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Review Article

Association between Genetic Variants and Obesity in Iranian Population: Review Article

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Abstract

Obesity is currently considered as a serious global health problem which is influenced by environmental and genetic factors. Association of genetic variants with obesity is widely scrutinized in recent years. The aim of this study was to evaluate present data on genetics of obesity in Iranian population in a systematic review study. To obtain all related studies, Google Scholar, PubMed, and Persian web databases; IranMedex and Magiran were searched up to January 2013. The search terms were; "gene" , "polymorphism , "obesity" , "waist circumference" , "BMI" affiliated to Iran. Non-population cross sectional studies, experimental studies, *in vitro* studies, case reports, review articles, letters to editor, short communications and dissertations were excluded. Finally 11 articles that investigated association of different gene variants with obesity were included. Due to the heterogeneity of data, it was impossible to perform a Meta-analysis. Our study showed that males with TT genotype for +45T>G variant of adiponectin gene, GG genotype for -11391G>A polymorphism of adiponectin, GC+GG genotype for Pro12Ala PPARγ2 gene variant, 1484insG carriers of PTP1B and AA genotype of 4223A>C ADA gene variant had significant positive association with obesity in Iranian population. However gene variants of glucokinase, TNF-α, UCP2, MTHFR, β3-adrenoreceptor and apolipoprotein E were not significantly associated with obesity. There are discrepancies in association between obesity and genetic variants in Iranian population compared to other populations. Therefore we suggest large scale genome wide association studies on defined populations with distinct clinical features are necessary in future to further investigate underlying genetic variants associated with obesity in Iranian population.

Keywords: Gene, Polymorphism, Obesity, Iran

Introduction

A condition of abnormal or excessive fat accumulation in adipose tissue is defined as obesity (1). Obesity is currently considered as a serious global issue due to its important effect on health, economy and quality of life. The prevalence of obesity is growing worldwide. According to current reports, one billion people in the world are overweight and 300 million are obese (2). It has been estimated that the number of overweight subjects will reach to 2 billion and for obese to 1.2 billion people until 2030 (3).

A number of chronic diseases are developed as a consequence of increased body weight, such as type 2 diabetes, cardiovascular disease, hypertension, gall bladder disease and certain types of cancer (1).

Obesity is influenced by several factors including environment, genetic and behaviors (4). In recent years the association of genes with obesity has been of major interest. Genes which are associated with obesity are categorized into 5 groups:

1) Genes responsible for monogenic forms of obesity. Mutation in leptin, leptin receptor (LEPR), melanocortin 4 receptor (MC4R) and proopiomelanocortin pathway (POMC) could be categorized in this group (4). Leptin is an important hormone being secreted in adipocyte tissue. Mutation in leptin or its receptor would alter satiety pathway and results in obesity (5).
2) Free fatty acid metabolism regulator genes. Adiponectin, β-adrenergic receptor and lipases are in this group (5). Adiponectin is an autocrine factor in adipose tissue that promotes cell proliferation and differentiation from preadipocytes into adipocytes. As a result programmed gene expression responsible for adipogenesis is augmented and lipid content and insulin responsiveness of the glucose transport system in adipocytes is increased (6).
3) Genes related to inflammation including Tumor Necrosis Factor α (TNF-α) and C-reactive protein (CRP) (4). Obesity leads to an increased production of TNF-*a* (2).
4) Genes associated with fat metabolism such as CD36, apolipoprotein E, 11-β-hydroxy steroid dehydrogenase (4).
5) Genes associated with insulin resistance such as Protein Tyrosine Phosphatase 1B (PTP1B) and Peroxisome proliferators activated receptors γ2 (PPARγ) (4).
Other genes which their association with obesity are studied, include insulin gene Variable Number of Tandem Repeat (VNTR) (7), Insulin-like Growth Factor I (IGF-I) (8), Glucose Transporter (GLUT) 2, GLUT4, Phosphoinositide 3 Kinase (PI3K), Glutamic Acid Decarboxylase (GAD) 2, GAD65 (9), polymorphisms of Uncoupling Protein 1 (UCP1) gene (10), Visfatin, Growth Hormone Secretagogue Receptor (GHSR) (11), catalytic subunit of telomerase (hTERT) (12) and fat mass and obesity associated (FTO) gene (4).
The body mass index (BMI) is the most widely used index for assessing the obesity because of high correlation between BMI and adiposity. Waist circumference (WC), hip circumference and waist to hip ratio (WHR) which determines abdominal obesity are other indicators used as implementation for BMI index (1, 13).

