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The Obesity-related Single Nucleotide Polymorphisms *FTO* and *GHSR* Genes and the Postprandial Feeling of Fullness in Filipino Adults

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Obesity-related single nucleotide polymorphisms (SNPs) may impact the control of energy intake and eating behavior. However, the effect size of those individual SNPs is not yet fully elucidated. Intervention studies using a standardized test meal coupled with a validated visual analogue scale (VAS) is important in understanding the influence of SNPs in the subjective feeling of appetite. This study aimed to assess the influence of obesity-related SNPs on appetite responses of Filipino adults following consumption of equicaloric breakfast meals. In an intervention study, thirty-four apparently healthy Filipino adults were genotyped for SNPs in the fat mass and obesity-associated gene (*FTO*) and growth hormone secretagogue receptor (*GHSR*). A validated VAS was used to capture the pre- and post-prandial feeling of the appetite of the study participants. Analysis of covariance (ANCOVA) was used to determine the differences between the subjective ratings of appetite (hunger, fullness, desire to eat, and prospective consumption) relative to the genotype of the study participants. The mean rating of fullness was 5.6% lower in carriers of the risk-allele A for *FTO* rs9939609 and 16.6% higher in carriers of the risk-allele A for *GHSR* rs572169. The levels of fullness after a meal is significantly influenced by the obesity-related SNPs *FTO* rs9939609 and *GHSR* rs572169 after controlling for age, sex, height, weight, BMI, and baseline appetite scores of the study participants. Our result implies that genetic polymorphisms might pose control of subsequent food intake.

Key words: appetite, food intake, fullness, obesity, single nucleotide polymorphisms

INTRODUCTION

According to the World Health Organization (WHO 2018), in 2016, a total of more than 650 million adults were obese worldwide. The worldwide obesity prevalence has gone triple since 1975 and it continues to pose serious debilitating clinical conditions (WHO 2018).

In the Philippines, the Food and Nutrition Research Institute (DOST-FNRI) reported that in 2013, three in every 10 adults were overweight and obese. Obesity as classified by either BMI, waist circumference (WC), or waist-hip ratio (WHR) is found to be high in prevalence (DOST-FNRI 2015). As such, the problem of overweight and obesity has been one of the key issues being addressed by the Philippine Plan of Action for Nutrition 2017-2022 – along with stunting and wasting among children, deficiencies in vitamin A, iron, and iodine, hunger and food insecurity, maternal nutrition, and poor infant and young child feeding (NNC 2017). Eating patterns, access and availability of foods, physical inactivity,

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and home habits (such as parents who do not eat well setting the wrong example to their children) were found as contributing factors of overweight and obesity in the Philippines (EIU 2017).

In the context of biology, the obesity epidemic can be deemed a result of energy imbalance coupled with excessive fat deposition (Racete et al. 2003). What is crucial in this disparity is the careful attention required to balance the interaction among multiple factors such as biology, environment, and behavior (Kadouh et al. 2016). The essential drivers for such a conundrum are the interplay of genetics, behavior, environment, physiology, social and cultural factors, food consumption, and eating traits – as well as the increasing palatability, variety, and availability of food (Racete et al. 2003; Rolls 2007).

The recent progress in the genetic basis of obesity has supported the 'thrifty genotype' hypothesis originally proposed by Neel (1962), where he suggested that genes that predispose a human being to obesity would have had an impact in populations that frequently experienced starvation. Decades after, intensive research in the field of genetics and obesity has proven the existence of a continuum between monogenic and polygenic obesity that further explains the role of genes in the regulation of food intake and genetic predisposition to obesity (Choquet & Meyre 2011). In 2016, genome-wide association studies (GWAS) findings revealed that there were about 127 sites in the human genome that have been linked to the development of obesity (Alonso et al. 2016). To date, available evidence suggests that genetic polymorphisms can also influence appetite responses (Dougkas et al. 2013; den Hoed et al. 2008) particularly on the phenotypes involved in snacking, eating patterns, energy intake, and uncontrolled eating (Bienertová-Vašku et al. 2010; De Krom et al. 2007; Qi et al. 2008; Konttinen et al. 2015).

