Individual Dietary Fat Sensitivity and Postprandial Lipid Handling

Genetic Modifiers of Body-Weight and Cardiometabolic Response to Dietary Fat — A Literature Review

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ABSTRACT

Background. **Individual body-weight and cardiometabolic response to dietary fat composition varies substantially. Some patients experience marked weight gain, central adiposity and dyslipidaemia in response to high-saturated-fat intake, while others are relatively insensitive. Common variants in APOA2 (rs5082), FABP2 (rs1799883), APOA5 (rs662799) and ADRB2 (rs1042714) contribute to this variability by modifying intestinal fat absorption, chylomicron handling, postprandial triglyceride clearance and catecholamine-driven lipolysis.**

Methods. **Narrative literature review of PubMed-indexed gene–diet interaction and controlled feeding studies addressing dietary fat type, quantity and postprandial lipid response. Evidence is summarised at the individual-variant level rather than aggregated into a composite score.**

Results. **APOA2 rs5082 CC homozygotes show higher BMI and central adiposity specifically on high-saturated-fat diets; switching to predominantly unsaturated-fat intake attenuates the genotype effect (Corella et al., 2009). FABP2 Thr54 carriers have altered intestinal fat absorption and modestly different postprandial responses. APOA5 −1131C reduces triglyceride clearance and exaggerates postprandial lipaemia. ADRB2 Gln27Glu modifies adipocyte β2-adrenergic responsiveness.**

Discussion. **For patients with clinical features of dietary fat sensitivity — elevated postprandial triglycerides, central adiposity at moderate BMI, family history of hypertriglyceridaemia — a Mediterranean-pattern diet that emphasises unsaturated fats (olive oil, nuts, oily fish) while moderating saturated-fat sources (processed meat, full-fat dairy, tropical oils) is a mechanistically supported first-line recommendation. Alcohol moderation, refined-carbohydrate reduction and regular exercise remain foundational.**

Subjects: Genetics, Nutrition, Lipid Metabolism. **Keywords:** dietary fat; saturated fat; APOA2; FABP2; APOA5; gene–diet interaction; postprandial lipaemia.

INTRODUCTION

The phrase 'dietary fat sensitivity' describes a clinical phenotype in which patients show disproportionate weight gain, central adiposity and adverse lipid response to a diet high in saturated fat, compared with patients of similar age, sex and energy intake. Like carbohydrate sensitivity, it is not a discrete genetic disorder but a useful summary of converging physiological responses that cluster in certain patients.

The relevant biology involves intestinal fat absorption (FABP2), chylomicron assembly and clearance (APOA2, APOA5), postprandial triglyceride handling (APOA5, lipoprotein lipase), and adipocyte lipolysis (ADRB2). Common variants at these loci contribute modest individual effects that together help explain why some patients tolerate moderate-to-high saturated-fat diets while others benefit markedly from unsaturated-fat substitution. This review summarises the evidence at the individual-variant level; the clinically useful unit is the overall phenotype rather than any fixed composite score.

KEY GENETIC MODIFIERS OF DIETARY FAT RESPONSE

APOA2 rs5082 (−265T>C) produces one of the clearest gene–diet interactions in nutrigenetics. CC homozygotes show approximately 1 kg/m² higher BMI and increased central adiposity when saturated-fat intake is high, but not when it is low (Corella et al., 2009). The effect has been reproduced in North American, Mediterranean and Asian cohorts. The underlying mechanism is thought to involve altered chylomicron processing and intestinal satiety signalling.

FABP2 rs1799883 (Ala54Thr) encodes a variant intestinal fatty-acid-binding protein with altered affinity for long-chain fatty acids. Thr54 carriers show altered intestinal fat absorption kinetics and modestly different postprandial triglyceride responses (Baier et al., 1995).

APOA5 rs662799 (−1131T>C) reduces APOA5 expression and impairs lipoprotein-lipase-mediated triglyceride clearance; C-allele carriers show 20–40 % higher fasting triglycerides and exaggerated postprandial lipaemia, as discussed in the dedicated triglyceride review. ADRB2 rs1042714 (Gln27Glu) modifies adipocyte β2-adrenergic signalling and therefore catecholamine-driven lipolysis during fasting and exercise.

CLINICAL PHENOTYPE AND DIETARY IMPLICATIONS

Clinical features that most reliably identify dietary-fat-sensitive patients include elevated fasting and non-fasting triglycerides, central adiposity at moderate BMI, reduced HDL cholesterol, and a personal or family history of hypertriglyceridaemia, pancreatitis or familial combined hyperlipidaemia. In these patients, shifting dietary fat composition toward predominantly monounsaturated and long-chain polyunsaturated sources produces measurable improvements in lipid profile and body composition, independent of total energy or macronutrient ratio.

The preferred pattern emphasises olive oil, nuts and seeds, oily fish (EPA and DHA), avocado, eggs and lean meat, while moderating saturated-fat sources — particularly processed meat, full-fat dairy, butter, tropical oils (coconut, palm) and commercial baked goods. Alcohol is an important modifier: it acutely raises triglycerides and undermines the benefit of dietary-fat changes, particularly in APOA5 C-allele carriers.

Refined-carbohydrate reduction provides additional benefit because de novo lipogenesis from carbohydrate excess is a major driver of VLDL triglyceride production.

