

ORIGINAL ARTICLE

Can study of the ADRB3 gene help improve weight loss programs in obese individuals?[☆]

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Abstract

Introduction: Obesity is a chronic disease of multifactorial origin characterized by excess weight and excess fat accumulation, and whose etiology includes intrinsic (genetic, physiological, and metabolic) and extrinsic (social and cultural) factors. Fat accumulation is caused by a prolonged imbalance in the energy balance influenced, among other factors, by adaptive thermogenesis, which is triggered by cold environmental conditions, or by hypercaloric intake. Thermogenesis is regulated by the sympathetic nervous system (SNS) and occurs in the muscle and brown adipose tissue (BAT). There are adrenergic receptors in BAT, including the beta-3 adrenergic receptor (ADRB3), the main receptor for the regulation of thermogenesis. The presence in heterozygosis of a SNP-type polymorphism in the ADRB3 gene (Trp64Arg; rs4994) is associated with lower lipolytic activity, a predisposition to obesity, and resistance to weight loss. The objective of this study was to analyze through a systematic review the weight loss program most appropriate for carriers.

Methods: A retrospective study of published papers on rs4994 polymorphism in the SNP and PubMed databases was conducted.

Results: Most published studies suggest the presence of obesity and resistance to weight loss in carriers, and report significant improvements in anthropometric parameters when patients receive fat-rich hypocaloric diets.

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Conclusions: Based on these conclusions, specific nutritional and physical exercise guidelines are proposed for individuals carrying the Trp64Arg allele.

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PALABRAS CLAVE

Gen ADRB3;
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Ejercicio;
Termogénesis

¿Puede el estudio del gen ADRB3 ayudar a mejorar los programas de pérdida de peso en individuos obesos?

Resumen

Introducción: La obesidad es una enfermedad crónica de origen multifactorial, caracterizada por exceso de peso y acumulación excesiva de grasa, y cuya etiología incluye factores intrínsecos (genéticos, fisiológicos y metabólicos) y extrínsecos (sociales y culturales). El sobrepeso graso se produce por un desequilibrio prolongado en el balance energético, en el que influyen, entre otros, la termogénesis adaptativa, desencadenada por condiciones ambientales de frío, o a una ingesta hipercalórica. La termogénesis está regulada por el sistema nervioso simpático (SNS), y tiene lugar en el músculo y tejido adiposo pardo (TAP). En el TAP se encuentran receptores adrenérgicos, siendo el receptor β -3 adrenérgico (ADRB3), el principal receptor en la regulación de la termogénesis. La presencia en heterocigosis de un polimorfismo tipo SNP en el gen ADRB3 (Trp64Arg; rs4994) estaría asociado a una menor actividad lipolítica, predisposición a la obesidad y resistencia a la pérdida de peso. El objetivo de este estudio ha sido analizar mediante una revisión sistemática el tipo de programa más indicado para pérdida de peso para individuos portadores.

Métodos: Se realizó un estudio retrospectivo de los trabajos publicados sobre el polimorfismo rs4994 en las bases de datos SNP y PubMed.

Resultados: La mayor parte de los trabajos publicados indican la presencia de obesidad y resistencia a la pérdida de peso en individuos portadores, mostrando importantes mejoras en los parámetros antropométricos los individuos sometidos a dietas hipocalóricas altas en grasas.

Conclusiones: Teniendo en cuenta estas conclusiones, se proponen unas pautas nutricionales y de ejercicio físico específicas para individuos portadores del alelo Trp64Arg.