Both the *FTO* and the *GHSR* gene have been associated with obesity and obesity-related phenotypes in different populations. The *FTO* gene was the first locus found to be associated with obesity in cohorts done among Europeans, European Americans, and Hispanic Americans (Frayling et al. 2007; Scuteri et al. 2007) and appears to influence obesity and obesity-related traits among Asians (Li et al. 2012; Rees et al. 2011). The relationship of the *FTO* gene with diet and appetite, particularly of the SNP rs9939609, was demonstrated in studies among children where it was found that participants carrying the minor variant tend to consume more fat and energy (Timpson et al. 2008) and show hyperphagic-like characteristic indicated by profound preference for energy-dense foods (Cecil et al. 2008). A study by den Hoed and co-authors (2008) conducted among adults with BMI ranging from 19-31 kg/m^2 revealed that the A allele of rs9939609 caused a significant reduction in postprandial satiety and a potential contribution towards consumption of excess calorie. Conversely, in a review conducted by Livingstone and co-authors in 2015, it was found that in each copy of the A allele of the *FTO* gene, individuals aged 31-75 years tend to report lower energy intake.

Attributing the *GHSR* gene in the genetic etiology of obesity is due in part to its location and function. It is located in the chromosome 3 (3q27), a region found to have a strong link with metabolic syndrome and obesity (Kissebah et al. 2000). The physiological role of the *GHSR* gene is in food intake regulation and energy homeostasis. Using a rat model, it was found that rats lacking a functional *GHSR* tend to eat less despite different exposures such as acute fasting, long-term high-fat diet, and presence of palatable dessert (MacKay et al. 2016). Among humans, den Hoed and co-authors (2008) demonstrated that the coding SNP rs572169 in the *GHSR* gene contributes to the variations of energy and food intake by influencing dietary restraint and disinhibition.

This study aims to provide preliminary insights on the influence of two known obesity SNPs in appetite perception through an intervention study. It aimed to assess the changes in the level of subjective feeling of appetite as they relate to *FTO* rs9939609 and *GHSR* rs572169 following consumption of equicaloric breakfast meals.

MATERIALS AND METHODS

Recruitment, Study Population, and Ethical Considerations

The study participants were recruited from different agencies of the Department of Science and Technology (DOST) within the Bicutan cluster in Taguig City through printed and electronic advertisements. Potential study participants were invited to participate in the orientation to discuss the inclusion and exclusion criteria, procedures for blood sample collection, the study protocol, and to offer an opportunity for the potential participants to ask questions about the study.

The study adhered to the guidelines stipulated in the Declaration of Helsinki and all procedures involving the study participants were approved by the Food and Nutrition Research Institute Institutional Ethics Review Committee (FIERC). The participants provided written informed consent before commencing the study.

A total of 34 adults (male=15; females=19) with normal BMI (18.50-24.99 kg/m^2) participated and completed the intervention study. All participants had normal fasting blood glucose (FBG) (3.89-5.49 mmol/L) and blood pressure levels (≥120/80 mm/Hg) at the time of the study.

The BMI was derived after taking the participants' weight using a platform scale (Detecto, USA) and height with a portable stadiometer (Model 213, Seca, Germany). The age of the participants was self-declared. Fasting blood samples to determine fasting blood glucose (FBG) levels were submitted to Hi-Precision Diagnostics and were measured using enzymatic hexokinase method. Blood pressure levels were taken by the registered physician who also conducted the medical evaluation of the participants. Participants were non-smokers and have not taken any medications and/or food supplements, have no recent weight loss or weight gain, and have no food allergy or intolerance in the food items that were used in the study as declared in the self-administered screening questionnaire. Those who were below- or above- the normal BMI cutoff, diabetic, hypertensive, with self-declared thyroid conditions, with a self-declared gastrointestinal disease, pregnant, lactating, and those who were taking anti-obesity or anti-satiety drugs were excluded from the study. All participants underwent a medical evaluation by a registered physician prior to the conduct of the study.

Study Protocol

The study participants were asked to be on an overnight fast, with nothing to eat and drink (including water, coffee, and tea) for 8-10 h on the night of every meal intervention. The meal intervention lasted for 12 days and the study participants were required to report directly from their homes to the test center (Life Stage Nutrition Laboratory of the Food and Nutrition Research Institute) during the scheduled intervention sessions. Upon arrival in the test center on the first day of the intervention period, the participants were weighed using a platform scale (Detecto, USA) and were asked to fill in a standard visual analogue scale (VAS) questionnaire as pre-prandial appetite levels. Breakfast meal sets along with a booklet of VAS questionnaire were distributed among the participants throughout the intervention period.

