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REVIEW ARTICLE

Association of Genetics traits with obesity in men: A review on the current knowledge in Iran

Arezoo Akhoundi Khoranaghi[1], Shahrzad Nematollahi[2]*, Fereshteh AliAkbary[2], Samira Shariatpanahi[2]

1. M.Sc student of Genetics, Kharazmi university, Tehran, Iran.
2. Men's Health & Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Abstract: Today, obesity is one of the leading causes of death. It also causes other diseases such as diabetes, cardiovascular disease, and various types of cancer. Obesity is a multifactorial disease caused by factors such as genetics and lifestyle. However, scientists imagine that about 40-70% of the disease originates from genetics. In this review, we examined the role of different genes in obesity by examining 30 articles published on the role of genetics in the obesity of Iranian men, according to their BMI, comorbidities and family history. We concluded that most of the research has been done on the FTO, Hind III and S447 genes. We also showed an apparent relationship between these genes and obesity. Finally, according to studies, FTO can be considered as the most important and strongest contributor to obesity.

Keywords: Obesity; BMI; Genetic; Iran

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1. Introduction

Obesity has become a major global problem and is recognized as the fifth leading cause of death worldwide (1). Recent estimates by the World Health Organization (WHO) show that in 2016, more than 1.9 billion and 650 million adults were overweight and obese, respectively. The proportion of overweight by gender also shows that 39% of men and 40% of women are overweight worldwide (2). Many developing countries, such as Iran, are currently struggling with obesity and problems associated with excess weight (3).

Obesity is a multifactorial disease caused by a constellation of various elements such as genetics, environmental, social, and lifestyle-related factors (4). Raised BMI is a major risk factor for non-communicable diseases such as cardiovascular diseases (mainly heart disease and stroke), diabetes mellitus, musculoskeletal disorders (especially osteoarthritis), and some cancers, including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon (2).

It is estimated that the cause of obesity in about 40 - 70% of the cases is presumed to be genetics (5). According to the Genome-Wide Association Studies (GWAS), about 97 gene loci and 835 genes in relation to obesity have been found (5, 6). Several genes implicated in monogenic obesity are in or near loci, and subsequently associated with obesity-related traits, including MC4R, BDNF, PCSK1, POMC, SH2B1, LEPR, and NTRK2 (7). The most important of these genes are FTO (5/ 8/11/ 13/ 22/ 23/ 24/ 25/ 26/ 27) Hind III, S447 (18/19/28) PPARÎş2 (16/29), and UCP2 (30/ 31). The FTO gene is known to be the most important gene causing obesity by increasing the appetite (8).

Investigators pursue the susceptibility genes to improve our understanding of the etiology of obesity. The primarily goal is to utilize this knowledge for the improvement of human health conditions through the development of new therapeutic or preventive treatments. Although this goal requires operational information (which is widely unavailable today), genetic variants for obesity-related traits have been exploited to provide numerous insights into the biology of obesity and its complications, as reviewed below. The purpose of this review article is to examine the role of genetics in obesity in Iranian men based on body mass index (BMI) and family history. To prepare this review, international and national databases (including Medline, Scopus, Clarivate Analytics, Magiran, SID) were searched with keywords including: Obe-

***Corresponding Author:** Shahrzad Nematollahi, Address: Men's Health & Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: shrzd.nematollahi@outlook.com, Phone: 2122712234 / Fax: (+98)2122716383

sity, Body Mass Index, Familial obesity, morbid obesity, Iran, Gene, Genetics. In total, 78 articles were extracted, which finally 26 were used for the present review. Examining these articles, we found no review article and no systematic review in this regard. (Figure-1)