Since, the outcome of genetic association studies is influenced by different factors including study population, this systematic review aimed to investigate the association of genetic variants with obesity in Iranian population which was published until 2013.

Methods

Study population

PubMed and Google Scholar web databases were searched up to January 2013. The search terms were; "gene", "polymorphism, "obesity", "waist circumference", "hip circumference", "waist to hip ratio", and "BMI" affiliated in Iran and their equivalences in Persian web databases; Magiran and IranMedex. All cross sectional, cohort and case control studies which investigated the association between genetic variants and obesity in Iranian population were included. BMI was defined as weight/height (kg/m^2), waist circumference is defined as measuring the midpoint between the lower margin of the least palpable rib and the top of iliac crest (cm) and hip circumference is measured around the widest portion of buttocks (13). According to world health organization criteria overweight is defined as 25<BMI<30 while obesity and morbid are defined as BMI≥30 and ≥35 respectively (1). In addition, WC≥102 (cm) for men and ≥88 for women or WHR≥0.9 for men and ≥0.8 for women are another definitions of obesity (14). Animal studies, in-vitro studies, clinical trials, case reports, review articles, letters to editor, short communications and dissertations were excluded. Population-based studies with <100 sample size were also excluded.

Data extraction

Two reviewers independently investigated title, abstract and full text of each article according to inclusion and exclusion criteria to choose eligible articles and eliminate duplicate publications. At least 3 emails were sent to the corresponding authors of articles which their full texts were not accessible or had incomplete data. In addition, the reference lists of articles were reviewed for additional relevant studies. When there were multiple

publications from the same population, only the most relevant data was included.

Statistical Analysis

Although all included studies used DNA extraction from blood and PCR-RFLP method for genotyping, only one gene variant of each categorized genes' related to obesity was studied in Iranian population. Therefore, performing Meta analysis was impossible.

Results

The initial search resulted in 1814 records from which 1766 records by title and 35 records by abstract were excluded. Figure 1 shows the flow diagram of the study selection processes. Finally 11 studies were eligible (14-24) which the summary of their results is shown in Table 1.
Details of included studies are as follows.

Table 1: Iranian population-based studies investigated association between gene variants and obesity

Reference	Genes / Polymorphisms, Alleles	City	Sex	Sample size (n)	Age(yr)	Study design	Results
(18)	TNF-α / -308G>A -238G>A	Tehran	Both	Total(T):244 Male(M):102 Female:142	<18 & > 18	Cohort	No significant association with BMI or WHR
(21)	Glucokinase / -30G>A	Mashhad	Both	T:542 M:256 F:286	18-65	Cross sectional	No significant association with BMI
(22)	UCP2 / -866G/A	Tehran	Both	T:225 M:93 F:132	35-76	Case control	No significant association with BMI
(16)	Adiponectin / -11377C>G	Tehran	Female (F)	F:163	> 18	Cross sectional	No significant association with BMI, WC, or WHR
(15)	Adiponectin / +45T/G	Rafsanjan	Both	T:413 M:200 F:213	37-65	Cross sectional	Significant positive association between male TT carriers and BMI
(15)	Adiponectin / -11391G/A	Rafsanjan	Both	T:342 M:128 F:214	37-65	Cross sectional	Significant positive association between male GG carriers and BMI, significant positive association between female GG carriers and WC
(23)	MTHFR / 677C>T	Tehran	Both	T: 688 M:260 F:428	30-63	Case control	No significant association with BMI
(20)	PPARγ2 / C>G in codon 12 (Pro12Ala)	Tehran	Both	T:156	25-65	Case control	Significant positive association between GC+GG carriers and BMI
(24)	ADA / 4223A>C	Tehran	Both	T:138 M:42 F:96	25-64	Case control	Significant positive association between AA carriers and BMI
(17)	β3-adrenoreceptor / 190T>C (Trp64Arg)	Tehran	Both	T:401 M:197 F: 204	> 18	Cross sectional	No significant association with BMI
(19)	Apolipoprotein E / E2,E3,E4	Tehran	Both	T:329 M:150 F:179	> 30	Cross sectional	No significant association with BMI or WHR
(14)	PTP1B / 1484insG	Tehran	Both	T:346	20-80	Case control	Significant positive association between1484insG carriers and BMI