Measurement of Appetite-related Variables

Participants were provided with the test meal and completed their VAS ratings at 0 minutes (pre-prandial), 15, 30, 45, 60, 90, 120, 150, 180, and 240 min postprandial. The VAS questionnaire for a single meal study (Flint et al. 2000) was completed by the participants in pen and paper form. The questionnaire was composed of five standardized questions as follows: 1) How hungry do you feel right now? ("Not hungry at all" to "Extremely hungry"); 2) How full do you feel right now? ("Not full at all" to "Extremely full"); 3) How satiated do you feel right now? ("Not satiated at all" to Extremely satiated"); 4) How much food do you think you can eat right now? ("Nothing at all" to "A lot"); and, 5) How much is your appetite to eat food right now? ("Nothing at all" to "A lot").

Each VAS question consisted of a 100-mm line anchored at the beginning and end by opposing statements. Participants marked a vertical line to indicate their feelings at that given moment.

Test Meals

The breakfast test meal was comprised of one cup cooked rice (160 g) with either egg (60 g), meat (50 g), fish (60 g), vegetables (90 g), and fruits (60 g). These were standardized in energy content at approximately 500 kcal with macronutrient composition of 55% carbohydrates, 15% protein, and 30% fat. Table 1 shows the average composition of the test meals calculated using the Philippine Food Composition Tables (FCT) (DOST-FNRI 1997).

Table 1. Average energy and macronutrient composition of breakfast test meals.

	Breakfast test meals
Energy, kcal	505
Protein, g	19.2
Carbohydrate, g	71.9
Fat, g	15.2

All food items were weighed by a compact high-resolution top-loading scale (Model SC-3000, UWE, South Africa) prior to serving. The participants were instructed to fully consume the test meals. During the 240-min postprandial period, the participants were prohibited from drinking and eating any food item.

Genomic DNA Isolation and SNP Genotyping

Genomic DNAs were extracted from 250 µL EDTA-anticoagulated whole blood samples using the QIAamp DNA Mini Kit (Qiagen Ltd., Amsterdam, The Netherlands) following the manufacturer's instructions. The blood samples were collected during the first day of meal intervention by a registered medical technologist. Genotyping of *FTO* rs9939609 and *GHSR* rs572169 was conducted via high-resolution melt (HRM) assay using the Bio-Rad CFX™ software (Bio-Rad, USA). Experiments were run in duplicates with the incorporation of no template control (NTC). The overall calling rate was 99.2% for rs99309609 and 98.6% for rs572169. We randomly selected samples with different genotypes for capillary sequencing and the consistent rate was 100%. The set of forward and reverse primers used in SNP genotyping were as follows: (1) *FTO* rs9939609 forward: ATTCTAGGTTCCTTGCGAC, reverse: CAGTTTGCTTTTATGCTCTC; (2) *GHSR* rs572169 forward: GCTACTTCGCCATCTGCTTC, reverse: GGTGCCGTTCTCGTGCT.

Statistical Analyses

Subject characteristics were analyzed using descriptive statistics and presented as means ± SD. All VAS ratings were measured in millimeters (mm) from left to the right end of the scale and the mean of average ratings (± SD) at each time point were computed. The ratings that were presented in this paper were mean of means of the VAS ratings (in mm) at each subjective parameters of appetite taken at each time point during the 12-day breakfast meal intervention. A repeated measures ANOVA with a Greenhouse-Geisser correction was employed to assess the subjective measures of appetite by genotype.

The departure of the genotype distribution from Hardy-Weinberg equilibrium was assessed by Chi-square analysis. The three models of inheritance (additive, recessive, and dominant) were considered during the analyses. The genetic model of inheritance was based on the number of copies of an allele needed for increased susceptibility and was described as (1) additive, the susceptibility is increased having 0, 1, and 2 copies of the risk allele with the risk of 0 alleles < 1 allele < 2 alleles; (2) recessive, 2 copies of the risk allele are needed; (3) dominant, 1 or 2 copies of the risk allele are equally related to the likelihood of possessing the trait (Dougkas et al. 2013). All models were tested for normality and residuals.

Analyses of covariance (ANCOVA), accounting for age, sex, weight, height, BMI, and baseline appetite scores were used to determine the changes on appetite ratings (as measured by VAS) relative to *FTO* rs9939609 and *GHSR* rs572169. Reported means and SDs were adjusted for all variables. Bonferroni corrections were used to correct for multiple testing and the criterion for significance was set at $P<0.05$. All analyses were performed with SPSS version 23.0 (IBM Corporation, USA).

