Sex Modifies the Association between Diet Intake-Regulation Related Genes and BMI z-scores in Children

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Background

- Excessive energy intake is a critical contributor to the development of childhood obesity.
- Genes involved in the brain eating regulatory systems (hypothalamus and food reward circuitry) may play a role in dietary intake and consequently weight gain.

Objective

The aim of this study was to assess the association between genetic variants mapped to three genes involved in the brain eating regulatory circuitry with the standardized BMI in school-age children.

DRD2 (rs1800497) – Mesolimbic dopaminergic pathway
CLOCK (rs1801260) – Circadian rhythms
NR3C1 (rs56149945) – Stress
FTO (rs9939609) – Obesity

Methods

- Anthropometric measurements and genotypes were available in 121 school-age children in the *Fuel for Fun (FFF)* study.[1]
- *Fuel for Fun* study is a multi-component, school- and family-based, cluster-randomized intervention trial (NCT02491294). The intervention is designed to improve culinary skills, dietary intake, and physical activity.
- Anthropometric measures were assessed at the baseline and 12-month follow-up.
- Age- and sex-specific standardized BMI scores (BMIz) were calculated based on the growth chart developed by the US Centers for Disease Control and Prevention.

- The children's DNA was obtained from buccal swab samples, and genotyping was performed by The Pennsylvania State University Genomics Core using the Thermo Fisher TaqMan assay (Thermo Fisher Scientific, CA, USA).
- Mixed-effects linear regression was applied to assess the genetic association and control clusters within families and schools.
- Covariates: age, sex, race, screen time, and intervention arms.

Table 1. Characteristics of the *FFF* Youth Participants (n=121)

Characteristic	Baseline	12-month follow-up
Overweight (BMI percentile ≥85)	14%	29%
Age mean (s.d.)	9 (0.5)	10 (0.3)
Boys	56%	
Caucasian	81%	
Screen time (hr/day)	3.4/2.5	3.2/2.1
Intervention		50%

Results

- Obesity affected 6% children at baseline and 17% at the 12-month follow-up.
- rs9939609 at *FTO* (AG vs. GG alleles, p=0.039) was significantly associated with the follow-up BMIz scores (Figure 1).
- Sex significantly modified the associations of BMIz at baseline with loci at the *DRD2* (p=0.047), *CLOCK* (p=0.029), and *FTO* (p=0.034) genes (Figure 2-4).

