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Interaction between genes and lifestyle factors on obesity

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Obesity originates from a failure of the body-weight control systems, which may be affected by changing environmental influences. Basically, the obesity risk depends on two important mutually-interacting factors: (1) genetic variants (single-nucleotide polymorphisms, haplotypes); (2) exposure to environmental risks (diet, physical activity etc.). Common single-nucleotide polymorphisms at candidate genes for obesity may act as effect modifiers for environmental factors. More than 127 candidate genes for obesity have been reported and there is evidence to support the role of twenty-two genes in at least five different populations. Gene–environment interactions imply that the synergy between genotype and environment deviates from either the additive or multiplicative effect (the underlying model needs to be specified to appraise the nature of the interaction). Unravelling the details of these interactions is a complex task. Emphasis should be placed on the accuracy of the assessment methods for both genotype and lifestyle factors. Appropriate study design (sample size) is crucial in avoiding false positives and ensuring that studies have enough power to detect significant interactions, the ideal design being a nested case–control study within a cohort. A growing number of studies are examining the influence of gene–environmental interactions on obesity in either epidemiological observational or intervention studies. Positive evidence has been obtained for genes involved in adiposity, lipid metabolism or energy regulation such as PPARγ2 (Pro12Ala), β-adrenoceptor 2 (Gln27Glu) or uncoupling proteins 1, 2 and 3. Variants on other genes relating to appetite regulation such as melanocortin and leptin receptors have also been investigated. Examples of some recently-identified interactions are discussed.

Obesity risk: Mutations: Physical activity: Diet: Gene–environment interaction

Genetics of obesity

Nowadays, the availability of genomics technology represents a major advance in the study of the genetics of obesity[1,2]. Human genetic differences appear at the level of single-nucleotide polymorphisms, copy-number polymorphisms and the specific combinations of alleles (haplotypes)[3,4]. The configuration of multiple genes can range from polygenic (i.e. many genes with a relatively small contribution) to oligogenic (i.e. few genes with large measurable effects often expressed on a residual polygenic background). Indeed, it is this oligogenic architecture that has justified the current efforts to map genes for complex phenotypes. In the present paper the influence of a number of single-nucleotide polymorphisms in genes encoding factors regulating food and energy intake and factors implicated in energy expenditure and adiposity will be summarised.

Genes encoding factors regulating food and energy intake

It is generally accepted that hypothalamic and brain stem centres are involved in the regulation of food intake and energy balance but only in the last decade has information on the relevant regulatory factors and their genes become available[5]. Insulin was regarded as the only candidate for the key role in body-weight regulation until the discovery of leptin by Friedman and colleagues[6], one of the most exciting findings of the last decade[7,8]. This cytokine-like

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Abbreviations: ADRB, β-adrenoceptor; CHO, carbohydrate; MC4R, melanocortin 4 receptor; M/S, metabolic equivalent-hours per week:time spent sitting down during leisure time; TV, television; UCP, uncoupling protein.
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peptide, which is mainly expressed by adipocytes, is now believed to be a key regulator of fat metabolism and energy intake together with other adipokines[9].

Certain areas of the hypothalamus are rich in specific receptors binding regulatory peptides and triggering central regulatory mechanisms. Factors acting at the central nervous system level include neuropeptide Y, cortico-trophin-releasing hormone, pro-opiomelanocortin, α-melanocyte-stimulating hormone, agouti-related protein, melanin-concentrating hormone and cocaine- and amphe-tamine-regulated transcript[10]. Interactions between these molecules involving complex neuronal mechanisms even-tually influence behaviour and provide important links with neuroendocrine regulation of other vital functions of the organism[11].

Evidence is accumulating that most of the genes encoding central peptide factors as well as their receptors (leptin receptors, melanocortin receptors, neuropeptide Y receptors) are polymorphic[12]. Dominant inheritance of obesity conferred by missense, nonsense and frameshift mutations in the melanocortin 4 receptor (*MC4R*) gene has been extensively reported in many populations, including Spanish individuals[13,14]. It has been estimated that 1–6 % of extremely-obese individuals harbour functionally-relevant *MC4R* mutations[15]. More than seventy mutations of *MC4R* (fifty-seven non-synonymous, five nonsense and ten frameshift mutations) have been reported, many of them associated with dominant inheritance of obesity[14]. Functional studies showed that many of the missense mutations also lead to a loss of function of MC4R[15]. Meanwhile, other mutations (i.e. Thr11Ser, Arg18Cys) and two polymorphisms (Val103Ile, Ile251Leu) do not modify the function of the MC4R *in vitro*[14].

A number of peptides synthesised along the gastro-intestinal tract also affect food intake. They include ghrelin (an orexigenic peptide mainly produced in the stomach), cholecystokinin (produced in the small intestine and acting as a short-term satiety signal) and peptide YY3–36 (produced in the colon and suppressing appetite for ≤12 h)[16]. Exploration of these signalling pathways has started and it is becoming clear that polymorphism in relevant genes may have important functional con-sequences. For the ghrelin receptor gene two single-nucleotide polymorphisms have been reported: Ala204Glu and Phe279Leu, which selectively impair the constitutive activity of the receptor in human subjects leading to short stature and obesity that apparently develops during puberty[17].

Genes encoding factors implicated in energy expenditure

Adaptive thermogenesis in human subjects is closely re-lated to the active mobilisation of lipids from fat tissues and is of particular interest in relation to obesity[18]. Central neural pathways responsible for food-intake and energy-expenditure regulation are closely interconnected. The peripheral transmission of central commands to the fat stores is mediated by the sympathetic nervous system. The β-adrenoceptor (*ADRB*) gene family members (*ADRB2*, *ADRB3*, *ADRB1*) are extensively-studied candidate genes

in the obesity field because of their participation in energy-expenditure regulation[19].