Lifestyle measures — regular aerobic and resistance exercise, adequate sleep, normal body weight — remain quantitatively more important than any genetic consideration. Genetic information refines 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
Corella et al., 2009	**Population:** 3 462 adults across three populations.	**Design:** Gene–diet interaction in multi-ethnic cohorts. **SNP:** APOA2 rs5082 × saturated-fat intake.	APOA2 −265CC homozygotes had higher BMI and central adiposity when saturated-fat intake was high but not when it was low — one of the clearest and most reproducible gene–diet interactions in human nutrigenetics (Corella et al., 2009).
Corella et al., 2011 (PREDIMED sub-study)	**Population:** Adults in PREDIMED at elevated cardiovascular risk.	**Design:** Mediterranean-diet trial sub-analysis. **SNP:** APOA2 rs5082 × dietary fat composition.	Mediterranean-pattern unsaturated-fat substitution attenuated the APOA2 CC-associated adiposity phenotype, supporting dietary fat composition as an effective genotype-informed lever (Corella et al., 2011).
Baier et al., 1995	**Population:** Pima Indians.	**Design:** Functional and population study. **SNP:** FABP2 rs1799883 (Ala54Thr).	Thr54 carriers had altered intestinal fatty-acid binding and modestly altered insulin sensitivity and postprandial fat handling (Baier et al., 1995).
Pennacchio et al., 2001	**Population:** Human and murine.	**Design:** Gene discovery and functional study. **SNP:** APOA5 rs662799.	Identified APOA5 as a major regulator of plasma triglycerides; the −1131C allele reduces APOA5 expression and increases fasting and postprandial triglycerides (Pennacchio et al., 2001).
Talmud et al., 2002	**Population:** UK adults (Whitehall II).	**Design:** Population genetic association. **SNP:** APOA5 rs662799.	C allele was associated with elevated fasting triglycerides and exaggerated postprandial lipaemia in healthy adults (Talmud et al., 2002).
Large et al., 1997	**Population:** Obese adults.	**Design:** Functional and clinical study. **SNP:** ADRB2 rs1042714 (Gln27Glu).	Glu27 carriers had modified adipocyte β2-adrenergic responsiveness, with implications for catecholamine-driven lipolysis and regional fat distribution (Large et al., 1997).

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Mozaffarian et al., 2010	**Population:** > 90 000 adults in controlled trials.	**Design:** Meta-analysis of dietary fat trials. **Focus:** Saturated-fat substitution with polyunsaturated fat.	Replacement of saturated fat with polyunsaturated fat reduced coronary heart disease by approximately 19 %; benefit was greater in those with baseline hypertriglyceridaemia and dyslipidaemia (Mozaffarian et al., 2010).
PREDIMED, 2013	**Population:** 7 447 adults at high cardiovascular risk.	**Design:** Randomised controlled cardiovascular-outcome trial. **Focus:** Mediterranean diet with olive oil or nuts vs low-fat control.	Mediterranean-pattern diet reduced major cardiovascular events by approximately 30 % compared with a low-fat control, with the benefit plausibly mediated by dietary fat composition and polyphenol content rather than by weight change (Estruch et al., 2013).

INTERVENTION RATIONALE

For patients with clinical features of dietary fat sensitivity, Mediterranean-pattern unsaturated-fat emphasis is the most effective dietary framework. Specific implementation includes extra-virgin olive oil as the primary cooking fat, two or more servings of oily fish per week (salmon, mackerel, sardines, herring), one handful of unsalted nuts most days, avocado, seeds and legumes as regular inclusions, and deliberate moderation of saturated-fat sources (processed meat, full-fat dairy, butter, tropical oils). In APOA5 C-allele carriers, alcohol moderation is particularly important because alcohol acutely raises triglycerides.

Refined-carbohydrate reduction is a complementary strategy in dietary-fat-sensitive patients, because carbohydrate excess drives hepatic de-novo lipogenesis and VLDL triglyceride production — often dominating postprandial lipid response in modern diets. The combined Mediterranean-pattern, low-glycaemic-load dietary framework addresses both the dietary fat and refined-carbohydrate arms of postprandial dyslipidaemia.

Pharmacological options — icosapent ethyl (high-dose purified EPA), fibrates, statins depending on the lipid panel — are available for patients who do not achieve adequate control with lifestyle measures, and have been discussed in the triglyceride and LDL-cholesterol reviews.

OPEN QUESTIONS AND DIRECTIONS FOR FURTHER RESEARCH

Individual-variant effects on dietary fat response are modest, and no clinically validated composite tool integrates them into routine dietary counselling. Current best practice identifies dietary-fat-sensitive patients through biomarker-based phenotyping (fasting and non-fasting triglycerides, HDL, waist circumference, family history) supplemented where available by genotype data. Randomised feeding trials that stratify by phenotype and by key individual variants are the most informative next step and are the basis on which genotype-informed clinical advice will continue to evolve.

CONCLUSION

Individual response to dietary fat composition varies substantially and is partly genetically determined. Common variants in APOA2, FABP2, APOA5 and ADRB2 contribute modest individual effects that together help to explain why some patients tolerate higher saturated-fat intake while others show improved cardiometabolic outcomes on Mediterranean-pattern unsaturated-fat-emphasising 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, alcohol moderation, refined-carbohydrate reduction, regular physical activity and normal body weight remain the dominant modifiable determinants of lipid health.

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