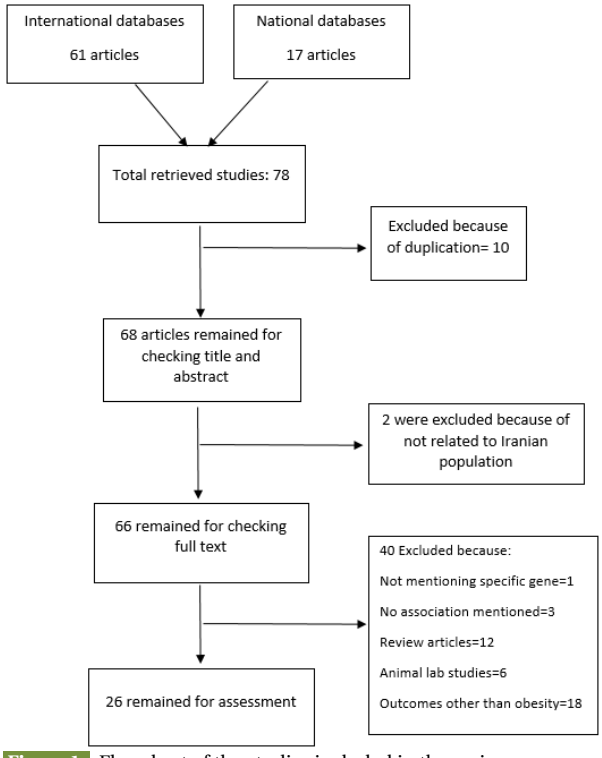

Figure 1: Flowchart of the studies included in the review.

1.1. Obesity based on BMI

Body Mass Index (BMI), calculated as the division of weight (Kg) by squared height (in meters), is a global index used to diagnosis obesity and overweight (9). According to the definition, overweight is defined as a BMI between 25 and 29.9; while, obesity I defined as a BMI equal or greater than 30.

Research on the role of genes in human BMI is rising in popularity in Iran (10). A kernel machine SNP analysis on the cohort participant of Tehran Lipid and Glucose study (TLGS) has shown that 97 genetic variants are involved in 2.7% of overweight individuals (defined as (25<BMI< 29.9)) (11).

A study on the C825T polymorphism in the GNB3 gene identified an association between TT genotype in the C825T polymorphism and obesity. The authors estimated that the probability of obesity in people with TT genotype in the C825T polymorphism is nearly 75% (10). Another study on adolescents showed a significant relationship between the T allele in UCP3 C-55T polymorphism and obesity. The prevalence of T allele of this polymorphism was estimated as 72% in obese individuals in contrast to 40% in normal individuals (12).

It has been shown that the FTO gene has had the strongest association with obesity. Several polymorphisms of this gene such as; rs1558902, rs3751812, rs9939609, rs9930506, rs1421085, rs17817449, rs9930501 & rs9932754 have been found to be related to obesity in human population (13). On the other hand, investigation has shown that intake of protein, carbohydrates, and fiber might reduce the risk of rs1558902 polymorphism (8, 14). A 3.5-year follow-up study on 4292 participants of Tehran Lipid and Glucose Study showed that in carriers of the risk alleles rs1121980, rs1421085, rs8050136, rs1781799 and rs3751812, BMI was approximately 2-fold higher in individuals in the higher quartile of western dietary pattern (full of processed red meat and full-fat diary) compared with the first quartile. The authors concluded that adults with higher genetic predisposition to obesity are more susceptible to the harmful effects of western dietary pattern (8). The association of healthy diet with obesity-associated variants (FTO) also has been shown in a nested case-control study, indicating that individuals with minor allele carriers of rs9939973, rs8050136, rs1781749, and rs3751812 had lower risk of obesity when they had higher scores on Mediterranean diet, compared to wild-type homozygote genotype carriers. However, the authors found no significant interaction between the genetic risk score and Mediterranean diet on abdominal obesity. The authors concluded that compared to those with lower adherence to the Mediterranean diet and lower genetic risk scores, higher adherence to the Mediterranean diet was associated with lower obesity risk in subjects with more genetic predisposition to obesity (15).

Mediterranean diet has also been studies on the context of the rs3751812 polymorphism, which carries the T allele in the TG + TT genotype (5). People with the AT or AA allele in the rs9939609 polymorphism are more likely to be obese, especially with a diet containing sweeteners and fried foods (8). Because this polymorphism is associated with a lower level of lipolysis in adipose tissue (23), people carrying this type of polymorphism have a higher weight loss than non-carriers if they use a healthy diet (8). The rs9930506 polymorphism with the GG genotype also has the strongest association with BMIs greater than 30. In a school-based study on male adolescents with body mass index (BMI) higher than +âĂĽ1 Z-score, it is shown that compared to male adolescents without extra weight, higher BMI and body fat percent and lower skeletal muscle percent were more likely to have a newly found haplotype of rs9930506, rs9930501 & rs9932754 (GGT) in the first intron of the FTO with complete linkage disequilibrium (LD). The association was remained after controlling for age, calorie intake and physical activity (13). Another study showed that compared