Keys: WC, waist circumference; **BMI**, body mass index; **WHR**, waist to hip ratio; **TNF-α**, tumor necrosis factor α; **UCP2**, uncoupling protein 2; **MTHFR**, methylenetetrahydrofolate reductase; **PPRAγ2**, peroxisome proliferators activated receptor –γ2; **PTP1B**, protein tyrosine phosphatase 1B; **ADA**, adenosine deaminase; **Pro**, proline; **Ala**, alanine; **Trp**, tryptophan; **Arg**, arginine; **ins**, insertion

Free fatty acid metabolism regulator genes

Within this group, we found that +45T>G, -11391G>A and-11377C>G polymorphisms of adiponectin gene; and also 190T>C polymorphism of β3-adrenoreceptor gene have been studied in Iranian population (4).

Adiponectin gene

Genetic polymorphisms of Adiponectin that have been investigated include -11391G>A, -11377C>G and +45T>G (15, 16). These studies showed gender differences in association between these gene polymorphisms and BMI or WC (15, 16).

In one study 416 participants were investigated and the frequency of +45TT/TG/GG genotypes in men were 136/55/9, while their frequencies in women were 152/54/7 (15). Overall, mean BMI among women was higher than men. Significant higher mean BMI was found in male carriers of the TT genotype of +45T>G polymorphism compared to male GG homozygotes (26±4 versus 23±3 kg/m^2, *P*=0.018). Also, in female group the mean BMI in TT carriers was higher than GG carriers (27±4versus 24±6 kg/m^2), without any significant differences (15). In contrast to BMI, mean WC among men was higher than women. The mean of WC in males with TT genotype was higher than those with GG genotype; 97±10 versus 91±8 cm, without any significant difference. These figures for females were 91±9 versus 84±12 cm, respectively in subjects with TT and GG genotypes of +45T>G polymorphism, without any significant differences (15).

Genotype frequencies of -11391GG/GA/AA polymorphism in males were 120/8/0, while in females these frequencies were 199/14/1 (15). The mean of BMI among women was higher than men. Significantly higher mean BMI was shown in subjects with GG genotype of -11391G>A polymorphism compared to GA+AA genotype; 24±4 versus 21±3 kg/m^2 (*P*=0.041) (15). These figures among female with GG genotype were 27±4 versus 25±5 kg/m^2 in GA+AA genotypes, without any significant differences. Against BMI, mean WC among men was higher than women. The mean of WC in male subjects with GG genotype was higher than those with GA+AA genotype; 93±10 versus 91±11 cm, without any significant difference. In females with GG genotype of -11391G>A, significant higher WC was shown compared to females with GA + AA genotype; 91±9 versus 86±6 cm (*P*=0.038) (15).

Investigating -11377C>G polymorphism of adiponectin in females showed that the frequencies of -11377CC/GC/GG genotype were 108/44/11 respectively (16). Mean BMI among women was higher than men. Mean BMI in female carriers of CC genotype was higher than GG carriers (26.99±0.57 versus 25.28±1.67) without any significant differences. Mean WC and WHR for females were 85.94±1.4 cm and 0.84±0.008 in CC carriers versus 82.82±4.47 cm and 0.83±0.03 in GG carriers without any significant differences (16).

