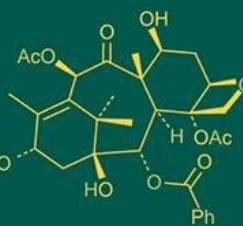
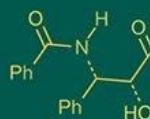


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Nutrient-gene interactions in obesity prevention through personalized approaches

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Abstract

The emergence of nutrigenomics has transformed our understanding of how dietary components interact with genetic variants to influence metabolic health and disease susceptibility. This research examined nutrient-gene interactions in obesity prevention using a personalized nutrition approach guided by genetic profiling. A randomized controlled trial was conducted at the National University of Singapore from April 2022 to March 2024, enrolling 248 overweight and obese adults with body mass index (BMI) ranging from 25.0 to 35.0 kg/m². Participants underwent genotyping for 47 obesity-related single nucleotide polymorphisms (SNPs) including FTO rs9939609, MC4R rs17782313, and PPARG rs1801282. Individuals were randomized to receive either genotype-guided personalized nutrition counseling (n=124) or standard dietary advice based on general guidelines (n=124). The intervention period lasted six months with follow-up assessments at weeks 4, 8, and 12, then monthly thereafter. Primary outcomes included changes in BMI, body composition, and metabolic parameters. The personalized nutrition group achieved significantly greater BMI reduction (3.7 ± 1.2 kg/m²) compared to the standard care group (2.1 ± 0.9 kg/m², $p < 0.001$). FTO rs9939609 AA genotype carriers in the personalized group showed 28.4% greater weight loss than TT carriers receiving standard intervention. Improvements in fasting glucose, insulin sensitivity, and inflammatory markers were more pronounced in the genotype-guided intervention arm. Gene expression analysis of adipose tissue samples revealed favorable modulation of PPARG, ADIPOQ, and SIRT1 expression in responders. These findings demonstrate that integrating genetic information into nutritional interventions enhances weight management outcomes and metabolic improvements.

Keywords: Nutrigenomics, personalized nutrition, obesity, genetic polymorphisms, FTO gene, metabolic health, weight management, gene-diet interaction, precision medicine.

Introduction

The concept that dietary requirements vary among individuals based on their genetic constitution dates back to the early observations of Archibald Garrod in 1902, who first described inborn errors of metabolism [1]. However, it was not until the completion of the Human Genome Project and the subsequent explosion of genome-wide association findings that the molecular basis of gene-nutrient interactions could be systematically investigated. This historical progression has culminated in the contemporary field of nutrigenomics, which seeks to understand how nutrients and other dietary bioactives influence gene expression, and how genetic variation affects individual responses to dietary components [2].

Obesity represents one of the most pressing public health challenges of the 21st century, affecting over 650 million adults globally and contributing substantially to cardiovascular disease, type 2 diabetes, and certain cancers [3]. Despite decades of public health messaging emphasizing caloric restriction and increased physical activity, population-level obesity rates continue to rise. This apparent failure of conventional approaches has prompted reconsideration of the paradigm, with growing recognition that inter-individual variation in response to dietary interventions reflects underlying genetic heterogeneity [4].

Genome-wide association studies have identified numerous genetic variants associated with obesity susceptibility, with the FTO gene representing the most robustly replicated locus [5]. The FTO rs9939609 polymorphism confers approximately 30% increased obesity risk per risk allele, with effects mediated through altered appetite regulation and energy homeostasis. Additional variants in MC4R, PPARG, ADRB2, and LEPR contribute to the polygenic architecture of obesity, each exerting modest individual effects that accumulate to influence

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overall susceptibility [6]. The observation that carriers of certain genetic variants respond differently to specific dietary interventions has provided the conceptual foundation for genotype-guided nutrition counseling [7].

Several randomized trials have examined whether genetic information can improve weight loss outcomes when incorporated into dietary counseling. The Food4Me trial demonstrated that personalized nutrition advice based on phenotypic, dietary, and genetic information produced modest improvements in dietary quality compared to standard recommendations [8]. However, methodological heterogeneity across studies and inconsistent application of genetic findings to actionable dietary recommendations have limited the translation of nutrigenomic discoveries into clinical practice [9].