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Introduction

According to the World Health Organization (WHO), obesity and overweight have reached epidemic proportions worldwide; over 1000 million adult individuals are overweight, and approximately 300 million are obese. These numbers suggest that obesity is currently one of the most important public health problems.¹

Obesity is a chronic disorder of multifactorial origin characterized by excess weight due to excessive body fat accumulation. The underlying etiology includes both intrinsic (genetic, physiological and metabolic) and extrinsic factors (social and cultural patterns). Only some types of obesity are considered to be of genetic origin, with a clear hereditary pattern, such as obesity associated with Prader-Willi syndrome. In most cases, the phenotypic variation seen in obese individuals is attributable to gene-environmental interaction. At present, it is considered that 40–70% of such phenotypic variation is genetically mediated, with candidate genes having been found in 190 different loci. Some of these genes are involved in the function of the food intake control systems or in the stimulation of orexigenic neuronal circuits. These loci include the gene encoding for leptin and its receptor, the melanocortin receptor 4 gene,

and the neuropeptide Y gene.² Until the discovery of leptin, insulin was recognized as the only hormone candidate for long-term body weight regulation. However, we now know that mutations in leptin and its receptor genes are related to the most severe types of obesity, causing lack of satiety and increased food intake from birth.^{3,4} The melanocortin receptor 4 gene is expressed in the paraventricular hypothalamic nucleus and in the lateral hypothalamic area, these being regions involved in the control of appetite.³ Mutations in the melanocortin 4 receptor gene are associated with multifactorial obesity and, in some cases, with monogenic inheritance. Neuropeptide Y is released from the arcuate nucleus of the hypothalamus under fasting and hypoglycemic conditions, and its secretion is inhibited after food intake. A single nucleotide polymorphism (SNP) in the coding region of the neuropeptide Y gene, Leu 7 Pro, appears to be involved in the regulation of lipid metabolism, though it is also a marker of inflammation and vascular problems in individuals with type 2 diabetes mellitus.⁵

Some of the identified genes are related to the occurrence of obese phenotypes, and their function is usually related to the regulation of calorie expenditure and energy balance mechanisms, and to thermogenesis.⁶ Thermogenesis is regulated by the sympathetic nervous system, and

takes place in muscle and brown adipose tissue (BAT), the latter producing heat via a mitochondrial protein called thermogenin. These tissues regulate the energy balance, controlling the homeostasis of glucose metabolism and the active mobilization of lipids from fatty tissues to generate heat and maintain body temperature. Brown adipose tissue in humans is found in the fetus and in the newborn infant. However, recent studies based on positron emission tomography (PET) also show the presence of BAT in adults. Furthermore, the BAT regions are highly innervated by the peripheral nervous system, in contrast to the adjacent white adipose tissue regions.⁷ Its initial purpose is to protect the individual from exposure to cold and to regulate the energy balance by adapting it to new food intake conditions following environmental change. Brown adipose tissue contains adrenergic receptors, with α -3 (ADRB3) being the main receptor involved in the regulation of thermogenesis.

In 1989, Marullo et al.⁸ isolated ADRB3, the main receptor involved in the regulation of catecholamine-mediated thermogenesis and lipolysis in BAT.⁸ Individuals with altered thermogenesis present mutations in the α -adrenergic receptor genes. It has been reported that the presence of the SNP Trp64Arg (polymorphism rs4994) in heterozygosis with the Trp64 wild-type allele could be associated with decreased basal metabolism and lower lipolytic activity, contributing to lipid accumulation in adipose tissue, and probably being responsible for the prevalence of higher body mass index (BMI) values in carrier individuals.^{9–11} *In vitro* studies in isolated adipocytes indicate that carriers of polymorphism rs4994 have decreased lipolytic activity against an agonist as compared to those who are homozygous for the wild-type allele.¹⁰ The prevalence of carriers of polymorphism rs4994 in the obese population is estimated to be approximately 15%, with the observation in some cases of mutations related to a decrease in lipid oxidation and to the energy used in thermogenesis.¹¹

In view of the above, the present study was carried out to offer a detailed analysis of the existing literature on polymorphism rs4994, in order to determine whether the existing data indicate the need to conduct genetic screening of this polymorphism in the obese population.

