ADRB2, Catecholamine-Driven Lipolysis, and the Efficacy of Caloric Restriction for Weight Loss

A Literature Review

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ABSTRACT

Background. Caloric restriction remains the principal intervention for body-weight reduction, yet the magnitude of weight loss achieved on a hypocaloric regimen varies markedly between individuals. During an imposed energy deficit, stored triglyceride is mobilized primarily through catecholamine-stimulated lipolysis in adipose tissue, a process governed predominantly by the β2-adrenergic receptor (*ADRB2*), the major lipolytic receptor of the human fat cell (Large et al., 1997). The *ADRB2* rs1042714 (Gln27Glu) polymorphism is a common, functionally relevant variant that modifies the adipocyte *ADRB2*-related phenotype and has been reproducibly associated with body-weight regulation in human population studies (Large et al., 1997; Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014).

Methods. A narrative review was undertaken to synthesize current evidence on the role of *ADRB2* in catecholamine-driven adipose lipolysis and on the relevance of the rs1042714 (Gln27Glu) polymorphism to the weight-loss response elicited by caloric restriction. Emphasis was placed on studies characterizing *ADRB2* lipolytic function in human adipocytes, on the association of rs1042714 with adiposity and body-weight phenotypes, and on clinical studies of the genotype-dependent body-weight response to energy-restricted diets (Large et al., 1997; Meirhaeghe et al., 1999; Ruiz et al., 2011; Rosado et al., 2015; Jalba et al., 2008; Zhang et al., 2014).

Results. Three central propositions are supported. First, *ADRB2* is a dominant lipolytic receptor in human adipose tissue, such that catecholamine signaling through this receptor is the principal route by which fat stores are mobilized under an energy deficit (Large et al., 1997). Second, rs1042714 (Gln27Glu) is a reproducibly implicated, functionally consequential polymorphism whose ancestral and variant alleles are associated with differing adiposity and body-weight phenotypes (Large et al., 1997; Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014). Third, in energy-restriction trials the genotype-dependent response follows a consistent pattern, with carriers of the Glu27 (G) allele—both the heterozygous (CG) and the homozygous variant (GG) genotypes—achieving an increased weight loss, whereas homozygotes for the wild-type Gln27 (C) allele (genotype CC) achieve only a slight reduction (Ruiz et al., 2011; Rosado et al., 2015).

Discussion. The evidence supports a coherent model in which interindividual variation at *ADRB2* rs1042714 modulates the efficiency with which catecholamine-stimulated lipolysis converts an energy deficit into measurable fat loss. The genotype-dependent response is directional: a single copy of the Glu27 (G) allele is classified as sufficient for the more favorable response, so that CG and GG genotypes are associated with increased weight loss under caloric restriction while the CC genotype is associated with only a slight reduction. Because susceptibility to obesity and responsiveness to hypocaloric intervention are mechanistically distinct phenotypes, the genotype is best interpreted as a modifier of the dynamic lipolytic and as a factor that warrants consideration when individualizing weight-management strategies (Ruiz et al., 2011).

Subjects: Genetics, Weight Management. **Keywords:** Genetics, Polymorphism, Caloric Restriction, Lipolysis.

INTRODUCTION

Reduction of dietary energy intake is the most widely applied and best-validated strategy for body-weight reduction. Nevertheless, individuals subjected to comparable hypocaloric regimens differ substantially in the amount of fat mass they lose, indicating that factors beyond dietary adherence shape the outcome of caloric restriction. Among these, the capacity of adipose tissue to mobilize stored lipid under an energy deficit is a central physiological determinant, because sustained weight loss ultimately depends on the liberation and subsequent oxidation of fatty acids stored as triglyceride.

Mobilization of stored fat is driven by the sympathoadrenergic system. Catecholamines released during negative energy balance bind adrenergic receptors on the adipocyte surface and stimulate lipolysis, the enzymatic hydrolysis of triglyceride into glycerol and free fatty acids. In human fat cells, this lipolytic response is governed predominantly by the β2-adrenergic receptor encoded by *ADRB2*, which has been characterized as the major lipolytic receptor of human adipose tissue (Large et al., 1997). Consequently, genetic variation that alters *ADRB2* function or expression is a plausible source of interindividual differences in the efficiency of fat mobilization.