β3-adrenoreceptor gene

Another studied gene variant that is belonged to this group, was the 190T>C polymorphism of β3-adrenoreceptor gene resulting in the replacement of tryptophan by arginine in codon 64 of this gene. In this study 401 subjects; 197 men with mean age of 46±14 years and 204 women with mean age of 42±13 years participated. Between them, 61 participants were arginine carries with mean BMI of 27±6 and 340 participants were non arginine carriers with mean BMI of 25±5 kg/m^2. No significant BMI change was found between tryptophan or arginine carriers (*P*=0.072) in this study (17). Mean WC was higher in arginine carriers than tryptophan carriers (91±13 versus 87±13 cm) without any significant difference. WHR was also higher in arginine carriers than tryptophan carriers (0.9±0.1 versus 0.8±0.1) without any significant difference. Overall, 104 participants were overweight and 102 subjects were obese. The most prevalent of overweight and obese subjects were among TT carriers; 89 subjects (85.6%) for overweight and 81 subjects (79.4%) for obese (17).

Genes related to inflammation

As it was mentioned before, TNF-α is one of the most important genes included in this group (4). G-308A and G-238A polymorphisms of TNF-α

promoter gene were studied in two aged group; <18 and > 18years in a cohort study (18).
The frequency of -308GG/GA/AA genotypes in <18years age group was 34/7/1 while in >18years age group was 175/25/2 respectively. Although only one person had AA genotype, higher mean BMI was shown in subjects with AA genotype compared to GG genotype (26.71 versus 19.73±3.84 kg/m^2) in <18 years age group without any significant difference. The same results was found in >18 years age group (32.18±2.7 versus 26.65±4.55 kg/m^2) without any significant difference. AA subjects had higher WHR than GG subjects in <18 and >18 years age groups (0.98 versus 0.83±0.05, and 0.95±0.06 versus 0.87±0.08) without any significant difference. In <18 years age group 16 subjects were obese that most of them; 13 numbers (81.2%) had GG genotype. In >18 years age group 81 and 46 subjects were overweight and obese, respectively and most of them; 71 overweight subjects (87.7%) and 37 (80.4%) obese subjects had GG genotype (18).
The frequency of -238GG/GA/AA genotypes were 33/8/0 respectively in <18 years group and 175/38/3 in >18years group. None of the subjects had AA genotype. No significant association between G-238A polymorphism of TNF-α and BMI or WHR was found in both aged groups. In <18 years age group 16 subjects were obese that most of them; 13 (80%) had GG genotype. In >18 years age group 81 and 46 subjects were overweight and obese, respectively and most of them; 60 overweight subjects (77.9%) and 32 (78%) obese subjects had GG genotype (18).

Genes associated with fat metabolism

Different polymorphisms of apolipoprotein which is included in this group (4), has been investigated (19). The authors have studied 329 subjects; 150 men and 179 women. The frequency of E2/E3/E4 alleles was 0.065/0.851/0.083 respectively. Mean BMI in male carriers of E2/E3/E4 were 26.9±4.2/27±4.5/27.7±4.8 kg/m^2 while in female carriers were 28±6/28±5/27±5 kg/m^2. Female carriers of E2/E3/E4 had lower mean WHR than male carriers (0.84/0.84/0.83 versus 0.96/0.95/0.95). No significant association between E2, E3 and E4 polymorphisms of ApoE gene and BMI or WHR was found in both sexes (19). Most of the participants were overweight and most prevalent allele between them was E3.

Genes associated with insulin resistant

The most important genes in this group include PPAR-γ2 and PTP1B genes (4). Both of these genes were studied in Iranian population.

PPAR-γ2

Pro12Ala polymorphism caused by C>G mutation in codon 12 of this gene was studied. The association of this polymorphism with obesity was investigated in a case control study which 78 subjects with BMI<30 kg/m^2 were selected as control group and 78 subjects with BMI≥30 kg/m^2 as case group (20). The frequency of CC/GC/GG genotypes was 53/24/1 respectively in cases and 65/12/1 in controls. The most prevalent genotypes among obese subjects were GG and GC. Mean BMI of subjects with GC+GG genotypes was significantly higher than mean BMI of subjects with CC genotype (27±2 versus 25±3 kg/m^2, *P*=0.033) (20).