Table 1: Table of genes and polymorphisms affecting obesity

Genes	Polymorphism	Genotype
Based on BMI		
GNB3	C825T	TT
UCP3	C-55T	T
FTO	rs3751812	TG+TT
FTO	rs9939609	AT+AA
FTO	rs9930506	GG
FTO	rs9932754, rs9930501	First intron
Based on MetS		
LPL	D9N	AG+GG
LPL	rs328	GG+GC
LPL	rs5882	G
LPL	S447X,HindIII	
AZFa, AZFb, AZFc		microdeletion
MC4R	rs17782313	CC
RBP4	rs3758539	GA + AA
CD36	rs10499859	A
CD36	rs132246513	T
VEGF	rs6993770	AT + TT
HSP70	126HSP70-2	AA
based on family history		
IRS1	RR + GR (reduce risk of obesity)	

to normal adolescent males, male adolscents with very high BMI and lower skeletal muscle volume had the rs9930506, rs9930501 and rs9932754 haplotypes in their first FTO gene intron (23).

1.2. Sperm Factors

Metabolic Syndrome (MetS) as the most common form of lipid abnormalities can increase Triglyceride (TG) level and decrease High-Density Lipoprotein cholesterol (HDL) level. The lipoprotein lipases (LPL), located at the 8p22 locus, plays an important role in controlling MetS (16). A study on blood samples of 750 students aged 10-18 years showed that there were significant interactive effects from LPL polymorphisms and birth weight on HDL-C concentration, and also effects from LPL polymorphisms and BMI on TG and HDL-C concentrations. More specifically, the AG/GG genotype in D9N polymorphism was associated with higher LDL-C (low-density lipoprotein cholesterol) and lower HDL-C concentration. Significant interactions were found for D9N polymorphism and birth weight in association with plasma HDL-C concentration, and also for D9N polymorphism and BMI in association with plasma triglyceride (TG) and HDL-C levels. Significant interactions were found for S447X polymorphism and BMI in association with plasma TG and HDL-C concentrations (16). Another investigation on the association of a polymorphism of the lipoprotein lipase (LPL) rs328 and cholesteryl-ester-transfer-protein (CETP) rs5882 genes in relation to lipid profile concluded that there was a significant association of LPL and CETP polymorphisms with serum triglycerides and HDL-cholesterol. The results showed that in comparison to normal-weight subjects, obese subjects had a significantly higher level of triglyceride (TG), blood pressure, waist-circumference and fasting-blood-glucose, and lower level of HDL-C. The LPL rs328-GG-GC genotype was significantly related to a higher concentration of TG, compared to the CC wild-type; however, LPL and CETP polymorphisms were not associated with obesity. Additionally, the authors reported that obese-subjects carrying the G allele of CETP had a significantly lower level of HDL-C compared to those with C allele (17).

The most common LPL gene polymorphism is Hind III which occurs when the thymine is converted to guanine at position + 495 in intron 8 and correlates with birth weight in terms of HDL-C and BMI for TG and HDL-C. In a study on 233 obese adolescents with BMI> 30 and 156 healthy adolescents with BMI less than 25 as the control group, using the PCR- RFLP examined the Hind III and S447X polymorphisms of the LPL gene. The results of this experiment confirmed the relationship between sex and LPL gene polymorphisms and the risk of metabolic syndromes in the population of northern Iran (16).

Another example of factors contributing to obesity is the MSY region on the Y chromosome. This region consists of 3 segments AZFa, AZFb and AZFc, each of which contains different genes. Researchers have found that microdeletions in this area decrease androgen levels and increase BMI. In a study on 180 subjects (44 obese, 94 overweight, and 42 normal) in Golestan Province of Iran, the authors found that obese individuals with AZFc microdeletions, including gr/gr, had reduced testosterone levels and increases obesity, especially in men (4). The balance between energy intake and consumption is another factor contributed to the obesity. Melanocortin-4-receptor (MC4R) is one of the most important genes in energy homeostasis (18). There is a variant in the 188 kb downstream region of this gene, called rs17782313, which plays a role in increasing BMI. Research on Iranian population shows that people with the CC genotype had a higher fat level than those with the TT genotype and are more likely to have a BMI greater than 25 (19). Another gene involved in balancing energy intake is the ADRB3 gene at the 8p12-p11.2 gene locus. This gene is mainly expressed in adipose tissue and it plays a key role in regulating lipid metabolism and thermogenesis. This gene has a B3 receptor which, if translocation of Trp to Arg at position 64 of this receptor, decreases lipid metabolism by this gene and increases BMI (20). Another gene that plays a role in the volume of adipose tissue is the RBP4 gene, which is located in the 10q23-q24 gene locus and is released from the liver and adipose tis-

sue. This gene has two variants rs3758539 and rs10882273. An investigation on 321 people in Isfahan city found a significant association between the G and A allele in the rs3758539 variant, which was significantly higher in individuals with higher BMI and obesity. The authors also reported that people with higher BMI had GA + AA genotypes more frequently (21).

