Individual Carbohydrate Sensitivity and Glycaemic Response

Genetic Modifiers of Body-Weight and Metabolic Response to Carbohydrate Intake — A Literature Review

Magdalena Behensky[1], René Rohrmanstorfer[1], Thomas Dullnig[1], Daniel Wallerstorfer[1]

[1]*Laboratory, Novogenia GmbH, Salzburg, Austria*

Corresponding Author: Daniel Wallerstorfer (ceo@novogenia.com)

ABSTRACT

Background. **Individual metabolic and body-weight response to dietary carbohydrate intake varies substantially. At the same caloric load, some patients gain weight, develop insulin resistance and show elevated postprandial glucose in response to a moderate-to-high-carbohydrate diet, while others tolerate the same intake without adverse effect. Common variants in FTO (rs9939609), PPARG (rs1801282, Pro12Ala), TCF7L2 and IRS1 contribute measurably to this variability, producing a clinically useful 'carbohydrate-sensitive' phenotype at the intersection of hypothalamic appetite regulation, adipocyte insulin sensitivity and pancreatic β-cell function.**

Methods. **Narrative literature review of PubMed-indexed genetic-association, gene–diet interaction and controlled feeding studies addressing carbohydrate sensitivity, insulin resistance and body-weight response to carbohydrate intake. Evidence is summarised at the individual-variant level rather than aggregated into a composite score.**

Results. **Each FTO rs9939609 A allele is associated with approximately 1.5 kg higher body weight, higher reported hunger and larger meal sizes; physical activity attenuates the effect by approximately 30 %. PPARG Pro12Ala Pro/Pro homozygotes show reduced insulin sensitivity and increased susceptibility to diet-induced type 2 diabetes compared with Ala carriers. In randomised controlled feeding trials (notably DIETFITS and POUNDS LOST), mean weight-loss outcomes do not differ substantially between low-fat and low-carbohydrate assignments, but within-group variability is large and partly explained by individual genetic profile and by baseline insulin sensitivity.**

Discussion. **For patients who show clinical features of carbohydrate sensitivity — central adiposity, elevated postprandial glucose and insulin, dyslipidaemia, insulin resistance — a Mediterranean-pattern moderate-carbohydrate diet that emphasises unrefined complex carbohydrates, high fibre, unsaturated fats and adequate protein is a mechanistically supported first-line recommendation. Regular physical activity, adequate sleep and normal body weight remain the dominant modifiable influences across all genotypes.**

Subjects: Genetics, Nutrition, Metabolism. **Keywords:** carbohydrate sensitivity; insulin resistance; FTO; PPARG; gene–diet interaction; weight management.

INTRODUCTION

The phrase 'carbohydrate sensitivity' describes a clinical phenotype in which individuals experience disproportionate weight gain, central adiposity, elevated postprandial glucose and insulin, and higher triglycerides in response to a moderate-to-high-carbohydrate diet, compared with patients of similar age, sex and body weight. It is neither a discrete genetic disorder nor a validated biomarker-based diagnosis, but a useful summary of a set of physiological responses that cluster in certain patients and that inform dietary counselling.

Several common polymorphisms contribute to individual variability in this phenotype. The dominant loci are FTO (appetite regulation), PPARG (adipocyte insulin sensitivity), TCF7L2 (pancreatic β-cell insulin secretion) and IRS1 (insulin receptor signalling). Each variant produces a modest individual effect, but together they help to explain why some patients respond favourably to moderate-carbohydrate Mediterranean patterns while others benefit from lower-carbohydrate approaches. This review summarises the evidence, emphasising that the clinically useful unit is the overall phenotype rather than any single gene or any fixed composite score.

KEY GENETIC MODIFIERS OF CARBOHYDRATE RESPONSE

FTO rs9939609 is the most extensively replicated common obesity variant. Each A allele is associated with approximately 1.5 kg higher body weight and modestly higher hunger scores, larger meal sizes and higher total energy intake — the behavioural pathway most clearly linked to FTO's hypothalamic expression (Frayling et al., 2007; Cecil et al., 2008). Physical activity attenuates the FTO–obesity association by approximately 30 %, suggesting that the genotype effect is partly mediated through activity-related energy expenditure and appetite modulation (Kilpeläinen et al., 2011).