RESULTS AND DISCUSSION

Results of the Study

The baseline characteristics of the study participants are shown in Table 2.

The appetite scores (hunger, fullness, satiation, desire to eat, and prospective consumption) in 100-mm VAS with 30-min to 1-h intervals over a 4-h period postprandial are shown in Table 3. Scores for hunger, desire to eat and prospective consumption decreased significantly ($P<0.05$; range 0.01 – 0.04) 15 min after full consumption of breakfast test meal; however, scores for these parameters started to increase gradually thereafter. Meanwhile, ratings for fullness and satiation increased significantly over the 4-h period after full consumption of the breakfast test meal. However, a gradual decrease was noted thereafter. The time effect remained significant ($P<0.05$; range 0.01 – 0.04) across all the time points of the five parameters of subjective appetite being measured.

Table 2. Characteristics of study participants categorized by sex (mean ± SD), n=34.

	Male (n=15)	Female (n=19)	All (n=34)
Age (years)	28.7 ± 6.8	26.8 ± 5.7	27.6 ± 6.2
Weight (kg)	62.9 ± 6.8	50.5 ± 5.5	56.0 ± 8.7
Height (cm)	165.6 ± 6.5	153.1 ± 5.4	158.6 ± 8.6
Body mass index (kg/m^2)	22.9 ± 1.8	21.5 ± 1.7	22.1 ± 1.9
Fasting blood glucose (mmol/L)	5.03 ± 0.3	4.84 ± 0.3	4.93 ± 0.3
Systolic BP (mm/Hg)	114.00 ± 10.8	104.21 ± 9.0	108.52 ± 11.0
Diastolic BP (mm/Hg)	79.29 ± 8.8	68.59 ± 8.1	73.53 ± 9.8

Table 3. Fasting and postprandial hunger, fullness, satiation, desire to eat and prospective consumption ratings (100-mm VAS; mean ± SD) following consumption of breakfast test meals (500 kcal).

Time (min)	Hunger (mm)	Fullness (mm)	Satiation (mm)	Desire to eat (mm)	Prospective consumption (mm)
0	76.5 ± 24.5	13.2 ± 15.3	18.2 ± 22.4	75.3 ± 19.7	77.8 ± 21.3
15	8.2 ± 10.8*	84.6 ± 17.1*	78.5 ± 24.5*	13.4 ± 16.1*	13.8 ± 17.3*
30	10.7 ± 12.2*	83.4 ± 16.9*	77.2 ± 24.4*	15.9 ± 17.6*	16.7 ± 18.9*
45	14.6 ± 13.6*	79.6 ± 17.5*	74.7 ± 22.3*	18.9 ± 17.8*	19.7 ± 18.5*
60	18.8 ± 15.3*	75.9 ± 18.4*	71.8 ± 21.3*	23.2 ± 18.8*	24.2 ± 19.4*
90	24.9 ± 17.2*	71.1 ± 18.6*	67.6 ± 20.4*	27.9 ± 18.8*	29.4 ± 19.8*
120	32.5 ± 19.7*	65.2 ± 20.7*	63.1 ± 21.2*	34.0 ± 21.4*	36.1 ± 22.4*
150	39.8 ± 21.9*	58.3 ± 22.9*	59.1 ± 21.3*	39.9 ± 22.3*	41.7 ± 22.8*
180	49.9 ± 23.0*	48.9 ± 23.6*	51.4 ± 23.2*	49.0 ± 23.3*	51.4 ± 23.9*
240	68.3 ± 23.3*	31.7 ± 24.5*	36.4 ± 26.6*	65.1 ± 23.3*	68.0 ± 24.1*

*$P>0.05$

The genotype distribution (Table 4) of the *FTO* rs9939609 and *GHSR* rs572169 conformed to Hardy-Weinberg equilibrium ($P>0.05$). The minor allele frequency (MAF) for *FTO* rs9939609 and *GHSR* rs572169 is 0.25 and 0.32, respectively.

The mean postprandial responses of appetite according to genotypes are presented in Table 5. There was no observed difference between genotype groups for *FTO* rs9939609 and *GHSR* rs572169 with respect to postprandial appetite responses, except for the feeling of fullness. There were significant changes on the levels of fullness for the dominant model for *FTO* rs9939609 after controlling for age, sex, weight, height, BMI, and baseline appetite score [$F(2,4337)=4.32$, $P=0.023$]. The mean rating of fullness score was 5.6% lower ($P=0.023$) in carriers of the risk A allele compared with the TT homozygotes for *FTO* (dominant model).