PTP1B

The 1484insG polymorphism of PTP1B gene was investigated in 346 subjects (14). Most of them (264 subjects) were non-diabetics and others were diabetics. Frequency of 1484insG/wt was 7.6% (21 numbers) and 12.7% (9 numbers) respectively in non-diabetics and diabetics. Mean BMI was significantly higher in 1484insG carriers compared to wild type carriers in non-diabetics (28.48±5.45 versus 25.91±4.26 kg/m^2, *P*=0.012) (14).

Other genes

Some genes were studied from these groups which are as following; glucokinase, UCP2, MTHFR and adenosine deaminase.

Glucokinase

Association of -30G>A polymorphism of glucokinase gene with obesity was investigated in 542 subjects, which were divided into 3 groups; normal BMI (220 subjects), overweight (135 subjects)

and obese (187 subjects). The frequency of AA/GA/GG genotypes was 57/6/157 respectively in normal BMI, 30/9/96 in overweight and 41/17/129 in obese groups. The results showed no significant association between this polymorphism and BMI (*P*=0.091) (21).

UCP2

The -866G/A polymorphism of UCP2 was studied in 225 subjects; 75 non-obese diabetics, 75 non-diabetics obese, and 75 control subjects (22).The frequency of AA/GA/GG genotypes of -866G/A was 11/48/16 in obese group and 7/41/27 in control group. Mean of BMI in subjects with AA genotype was lower than subjects with GG genotype in obese group. However, no significant association was found between -866G/A polymorphism of UCP2 and obesity after the results were adjusted for age, gender and BMI (*P*=0.119) (22). Mean WC in those with AA genotype was higher than subjects with GG or GA genotypes with no significant differences. There was also no significant difference between subjects with AA, GA or GG genotype.

MTHFR

Association between C677T polymorphism of MTHFR and obesity was studied in 688 subjects. The study group comprised of 260 men and 428 women divided into 4 groups; healthy control group (207), obese (74), diabetics (281), and obese diabetics (120). The frequency of CC/CT/TT genotypes was 113/80/14 in control group and 44/21/9 in obese group. Mean BMI in control group was 24.8±2.9 and 33.8±3.4 kg/m^2 in obese group. They have found no significant association between obesity and C677T polymorphism (*P*=0.1) (23).

ADA

Association of 4223A/C polymorphism of Adenosine deaminase (ADA) gene with obesity was investigated in 138 subjects; 68 control and 91 obese subjects as cases (70 obese and 21 morbid obese). The frequency of AA/CA/CC genotypes was 5/39/24 in control group and 15/31/24 in obese group. A significant positive association between AA genotype of 4223A/C polymorphism and BMI was found in obese and morbid obese subjects (*P*= 0.01, and 0.03, respectively) (24).