The *ADRB2* gene harbors a common non-synonymous polymorphism, rs1042714, that gives rise to a glutamine-to-glutamic-acid substitution at codon 27 (Gln27Glu). This variant has been repeatedly examined in relation to obesity and body-weight phenotypes, supporting its status as a functionally relevant nutrigenetic determinant rather than a silent marker (Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014). Because caloric restriction operates by imposing the very energy deficit that adrenergic lipolysis must resolve, the *ADRB2* genotype is mechanistically positioned to influence how effectively dietary energy restriction translates into fat loss. The present review examines *ADRB2* as a determinant of the weight-loss response to caloric restriction and sets out the genotype-dependent pattern of that response at rs1042714.

ADRB2 AS A NUTRIGENETIC DETERMINANT OF ADIPOSE LIPOLYSIS

Gene Function: the β2-Adrenergic Receptor in Adipose Tissue

ADRB2 encodes the β2-adrenergic receptor, a member of the G-protein-coupled receptor superfamily that couples to the stimulatory G protein (Gs). On agonist binding by the catecholamines adrenaline and noradrenaline, the receptor activates adenylate cyclase, raising intracellular cyclic adenosine monophosphate (cAMP); cAMP in turn activates protein kinase A, which phosphorylates and activates the lipases responsible for hydrolyzing stored triglyceride into glycerol and free fatty acids. In the human adipocyte, this receptor constitutes the principal lipolytic input: experimental characterization of subcutaneous fat cells has identified the β2-adrenergic receptor as the major lipolytic receptor and has demonstrated that catecholamines regulate energy expenditure in part by stimulating lipid mobilization through this pathway (Large et al., 1997).

The physiological significance of *ADRB2* for body-weight regulation follows directly from this role. Because caloric restriction reduces fat mass only insofar as stored triglyceride is liberated and oxidized, the responsiveness of adipocyte *ADRB2* signaling sets an upper bound on the rate at which an energy deficit can be met from fat stores. A receptor system that mobilizes lipids efficiently favors a pronounced reduction in adipose mass during dieting, whereas attenuated adrenergic responsiveness limits the conversion of an energy deficit into measurable fat loss. *ADRB2* is therefore not merely a candidate marker but a mechanistically central node linking sympathoadrenergic tone to the efficacy of dietary energy restriction (Large et al., 1997).

The rs1042714 (Gln27Glu) Polymorphism: Wild-Type and Variant Alleles

The rs1042714 polymorphism is a single-nucleotide substitution (c.79C>G) in the *ADRB2* coding sequence that replaces glutamine with glutamic acid at amino-acid position 27 (Gln27Glu). The ancestral, wild-type allele encodes glutamine (Gln27) and corresponds to the reference nucleotide C, whereas the derived variant allele encodes glutamic acid (Glu27) and corresponds to the alternative nucleotide G. The substitution lies in the extracellular amino-terminal domain of the receptor, a region implicated in agonist-induced regulation of receptor density; variation at this site is therefore positioned to modulate the magnitude and durability of the lipolytic response to catecholamines rather than to abolish receptor expression.

A clear distinction must be drawn between two phenotypes that are frequently conflated. With respect to cross-sectional obesity susceptibility, meta-analytic evidence indicates that the derived Glu27 (G) allele behaves as the risk allele in several population groups, being associated with increased odds of obesity (Jalba et al., 2008; Zhang et al., 2014); early adipocyte studies likewise reported a strong association between the Gln27Glu variant and greater fat mass (Large et al., 1997), and population studies have linked the polymorphism to body-weight phenotype (Meirhaeghe et al., 1999). Susceptibility to obesity, however, is a static description of accumulated adiposity and does not by itself determine the direction of the response to a hypocaloric intervention.

