The Association between FTO, MC4R Variants and Obesity in Different Populations and the Possible Reasons

Hanyu Zhang
Academy of life science biology engineering, Henan University, Shandong, China

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Abstract: Obesity is one of the diseases which have bad effects on human health. The finding of obesity genes is a breakthrough in the related area for sure. The association between obesity genes and obesity have certain differences in different population which never be investigated systematically. FTO genes and MC4R genes are common obesity genes. Furthermore, the paper concerning the roles of two genes in different populations and their mechanisms are abundant. However, limits still exist, including the lack of detailed researches on the interaction between two genes. There is less papers on whether other genes'effects cause this phenomenon and how the genes' interactions cause it. Topic and method: This paper aimes at exploring the differences of FTO and MC4R's functions in different populations. The author investigates it by looking through papers and analysis and comparing. Results and conclusions: Two hypotheses to the topic are proposed. Firstly, the reasons may be the genes' differences or the influences from other genes. Secondly, two possible influences from other genes are also mentioned, namely influence directly or indirectly. By analysing the results of existing literature and research, both two possibilities, including one hypothesis that the same genes have certain distinct features in different populations and another possibility that other genes may make effects on it, tend to be reasonable and for the latter circumstance, the effects made by other genes can be directly and indirectly.

1 INTRODUCTION

In recent years, with the improvement of life level, the number of obese people increase a lot. Obesity becomes one of the most severe diseases which influence people's health. Obesity causes trouble to people's life and every nations are eager to solve or relieve obesity through doing research on obesity. As varied obesity genes are found in turn, the mechanism of obesity genes, the methods to cure obesity become the focus of the researches. The topic of this paper is to explore the differences of obesity genes' functions among different populations and the possible reasons, analyzing the differences to find possible reasons to explain them. FTO genes and MC4R genes are proven to be one of the most significant obesity genes, which are related to human obesity. However, after research on the association between these two genes and obesity, the author finds that two genes' roles are different in different people are varied, showing the degree of functions, namely strong or poor, or even showing to have opposite functions. Questions are got and discussed. By looking through materials, two hypothesis about this phenomenon are made and then by analyzing papers, rationality of the two hypothesis will be described,including whether the genes themselves cause differences in different populations or other genes' influences lead these kinds of differences; if the latter description is correct, then, how the genes interact, directly or indirectly. Moreover, it can be used as an example to explore the differences of obesity genes among different populations.

This research has certain meanings for exploration of the differences of obesity genes in different population and may direct the direction to the further research to certain extent.

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2 ASSOCIATION BETWEEN FTO GENES AND OBESITY, MC4R GENES AND OBESITY IN DIFFERENT POPULATIONS AND AN INTERESTING PHENOMENON

FTO genes and MC4R genes all tend to have varied influence in different populations. It is shown as the reduction or increase of their functions or even showed to have opposite effects which is interesting. The two genes seemed to be able to influence each other. Both FTO genes and MC4R genes are genes related to obesity significantly. However, these two genes are proven to have different effects in different populations in recent researches. In specific regions, researchers selected obese people and healthy people in random. They used real-time polymerase chain reaction to measure the prevalence of FTO variants and MC4R variants in participants and also took certain methods to measure related obesity markers, including body wight, body mass index, fat mass percentage, hip circumference, waist circumference, waist-to-hip ratio and so on. According to these data they collected, they built linear regression analysis and other mathematical models to analyze the relationship between these variants and obesity. The results found that polymorphisms in the first intronic region of the FTO gene are associated with obesity-related characteristics such as increased body weight, hip circumference, and waist/hip circumference ratio in European, Asian, African(Adeyemo 2010, Dina 2007, Tan 2008, Peeters 2008, Hess 2014). However, actually, the associations between FTO genes and obesity are very complex among people. Factors including races, regions where they live and so on may affect it. There is a research showing that FTO genes have no apparent relationship with obesity in Egypt (Abdelmajed 2017), though this gene is shown to be related to some factors related to obesity, like LDL. For Portugal, FTO genes are associated with obesity significantly, as it is related to many characteristics including BMI (Albuquerque 2013). At the same time, though the participants are from the same population, some differences of FTO's effects for obesity exist in females and males or in different age ranges.