Methods

A retrospective study was made of the studies published on polymorphism rs4994. The search was performed in February 2018. The identifier rs4994 of this polymorphism was entered in the SNP database of the NCBI (<https://www.ncbi.nlm.nih.gov/snp/>). This database allowed us to conduct a cross-search in the PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed/>) of the same server, with the reporting of 37 studies. In parallel, another search was made in the PubMed database of the NCBI using the keywords “ADRB3”, “Trp64Arg” and “rs4994” of articles published since 1997. A total of 87 studies were identified, of which those carried out in human populations were selected, most of them corresponding to Caucasian and Japanese populations (Fig. 1). For inclusion in our study, we considered the number of individuals in the population sample, their gender and genotype, the type of intervention made, and whether biochemical parameters

were analyzed or not. The studies were classified according to the type of intervention: no intervention (observation only), dietary intervention, physical exercise intervention, and combined diet and physical exercise intervention. Of all the publications analyzed, only the 17 studies shown in Table 1 met these conditions. Many of the studies were discarded during screening, since they failed to specify the population, study design or type of intervention involved (Fig. 1).

Results

Single nucleotide polymorphism rs4994 and differences in responses to intervention programs in obese individuals

A meta-analysis analyzing approximately 9000 individuals from different populations recorded a statistically significant association between individuals carrying polymorphism rs4994 and the BMI. Carriers of this allele were common among individuals with morbid obesity. The Trp64Arg allele was suggested as being related to susceptibility to obesity and probably to increased resistance to weight loss.¹² Studies in different groups of individuals confirmed this tendency towards resistance to weight loss in obese carriers in both observational studies^{13–15} and dietary intervention studies,^{19,20} including physical exercise in the intervention^{21,22} or combining diet and exercise.^{23–26} An association was also found between carrier status of the Trp64Arg allele and having a greater weight and BMI,¹⁵ as well as a greater tendency towards insulin resistance and an increased risk of type 2 diabetes mellitus.¹⁸ However, other follow-up or physical exercise intervention studies in obese patients found no differences between carriers and non-carriers in both observational¹³ and intervention studies involving physical exercise^{21,22} or the combination of diet and physical exercise.²³ All these studies, together with their main conclusions, are summarized in Table 1.

Although these data come from studies with very diverse methodologies, they appear to indicate that carriers of polymorphism rs4994 in the ADRB3 gene tend to have greater body weight, as well as greater difficulty losing weight.

Nutritional guidelines for carriers of SNP Arg64 of the ADRB3 gene

Many weight losing diets have been introduced, all of them showing considerable differences in their effects upon the individuals that follow them. Most obese patients present an energy imbalance, i.e., the balance between energy ingested and calorie expenditure is altered. Most studies analyzed in the present study (and included in Table 1) in which dietary interventions were performed reflect differences in the response to weight losing treatments between Trp64/Trp64 homozygous individuals and carriers of the Arg64 allele.^{14,21–23,27–29} These differences refer to improvements in anthropometric parameters after follow-up or intervention (the BMI, weight, body fat, or hip circumference), and in leptin levels.^{22,23} However, the differences are more evident when biochemical parameters (insulin

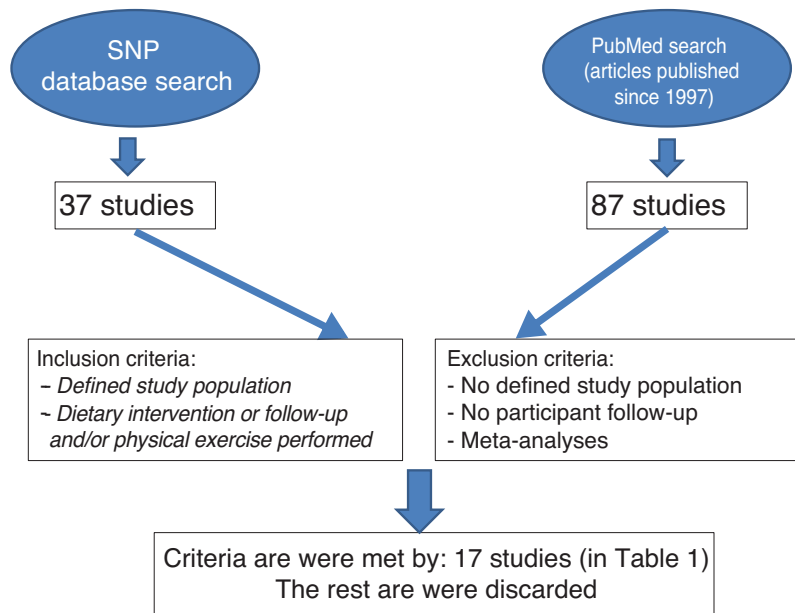


Figure 1 Flowchart of the studies carried out in human populations.