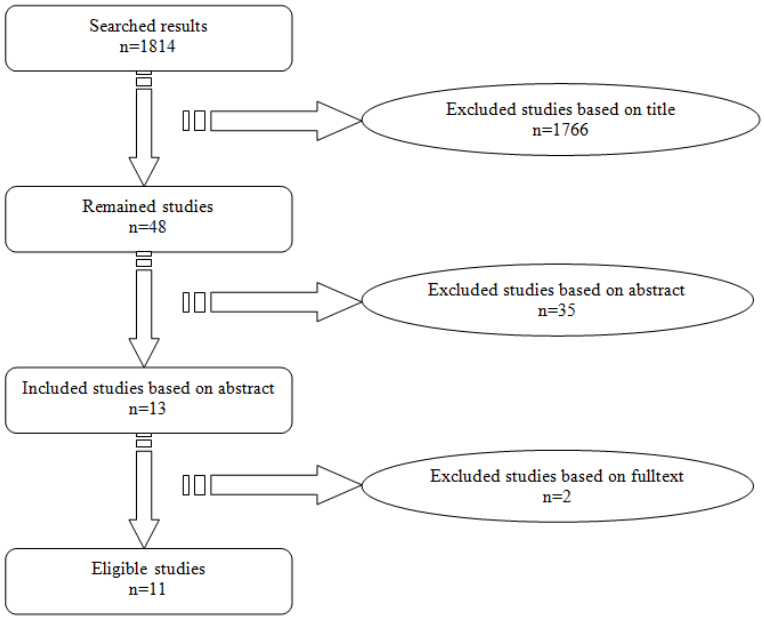

Fig. 1: Diagram of study selection process

Discussion

Studies have shown almost doubled prevalence of adult obesity over the past three decades. Parallel to that mean BMI has also been increased and it has reached to 23.8 kg/m^2 for men and 24.1 kg/m^2 for women (25). Studies have shown that obesity is mostly prevalent in eastern Mediterranean countries including Iran, Qatar, Saudi Arabia, Kuwait and etc. In Iran studies have shown that 42.8% of men and 57% of women are obese. Mean BMI in Iran was estimated 26 kg/m^2 in men and 27.5 kg/m^2 in women during 2004-2005. These findings show that obesity is more prevalent among women than men in Iranian population (4). As mentioned previously, interactions of environmental, genetic and behavioral factors are main causes of obesity. Among these factors, lifestyle has been considered as the most important cause in addition to the genetic background which is also important in obesity. It has been shown that there is an interaction between human genome and nutrition making a new line of study as nutrigenomics. Two concepts are indicated in nutrigenomics; first it shows that nutrients, metabolic response and susceptibility to nutrition related diseases are associated with human genome. Second nutrigenomic shows that nutrients interact with transcription factors regulating gene expression or metabolic response change (4). Nowadays, the association of different genes with monogenic obesity has been under attention worldwide. Studies have shown implication of β2-adrenoceptor gene in association with body weight regulation and onset of obesity in French men (26). Association of Gly16Arg polymorphism of this gene with BMI was also found in Caucasian women (27). Two mutations (c.2396-1 G>T and c.1675 G>A) in leptin receptor gene (LEPR) was found in obese Pakistani children (28). In line with these results, a 66bp deletion in codon 514 of LEPR gene was detected in an 18 month old boy (29). Two other mutations in LEPR (Trp646Cys and Pro316Thr) was also found in two sisters in Iran which altered leptin signaling and suppressed STAT3 phosphorylation and finally resulted in abnormal appetite and obesity (5). Mapping different obesity-related gene variants in obese animal models such as rats and pigs (because of their similarity to human genome), shows the importance of genetic association with obesity as well (30-33). At least 58 genetic loci which are strongly associated with obesity-related traits have been identified through large-scale genome-wide association studies (GWAS). Although the majority of these studies were done in European populations, studies which are now being performed in non-European populations are also mounting in number (25, 34-37).

In candidate gene based approaches alleles at polymorphic sites within the gene can be tested directly for a physiologically relevant association with a disease. Any disease associated allele could ultimately be used as a diagnostic or prognostic tool and also lead to the identification of novel targets for pharmacogenetic intervention.

In our study several gene variants were found which were significantly related to different clinical features of obesity including BMI, WC and WHR (14, 15, 20, 24). We found +45T/G and -11391G>A polymorphisms of adiponectin was positively associated with obesity in Iranian population with a gender differences (15), which was in line with studies in Swedish population that was investigated only in women (38). Another study in Japanese population confirmed our results although gender difference was not shown (39). Our findings for association between some gene variants and obesity were in contrast to other populations. The results on the association of PPARγ2 with obesity have been controversial (2). Our study showed the positive significant association between Pro12Ala polymorphism of PPARγ2 and BMI (20). Similar to our results, it was shown that there was an interaction between Ala allele and gender contributing to obesity susceptibility in European descent Brazilian men, and in White men from Italy. Besides that, Pro12Ala was shown to affected adiposity by measures of skin fold triceps and sub scapular in a gender specific manner in children of Greek origin (2). In another study the Ala allele was significantly associated with higher body weight, BMI, height and waist cir-

cumference. These data supports the notion of PPARγ2 genetic variability influence on body weight control and lipid homeostasis (40). However studies on French Caucasian and Qatari population showed no association between this polymorphism and obesity (2, 41, 42). We found significant positive association between 1484insG polymorphism of PTP1B with BMI in Iranian population (14) while in contrast there was no significant association between this polymorphism and obesity in Swedish population (43). Our results showed significant association between 4223A>C carriers of ADA gene and obesity (24), confirming the previous similar results that showed the association of increased serum levels of ADA with obesity in Turkish population (44).