Taking China as an example, some research concluded that FTO broad variant rs9939609 are linked with weight, BMI, waist-to-height ratio and fat(Wang 2012). This theory have differences in different sex, as this bond is stronger in girls than in boys. Whereas, the research-based on Egypt, the association between obesity and FTO genes is strongest in children aged 11. These differences may be led by the errors in sample selection, standard and data-analysis methods. Still, they are too little to be taken into considerations. Excluding these errors, from this phenomenon, a hypothesis is put forward. It may be because the influence from some special genes only play roles in certain populations or have different degree of activity on FTO genes or FTO genes themselves do play different roles in different populations. There is a research by Ningombam SS(Ningombam 2021), which can be cited as an evidence to justify the first hypothesis. In India Liangmai and Mizo tribes, rs17782313, a variant of MC4R, reduces the risk for people suffer from obesity which is very special and the FTO variants rs9939609 can increase the risk. However, if people have MC4R and FTO variants simultaneously, the extent of risks increased by FTO variants will be decreased to some degree. Theoretically, as an important obesity gene, MC4R genes are thought as a regulator working in hypothalamus to maintain physical homeostasis, control food intake and weight(Farooqi 2008). Its variants are justified to have close relationship with obesity in varied populations including Chinese(Wang 2017), German(Vogel 2011), Brazilian(Fernandes 2015), European-American and African-American(Grant 2009) and it does increase the risk of getting obesity through certain pathways. Contrasted by these data, the condition in India written above is very special and totally different from that, it can be guessed that obese genes have different expression in different people caused by other obese genes' roles. Nevertheless, this hypothesis needs more evidences to increase its persuasion. In the following content, mechanism will be investigated in order to explore whether this hypothesis is accurate.

Variables	Liangmai			
	Model	TBA	CVC	*p* Value
BMI	*FTO*	0.495	7/10	.15
	FTO, MC4R	0.505	8/10	.01*
	FTO, MC4R, MTHFR	0.509	5/10	<.001*
WC	*MC4R*	0.584	10/10	.007*
	FTO, MC4R	0.529	7/10	.001*
	MC4R, MTHFR, ACE	0.509	7/10	<.001*
WHR	*ACE*	0.450	5/10	.07*
	MC4R, ACE	0.589	9/10	.003*
	MC4R, MTHFR, ACE	0.452	6/10	<.001*
WHtR	*MC4R*	0.572	10/10	.01*
	FTO, MC4R	0.564	7/10	.003*
	FTO, MC4R, ACE	0.533	9/10	<.001*
TC	*FTO*	0.525	10/10	.316
	MC4R, ACE	0.458	6/10	.172
	FTO, MC4R, MTHFR	0.459	6/10	.071
TG	*FTO*	0.504	8/10	.072
	FTO, MTHFR	0.563	10/10	.013*
	FTO, MC4R, MTHFR	0.543	10/10	.005*
HDL	*MC4R*	0.570	10/10	.018*
	FTO, MC4R	0.543	8/10	.018*
	FTO, MC4R, MTHFR	0.553	5/10	.010*

Figure 1: Genetic interaction results between FTO rs9939609, MC4R rs17782313, ACE I/D rs4646994 and MTHFR C677T rs1801133 for somatometric and dyslipidaemia variables using generalized multifactor dimensionality reduction (GMDR). It comes from the paper of Somorjit.(Inandiklioğlu 2021).

Genotype	Obese patients $n = 100$	Control $n = 100$	*p*-Value
MC4R rs12970134 (AG and AA)			
GG	47	57	0.315
AG	42	36	
AA	11	7	
MC4R rs17782313 (CT and CC)			
TT	50	60	0.230
CT	37	33	
CC	13	7	
FTO rs1421085 (CT and CC)			
TT	25	41	0.019[a]
CT	47	44	
CC	28	15	
FTO rs9939609 (AT and AA)			
TT	26	46	0.002[a]
AT	48	44	
AA	26	10	

Figure 2: Distribution of polymorphisms of melanocortin-4 receptor and fat mass and obesity-associated genes between obese patient group and control group.This table is derived from paper written by Nihal (Inandiklioğlu 2021).

3 EXPLORING THE FUNCTION BETWEEN OBESITY GENES FROM THEIR MECHANISM

In 2019, Luca A.Lotta etc did research and found that there are 9 MC4R variants among 61 kinds of variants are connected to their activities and this kind of variations can make people reduce eating. This finding can work as an evidence for the first hypothesis which can explain that rs17782313 shows the function of obesity suppression in Indian tribes while in other districts, it increases the risk of suffering obesity. What is more, it proves that if the same variant' activity changes, it may cause changes in their functions. For hypothesis two, two possible situations exist. One is that two or more genes all work independently and different roles added up to have a general final results. Two is that genes' functions and pathways are similar, opposite or crossing, then same functions or opposite functions are added up or counteract which lead to the final results. Put these concepts into the analysis of the Indian tribes' phenomenon and it shows to have two possibilities. Namely, the pathways of FTO to play roles are opposite to MC4R's and then MC4R genes suppress the functions of FTO genes; or these two genes function through unrelated pathways but their direct functions are opposite completely, so MC4R genes can suppress FTO genes, for example, FTO may suppress the appetite while MC4R lead a good appetite or their direct effects have no associations but these effects can lead opposite results for obesity, for example, FTO can suppress appetite while MC4R can suppress the release of insulin and finally they have the opposite function to the possibilities of suffering obesity. Through the research, the mechanisms of FTO are below:

Under high-fat diet, FTO can influence the distributions of fat. Also, FTO can reduce glucose tolerance and influence leptin resistance. In 2015,Y.C.Tung etc found that WT mice given a HFD gained more visceral epididymal fat than subcutaneous fat(Tung 2015). But variant mice have opposite tendency. Moreover, its binding partner is NFκB's transcriptional coactivator, which can influence signaling pathway of NFκB to make effects on leptin.