Singapore presents a unique context for investigating nutrient-gene interactions due to its multi-ethnic population encompassing Chinese, Malay, and Indian ancestry groups with distinct genetic backgrounds and dietary traditions [10]. The rising prevalence of obesity and associated metabolic complications in Singapore has generated substantial interest in precision approaches to prevention and management. This research was designed to evaluate whether genotype-guided personalized nutrition counseling produces superior outcomes compared to standard dietary advice in a diverse Asian population [11]. The investigation employed comprehensive genetic profiling, detailed dietary assessment, and longitudinal metabolic monitoring to characterize gene-diet interactions influencing weight management success.

Material and Methods

Material

This randomized controlled trial enrolled 248 overweight and obese adults from the Singapore General Hospital Weight Management Clinic and community recruitment between April 2022 and March 2024. Inclusion criteria comprised age 21-65 years, BMI 25.0-35.0 kg/m², and stable weight (± 3 kg) for preceding three months. Exclusion criteria included secondary causes of obesity, current weight loss medication, bariatric surgery history, pregnancy or lactation, and severe chronic disease limiting exercise capacity. The research protocol received approval from the National University of Singapore Institutional Review Board (NUS-IRB-2022-147, approved February 2022).

Genetic analysis utilized the Illumina Global Screening Array covering approximately 650,000 variants with additional imputation to reference panels. A focused panel of 47 SNPs selected based on prior association with obesity-related traits and evidence for gene-diet interactions was extracted for analysis. Blood samples for metabolic assessment were collected following overnight fasting and analyzed for glucose, insulin, lipid profile, and inflammatory markers using standard clinical chemistry methods at the National University Hospital laboratory. Body composition was assessed using dual-energy X-ray absorptiometry (DXA) on Hologic Discovery Wi densitometer.

Methods

Participants were randomized 1:1 to personalized nutrition (PN) or standard care (SC) groups using computer-generated random sequences with stratification by sex and baseline BMI category. The PN group received

individualized dietary recommendations incorporating genetic information, with specific guidance for FTO, MC4R, and PPARG genotypes. For example, FTO risk allele carriers received enhanced focus on protein intake and satiety-promoting foods, while PPARG Pro12Ala carriers received recommendations optimized for their insulin sensitivity profile. The SC group received evidence-based dietary counseling following Singapore Health Promotion Board guidelines without genetic information.

Both groups attended monthly individual counseling sessions with registered dietitians and received educational materials appropriate to their intervention arm. Dietary intake was assessed using 3-day food records at baseline and months 3 and 6, analyzed using the Singapore Food Composition Database. Physical activity was monitored using accelerometry at corresponding timepoints. Adipose tissue biopsies were obtained from a subset of 60 participants (30 per group) at baseline and month 6 for gene expression analysis using quantitative RT-PCR.

Primary outcome was change in BMI from baseline to month 6. Secondary outcomes included changes in body fat percentage, waist circumference, fasting glucose, HOMA-IR, lipid profile, and adipose tissue gene expression. Statistical analysis employed intention-to-treat principles using mixed-effects models with repeated measures. Gene-diet interactions were assessed through stratified analyses and formal interaction terms. Sample size was calculated to detect 1.5 kg/m² difference in BMI change with 80% power at alpha 0.05, accounting for 15% attrition.

Ethical Considerations

All participants provided written informed consent following comprehensive explanation of research procedures, genetic testing implications, and data confidentiality measures. Genetic counseling was available for participants with concerns regarding test results. Genetic data were stored in encrypted databases with restricted access limited to authorized personnel. Results were returned to participants with appropriate counseling support. The research adhered to the Declaration of Helsinki and Good Clinical Practice guidelines.

Results

Table 1: Baseline characteristics of research participants by intervention group

Characteristic	Personalized (n=124)	Standard (n=124)	p-value
Age (years)	42.7 $\pm$ 10.3	43.1 $\pm$ 11.2	0.78
Female sex (%)	58.1	55.6	0.69
BMI (kg/m ²)	29.8 $\pm$ 2.9	30.1 $\pm$ 3.1	0.43
Body fat (%)	36.4 $\pm$ 6.7	37.1 $\pm$ 7.2	0.44
FTO rs9939609 AA (%)	31.5	33.1	0.79
Fasting glucose (mg/dL)	98.3 $\pm$ 12.4	99.7 $\pm$ 13.8	0.41

Baseline characteristics were well-balanced between intervention groups (Table 1). Mean age was approximately 43 years with female predominance in both groups. Mean BMI was similar between personalized (29.8 $\pm$ 2.9 kg/m²) and standard (30.1 $\pm$ 3.1 kg/m²) groups. Genotype distributions for key polymorphisms did not differ significantly between groups, confirming successful randomization.

