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RESEARCH LETTER

Variation in the *FTO* gene locus is associated with cerebrocortical insulin resistance in humans

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To the Editor: In a genome-wide association study, the *FTO* locus has recently been identified as a gene associated with increased risks of obesity and type 2 diabetes mellitus in humans [1–3]. Dina et al. [4] reported that variation in this gene is strongly associated with childhood and severe adult obesity. In this paper, three single nucleotide polymorphisms are proposed to be functional and were reported to be in high linkage disequilibrium with the variants rs8050136 and rs9939609 reported by Scott et al. [1] and Frayling et al. [2], respectively. The overall weight effect of the risk genotype has been estimated to be approximately 3 kg and was detectable in children from age 7 years upwards [2]. These studies suggest that variants in the *FTO* gene cause an early onset deterioration of body weight regulation. Based on this, we investigated the relationship between the *FTO* variant rs8050136 and BMI using data obtained from the Tübingen Family (TÜF) Study [5]. BMI was higher in carriers of the risk allele than in wild-type individuals (AA [n=463] 27.2±0.3 kg/m^2, AC [n=732] 29.0±0.3 kg/m^2, CC [n=267] 29.5±0.5 kg/m^2, means±SEM, $p<0.001$) as a result of increased body weight (AA 79.8±0.9 kg, AC 84.7±1.0 kg, CC 84.8±1.5 kg, $p<0.001$). This finding replicates the previously reported weight difference in our population [1–4]. However, the mechanism by which *FTO* polymorphisms affect body weight in humans is still unclear. In mice, *FTO* is expressed in multiple tissues, including the brain. It is located on a region on chromosome 8 that is deleted by the Fused toes mutation [6]. The fused toes mutation causes a complex phenotype that features partial syndactyly of forelimbs and defects in brain morphogenesis [7]. However, in these animals, no conclusive evidence for a role of *Fto* or other deleted genes in energy homeostasis has been discovered. In their study Dina et al. [4] investigated the expression of *FTO* in human tissues, and in agreement with findings from animal studies, the *FTO* gene was found to be expressed in the brain. We recently described cerebrocortical insulin resistance in obese humans [8]. In lean humans, spontaneous cortical activity (beta and theta activity) is increased by insulin, while in obese individuals this effect was absent. In the brain, insulin acts as an adiposity and satiety signal and is critical for normal body weight regulation [9]. We therefore hypothesised that a reduced insulin response in the brain in carriers of a risk allele in *FTO* may be involved in the obesity effect and enrolled 47 subjects from the total database to study the effect of this polymorphism on the cerebrocortical insulin response. The genotype groups within this subgroup were matched for BMI, sex and age to exclude other obesity-

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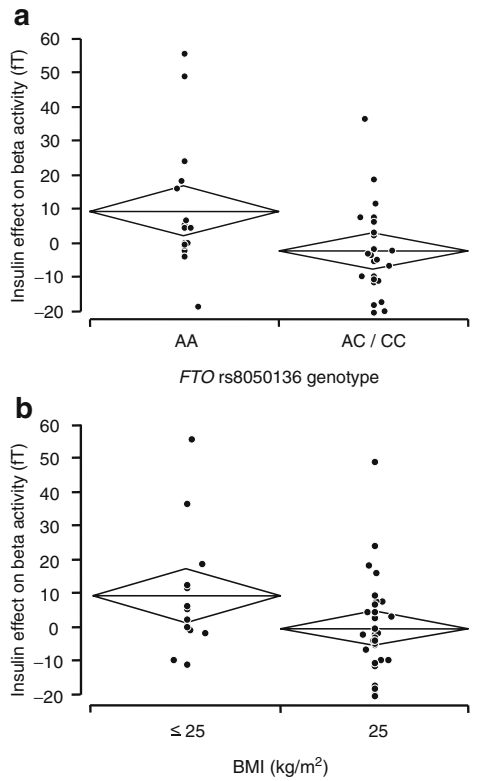

Fig. 1 **a** Insulin effect on beta activity in the genotype groups. In subjects carrying the rare allele of rs8050136 in the homozygous or the heterozygous form (CC [n=12] or AC [n=18], BMI 27.3±0.9 kg/m^2, mean±SEM) the insulin effect on beta activity was significantly reduced compared with wild-type carriers (AA [n=17], BMI 27.3±1.2 kg/m^2) (p=0.016 by two-tailed Wilcoxon test). **b** Insulin effect on beta activity in lean vs overweight/obese subjects. In overweight and obese subjects (BMI >25 [n=34]; 29.7±0.5 kg/m^2, mean±SEM) the insulin effect on beta activity was significantly lower than in lean subjects (BMI≤25 [n=13]; 21.5±0.5 kg/m^2) (p=0.046 by two-tailed Wilcoxon test), indicating insulin resistance of the brain. This difference between lean and overweight/obese humans has already been reported in 25 individuals [8]. These individuals are included here. The effect of the genotype was comparable to the difference between lean and overweight/obese subjects, even though the genotype groups were matched for BMI. This suggests that in carriers of the risk variant in *FTO* the effect of insulin on beta activity is as low as in obese subjects. The diamonds show the means of each group (horizontal line) and the confidence intervals of the means (upper and lower point)

related traits. The study protocol was approved by the Ethics Committee of the University of Tübingen and all participants gave written informed consent. We found that the obesity risk variant was associated with a reduced insulin effect on beta activity (Fig. 1a), which implicates a lower cerebrocortical response to insulin. Furthermore, in a multivariate model, the effect of the *FTO* polymorphism was independent of the Gly972Arg polymorphism in *IRS1*, which we have previously reported to reduce the cerebrocortical insulin effect (FTO p=0.014, IRS1 p=0.041, adjusted for BMI and age). The effect of being overweight/obese on the insulin effect on beta activity was similar to that of the *FTO* risk variant (Fig. 1b). This implies that even though participants were matched with respect to BMI, the overall genotype effect on cerebrocortical insulin sensitivity was similar to the effect of increased weight. At least in animals, insulin resistance in the brain has been shown to cause obesity [9]. It is therefore conceivable that the decreased cerebrocortical insulin effect in humans describes a mechanism by which variation in *FTO* contributes to the pathogenesis of obesity.

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