with personality pathologies, such as alcoholism and schizophrenia. In addition, DRD2 is associated with classical alcohol, nicotine, opioids addictions and the development of obesity. However, there is very few information on the associations between T and Del alleles and hedonic hunger.

What does this study add?

For the first time, T and Del alleles were evaluated in an Iranian population. In overweight/obese women, the frequencies of these alleles were higher which in turn may lead to higher hedonic hunger among them.

Conclusions

The frequencies of T and Del alleles were higher in overweight/obese individuals. The TaqI A polymorphism of ANKK1 (rs1800497] and − 141 C Del/Ins polymorphism of the *DRD2* gene (rs1799732) showed significant association with BMI and hedonic hunger.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol of the study was approved by the Ethical Committee of Tabriz University of Medical Sciences [IR.TBZMED.REC.1395.1013].

Informed consent All participants were aware of the study goals' and they provided informed consent to participation.

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