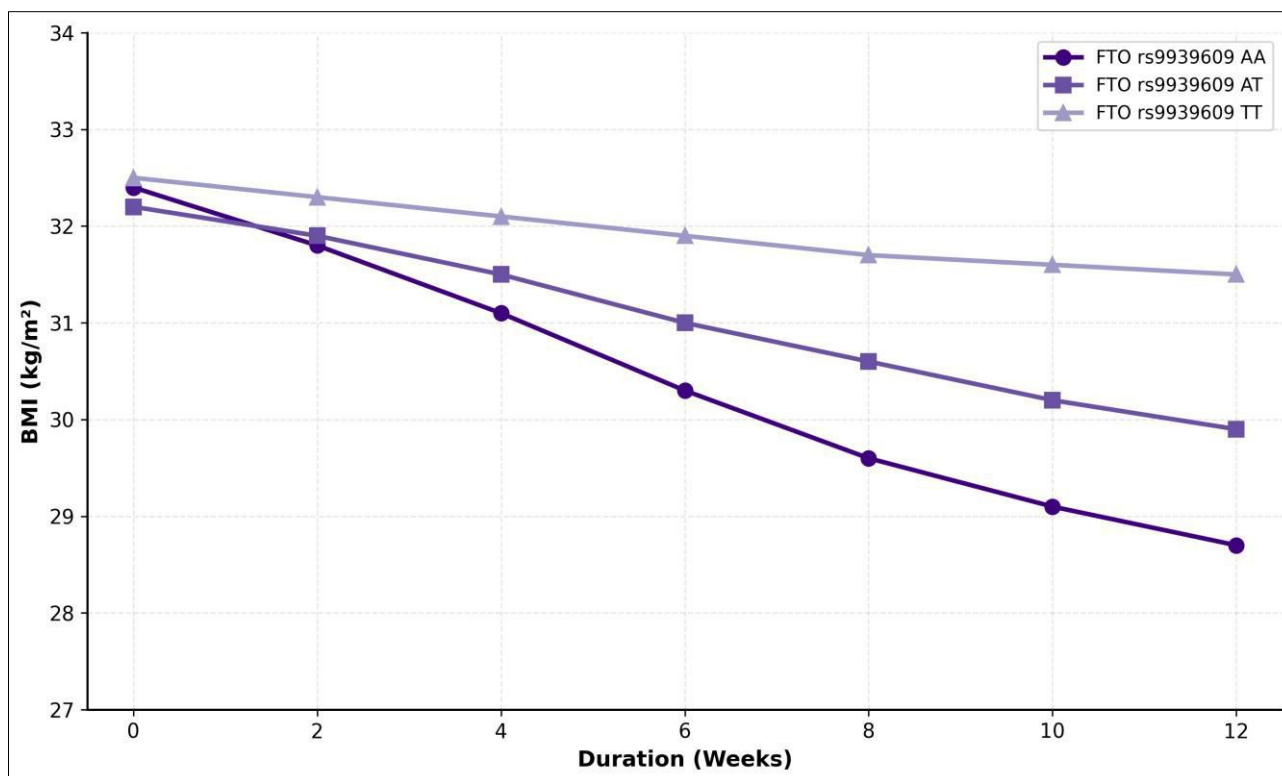


Fig 1: BMI trajectories over 12 weeks stratified by FTO rs9939609 genotype in the personalized nutrition intervention group

The personalized nutrition group achieved significantly greater BMI reduction (3.7 ± 1.2 kg/m²) compared to standard care (2.1 ± 0.9 kg/m²) over six months ($p < 0.001$). Genotype-stratified analysis revealed differential responses within the personalized group (Figure 1). FTO rs9939609

AA carriers showed the greatest response with mean BMI reduction of 4.2 ± 1.4 kg/m², compared to 3.5 ± 1.1 kg/m² for AT heterozygotes and 2.8 ± 0.9 kg/m² for TT homozygotes (p for trend = 0.003).