resistance and lipid profile) are assessed. Such parameters do not tend to improve or do so only slightly in carrier individuals.^{22,23}

Most of these dietary interventions involve low-calorie diets.^{20,27} Diets with a high intake of monounsaturated or polyunsaturated fatty acids show important improvements in the biochemical parameters referring to insulin resistance in obese carriers, but not in non-carriers.²² The findings are similar when low-fat or low-carbohydrate, or high-protein diets, are used.^{20,22}

However, the literature is not clear in this regard, and some studies have reported no differences between carriers and non-carriers.^{13,20,24–26} Most of these studies reporting no differences have been conducted in the Japanese population; the ethnic factor therefore may be important.^{24–26}

Response to physical exercise

In some cases, nutritional improvement regimens are insufficient as treatment for any kind of obese or overweight individual; it is therefore advisable to include physical exercise as part of the intervention plan.

Of the different physical exercise interventions analyzed, one of the strategies showing the best results is the intervention proposed by Phares et al., where carriers of the Arg64 allele showed a significant loss of body and trunk fat in response to aerobic training for 24 weeks after a dietary intervention.²⁷ This proposal included resistance exercises three days a week for 24 weeks, with an increase in VO_2 max (the maximum amount of oxygen which the body can absorb, transport and consume in a given time) from 50% to 70% in the first 10 weeks, and 70% in the subsequent weeks. Bea et al. obtained similar results, concluding that an intense physical exercise intervention lasting at least 12

months can counteract the adverse effects of genetics upon the body composition parameters.²⁸

An observational study conducted in obese Brazilian adolescents found the fat-burning capacity (FATmax) to be decreased in carriers of the Arg64 allele.¹⁹ FATmax represents the exercise intensity associated with maximum fatty acid oxidation in absolute and relative terms.³⁰ These values appear to corroborate the results obtained in the dietary intervention studies mentioned in the previous section, where low lipolytic activity was found among carriers (Table 1). However, there are no data on whether this lipolytic activity is modified when the physical exercise intervention is conducted over time or when it is combined with other types of exercise, such as resistance exercise.

Discussion

Although lifestyle interventions generally improve lipid metabolism and reduce cardiovascular risk, some individuals fail to show the expected results, and genetic factors appear to play an important role in this respect.

Although the data are not particularly clarifying, the research conducted over the last 20 years on the role of the ADRB3 gene in the development of obesity and resistance to weight loss suggests that special attention should focus on carriers of the Arg64 allele in the designing of diet and physical exercise regimens in weight loss programs.

The improvements in anthropometric and body composition parameters experienced by patients carrying the Arg64 allele are considerable in comparison with the observed lack of improvement in biochemical parameters such as insulin levels and the HOMA index,^{22,23} reflecting the lower lipolytic activity of their adipose tissue, which presumably affects insulin resistance or is indicative of lower adipokine activity. These patients, moreover, usually have a greater

Table 1 Findings of some intervention/follow-up studies on carriers of the Arg64 allele versus non-carriers of the Arg64 allele of the ADRB3 gene.

