Influence of Fat Mass- and Obesity-Associated Genotype, Body Mass Index, and Dietary Intake on Effects of Iroquois-related Homeobox 3 Gene on Body Weight

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To the Editor: Iroquois-related Homeobox 3 (IRX3) is a member of the Iroquois homeobox gene family that encodes a protein known for its essential role in spinal cord development.[1] Recent studies reported that the expression level of this gene in hypothalamus is related to calorie intake and body composition.[2] There are some evidences that polymorphisms of IRX3 gene and the level of IRX3 gene expression are both related to obesity through various mechanisms. An interesting point is that in some studies, upregulation of IRX3 was related to obesity,[2] while in some other studies, decrease of its expression was related to obesity.[3] Several mechanisms have been identified for the association between IRX3 gene and obesity. Knockout of IRX3 expression in brain resulted in a decrease of body fat mass by increasing basal metabolism rate and browning white adipose tissue. Knockout of IRX3 expression in mice caused an increase in uncoupling protein 1 (UCP1) gene expression in white adipose cells which is an important factor of browning white adipocytes.[4] However, contradictory results were found in this area. In the study by Zou et al.[1] it was observed that increasing the expression level of IRX3 is positively related with browning adipocytes. In this study, the researchers reported that IRX3 knockdown could decrease the expression of UCP1 and thermogenesis and increase obesity. It seems that some metabolic factors influence the effect of IRX3 on body weight that may lead to contradictory results.

The contradiction in the results across studies can be related to the differences in genotype and the level of expression of fat mass- and obesity-associated (FTO) gene. One possible hypothesis is based on the effects of FTO genotype on the level of IRX3 gene expression. Smemo et al.[5] showed that the polymorphism of FTO gene has a relationship with the expression of IRX3 gene in human brain. Claussnitzer et al.[5] observed that FTO gene variant can disrupt AT-rich interactive domain 5B repressor binding; this disruption results in derepression of IRX3 during early adipocyte differentiation. This process could lead to a cell-autonomous shift from white adipocyte browning and thermogenesis to lipid storage, increased fat stores, and body weight gain. Moreover, Tews et al.[3] interestingly concluded that FTO knockout could increase the expression of UCP1 and the browning of white adipose tissue. Interestingly, Landgraf et al.[3] showed that risk allele of FTO for obesity is related to IRX3 expression only in children with body mass index (BMI) higher than 95th percentile. Therefore, people’s BMI may also play a significant role in the relationships between FTO and IRX3 [Figure 1].

On the other hand, diet can also affect IRX3 expression and the results appear to be contradictory in different studies. It is reported that a high-fat diet causes an increase in IRX3 expression.

Figure 1: The effects of Iroquois-related homeobox 3 on body metabolism and obesity which is influenced by fat mass- and obesity-associated gene, diet, and obesity.

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in adipose tissues, while in another study, the expression of IRX3 was upregulated in adipose tissues after a low-fat diet. However, a reason for this contradiction can be the fact that IRX3 expression reacts differently under the influence of different variants of FTO, and IRX3 gene is upregulated in FTO knockout mice after a high-fat diet. However, the exact mechanism of these changes has not been determined yet, and more studies are required in this area.

Totally, the results of the studies existing in this area showed that the association between IRX3 and obesity can be influenced by FTO genotype, BMI, and dietary intake. More human studies are required to examine the suggested mechanisms of the effects of these genes on body weight.

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Conflicts of interest
There are no conflicts of interest.

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