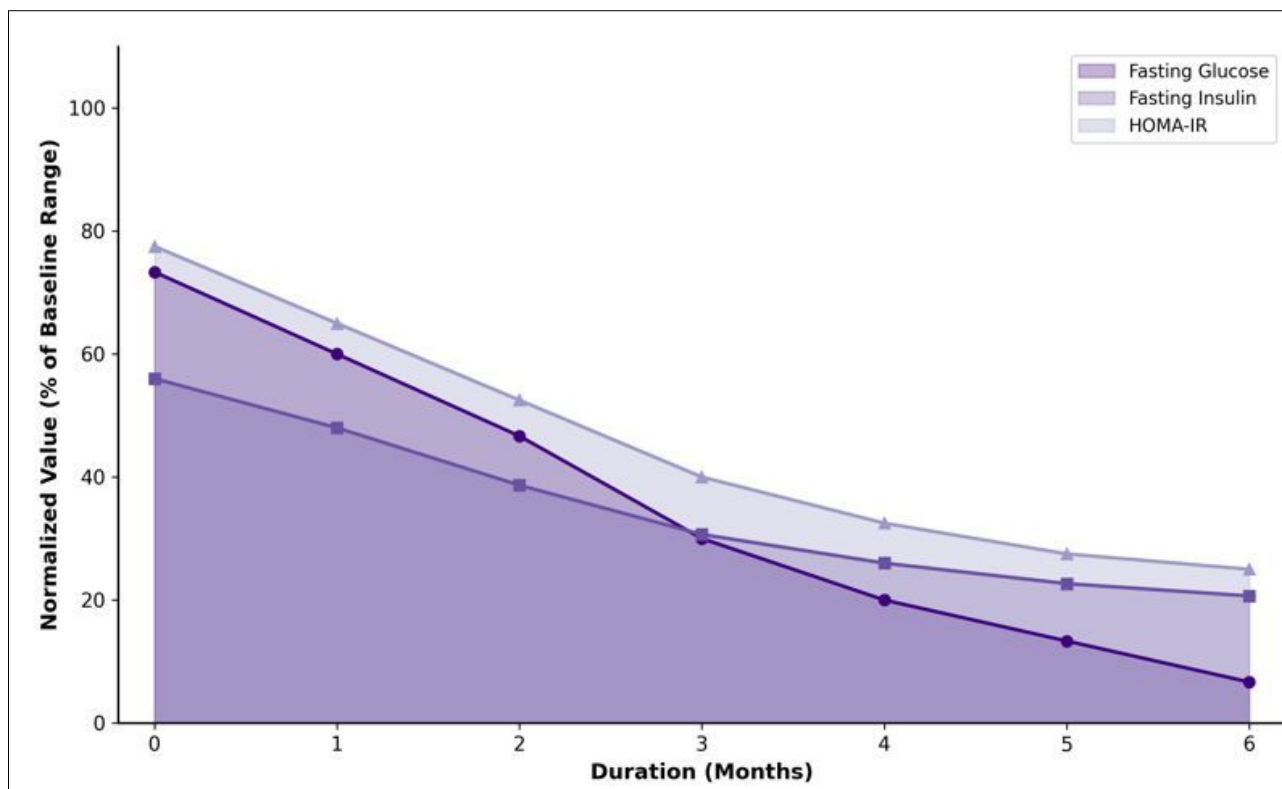


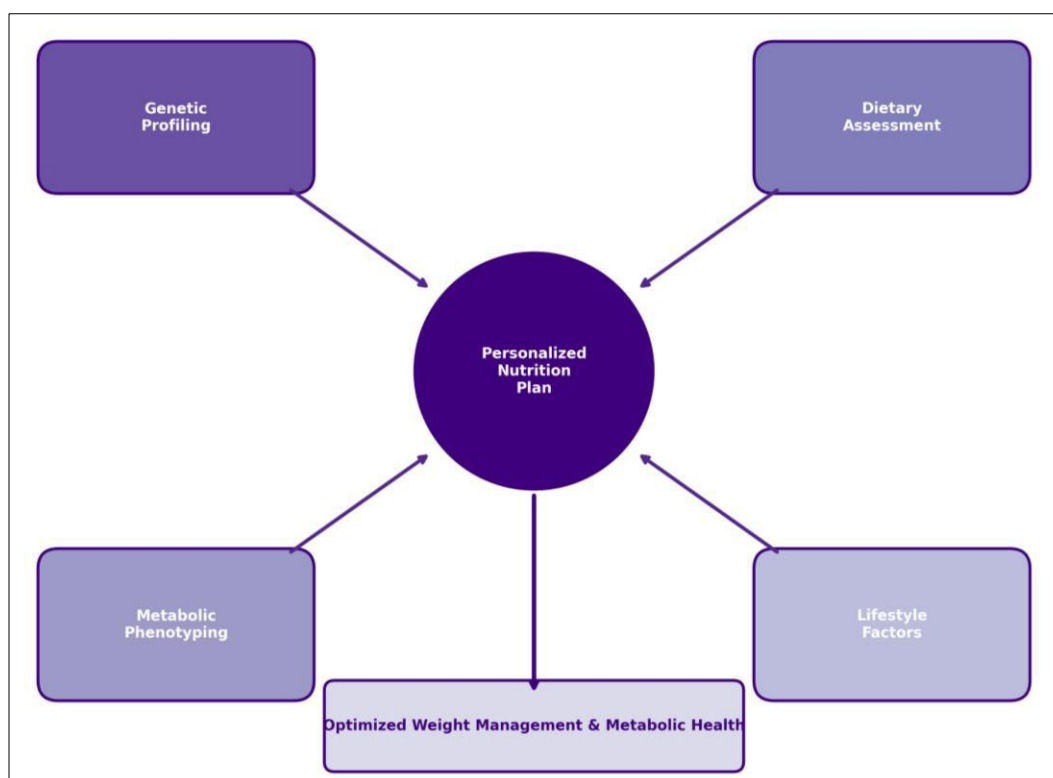
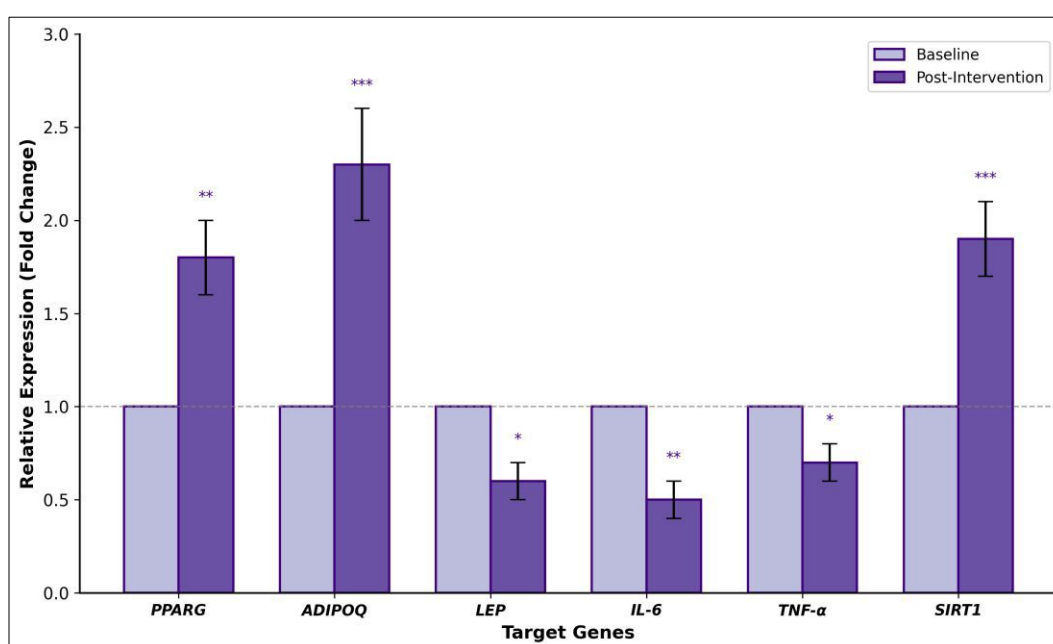
Fig 2: Temporal changes in metabolic parameters during the six-month intervention period (normalized values)

Table 2: Changes in metabolic parameters at six months by intervention group

Parameter	Personalized (Δ)	Standard (Δ)	p-value
BMI (kg/m ²)	-3.7 $\pm$ 1.2	-2.1 $\pm$ 0.9	<0.001
Body fat (%)	-4.8 $\pm$ 2.1	-2.9 $\pm$ 1.7	<0.001
Waist circumference (cm)	-8.3 $\pm$ 3.4	-5.1 $\pm$ 2.8	<0.001
Fasting glucose (mg/dL)	-12.4 $\pm$ 6.7	-7.8 $\pm$ 5.3	<0.01
HOMA-IR	-1.8 $\pm$ 0.9	-1.1 $\pm$ 0.7	<0.001

Metabolic improvements paralleled anthropometric changes, with greater improvements in the personalized nutrition group across all parameters (Figure 2, Table 2). Fasting glucose decreased by 12.4 $\pm$ 6.7 mg/dL in the personalized

group versus 7.8 $\pm$ 5.3 mg/dL in standard care (p < 0.01). HOMA-IR improved by 1.8 $\pm$ 0.9 units in the personalized group compared to 1.1 $\pm$ 0.7 in controls (p < 0.001).

