Genetic Determinants of Body-Fat Distribution

PPARG, FTO, APOA2, ADRB2 and FABP2 Polymorphisms and the Balance Between Visceral and Subcutaneous Adiposity — A Literature Review

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ABSTRACT

Background. Body-fat distribution — in particular the balance between visceral (intra-abdominal) and subcutaneous (peripheral) adipose tissue — is a stronger determinant of cardiometabolic risk than total adiposity. Visceral adiposity is associated with insulin resistance, dyslipidaemia, hypertension and cardiovascular events; gluteofemoral subcutaneous adiposity is relatively metabolically protective. Fat distribution is partly heritable and modified by variants in PPARG, FTO, APOA2, ADRB2 and FABP2.

Methods. Narrative review of PubMed-indexed studies on genetic determinants of body-fat distribution.

Results. PPARG Pro12Ala Ala carriers have smaller, more insulin-sensitive adipocytes and show favourable fat-distribution phenotype. FTO A-allele increases total adiposity and visceral fat. APOA2 rs5082 CC homozygotes accumulate visceral fat specifically on high-saturated-fat diets. ADRB2 variants modify regional lipolysis and affect the responsiveness of different depots. FABP2 Thr54 reduces intestinal fat absorption and modestly reduces ectopic fat deposition.

Discussion. Genotype-informed advice emphasises interventions that preferentially reduce visceral fat: resistance plus aerobic exercise, Mediterranean-pattern diet, avoidance of alcohol excess, adequate sleep, and stress management. Visceral-fat-reducing interventions reliably improve metabolic outcomes across genotypes.

Subjects: Genetics, Obesity, Cardiometabolic Risk. **Keywords:** PPARG; FTO; APOA2; ADRB2; FABP2; visceral fat; subcutaneous fat; fat distribution.

INTRODUCTION

Visceral adipose tissue — the fat surrounding abdominal organs — is metabolically distinct from subcutaneous adipose tissue. It drains directly into the portal circulation, is highly lipolytically active, is infiltrated by pro-inflammatory macrophages, and produces a profile of adipokines (lower adiponectin, higher TNFα, IL-6) that drives insulin resistance and atherogenic dyslipidaemia. Excess visceral fat is therefore a stronger cardiometabolic risk factor than total body fat.

Body-fat distribution is heritable with heritability estimates of 30–60 % for waist-hip ratio after adjustment for BMI. Common variants at multiple loci contribute, including those discussed in the nutritional-type review (PPARG, FTO, APOA2, ADRB2, FABP2) plus dedicated fat-distribution loci identified in GWAS (including near TBX15, LYPLAL1, KLF14).

KEY FAT-DISTRIBUTION GENES

PPARG Pro12Ala Ala12 carriers show smaller, more insulin-sensitive adipocytes and a relatively favourable fat-distribution phenotype with reduced ectopic fat deposition. FTO A-allele carriers show higher total adiposity with modest preferential accumulation in visceral depots. APOA2 rs5082 CC genotype, combined with high saturated-fat intake, favours visceral fat accumulation (Corella et al., 2009).

ADRB2 variants modify regional lipolysis: Gly16 is associated with enhanced desensitisation in subcutaneous depots; Glu27 alters adipocyte β2-responsiveness. The net effect on distribution is modest and context-dependent. FABP2 Thr54 reduces intestinal fat absorption and is associated with slightly lower ectopic fat deposition.

Beyond these variants, sex is a major determinant: pre-menopausal women show preferential gluteofemoral subcutaneous fat deposition; men and post-menopausal women show preferential visceral accumulation. Hormonal changes, alcohol, stress and sleep deficits all influence visceral fat accumulation independently of genotype.

TABLE 1 — SUPPORTING HUMAN STUDIES

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Altshuler et al., 2000	**Population:** Type 2 diabetes case–control studies.	**Design:** Meta-analysis. **SNP:** PPARG Pro12Ala.	Ala12 allele was associated with reduced type 2 diabetes risk; functional studies showed smaller, more insulin-sensitive adipocytes (Altshuler et al., 2000).
Corella et al., 2009	**Population:** 3 462 multi-ethnic adults.	**Design:** Gene–diet interaction study. **SNP:** APOA2 rs5082.	APOA2 CC carriers showed higher BMI — particularly central adiposity — on high-saturated-fat diets (Corella et al., 2009).
Shungin et al., 2015 (GIANT)	**Population:** Over 200 000 individuals.	**Design:** GWAS meta-analysis. **Focus:** Waist-hip ratio adjusted for BMI.	Identified 49 loci for waist-hip ratio including KLF14, TBX15, LYPLAL1; demonstrated sex-specific fat-distribution genetic architecture (Shungin et al., 2015).
Frayling et al., 2007	**Population:** 39 000 adults.	**Design:** GWAS. **SNP:** FTO rs9939609.	FTO A allele associated with higher total adiposity including modest preferential visceral accumulation (Frayling et al., 2007).
Baier et al., 1995	**Population:** Pima Indians.	**Design:** Functional study. **SNP:** FABP2 rs1799883 (Ala54Thr).	Thr54 affected intestinal fat absorption kinetics with implications for ectopic fat deposition (Baier et al., 1995).

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Visceral-fat-reduction trials	**Population:** Adults with visceral obesity.	**Design:** Lifestyle intervention trials. **Focus:** Exercise, diet, sleep, alcohol.	Combined aerobic-plus-resistance exercise, Mediterranean-pattern diet, alcohol moderation and adequate sleep reliably reduced visceral fat across populations; benefit was greater in high-genetic-risk subgroups in some studies.

INTERVENTION RATIONALE

Interventions that preferentially reduce visceral fat include combined aerobic and resistance exercise (at least 150 min/week moderate or 75 min/week vigorous aerobic activity plus 2 resistance sessions), Mediterranean-pattern diet (emphasising vegetables, fruit, legumes, whole grains, fish, nuts, olive oil), moderation of alcohol (major contributor to central adiposity), stress management, adequate sleep and smoking cessation.

For patients with genetic susceptibility to visceral accumulation (compound genotypes including FTO A, APOA2 CC with high saturated fat, PPARG Pro/Pro), the relative benefit of these interventions is larger, although effect sizes are modest at individual variant level. Pharmacological interventions with demonstrated visceral-fat benefit include GLP-1 receptor agonists and, in diabetes, SGLT2 inhibitors.

OPEN QUESTIONS

Polygenic risk scores for fat distribution are improving in predictive value and may help identify patients who will benefit disproportionately from specific interventions. Sex-specific genetic architecture of fat distribution is an active research area.

CONCLUSION

Body-fat distribution is partly genetically determined and is a stronger cardiometabolic risk factor than total adiposity. PPARG, FTO, APOA2, ADRB2 and FABP2 variants contribute to individual distribution patterns. Combined exercise, Mediterranean-pattern diet, alcohol moderation, adequate sleep and stress management reliably reduce visceral fat and improve metabolic health across genotypes.

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