The influence of genotype on the postprandial feeling of fullness was most profound among carriers of the risk A allele in *GHSR* rs572169 (dominant model) where the mean rating of fullness score was 16.6% higher ($P=0.025$) compared with GG homozygotes. There was a significant influence of *GHSR* rs572169 alleles on the levels of fullness after controlling for the age, sex, weight, height, BMI, and baseline appetite score [$F(2,30)=4.20$, $P=0.025$].

A repeated measures ANOVA with Greenhouse-Geisser correction determined that the mean rating of fullness when comparing both dominant models of *FTO* rs9939609 and *GHSR* rs572169 differed statistically between time points [$F(2.353, 75.285)=107.048$, $P=0.040$, and $F(2.312, 73.985)=108.963$, $P=0.030$, respectively]. Post hoc test using the Bonferroni correction revealed that participants carrying the risk A allele for *FTO* rs9939609 (dominant model) exhibited an attenuated suppression of fullness as compared with the participant carrying the TT genotype (Figure 1A), while participants carrying the risk A allele for *GHSR* rs572169 (dominant model) showed a higher perception of fullness as compared to their TT counterparts (Figure 1B).

DISCUSSION OF THE RESULTS

The present study indicates that the perception of fullness after a meal is significantly influenced by *FTO* rs9949609 and *GHSR* rs572169, independent of age, sex, height, weight, BMI, and baseline appetite score in this particular group of Filipino adults.

The feeling of fullness and its relationship with *FTO* rs9939069 was previously demonstrated by Dougkas and co-authors in 2013 when he examined the relationship between *FTO* rs9939609 and appetite responses and energy intake in overweight men. It was found that carriers of the risk allele A had 17.2% lower fullness score ($P=0.026$) compared with the TT homozygotes. For this

Table 4. Distribution of genotypes and alleles.

		Genotype frequency									Allele frequency					
Genes	**SNP**		**n**	**%**		**n**	**%**		**n**	**%**		**n**	**%**		**n**	**%**	***P***
FTO	rs9939609	TT	18	52.9	TA	15	44.1	AA	1	2.9	T	51	75.0	A	17	25.0	0.30
GHSR	rs572169	GG	17	50.0	GA	12	35.3	AA	5	14.7	G	46	67.6	A	22	32.4	0.26

**P* value for the X^2 analysis of Hardy-Weinberg equilibrium, $P>0.05$

Table 5. Mean appetite responses using repeated 100 mm visual analogue scale rating over the whole duration of the study following intake of breakfast meals according to SNPs (dominant model).

Phenotype[a]	**SNP**		**Mean (mm)**[b]	**SD**		**Mean (mm)**[b]	**SD**	***P****
Hunger	rs9939609	TT	33.2	4.0	TA+AA	39.7	6.0	0.056
Fullness	rs9939609	TT	64.9	3.2	TA+AA	62.1	4.8	0.023
Prospective consumption	rs9939609	TT	36.1	4.0	TA+AA	36.9	5.9	0.068
Desire to eat	rs9939609	TT	38.2	4.2	TA+AA	36.6	6.3	0.138
Hunger	rs572169	GG	35.5	3.8	GA+AA	29.5	3.8	0.304
Fullness	rs572169	GG	60.8	2.9	GA+AA	69.1	2.9	0.025
Prospective consumption	rs572169	GG	36.9	4.0	GA+AA	35.6	5.1	0.138
Desire to eat	rs572169	GG	38.0	4.1	GA+AA	31.9	4.1	0.236

[a]Appetite responses (hunger, fullness, prospective consumption, and desire to eat) were assessed using a visual analogue scale
[b]Mean of means of VAS ratings
**P* value for the difference between genotypes after adjustment for age, sex, weight, height, BMI, and baseline appetite score ($P<0.05$)