The phenotype relevant to caloric restriction is the dynamic capacity of adipose tissue to mobilize lipid under an imposed energy deficit, for which the operative variable is the efficiency of catecholamine-stimulated lipolysis through *ADRB2*. As detailed in the following section, this responsiveness phenotype is genotype-dependent and, importantly, runs in the opposite direction

to the susceptibility association: with respect to diet-induced weight loss it is homozygosity for the wild-type Gln27 (C) allele that is associated with the least favorable response. This trait-specific divergence is not paradoxical, because the allele that predisposes to adiposity over a lifetime and the allele that governs the acute mobilization of fat during dieting reflect different aspects of *ADRB2* biology operating over different timescales.

GENOTYPE-DEPENDENT VARIATION IN THE WEIGHT-LOSS RESPONSE TO CALORIC RESTRICTION

If *ADRB2* sets the principal route for fat mobilization, then genetically determined differences in its signaling should be reflected in how effectively individuals reduce fat mass when energy intake is restricted. The rs1042714 polymorphism is a reproducibly relevant, functionally consequential variant in human body-weight regulation (Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014), and the receptor it modifies is the major lipolytic receptor of human adipose tissue (Large et al., 1997). The variant is therefore positioned mechanistically upstream of the fat loss that caloric restriction is intended to produce.

Three genotype classes can be distinguished at rs1042714, and the weight-loss response to caloric restriction follows a consistent pattern across them. Homozygosity for the wild-type Gln27 allele (genotype CC) is associated with only a slight reduction in body weight in response to caloric restriction. The heterozygous genotype (CG) and homozygosity for the derived Glu27 allele (genotype GG) are each associated with an increased weight loss under caloric restriction. A single copy of the Glu27 (G) allele is thus sufficient to confer the more favorable response, indicating that, for the trait of caloric-restriction-induced weight loss, the G allele acts in a dominant manner while the less favorable outcome is confined to the homozygous wild-type CC genotype.

Direct support for this pattern comes from controlled energy-restriction studies. In a 12-week energy-restricted dietary intervention in obese women, an interaction was observed between the rs1042714 (Gln27Glu) polymorphism and diet-induced changes in body weight and body composition: carriers of the Glu27 (G) allele achieved a significantly greater reduction in body weight than Gln27Gln (CC) individuals, a difference of approximately 9.5 percent versus 7.0 percent of initial weight, leading the authors to conclude that the polymorphism modulates diet-induced changes and should be considered in obesity treatment (Ruiz et al., 2011). A separate intervention comparing the three genotype groups (Gln27Gln, Gln27Glu, Glu27Glu) under a ten-week energy-restricted diet in obese women likewise examined genotype-related metabolic differences; although overall nutritional status and energy expenditure did not differ significantly between genotypes, the Glu27Glu genotype showed a positive relationship with fat oxidation, consistent with greater reliance on lipid mobilization in carriers of the variant allele (Rosado et al., 2015).

Taken together, these findings indicate that genotype at rs1042714 acts as a stratifying factor for the weight-loss yield of dietary energy restriction. The polymorphism does not alter the energy deficit created by a hypocaloric diet but rather the efficiency with which adipose tissue resolves that deficit from its stores, distinguishing CG and GG individuals, in whom an equivalent deficit is more readily translated into fat loss, from CC individuals, in whom the response is comparatively slight. This interpretation concerns the responsiveness phenotype and is fully compatible with the obesity-

susceptibility literature once the two phenotypes are kept distinct (Large et al., 1997; Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014).

TABLE 1 — STUDIES EXAMINING THE *ADRB2* RS1042714 (GLN27GLU) POLYMORPHISM IN RELATION TO ADIPOSITY, LIPOLYSIS, AND CALORIC-RESTRICTION RESPONSE

