ADRB2 and ADRB3 Polymorphisms and the Relative Efficacy of Exercise versus Calorie Restriction

Genetic Determinants of Sympathetic Lipolysis and Weight-Loss Response — A Literature Review

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ABSTRACT

Background. Weight loss can be achieved through negative energy balance produced by calorie restriction, increased physical activity, or their combination. Individual responsiveness to each strategy varies substantially and is partly modified by common variants in the β-adrenergic receptors ADRB2 (rs1042714 Gln27Glu, rs1042713 Arg16Gly) and ADRB3 (rs4994 Trp64Arg), which govern catecholamine-mediated lipolysis during exercise and fasting.

Methods. Focused literature review. PMIDs from the source report include 32335043, 26365669, 26524954, 21209257, 20696075, 19828688, 17211608 and others on exercise genetics; 12888635 for ADRB3.

Results. ADRB3 Trp64Arg carriers have modestly reduced β3-adrenergic-mediated lipolysis and lower resting energy expenditure. ADRB2 Gly16 homozygotes have enhanced receptor desensitisation and may respond less to aerobic exercise. Genotype-stratified exercise interventions show small but measurable differences in fat loss between exercise and calorie-restriction arms. Both interventions remain effective across genotypes.

Discussion. Genotype-informed weight-management advice emphasises combined interventions — moderate calorie restriction plus structured physical activity including both aerobic and resistance components — with specific attention to adequate protein intake and sleep. Genotype may inform the relative balance but should not override evidence-based principles.

Subjects: Genetics, Exercise Physiology, Weight Management. **Keywords:** ADRB2; ADRB3; rs1042714; rs4994; catecholamines; lipolysis; exercise; weight loss.

INTRODUCTION

Negative energy balance — whether produced by calorie restriction, physical activity or their combination — is the necessary condition for body-fat loss. Observational and interventional studies show that calorie restriction is typically more effective than exercise alone for short-term weight loss, but combined interventions produce better long-term maintenance and metabolic outcomes.

The β-adrenergic receptors mediate catecholamine-driven lipolysis during exercise and fasting. Variants in ADRB2 and ADRB3 modify this response and contribute to individual variability in the relative efficacy of exercise versus calorie restriction.

ADRB2 AND ADRB3 VARIANTS

ADRB2 is the major β-adrenergic receptor on human adipocytes. Two common non-synonymous variants — rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu) — modify receptor desensitisation kinetics and downstream lipolysis. Gly16 promotes enhanced receptor internalisation and desensitisation; Glu27 is linked to altered β2 responsiveness. These variants have been associated with variable responses to exercise and to β-agonist therapy.

ADRB3 rs4994 (Trp64Arg) substitutes arginine for tryptophan in transmembrane domain 1 and produces a receptor with approximately 50 % reduced activity. Arg64 carriers have lower resting energy expenditure, reduced cold-induced thermogenesis and a modestly increased propensity to weight gain (Walston et al., 1995).

CLINICAL IMPLICATIONS

In exercise interventions, Gly16 homozygotes and Arg64 carriers show modestly blunted fat-loss responses to aerobic exercise compared with Arg16 or Trp64 wild-type carriers. Effect sizes are small at individual level but can accumulate over sustained intervention periods. Combined exercise-plus-calorie-restriction interventions generally overcome this attenuation.

For calorie-restriction-based interventions alone, ADRB genotype has less clear differential effect, because catecholamine-driven lipolysis is a smaller component of fat mobilisation during sustained hypocaloric feeding compared with during exercise. The practical recommendation is therefore consistent across genotypes: combined diet plus exercise including resistance training, adequate protein intake (1.2–1.6 g/kg/day during weight loss to preserve lean mass), and consistent sleep.

TABLE 1 — SUPPORTING HUMAN STUDIES

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Walston et al., 1995	**Population:** Pima Indians.	**Design:** Genetic association study. **SNP:** ADRB3 rs4994 (Trp64Arg).	Arg64 carriers had earlier onset of type 2 diabetes and modestly lower resting energy expenditure; established ADRB3 as a functional obesity-associated variant (Walston et al., 1995).
Large et al., 1997	**Population:** Obese adults.	**Design:** Functional and clinical study. **SNP:** ADRB2 Gln27Glu.	Glu27 carriers had altered adipocyte β2-adrenergic function consistent with modified lipolysis during catecholamine stimulation (Large et al., 1997).

STUDY (AUTHOR, YEAR)	POPULATION	DESIGN · SNP / FOCUS	PRIMARY OUTCOME / KEY FINDINGS
Meirhaeghe et al., 2001	**Population:** Adults with varying physical activity.	**Design:** Population cohort. **SNP:** ADRB2 rs1042713 × physical activity.	Arg16/Gly16 genotype modified the association between physical activity and BMI; ADRB2 variation contributes to exercise-response variability (Meirhaeghe et al., 2001).
Bray et al., 2009 (HERITAGE)	**Population:** Adult families in HERITAGE Family Study.	**Design:** Large exercise-training cohort. **Focus:** Genetic predictors of training response.	Identified multiple loci influencing cardiorespiratory-fitness response to standardised exercise training; supported the concept of genotype-modified exercise responsiveness (Bray et al., 2009).
Genotype-stratified exercise trials	**Population:** Adults stratified by ADRB2/ADRB3 genotype.	**Design:** Controlled exercise-training trials. **Focus:** Fat-mass change × genotype.	Modest but reproducible genotype-dependent differences in fat loss with exercise-only protocols; combined diet + exercise interventions produced consistent benefit across genotypes.
Donnelly et al., 2009 (ACSM)	**Population:** Adults attempting weight loss.	**Design:** Evidence-based position stand. **Focus:** Exercise prescription and weight management.	Established the effectiveness of combined diet plus moderate-to-vigorous exercise (≥ 250 min/week) for significant weight loss and maintenance (Donnelly et al., 2009).

INTERVENTION RATIONALE

For most overweight and obese adults, combined diet plus structured physical activity is the most effective approach. Targets of approximately 500–750 kcal/day deficit, 30–60 minutes of moderate physical activity most days, and 2–3 resistance-training sessions per week produce reliable fat loss with lean-mass preservation. Protein intake of 1.2–1.6 g/kg/day during active weight loss preserves lean mass; adequate sleep (7–9 hours) supports hunger/satiety regulation.

For ADRB3 Arg64 carriers and ADRB2 Gly16/Gln27 carriers, a slightly greater emphasis on exercise intensity (including resistance training and high-intensity interval sessions) may help overcome the modestly attenuated catecholamine-driven lipolysis. For Trp64 and Arg16 wild-type individuals, standard recommendations are fully effective.

OPEN QUESTIONS

Genotype-stratified long-term randomised trials of exercise versus calorie-restriction interventions remain limited. The interaction between β-adrenergic genotype and specific exercise modalities (high-intensity interval, resistance, endurance) is an active research area.

CONCLUSION

ADRB2 and ADRB3 variants modify catecholamine-driven lipolysis and contribute to interindividual variability in response to exercise-based weight-loss interventions. Combined diet-plus-exercise approaches remain effective across genotypes and form

the evidence-based foundation of weight management; genotype-informed refinement of modality emphasis is a useful complement.

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