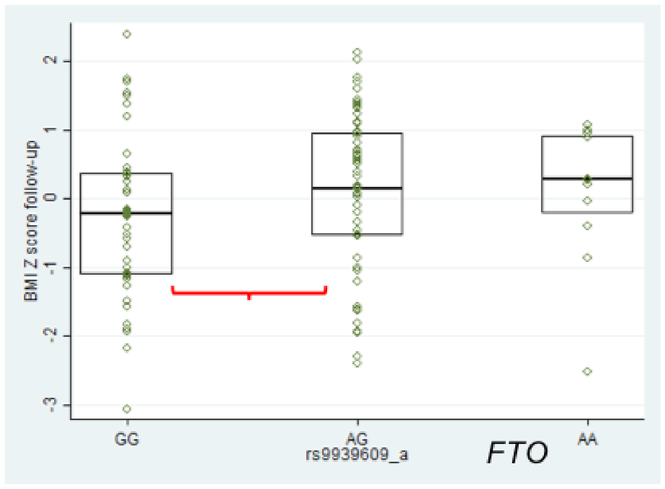

Figure 1

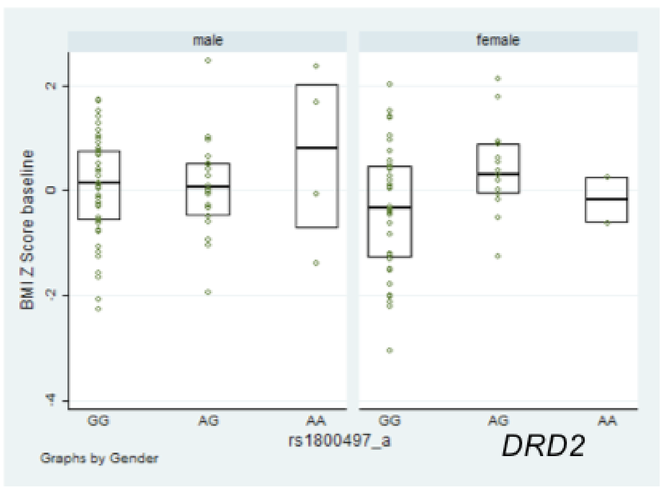

Figure 2

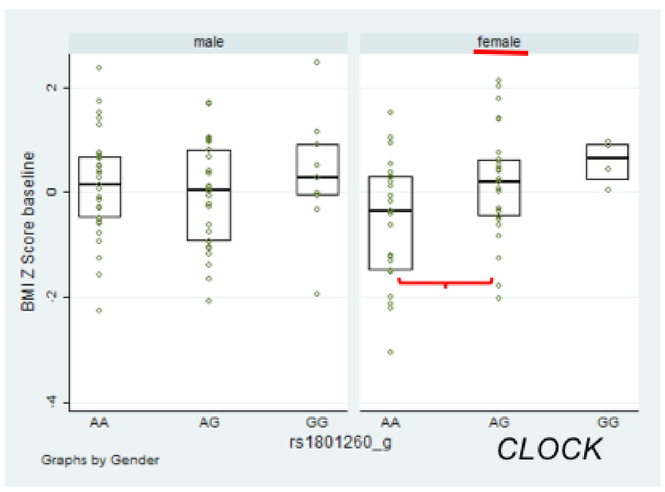

Figure 3

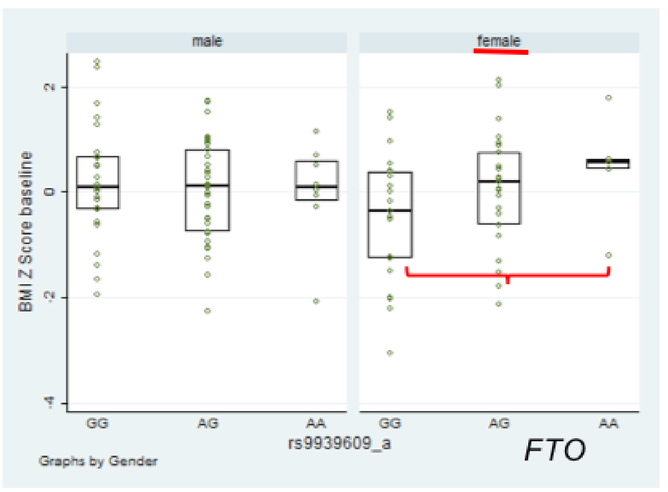

Figure 4

- At the follow-up, sex significantly modified the associations of BMIz with loci at the *CLOCK* (p=0.039) and *NR3C1* (p=0.015) genes (Figure 5).

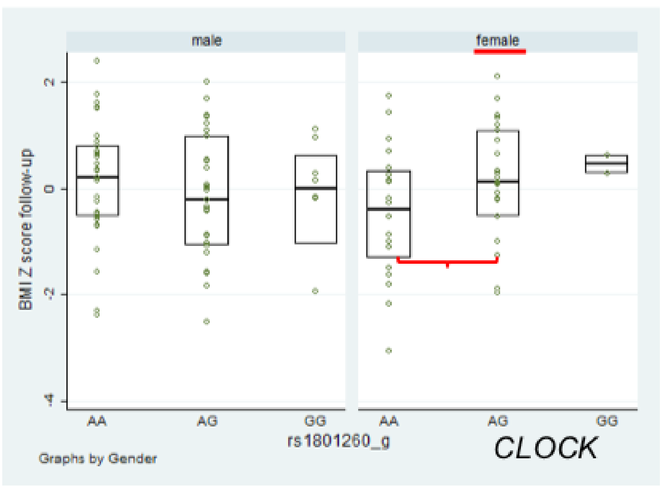

Figure 5

- Function analysis of the three variants indicates that the variants located within *DRD2* and *NR3C1* are missense variants and the variants located within *DRD2* and *CLOCK* are gene expression quantitative trait loci (eQTL).
- Gene function analysis indicates that *DRD2* is involved in the food reward circuitry.[2] *CLOCK* is associated with sleep duration and potentially dietary intake.[3,4] *NR3C1* plays a role in stress and may be associated with stress eating behavior.[5]

Conclusion

- Our results indicated that sex could be a critical modifier for the relationship between potential eating regulatory genes and body weight in children.
- Further investigation is warranted to delineate the relationship between sex hormones and eating regulatory circuitry.

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