Obesity can be considered as both outcome and etiologic cause for other disorders/diseases. Obesity is heavily associated with cardiovascular diseases while Apo E gene, which plays a role in cardiovascular disease (42), also has a close relationship with its polymorphism and obesity. Although the association between this gene and obese individuals is controversial (22, 23). Unlike the two Apo E and NR1H3 genes, the CD36 gene in the 7q11.2-7q21.11 gene locus has been proposed as a candidate for BMI and MetS (24). The protein from this gene has two polymorphisms rs10499859A> G and rs13246513C> T.

According to other studies, another gene involved in MetS is the VEGF gene with rs6921438, rs4416670, rs6993770, and rs10738760 polymorphisms (25). The association between AT and TT genotype in rs6993770 polymorphism was reported as 49% and 15% in a study, respectively. The study concluded that the AT and TT genotypes were associated with increased levels of FBS and TG, causing MetS and obesity (26).

Further study by Mardan-Nik et al. has identified the HSP70 gene as a candidate for obesity. The HSP70-2 gene encodes a protein likely to be involved in obesity and also in coronary heart diseases (27). Application of PCR-RFLP method on 317 Iranian individuals to confirm this hypothesis revealed that there was a significant relationship between obesity and polymorphism of 126HSP70-2.

1.3. Discussion

Many scientists now believe that there is a link between obesity and lipid levels (17), increased triglyceride (TG) (18) and LDL (19), decreased HDL-C (18), and also disrupted hormones (6) such as Diponectin (20).

Reports suggest that adherence to a healthy diet will reduce and modify the effect of the FTO on obesity (5). This is probably due to the role of fiber diet which produces fatty acids such as acetate, propionate, and butyrate. These compounds acetylate the histone tail of the FTO gene and do not allow transcription of this gene (35). This creates a theory that butyrate inhibits histone deacetylase and aids in the expression of genes such as PPAR, which, as PPAR- Ît' activator, decrease FTO gene expression and thereby reduce obesity (36). The other two polymorphisms of the FTO gene, rs1421085 and rs17817449, have less association with diet (26). In this review article, we tried to examine the role of different genes in obesity by examining about 30 articles published on the role of genetics in the obesity of Iranian men, according to their BMI, MetS and family history. In conclusion, most of this research has been done on the FTO, HindIII and S447 genes, all of which have shown the highest relationship between these genes and obesity. Finally, according to studies, FTO can be considered as the most important and strongest cause of obesity. Despite the earlier intention to include the association of genetic traits with obesity in men population, we realized later that there is not much to go in this field in Iran. In other words, our review team was unable to find studies on male population to adequately address the question in hand. To overcome this problem, we attempted to include genetic studies with subgroup comparisons based on gender; however, much of the literature did not address gender-specific genetic mechanisms for obesity. Another limitation of our review is that this study was investigated genes that are responsible for obesity; nevertheless, other interactions that can indirectly decrease or increase gene expression and subsequently lead to obesity are not included. Some of the interactions that are overlooked in our review include gene sensitivity, molecular mechanism, and gene methylation.

2. Conclusion

According to the literature, the effect of FTO gene alleles in men and women were almost equal, and we found that men with FTO gene polymorphisms were most associated with obesity. A healthy diet such as diets full of protein and fiber with removal of sweeteners and fried foods can control obesity. In other words, even with the influence of genetics and the susceptibility to obesity in these people, the environment and living conditions of individuals can still have a significant impact on their phenotype. However, diet has no effect on the frequency of genes in this disease and can only be a preventive or therapeutic agent.

3. Appendix

3.1. Acknowledgements

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3.2. Authors Contributions

All the authors have the same contribution.

3.3. Funding Support

None.

3.4. Conflict of Interest

No conflict of interest.

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