

Association between Polymorphisms of FTO Gene and Obesity

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Accepted 13 October 2016; Published Online Autumn-Winter2016

ABSTRACT

Introduction: Obesity is an important metabolic disorder. Obesity has complications in most of human body organs. In the other hand, the Fat-mass and obesity-associated gene (FTO) polymorphisms may associate with obesity. Purpose of present study is evaluation of association between polymorphisms in FTO gene and obesity. This study comprised a narrative review on credible original articles. These articles were searched from PubMed, Science Direct and Google Scholar. Most researches were based on the existence of association between FTO gene polymorphisms with obesity but in the some results of studies about polymorphisms of this gene, it was obtained the conflicting results from the association of some polymorphisms with obesity. These points maybe are indicative racial differences in susceptibility to obesity between the different populations. According to the results, polymorphisms of FTO gene may associate with obesity, because several studies are based on the role of FTO gene polymorphisms in the susceptibility of obesity. In the following, it should be noted that genetically predisposed individuals who are susceptible to obesity need to special attention for combating obesity-related problems and promotion of their health.

Key words: Body Weight, Body Mass Index, Obesity, FTO Protein-human

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Introduction:

Obesity is a very important problem of public health in the global area and it is a very important risk factor for the emergence of non-transmissible diseases. There are approximately 937 million and 396 million obese and overweight adult people around the world, respectively. Iran is in this group and this complication is a significant outbreak in Iran, so that 50% of adults in Iran are overweight and obese (1, 2). The rapid economic development, especially in developed countries, has made significant changes in the rate of physical activity and this matter has an important role in the development of obesity. On the other hand consumption of high calorie foods and occurrence of polymorphisms in genes are two of the causes of obesity (3-7). Unfortunately, obesity can cause a significant number of diseases. A bunch of these diseases increases the risk of heart diseases due to the fact that one of the indicators of lipid profiles, i. e. the level of blood cholesterol in obese persons, is removed from the body in a normal state and is pathogenic. Undoubtedly, these diseases are one of the most fundamental threats to life. If cholesterol levels were be in abnormal state, it is considered one of the major factors in the development of vascular diseases. One of these diseases is coronary artery disease, which is also a common problem in obese people due to the lack of normal and high levels of this index of lipid profile (8, 9). But problems due to obesity do not just end in cardiovascular problems because obesity can cause many problems and other illnesses. One of these cases is associated with the digestive system, which affects different parts of the digestive tract. Obesity can cause fatty liver and gastroesophageal reflux. One of the harmful effects of obesity is impact on the gallbladder. In obese people, gallstones have a significant outbreak. Gout also is common in obese people. Gout influenced the life quality of defected person due to inflammatory effects on the joints (10-12). It should be noted that one of the most important problems of obesity, which needs a lot of attention, a significant incidence of diabetes in obese people. Obesity is associated with a variety of cancers. Of the cancers that have been linked to obesity, it can be mentioned endometrial cancer, colon cancer, esophageal cancer and breast cancer. Obesity can also be considered as a risk factor in the development of

osteoarthritis and breathing problems during sleeping (13-16). Over 115 million people in the world suffer from problems, disorders and diseases caused by obesity. This case confirms that a significant increase in obesity is actually a concern and a dilemma in the general health of societies. And as it is known, obesity is a risk factor for non-communicable diseases and it is also a factor in emergence of these diseases in low-income countries (17-20). Obesity is an inevitable cause of mortality worldwide. So that, in the worldwide, obesity and having an abnormal weight and overweight, is the fifth indicator of mortality (21). In the World Health Organization (WHO) report, obesity is not just a proliferation factor in developed societies; this problem is also evident in developing nations (17).

On the other hand, the polymorphism of genes is an important issue in the development of diseases and disorders (22). In fact, polymorphisms create a barrier to normal cellular life. These problems can be linked to many diseases. For example, some polymorphisms can cause cancers such as colorectal cancer and renal cell carcinoma (23, 24). And or they can be associated with serious metabolic diseases such as diabetes (25). Fat mass and obesity associated gene, that was called FTO gene, is one of the key genes in managing, controlling, and sustaining the metabolic properties of the human body, and hence the presence of polymorphism in the gene, is certainly the prediction of problems associated with metabolic features such as the disturbance of normal weight and the development of obesity. Because one of the sustainability benefits of metabolic properties in humans is to adjust the weight of the individual. And this adjustment is normal for the individual's weight, which it can be said that this gene plays a significant role in the energy homeostasis (26-28). In addition to obesity, the disorder of the FTO gene is also associated with diabetes, and this has been consolidated and confirmed in numerous studies (29, 30). As it is known, the protein derived from this gene, which is similar to name of its gene, is associated with its normal functions in protecting human health. The location of this gene is on chromosome number 16 and on the long arm of this chromosome (16q12.2). One of the important actions of this gene and its protein is that it is involved in the normal activity of the lipase

enzyme that can be associated with obesity. In this regard, researchers have taken a prominent role in controlling hunger and satiety of the gene and its level of mRNA, by adjusting nutrition and energy metabolism, it affects the weight balance of individuals (31, 32). With regard to the issues about the importance of attention to the issue of obesity and, on the other hand, with regard to the important roles associated with the metabolic problems mentioned for the FTO gene and its results, it is necessary to investigate the relationship between different polymorphisms of FTO gene in associated with obesity.