PPARG Pro12Ala (rs1801282) is the master transcription factor of adipocyte differentiation. Carriers of the Ala12 allele produce smaller, more insulin-sensitive adipocytes and show approximately 25 % reduced risk of type 2 diabetes compared with Pro/Pro homozygotes (Altshuler et al., 2000). Pro/Pro homozygotes — the majority of the population — are correspondingly more susceptible to diet-induced insulin resistance and benefit proportionally more from lower-glycaemic-load dietary patterns.

TCF7L2 rs7903146 and IRS1 rs2943641 are additional common variants that modify pancreatic β-cell insulin secretion and peripheral insulin signalling respectively. Together with FTO and PPARG, they form the main biological substrates of carbohydrate sensitivity at the individual-variant level. No single variant is diagnostic; the clinical assessment is made at the phenotypic level through biomarker-based evaluation (waist circumference, fasting glucose and insulin, HOMA-IR, HbA1c, triglyceride-to-HDL ratio) combined with a carefully taken history.

CLINICAL PHENOTYPE AND DIETARY IMPLICATIONS

The clinical features that most reliably identify carbohydrate-sensitive patients are central adiposity, elevated fasting glucose or insulin, elevated triglycerides with low HDL

cholesterol, hypertension, and a strong personal or family history of type 2 diabetes or metabolic syndrome. In these patients, randomised trials consistently show better short- and medium-term metabolic benefit from moderate-carbohydrate Mediterranean-pattern diets than from low-fat, high-carbohydrate diets, although average weight-loss differences between patterns are small and largely determined by adherence (Gardner et al., 2018; Sacks et al., 2009).

The preferred pattern emphasises unrefined complex carbohydrates (legumes, whole grains, vegetables, moderate fruit), high fibre intake, unsaturated fats (olive oil, nuts, oily fish), adequate protein (1.0–1.6 g/kg/day, higher during active weight loss), and deliberate restriction of refined carbohydrate and sugar-sweetened beverages. The glycaemic load of a meal, rather than carbohydrate quantity in isolation, is the most useful clinical target.

Lifestyle measures — regular aerobic and resistance exercise, adequate sleep, and stress management — are quantitatively more important than any genetic consideration in determining insulin sensitivity and weight trajectory. Genetic information refines the dietary emphasis but does not override the primary importance of consistent lifestyle practice.

TABLE 1 — SUPPORTING HUMAN STUDIES

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Frayling et al., 2007	**Population:** 39 000 adults — initial GWAS discovery.	**Design:** Genome-wide association study. **SNP:** FTO rs9939609.	Each A allele of FTO was associated with approximately 0.4 kg/m² higher BMI and increased obesity risk, identifying the first common obesity locus (Frayling et al., 2007).
Cecil et al., 2008	**Population:** 150 children aged 4–10.	**Design:** Controlled feeding study in children. **SNP:** FTO rs9939609.	A-allele carriers showed impaired post-meal satiety and consumed approximately 100 kcal more per ad-libitum meal, consistent with the appetite pathway (Cecil et al., 2008).
Kilpeläinen et al., 2011	**Population:** > 218 000 adults, 19 000 children.	**Design:** Meta-analysis of physical-activity × genotype interactions. **SNP:** FTO rs9939609.	Physical activity attenuated the FTO–obesity association by approximately 30 %, with the largest benefit in homozygous A/A individuals (Kilpeläinen et al., 2011).
Altshuler et al., 2000	**Population:** Type 2 diabetes case–control studies.	**Design:** Meta-analysis. **SNP:** PPARG Pro12Ala (rs1801282).	Ala12 carriers showed approximately 25 % reduced type 2 diabetes risk; functional studies supported smaller, more insulin-sensitive adipocytes as the mechanism (Altshuler et al., 2000).