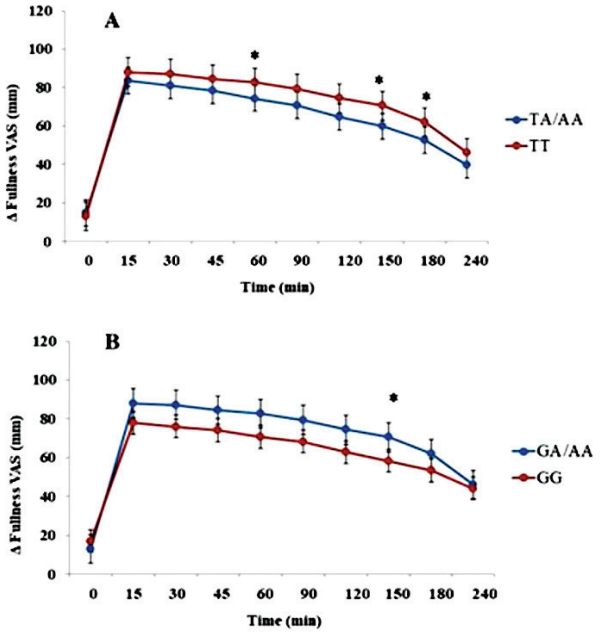

Figure 1. The comparison of mean fullness VAS ratings (mm) between alleles of *FTO* rs9939609 (A) and *GHSR* rs572169 (B) after consumption of equicaloric breakfast meals measured at different time points (0,15, 30, 45, 60, 90, 120, 150, 180, and 240 min).

present study, the mean rating of fullness score was 5.6% lower in A allele carriers compared with TT homozygotes for *FTO* rs9939609 when using the dominant model.

The *FTO* rs9939609 is being established to have a specific effect on macronutrient intake and was demonstrated by the meta-analysis conducted by Qi and co-authors (2014) from 40 studies with a total of 177,330 adults as participants. In this review, Qi and co-authors (2014) deduced that the risk A allele of the *FTO* rs9939609 was associated with lower total energy intake, higher dietary protein intake (percent of energy), and lower intake of dietary carbohydrate. A study by Huang and co-authors (2014) revealed a reduction of food cravings among overweight and obese adults who carry the A risk allele of *FTO* rs9939609. This reduction in food cravings was highlighted by the participants' shift to a hypocaloric and higher-protein weight-loss diet (Huang et al. 2014). The lower fullness score which can be translated as a suppressed feeling of hunger that was found in this study further supports the findings of Karra and co-authors (2013). Using normal-weight, adiposity-matched adult males, they found that participants carrying the risk A allele of *FTO* rs9939609 exhibited an attenuated postprandial suppression of both hunger and circulating acyl-ghrelin levels. Acyl-ghrelin is a ghrelin gene product that cues mealtime hunger and meal initiation (Chen et al. 2009).

The location and biological function of *GHSR* were identified as vital factors in its involvement in the pathogenesis of obesity (Baessler et al. 2005). *GHSR* appears to function in the central regulation of food intake (Nakazato et al. 2001) and that it is located within the quantitative trait locus (QTL) on chromosome 3q26-q29 that has been previously linked to six phenotypes of metabolic syndrome (Kissebah et al. 2000). The AA and GA genotype for 477G>A SNP of *GHSR* was found to pose higher perception of dietary restraint and disinhibition, suggestive of a reduction in the risk for overeating (den Hoed et al. 2008). In this study, we were able to identify 16.6% higher perception of fullness among carriers of the A allele (GA/AA) compared with GG homozygotes for *GHSR* rs572169. A limitation of the present study is the small participant population that contributed to our failure to provide statistically significant interaction between the SNPs and other postprandial satiety responses. Also, we were not able to control for environmental cues such as smell and sight of the food that might have affected the satiety signals.

We were not able to examine the epistatic interaction between *FTO* rs9939609 and *GHSR* rs572169 to further explain the mechanism affecting the significant disparity in the fullness ratings, and this is partly due to the small sample size used in this intervention study.

On the basis of the current influence of *FTO* and *GHSR* on appetite ratings, a larger sample size is needed to confirm the significant impact of the SNPs on other subjective measures of appetite such as prospective consumption and desire to eat. Future studies that will measure food intake and subjective measures of appetite by means of VAS using an extended period such as 24- or 48-h period is also warranted as additional data points pose better repeat-reliability of the perceptions being measured by the questionnaire.

CONCLUSION

We found a significant influence of *FTO* rs9939609 and *GHSR* rs572169 polymorphisms in the ratings of the subsequent feeling of fullness. This study has presented that carriers of the A allele of both SNPs might have an impaired ability to sense fullness as compared with their homozygote counterparts. This finding was supported by the lower rating of fullness for the carriers of the risk A allele of the *FTO* rs9939609 that is coexistent with a higher rating of fullness among the carriers of the A risk allele of *GHSR* rs572169. A detailed characterization of the phenotypes, as well as the functional studies on the polymorphisms, are being considered to further define the role of SNPs in influencing satiety.

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