Methods:

This study comprised a narrative review on credible original articles. These articles were searched from PubMed, Science Direct and Google Scholar for studies published between 2007 and 2016 using search terms of "Obesity", "FTO gene polymorphism" and "FTO gene Alleles" and then were evaluated.

Relationship between FTO gene polymorphisms and obesity:

As mentioned, the FTO gene can affect human weight by affecting several mechanisms, such as adjusting energy homeostasis, regulating energy metabolism, engaging in normal lipase enzyme activity, controlling hunger and satiety, and stabilizing metabolic properties. Certainly, the polymorphism in this gene changes the enzymatic activity of the obtained protein and causes the instability of the metabolic properties. It should be noted that in addition to the FTO gene, other genes associated with obesity such as the potassium channel tetramerization domain containing 15 gene (KCTD15) and the Fas apoptotic inhibitory molecule 2 gene (FAIM2). Also the researchers confirmed the relationship between the gene of SH2B adaptor protein 1 (SH2B1 gene), the gene of protein Mitochondrial carrier homolog2 (MTCH2 gene), the gene of enzyme glucosamine-6-phosphate deaminase 2 (GNPDA2 gene), the gene associated with Niemann-Pick disease type C i.e. the NPC1 gene, the transmembrane protein 18 gene (TMEM18) and the SEC16B gene (protein of leucine zipper transcription regulator 2 is encoded by this gene), with the incidence of obesity. It is worth noting

that the researchers stated that the polymorphism of rs10913469 in SEC16B gene and polymorphisms of rs7561317, rs2867125 and rs6548238 in the gene of TMEM18, is one of the most important polymorphisms in the above mentioned genes and they are associated with obesity (33, 34). Paying attention to the polymorphisms in these genes and in the FTO gene is one of the most urgent issues in the medical sciences. With regards to its important functions, the polymorphism in the FTO gene can be associated with obesity. Interestingly, in addition to the association with obesity, there are studies that indicate the association of FTO gene polymorphisms with diseases such as polycystic ovary syndrome, metabolic syndrome, endometrial cancer, and pancreatic cancer (35-37).

The association of FTO gene polymorphisms with obesity has been studied in valuable studies. In this regard, researchers have suggested that there is an interesting relationship between polymorphisms within intron 1 in the FTO gene (e.g., rs9926289, rs1421085, rs8043757 and rs17817449) and obesity (38-40). These articles have been emphasized on topics, for example childhood obesity and severe obesity in adults. In a study by Scuteri et al. it was concluded that there was a meaningful and significant relationship between rs9930506 polymorphism in the FTO gene with increased hip circumference, body weight and the incidence of obesity (6). In another study in Japan, the results of the reports revealed a significant relationship between obesity and the rs1558902 polymorphism in the FTO gene (41). Also, researchers in this field of genetics by investigating the relationship between obesity and rs16953002 polymorphism in the FTO gene in the urban population in Iran reported that obesity can be related to the expressed polymorphism (42). Also in this field, studies have been conducted on rs8050136 polymorphism in the FTO gene in relation to obesity. Research results on a population in southern China indicated that a correlation between rs8050136 polymorphism in the FTO gene and an increase in the BMI index. But these results were not confirmed in studies on people in northern China. Similarly, studies conducted on Caucasian-American populations and have similar results to those of the southern population of China (43, 44).

Table 1. Results of relationship between FTO gene polymorphisms with and obesity or BMI index

Polymorphisms	The population studied	Association with obesity or BMI index
rs16953002	Iranian population (42)	+
rs17817449	Thai population (38)	+
rs17817449	Caucasian Americans (48)	+
rs17817449	Indian population (50)	+
rs17817449	Slovak population (51)	-
rs8050136	Caucasian Americans (48)	+
rs8050136	Japanese population (49)	-
rs8050136	South China population (43)	+
rs8050136	North China population (43)	-
rs8050136	Caucasian Americans (44)	+
rs9926289	Polish population (40)	+
rs1588413	Indian population (52)	-
rs1588413	Chinese population (53)	+
rs1421085	Thai population (38)	+
rs8043757	Thai population (38)	+
rs1558902	Japanese population (41)	+
rs9930506	Italian population (6)	+
rs9939609	Oceanic population (45)	-
rs9939609	Japanese population (47)	+
rs9939609	Caucasian Americans (48)	+
rs9939609	American population(49)	-
rs9939609	Romanian population (46)	+
rs9939609	Asian/Pacific Islanders(49)	+
rs9939609	black/African Islanders (49)	+
rs9939609	Hispanic population (49)	+