Some researches find that FTO can control mitochondrial content and fat metabolism by moderating N6-methyladenosine(m6A) levels in hepatic cells which can be known from the figure 3 below(Kang 2018).

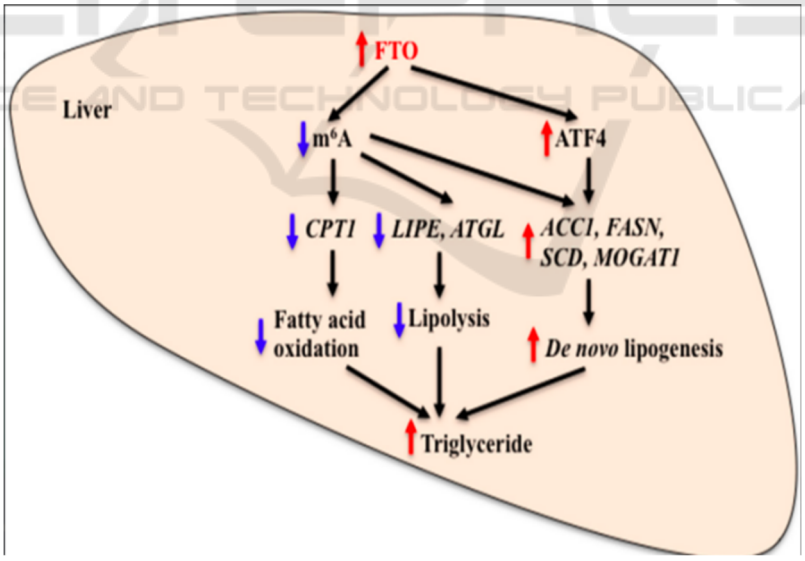

Figure 3: N6-methyladenosine(m6A) levels in hepatic cells.

FTO regulates hepatic lipid metabolism by altering the methylation state of genes that are involved in fatty acid oxidation, lipolysis and de novo lipogenesis. FTO also regulates hepatic lipid metabolism by altering the activity of transcription factors. Increased FTo expression and/or activity causes a reduction of m6A levels and reduces CPT1, LIPE and ATGL mRNA expression, leading to reduced fatty acid oxidation and lipolysis. It also causes an increase in ATF4 expression, which then stimulates expression of lipogenic genes, leading to increased de novo lipogenesis in the liver. Reduced

FTO expression and/or activity causes the opposite effect. FTO: Fat mass and obesity-associated, m6A: N6-methyladenosine, CPT1: Carnitine palmitoyltransferase 1, LIPE: Hormone sensitive lipase, ATGL: Adipose triglyceride lipase, ACC1: Acetyl-CoA carboxylase 1, FASN: Fatty acid synthase, SCD: Stearoyl-CoA desaturase, MOGAT1: Monoacylglycerol O-acyltransferase 1, ATF4: Activating transcription factor4. Red arrow: Stimulation. Blue arrow: Inhibition.

Under the moderation of metabolic signal, FTO encodes FTO protein and change FTO protein level can influence glucose and lipid metabolism.

However, MC4R genes are at the end of appetite regulation mediated by leptin and can encode MC4R receptor. When α－MSH combines with MC4R receptor in hypothalamus, the appetite will be suppressed. In addition, MC4R genes also take part in the regulation of leptin sensitive and glucose steady state.

From two genes' mechanisms, the two all participate in the regulation of leptin which means the first possibility is right. FTO genes are related to glucose tolerance while MC4R can regulate insulin and glucose state which are not the same but all influence glucose metabolism and obesity. It caters to the second possibility. Therefore, the hypothesis two is reasonable.

4 CONCLUSIONS

Through certain methods, the fact that some obesity genes have differences in different populations are judged. The fact is found that MC4R genes variant rs17782313 plays an opposite role in Liangmai and Mizo tribes in India, compared with other countries.The results of the two hypotheses are as follows.

In terms of the first hypothesis showed as resonable possibility , the author found some MC4R variants change activities, which do have an opposite result to those common variants, suppressing obesity. Hence, the reason for the differences of MC4R functions in Indian tribes may be related to the discrepancy of genes' activity. The second hypothesis is proved to be right. In Indian tribes, when FTO genes and MC4R genes exist together, FTO's acceleration to obesity is suppressed by MC4R genes, which prove the rationalities for hypothesis.

For the mechanism of two genes, two possibilities are put forward: their mechanisms are related; their mechanisms are opposite or the same or crossing. Taking MC4R genes and FTO genes as examples, according to the researches, it is found that both genes have relationship with leptin which prove the rationalities of possibility one. What is more, their roles in moderating glucose have differences, FTO genes can change glucose tolerance while MC4R can moderate insulin and glucose state which support possibility two. After research and discussion, the author finds that obesity genes do not work independently but are related and interact. The differences of genes in different population do lead to different results of obesity genes.

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