Study	Number of individuals in the study	Type of intervention or follow-up involved	Results
Observational Ukkola et al., ¹³	24 men (mean age 21 years)	Monitoring of physical and/or biochemical parameters over time. No intervention	No differences were seen between carriers and homozygous individuals
Corbalan et al., ¹⁴	159 Spanish subjects with obesity and no other diseases except diabetes	Case-control study. Follow-up of physical activity; no intervention	Greater susceptibility to obesity among carriers, but also more sedentary than non-carriers
De Luis et al., ¹⁵	217 obese, non-diabetic Caucasian individuals	Follow-up without intervention	Carriers had a greater BMI, weight, hip circumference, body fat, and C-reactive protein values
Takeuchi et al., ¹⁶	1355 healthy Japanese individuals	Follow-up without intervention	Carriers had a higher BMI, which correlated with elevated LDL-C levels
Sakane et al., ¹⁷	112 Japanese patients with altered glucose levels	6 months of follow-up with educational measures for lifestyle change	Carriers had less weight loss than non-carriers
De Luis et al., ¹⁸	531 obese women	Monitoring of parameters: bioimpedance, blood pressure measurement, 3-day food intake assessment, and biochemical analysis	Obese carriers were not more likely to suffer metabolic syndrome, but had higher insulin and HOMA levels
De Jesús et al., ¹⁹	72 non-obese adolescents (11–17 years of age)	Monitoring of physical and/or biochemical parameters over time. FATmax study (maximum fat oxidation after aerobic exercise). No intervention	The presence of the Arg64 allele was associated with lower FATmax values during aerobic exercise and higher LDL-cholesterol levels
Interventions Rawson et al., ²⁰	34 obese postmenopausal women (19 carriers and 15 non-carriers)	Prolonged caloric restriction as indicated by Diet II of the American Heart Association Guidelines (55% carbohydrates; 30% fats [15% polyunsaturated, 15% monounsaturated and < 7% saturated])	No differences were seen in body composition or energy expenditure between the two groups, though the authors did report difficulty in achieving visceral fat loss, with greater insulin resistance and cardiovascular risk among the carriers
De Luis et al., ²¹	193 obese Caucasian patients	Two low-calorie diets for 2 months: one low in fat, and the other low in carbohydrates	Anthropometric changes were seen that were not affected by the type of diet, but were influenced by the presence of the Arg64 allele. Although less than in homozygous individuals, carriers of the Arg4 allele had a significant decrease in their BMI, weight, fat mass, waist circumference and leptin levels, but there were no changes in insulin levels or the HOMA index

Table 1 (Continued)

Study	Number of individuals in the study	Type of intervention or follow-up involved	Results
De Luis et al., ²²	260 obese individuals	Aerobic exercise 3 days a week for 60 min Two low-calorie diets for 3 months, with a high intake of MUFAs versus a high intake of PUFAs, respectively	A high PUFA diet improved basal glucose levels, the lipid profile, insulin levels and the HOMA index in homozygous but not in heterozygous individuals. The high MUFA diet did not improve any of these parameters. The anthropometric parameters significantly improved with the 2 types of diet, as well as the leptin levels, which decreased
De Luis et al., ²³	284 obese individuals	Two low-calorie diets for 9 months: high in protein/low in carbohydrates versus standard diet	The effect of low-calorie diets upon the metabolic parameters was smaller in carriers of the Trp64Arg allele
Tahara et al., ²⁴	57 Japanese men (BMI > 23), classified as carriers and non-carriers	Aerobic exercise (walking) for 12 weeks with a pedometer	No differences were seen in weight loss
Nakashima et al., ²⁵	70 adult Japanese men exercising regularly	Physical exercise	No differences were seen in weight loss
Shiwaku et al., ²⁶	76 perimenopausal Japanese women carrying the Trp64Arg mutation	Diet and exercise	No differences were seen in weight loss
Phares et al., ²⁷	70 healthy sedentary men and 41 postmenopausal women with a BMI ≤ 37 kg/m ² (United States)	6 weeks of dietary stabilization (as indicated by the American Heart Association) prior to 24 weeks of supervised aerobic exercise	The ADRB3 gene genotype had effects upon weight loss, along with other genes
Bea et al., ²⁸	320 sedentary postmenopausal women	Supervised 12-month intervention with high-intensity resistance exercises at least 3 days a week, and an agreement not to gain weight	Based on the lifestyle changes of the participants, it was deduced that there were individuals who were more resistant to weight loss due to genetic reasons
Szendrei et al., ²⁹	173 subjects (91 women, 82 men) aged 18–50 years	6-month diet and exercise program	The ADRB3 gene influenced the amount of fat mass and percentage fat at individual level, and there was also an interaction among genotype, mass and exercise