Genetics researchers have reported that there is no relationship between the rs9939609 polymorphism in the FTO gene and the BMI index in oceanic populations. Conversely, in another study, it was confirmed the relationship between rs9939609 polymorphism in the FTO gene and the increase in BMI. In this study, researchers found a significant relationship between two cases in Romanian population (45, 46). It has also been reported in Karasawa et al. that the rs9939609 polymorphism in the FTO gene is significantly correlated with obesity in the Japanese population (47). Regarding FTO gene polymorphisms and their relationship with obesity in a study conducted on the Caucasian population, reports showed a significant relationship between rs8050136 and rs17817449 polymorphisms with obesity. In addition, the researchers pointed out in this paper that rs9939609 polymorphism is associated with high values of the BMI index (48). Song and his colleagues also stated about the relationship between rs9939609 polymorphism with the BMI and waist size in the Hispanic population

and the White American population, which stated that there is a significant and strong relationship between them. On the contrary, these results were not confirmed in the black and Asian / Pacific Islanders (49). Also the findings of other study in Japan were based on the absence of a relationship between rs8050136 polymorphism and obesity (50). In a study by Prakash et al., its results confirmed the existence of an acceptable relationship between rs17817449 polymorphism and obesity. It should be noted that this study investigate the relationship between obesity and polymorphisms of rs17817449 in the FTO gene in population of China (51). But similar results were not found in a study conducted in Slovakia (52).

In reports from studies that determined the presence or absence of association between rs1588413 polymorphism in the FTO gene with obesity, there was no correlation between this polymorphism and obesity in the Indian population, but mentioned correlation was observed in a study on a population of China (53, 54).

Interpretation:

By focusing on the results of studies conducted on different populations, it can be argued that there is a potential relationship between different polymorphisms in the FTO gene and obesity. In a more comprehensive view, it can be said that the FTO gene polymorphism, due to basic role of FTO gene, can be considered as a main factor in regulating the energy of the human body in the pathogenesis of obesity. The importance of the issue is that in addition to increase of weight and BMI index, this polymorphism is also an important factor in increasing the hip circumference. Also, according to studies, polymorphisms in the FTO gene is associated with metabolic diseases, cancers, and ovarian problems. Maybe, it can be considered that the stated problems and diseases are more likely to occur in obese people. But this subject requires thorough and extensive studies to obtain comprehensive results. As it is known, the FTO gene has an important relationship with metabolic problems in the human body. And in the present study, the topic of obesity was evaluated, but in the present study, the results of the studies had contradictory results, too. In order to justify these contrasts and contradictions, as well as to justify the difference in the incidence quantity of polymorphisms between different populations, it can discuss the racial difference and differences in lifestyle and method of live. So that, some races have different genetic backgrounds. These areas of creating a disorder in a race can make differences by causing the same disorder in other races. Or genetically, in a race with a specific polymorphism, people get sick or complication. While this complication or disease for another population have been result from another polymorphism or a different polymorphism in the same gene. For example, in the northern population of a country, there is no relationship between obesity and rs8050136 polymorphism in the FTO gene. But in the southern population of the same country, the result is converse (43). It can be also stated that probably a polymorphism in a particular position influences another gene, which causes the change in the susceptibility of disorders or diseases in individuals (42). On the other hand, due to some situations and lifestyles, the incidence quantity of polymorphisms in different races is affected. For example, alcohol intake results in the occurrence of rs12597786 and rs7204609 polymorphisms in the FTO gene, and

also, the consumption of this substance is forbidden in the Muslim religion. For this reason, due to lack of use this risk factor, there may be differences in the incidence of these polymorphisms and the development of obesity among races, because alcohol consumption causes increasing the incidence of mentioned polymorphisms in the FTO gene (24, 55). It has also been argued that physical activity and exercise can be countered by the destructive effects of polymorphisms and reduce destructive impacts. For example, in polymorphism rs9939609 in the FTO gene, which increases subcutaneous fat, physical activity can reduce the effects of malignancies of this polymorphism. Also low physical activity increases the above damaging effects (56, 57).

However, it is necessary to conduct researches in order to achieve precise and comprehensive results for above reasons confirmation.

Conclusion:

According to the results, polymorphisms of FTO gene may associate with obesity, because several studies are based on the role of FTO gene polymorphisms in the susceptibility of obesity. In the following, it should be noted that genetically predisposed individuals who are susceptible to obesity need to special attention for combating obesity-related problems and promotion of their health. Finally, it is recommended that in this important area of genetics, extensive studies be conducted to provide useful results in combating obesity and, subsequently, combating obesity-related problems.

Acknowledgment:

Hereby, we extend our gratitude to the medical scholar and professor of Education Office, Sayed Mojtaba Mirsane for their support of this paper.

Conflict of Interest:

The authors declare that they have no competing interests.

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