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Gardner et al., 2018 (DIETFITS)	**Population:** 609 overweight adults.	**Design:** Large randomised weight-loss trial. **Focus:** Healthy low-fat vs healthy low-carbohydrate diet for 12 months.	Both dietary patterns produced similar mean weight loss (approximately 6 kg at 12 months); genotype and insulin-secretion phenotype did not reliably predict which pattern worked best, although within-group variability was substantial (Gardner et al., 2018).
Sacks et al., 2009 (POUNDS LOST)	**Population:** 811 overweight adults.	**Design:** Large randomised weight-loss trial. **Focus:** Four diets varying in fat, protein and carbohydrate.	Diets of similar caloric deficit produced similar 2-year weight loss regardless of macronutrient composition, with adherence the dominant determinant of individual outcome (Sacks et al., 2009).
Qi et al., 2013 (PREDIMED and others)	**Population:** Adults at high cardiovascular risk.	**Design:** Secondary analysis of dietary-intervention trials. **Focus:** Genetic modifiers of response to Mediterranean diet.	Selected variants modified specific lipid and glycaemic responses to a Mediterranean diet, supporting the principle of individual variability within a shared dietary framework (Qi et al., 2013).
Grau et al., 2009 and successors	**Population:** European-descent adults with varying baseline insulin sensitivity.	**Design:** Dietary-intervention cohort. **Focus:** Insulin-resistant vs insulin-sensitive response to dietary composition.	Patients with low baseline insulin sensitivity derived greater metabolic benefit from moderate-carbohydrate Mediterranean-pattern diets than from low-fat, high-carbohydrate comparators, supporting a phenotype-based rather than a score-based approach to dietary individualisation.

INTERVENTION RATIONALE

For patients with clinical features of carbohydrate sensitivity — central adiposity, elevated fasting insulin or glucose, high triglycerides with low HDL, family history of type 2 diabetes — a Mediterranean-pattern moderate-carbohydrate diet is a defensible first-line recommendation. The specific implementation emphasises legumes, vegetables, whole grains in modest portions, moderate fruit, olive oil, nuts, oily fish, eggs, dairy and lean meat, while deliberately limiting refined carbohydrate, sugar-sweetened beverages, commercial baked goods and alcohol. For patients without these features, a broader range of healthy dietary patterns — including higher-carbohydrate Mediterranean, DASH, and plant-forward patterns — perform equivalently.

Physical activity (≥ 150 min/week moderate or 75 min/week vigorous aerobic activity plus 2–3 resistance-training sessions) improves insulin sensitivity independently of weight change and is particularly valuable in carbohydrate-sensitive patients. Adequate sleep (7–9 hours) and stress management support normal glucose and appetite regulation. For patients with established insulin resistance or type 2 diabetes,

pharmacotherapy (metformin, GLP-1 receptor agonists, SGLT2 inhibitors) should be considered alongside lifestyle measures.

OPEN QUESTIONS AND DIRECTIONS FOR FURTHER RESEARCH

Effect sizes of individual common variants are modest, and clinically validated composite tools for carbohydrate-sensitivity prediction are not yet in routine practice. Current best practice uses a combination of clinical history, anthropometry and routine biomarkers, with genetic information serving as one input among many. Randomised feeding trials that stratify by clinically defined insulin-resistance phenotype and by key individual variants — rather than by aggregate scores — are the most informative next step.

The intersection of genotype, gut microbiota composition, circadian and sleep regulation, and psychosocial context is an active research area and will shape future individualisation strategies.

CONCLUSION

Individual response to dietary carbohydrate varies substantially and is partly genetically determined. Common variants in FTO, PPARG and related loci contribute modest individual effects that together help to explain why some patients tolerate moderate-to-high-carbohydrate diets while others show improved metabolic outcomes on moderate-carbohydrate Mediterranean-pattern diets. The clinically useful unit is the overall phenotype, not any single gene nor a fixed composite score. Consistent adherence to an evidence-based dietary pattern, regular physical activity, adequate sleep and normal body weight remain the dominant modifiable determinants of metabolic health.

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