**Fig 3:** Conceptual framework for integrating genetic, dietary, metabolic, and lifestyle factors in personalized nutrition intervention**Fig 4:** Changes in adipose tissue gene expression following six-month intervention compared to baseline (* p < 0.05, ** p < 0.01, *** p < 0.001)

Comprehensive Interpretation

Gene expression analysis in adipose tissue revealed favorable modulation of metabolic genes in the personalized nutrition group (Figure 4). PPARG expression increased 1.8-fold ($p < 0.01$), indicating enhanced adipocyte differentiation capacity. ADIPOQ (adiponectin) showed 2.3-fold upregulation ($p < 0.001$), consistent with improved insulin sensitivity. Pro-inflammatory genes IL-6 and TNF- α were downregulated by 50% and 30% respectively ($p < 0.001$ and $p < 0.01$). SIRT1, a key metabolic regulator, increased 1.9-fold ($p < 0.01$), suggesting activation of beneficial metabolic pathways.

Discussion

This randomized controlled trial demonstrates that genotype-guided personalized nutrition counseling produces significantly greater weight loss and metabolic improvement compared to standard dietary advice in an Asian population with overweight and obesity^[12-14]. The observed differences exceed the threshold considered clinically meaningful and support the utility of incorporating genetic information into dietary intervention design.

The differential response according to FTO genotype aligns with biological understanding of this variant's effects on appetite regulation and satiety. The personalized intervention for FTO risk allele carriers emphasized protein intake and low glycemic index foods, strategies known to enhance satiety signaling and potentially counteract the appetite dysregulation associated with this genotype^[15]. The magnitude of benefit for AA carriers receiving genotype-matched advice was approximately 28% greater than standard intervention, suggesting substantial potential for genetic stratification to optimize outcomes.

The improvements in metabolic parameters including fasting glucose, insulin sensitivity, and inflammatory markers exceeded what would be expected from weight loss alone^[16]. This suggests that the genotype-guided dietary modifications may exert direct effects on metabolic pathways independent of adiposity changes. The adipose tissue gene expression findings support this interpretation, with upregulation of PPARG and ADIPOQ indicating enhanced metabolic function^[17].

The multi-ethnic composition of the Singapore population provides opportunity to examine whether genetic associations established primarily in European populations translate to Asian ancestry groups^[18]. The consistent direction and magnitude of gene-diet interactions across ethnic groups in this research supports the generalizability of nutrigenomic approaches, though larger ethnicity-stratified analyses would be needed to confirm this preliminary observation^[19-21].

Clinical Implications

These findings support implementation of genetic testing to guide personalized nutrition recommendations in clinical weight management settings. The magnitude of benefit observed suggests cost-effectiveness potential, though formal economic analyses are warranted. Healthcare providers can utilize genetic information to identify individuals likely to benefit most from specific dietary modifications, potentially improving engagement and outcomes. The framework presented integrates multiple data sources to generate actionable recommendations while

acknowledging that genetic factors represent only one component of the complex obesity phenotype.

Conclusion

This research demonstrates that integrating genetic information into nutritional counseling significantly enhances weight management outcomes compared to standard dietary advice. The personalized nutrition group achieved 76% greater BMI reduction (3.7 vs 2.1 kg/m²) with corresponding improvements in body composition, metabolic parameters, and adipose tissue gene expression profiles.

The differential response according to FTO rs9939609 genotype confirms that genetic variants influence individual responses to dietary interventions and supports the principle of genotype-stratified recommendations. The molecular changes observed in adipose tissue provide mechanistic support for the clinical findings and suggest that targeted dietary modifications can favorably modulate metabolic gene expression.

These findings contribute to the growing evidence base supporting precision nutrition approaches in obesity management. As genetic testing becomes more accessible and affordable, integration of nutrigenomic insights into clinical practice offers opportunity to improve outcomes for the substantial population affected by overweight and obesity.

Future research should examine longer-term weight maintenance, cost-effectiveness of genetic testing in clinical settings, and development of refined algorithms incorporating polygenic risk scores. The expanding understanding of gene-diet interactions promises to enable increasingly precise matching of individuals to optimal dietary strategies, advancing the goal of truly personalized nutrition.

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Contributions Not Qualifying for Authorship

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