FTO and APOA2 Polymorphisms in the Regulation of Hunger and Satiety

Genetic Determinants of Appetite Control and Eating Behaviour — A Literature Review

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ABSTRACT

Background. Hunger and satiety are regulated by hypothalamic and brain-stem circuits that integrate peripheral signals (ghrelin, leptin, GLP-1, PYY, insulin) with higher-order reward and executive-control pathways. Common variants influence appetite regulation and reported food intake. FTO rs9939609 A allele is associated with higher hunger scores, larger portion sizes and higher energy intake; APOA2 rs5082 modifies the satiating effect of saturated-fat-rich meals.

Methods. Narrative literature review of FTO, APOA2 and related variants in appetite regulation and eating behaviour.

Results. FTO A-allele carriers show higher appetite scores in controlled feeding studies, larger meal sizes and greater energy intake, consistent with hypothalamic effects of the variant. APOA2 rs5082 CC homozygotes show blunted satiety response to saturated-fat-rich meals. Behavioural strategies (portion control, high-protein and high-fibre meals, attention to hunger–satiety cues) reduce the behavioural impact of these variants.

Discussion. Genotype-informed advice for hunger regulation emphasises high-protein breakfast, fibre-rich meals, structured meal timing, adequate sleep and stress management. These strategies reduce the excess-intake phenotype associated with FTO A allele and reduce the saturated-fat dependence associated with APOA2 CC.

Subjects: Genetics, Appetite Regulation, Obesity. **Keywords:** FTO; rs9939609; APOA2; rs5082; hunger; satiety; appetite; eating behaviour.

INTRODUCTION

Appetite regulation is a central control problem for body-weight homeostasis. Peripheral signals from the stomach (ghrelin), adipose tissue (leptin), pancreas (insulin) and intestine (GLP-1, PYY, CCK) are integrated in the hypothalamic arcuate nucleus and in brain-stem regions, and are modulated by higher-order cortical control of food choice and portion.

Common variants at obesity-susceptibility loci — most prominently FTO — influence appetite regulation in measurable ways and contribute to the polygenic architecture of

obesity. Gene–diet variants such as APOA2 rs5082 additionally modify the satiety response to specific macronutrient patterns.

FTO AND APOA2 IN APPETITE REGULATION

FTO rs9939609 A-allele carriers show higher baseline hunger scores, larger meal sizes in controlled feeding studies, reduced post-meal satiety, and higher total energy intake — typically 100–200 kcal/day higher than non-carriers, cumulating in meaningful weight differences over time. Functional studies implicate the variant in hypothalamic melanocortin signalling and in reward-related food choice.

APOA2 rs5082 CC homozygotes show increased BMI specifically at high saturated-fat intake (Corella et al., 2009), with the mechanism thought to involve altered chylomicron processing and satiety signalling from the intestine. Switching to predominantly unsaturated-fat sources substantially attenuates the genotype effect.

BEHAVIOURAL IMPLICATIONS

The behavioural implications are practical. For FTO A-allele carriers, emphasis on higher-protein breakfast (reducing morning ghrelin surge and stabilising appetite), fibre-rich meals (increasing fullness signal from colon), structured meal timing and portion awareness is particularly valuable. For APOA2 CC homozygotes, reducing saturated-fat intake from processed meat, high-fat dairy and tropical oils directly addresses the gene–diet interaction.

Across both genotypes, adequate sleep (7–9 hours) improves leptin and ghrelin regulation; stress-management practice reduces cortisol-driven appetite dysregulation; regular physical activity improves insulin sensitivity and satiety signalling.

TABLE 1 — SUPPORTING HUMAN STUDIES

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Frayling et al., 2007	**Population:** 39 000 adults.	**Design:** GWAS. **SNP:** FTO rs9939609.	First identification of FTO as the main common obesity locus, with BMI effect per allele approximately 0.4 kg/m² (Frayling et al., 2007).
Cecil et al., 2008	**Population:** 150 children aged 4–10 years.	**Design:** Feeding study in children. **SNP:** FTO rs9939609.	FTO A-allele carriers had impaired post-meal satiety and ate approximately 100 kcal more per ad libitum meal than non-carriers (Cecil et al., 2008).
Wardle et al., 2008	**Population:** UK children.	**Design:** Behavioural study in children. **SNP:** FTO rs9939609.	A-allele carriers showed reduced satiety responsiveness on validated questionnaires, consistent with appetite dysregulation (Wardle et al., 2008).

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Corella et al., 2009	**Population:** 3 462 adults across multiple populations.	**Design:** Gene–diet interaction study. **SNP:** APOA2 rs5082 × saturated-fat intake.	APOA2 CC carriers had higher BMI when saturated-fat intake was high but not when it was low, establishing the gene–diet interaction (Corella et al., 2009).
Weigle et al., 2005	**Population:** Overweight adults.	**Design:** Controlled feeding trial. **Focus:** Protein intake and satiety.	Increasing dietary protein from 15 % to 30 % of energy produced sustained reduction in hunger and spontaneous weight loss, supporting high-protein strategies for appetite regulation (Weigle et al., 2005).
Behavioural-strategy trials	**Population:** Adults in weight-management programmes.	**Design:** Randomised lifestyle trials. **Focus:** Structured eating patterns, mindful eating.	Structured meal timing, portion-awareness training and mindful-eating strategies reduced ad libitum intake and improved weight-loss maintenance across populations, with greater effect in individuals with FTO risk-allele carriage in some cohorts.

INTERVENTION RATIONALE

For FTO A-allele carriers, the most effective appetite-regulation strategies are: high-protein breakfast (typically 25–30 g protein within an hour of waking), fibre-rich meals (≥ 8–10 g per meal, including vegetables, legumes and whole grains), structured meal timing with minimal snacking between meals, adequate sleep (7–9 hours), stress-management practice and regular physical activity. Portion awareness — using pre-portioned meals or measured servings rather than ad libitum serving — can substantially reduce excess intake.

For APOA2 CC homozygotes, minimising saturated-fat intake (particularly from processed meat, full-fat dairy, tropical oils and commercial baked goods) and emphasising Mediterranean-pattern fats (olive oil, nuts, seeds, oily fish) directly addresses the gene–diet interaction. Emerging evidence on GLP-1 receptor agonists (semaglutide, tirzepatide) suggests pharmacological appetite modulation is highly effective in patients who have not responded to lifestyle measures; genotype effects may help stratify need for pharmacotherapy.

OPEN QUESTIONS

The quantitative contribution of FTO A allele to long-term weight trajectory is modest but reproducible. Large genotype-stratified trials of specific appetite-management strategies remain limited, and the integration of FTO genotype with polygenic obesity risk scores is an active research area.

CONCLUSION

FTO and APOA2 variants contribute to interindividual variability in hunger, satiety and eating behaviour. Behavioural and dietary strategies — high-protein breakfast, fibre-

rich meals, structured timing, adequate sleep, and saturated-fat moderation in APOA2 CC — attenuate the excess-intake phenotype and form the foundation of genotype-informed appetite regulation.

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