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.[1,2] 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.[1,3] 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.[2] 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*.[2] showed that the polymorphism of FTO gene has a relationship with the expression of *IRX3* gene in human brain. Claussnitzer *et al*.[4] 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*.[5] 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

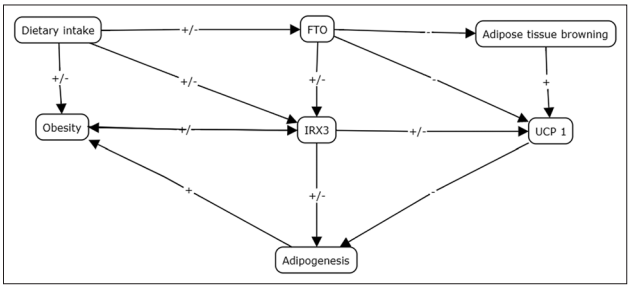

Figure 1: The effects of Iroquois-related homeobox 3 on body metabolism and obesity which is influenced by fat mass- and obesity-associated gene, diet, and obesity.

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in adipose tissues,[4] while in another study, the expression of *IRX3* was upregulated in adipose tissues after a low-fat diet.[2] 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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