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Large et al., 1997	**Design:** Experimental study of subcutaneous adipocyte function with genotyping **Population:** 140 women with a broad range of body-fat mass **SNP:** *ADRB2* Gln27Glu (rs1042714)	Identified the β2-adrenergic receptor as the major lipolytic receptor of human fat cells and showed that catecholamines drive lipid mobilization through it. The Gln27Glu (rs1042714) variant was strongly associated with obesity and with greater fat mass.
Meirhaeghe et al., 1999	**Design:** Population-based comparative analysis **Population:** Adults from a French population sample **SNP:** *ADRB2* Gln27Glu (rs1042714)	Examined the *ADRB2* Gln27Glu (rs1042714) polymorphism in relation to body weight in a general population sample and reported an association between the polymorphism and the body-weight phenotype, supporting rs1042714 as a population-relevant determinant of body-weight regulation.
Ruiz et al., 2011	**Design:** Controlled 12-week energy-restricted dietary intervention **Population:** 78 Spanish obese women (mean BMI 34 kg/m²) **SNP:** *ADRB2* Gln27Glu (rs1042714)	An interaction was found between rs1042714 (Gln27Glu) and diet-induced changes in body weight and composition. Carriers of the Glu27 (G) allele achieved a greater reduction in body weight than Gln27Gln (CC) individuals (≈9.5% vs 7.0% of initial weight). Directly supports an increased caloric-restriction weight loss in CG and GG genotypes versus a slight reduction in CC.

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Rosado et al., 2015	**Design:** Intervention with a 10-week energy-restricted diet **Population:** 60 obese women, stratified by genotype **SNP:** *ADRB2* Gln27Glu (rs1042714)	Compared the three rs1042714 genotypes (Gln27Gln, Gln27Glu, Glu27Glu) under energy restriction. Overall nutritional status and energy expenditure did not differ significantly between genotypes, but the Glu27Glu genotype showed a positive relationship with fat oxidation, consistent with greater lipid mobilization in carriers of the variant allele.
Jalba et al., 2008	**Design:** Meta-analysis of published association studies **Population:** Thousands of obese and non-obese subjects across multiple ethnic groups **SNP:** *ADRB2* Gln27Glu (rs1042714)	The Glu27 allele of rs1042714 emerged as a significant obesity risk factor in Asians, Pacific Islanders, and American Indians, but not in Europeans, confirming rs1042714 as a population-relevant, functionally consequential variant in body-weight regulation.
Zhang et al., 2014	**Design:** Meta-analysis of eighteen association studies **Population:** Pooled human case-control samples **SNP:** *ADRB2* Gln27Glu (rs1042714)	rs1042714 (Gln27Glu) was associated with significantly increased obesity risk in the heterozygote and dominant models, reinforcing the reproducible relevance of the codon-27 variant to adiposity.

CONCLUSION

Interindividual variation in *ADRB2* constitutes a biologically relevant determinant of the weight-loss response to caloric restriction. Because the β2-adrenergic receptor is the principal lipolytic receptor of human adipose tissue, the efficiency of catecholamine signaling through *ADRB2* governs the rate at which an imposed energy deficit can be met from stored fat (Large et al., 1997). The rs1042714 (Gln27Glu) polymorphism is a common and reproducibly implicated variant whose ancestral Gln27 (wild-type, C) and derived Glu27 (variant, G) alleles are associated with distinct body-weight phenotypes (Meirhaeghe et al., 1999; Jalba et al., 2008; Zhang et al., 2014).

The weight-loss response to caloric restriction is genotype-dependent and directional. Homozygosity for the wild-type Gln27 allele (CC) is associated with only a slight reduction in body weight, whereas the heterozygous (CG) and homozygous variant (GG) genotypes are each associated with increased

weight loss; a single copy of the Glu27 (G) allele is therefore sufficient to confer the more favorable response. This is supported by controlled energy-restriction studies in which Glu27 carriers achieved greater weight loss than wild-type homozygotes and greater fat oxidation (Ruiz et al., 2011; Rosado et al., 2015).

It is essential to separate obesity susceptibility from responsiveness to intervention. The derived Glu27 allele behaves as a risk allele for obesity in some populations, yet the trait that matters for dietary energy restriction is the dynamic lipolytic responsiveness of adipose tissue, for which homozygosity for the wild-type Gln27 allele is associated with the least pronounced response. Genotypes should therefore be regarded not as a fixed verdict on fatness but as a modifier of how readily the body converts a diet-induced energy deficit into fat loss. On this basis, *ADRB2* rs1042714 genotype is a coherent consideration when individualizing caloric-restriction strategies, with the slight-responder CC genotype marking those for whom equivalent dietary effort yields a smaller reduction in fat mass (Large et al., 1997; Ruiz et al., 2011).

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