initial visceral mass as compared to non-carriers,²² and a greater susceptibility towards high HDL-cholesterol levels and, therefore, greater cardiovascular risk (arterial hypertension, dyslipidemia), though no association has been found between the carrier genotype and metabolic syndrome.¹⁸ Data from transcriptomic studies show a decrease in the expression of proinflammatory genes, insulin response genes, and genes related to DNA damage after the intake of olive oil, which is rich in monounsaturated fatty acids.³¹

However, no improvements have been observed in biochemical parameters when this diet is applied to patients carrying the Arg64 allele.²²

It has been suggested that the Mediterranean diet, which is high in healthy fats (including olive oil) and quality proteins, and low in carbohydrates (with a predominance of fiber), could also be effective in improving cardiovascular parameters as well as different biochemical parameters (the HOMA index and insulin resistance).^{32,33} According to the

indications of these studies, all diets should contain between 10–25 g of soluble fiber a day, preferably obtained from citrus fruits and green leafy vegetables. Citrus fruits contain abundant soluble fiber and vitamin C, which are good for diabetes control or prevention. It has recently been suggested that foods rich in p-synephrine, such as some citrus fruits, could stimulate lipolysis, without a resultant rise in blood pressure.³⁴

Ketogenic diets have also been shown to be efficient in modifying biochemical parameters in obese individuals.³⁵ However, in carriers of the Arg64 allele, care should be taken to limit cholesterol intake to less than 200 mg/day, and a daily intake of about 2 g of stanols and sterols is advised in place of animal fats.

Some studies have reported an interaction between the ADRB3 and UCP3 genes. Individuals carrying mutant alleles in these genes had a greater BMI, body weight, fat mass, systolic blood pressure and waist circumference than patients with the genotype, suggesting a possible interaction of both genic products.³⁶ These data show that further studies are still needed to identify the complex relationship between the expression levels of these genes, whose interactions could be implicated in body fat accumulation. In fact, expression levels of the ADRB3 gene are decreased in obese individuals, and it has been suggested that the cell signaling pathway underlying the ADRB3 protein may be a potential therapeutic target for the treatment of obesity.³⁷

Most intervention programs targeted to obese individuals include dietary intervention and physical exercise. The recommendations regarding physical exercise should be no less than 13 METs (standard metabolic equivalents) a week. The MET is defined as the oxygen consumption that occurs during one minute while the individual is seated and at rest, and increases when physical activity raises oxygen consumption relative to the resting state.³⁸ Thirteen METs correspond to high intensity exercise and, therefore, the recommendations should include cardiorespiratory resistance exercises, muscle resistance and flexibility, and not be limited to light physical activity. A recent study in adolescents involving carriers of the Arg64 allele reported improved insulin levels after the dietary and physical exercise intervention, the latter being of high intensity (100 min of aerobic exercise, 20 min of stretching, three days a week and with at least 36 sessions).³⁹ For obese individuals in general, physical exercise indications have recently been proposed, working the activities at maximum FATmax ($41.3 \pm 3.2\%$ VO_2 max for women and $46.1 \pm 10.3\%$ VO_2 max for men).⁴⁰ It has, moreover, been reported that the ADRB3 gene also appears to influence athletic behavior of the individual in relation to resistance sports, demonstrating that training based on this type of exercise is more appropriate for carriers of the Arg64 allele.⁴¹

Based on the above, the study of the ADRB3 gene genotype may serve as a basis in clinical practice for developing personalized physical diets and exercise programs targeted to carriers of the Arg64 allele. A comprehensive approach to obese patients requires individualized diagnosis, treatment and follow-up. This is the approach sought by personalized or precision medicine, which aims to improve the individualized response to treatment, and should be taken into

account in patients where we are already aware of this difficulty due to genetic reasons.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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