Most of the gene variants which were investigated in our study showed no significant association with obesity (16-19, 21-23). Some of these results were controversial compared to studies in other populations; investigating -11377C>G polymorphism of adiponectin in Swedish Caucasian population showed significant positive association with BMI (45) in contrast to our study (16). For G-308A TNF-α gene variant and obesity (18), some studies reported significant interactions between dietary fat intake and TNF-α −308G/A polymorphism affecting obesity risk in a sub-Saharan women population (nutrigenomic) (2). In our study it was shown that the -866G/A polymorphism of UCP2 was not significantly associated with obesity (22). In a systematic review and a Meta analysis study it has been shown that this gene variant could be significantly associated with obesity in European but not in Asian population (30, 46).

Overall, as it was shown in our study quite similar to the others, some genetic variants show sex specific manner in association with the obesity (2, 4, 15). Therefore sex difference could be considered as an important factor in obesity-related genetic studies. We have shown that except for one study, which investigated TNF-α gene variants in association with obesity in <18 subjects (18), children obesity was not studied in Iran. Therefore more studies are needed to be performed covering all age ranges. Iran is a multi ethnic country and considering environmental and nutrigenomic factors and genetic background effect on obesity indices, it seems that more studies on this issue are needed. These studies could be done using appropriate methods such as large scale population based studies including genome wide association studies (GWAS).

Experience has now taught us that classical family based linkage analysis is more appropriate for finding the genes involved in monogenic disorders with simple Mendelian disease phenotypes. In contrast the power of linkage based approaches in identifying genes involved in complex diseases has proved to be relatively limited (47).

Case-control association studies, where cases of disease are compared with matched controls from the same population, are proving to give a greater chance of detecting small genetic effects in complex diseases (48). However this approach is proving to be invalid in the presence of population stratification when cases and controls are not fully matched. Furthermore misdiagnosis and misclassification of the cases are likely to lead to false negative or false positive results.

New technologies which allow the simultaneous amplification and quantification of specific nucleic acid sequences are also available which worth to be utilized in future studies. Recent progress in genotyping using high throughput techniques such as microarrays technologies enables the genome-wide screening of complex diseases using a dense map of single nucleotide polymorphism markers. Microarray technology is based on the principle of sequencing by hybridization and is capable of genotyping thousands of polymorphisms simultaneously (49). Genome wide association studies have been carried out to study obesity worldwide. In a GWAS study on Danish Duroc boars, different traits were investigated in association with feeding behavior and obesity. Pig-human comparative QTL (Quantitative Trait Loci) /genome mapping approach has also revealed many genes related to different obesity-related traits in human such as BMI, WC, fasting blood sugar (FBS) in addition to food intake (34). Another study, using GWAS method, was done on a very large sample size including 69,775 subjects (6,149 American

Indians, 15,415 African-Americans, 2,438 East Asians, 7,346 Hispanics, 604 Pacific Islanders, and 37,823 European Americans) investigating thirteen SNPs related to obesity in a multi racial group. They could replicate and generalize associations between 13 SNPs and BMI (35). Different LEPR gene variants in association with obesity were shown in GWAS study on Pima Indians. They have found several variants including rs2025804 variant related to BMI in Pima Indians. It has also been shown in this study that LEPR variants may be more important than FTO polymorphisms because the risk allele for LEPR is very common in this population (36). Association of the 3q25.31 locus with newborn body fat in four ethnic groups was found in another GWAS study (37).

Conclusion

Overall it seems that more studies are needed to be done in Iranian population to define the associated gene variants with obesity. Large scale population-based studies which include well defined clinical information using genetic markers across the genome using next generation association studies (50) could enhance our understanding of genetic variants underlying obesity.
The collection of samples from the distinct regions has been found to be highly appropriate for a case-control approach as it allows the study of a homogeneous and static population. A population which is ethnically diverse from other areas and has not experienced large-scale immigration or population mixing in recent history will be most suitable for conducting future studies.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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The authors declare that there is no conflict of interest.

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