The *ADRB2* gene encodes a major lipolytic receptor protein in human fat cells. Two common polymor-phisms of the *ADRB2* gene, characterised by an amino acid replacement of arginine by glycine in codon 16 (Arg16Gly) and glutamine by glutamic acid in codon 27 (Gln27Glu) have been explored in several diseases, e.g. hypertension and obesity[20–22]. A relationship between the Arg16Gly polymorphism and an altered function of ADBR2 has been reported, leading to decreased agonist sensitivity[23]. Meanwhile, the Gln27Glu variant has also been found to be linked to obesity in some populations. In men the 27Glu allele has been associated with increased BMI and subcutaneous fat and with elevated leptin and TAG levels, while in women the 27Glu variant has been reported to be linked to increased BMI, body fat mass and waist:hip ratio[24].

The ADRB3 protein plays a role in adipocyte metabo-lism, mediating the rate of lipolysis in response to catecholamines, and ADRB3 agonists have potential anti-diabetes and anti-obesity properties[19]. A common poly-morphism in this gene, characterised by an amino acid replacement of tryptophan by arginine at position 64 (Trp64Arg), has been identified and may be linked to lower lipolytic activity and may account for lipid accu-mulation in the adipose tissue[25]. A number of reports have indicated a relationship between the Trp64Arg variant of *ADRB3* and obesity-related phenotypes[25]. In relation to BMI, more than nine studies had shown an association between BMI and the Trp64Arg polymorphism in popu-lations varying from 134 to 856 subjects[25]. In addition, two meta-analyses examining the effect of this mutation on BMI have been published for Caucasian populations[25,26]. One of these meta-analyses included 2447 subjects and the summary weighted mean difference in BMI was 0·30 (95 % CI 0·13, 0·47) kg/m^2, indicating that variant carriers exhibited higher BMI (on the average, 0·30 kg/m^2 higher) than normal homozygous subjects[25]. The second involved 7399 subjects but the results indicated no association[26]. The Trp64Arg polymorphism has been associated with abdominal or visceral fat obesity in several populations such as Caucasians and Japanese subjects[2]. Similarly, several studies carried out among Mexican American, Japanese and Caucasians women have shown that carriers of the Arg allele have a higher BMI and lower reduction in visceral fat after weight loss[3]. Interestingly, a gene–gene interaction between the Trp64Arg variant of the *ADRB3* gene and the Pro12Ala variant of the *PPARγ2* gene has been reported in Spanish and Mexican populations[27].

Whereas ADRB participate in the regulation of adaptive thermogenesis as a component of sympathetic responses, uncoupling proteins (UCP) are involved in the modulation of heat-generating uncoupled respiration at the mitochon-drial level[28]. They represent a family of carrier proteins localised in the inner layer of mitochondrial membranes. There are different members: UCP 1 is mostly expressed in brown adipose tissue and has a role in thermogenesis; UCP2 is ubiquitously present in all tissues; UCP3 is mainly expressed in skeletal muscle and brown adipose tissue[29,30]. Their putative role as 'uncoupling proteins'

has been intensively explored. Like UCP1, UCP2 mediates mitochondrial proton leak, releasing energy stores as heat and therefore affecting the efficiency of energy metabolism[31]. The actual functions for UCP2 and UCP3 proteins are still under investigation. It has been proposed that UCP act as regulators of energy metabolism, being transmembrane fatty acid transporters in the mitochondria facilitating proton exchange[32,33].

Moreover, a number of human studies have indicated a relationship between UCP polymorphisms and exercise efficiency, resting energy expenditure, substrate oxidation, energy metabolism, BMI, obesity risk, type 2 diabetes risk, leptin, fat accumulation, body-weight changes, physical activity etc.[19]. These observations have led to the consideration of *UCP2* and *UCP3* as candidate genes for obesity, given their function in the regulation of fuel metabolism[34].

Several *UCP2* gene variants have been described: a G/A mutation in the promoter region –866G/A, a valine for alanine substitution at amino acid 55 in exon 4 (Ala55Val) and a 45 bp insertion/deletion in the untranslated region of exon 8[33]. The associations between these polymorphisms of *UCP2* and various aspects of obesity have been intensively studied. From the literature, it seems that the G allele in the promoter region of *UCP2* increases obesity risk, while affording relative protection for type 2 diabetes[33]. On the other hand, the Ala55Val polymorphism has been shown to be associated with increased exercise efficiency[19]. However, findings relating to the exon 8 insertion allele of the *UCP2* gene have been inconsistent. While no association with obesity has been observed in a number of the studies conducted in several populations, significant associations have been found between the exon 8 insertion of the *UCP2* gene and BMI, fat mass and the presence of obesity (ranging from $P < 0.01$ to $P < 0.001$)[19].

There are also several *UCP3* gene variants. In linkage studies some of the variants have been shown to be associated with a higher obesity risk. Specifically, the –55C/T polymorphism in the promoter region of this gene has been shown to be associated with an elevated BMI, an increased level of adiposity or a greater waist:hip ratio[19]. However, other authors have not found any relationship between this polymorphism and a higher risk of obesity or changes in metabolic rate[35]. Some studies have even reported an inverse correlation with BMI and the presence of the –55C/T polymorphism[36].

As the *UCP2–UCP3* gene cluster extends within a small region of 40 kb of the genome, a haplotype study is a useful tool to study its association with obesity. Using a study sample comprising 193 obese children and adolescents (cases) and 170 controls aged 6–18 years it has been found that the individual polymorphisms are not associated with obesity, but the (–866G; rs659 366)–(Del; 45 bp)–(–55T; rs1 800 849) haplotype is significantly associated with obesity and its presence in the control group increases the insulin resistance risk by about nine times[4].

Genes encoding factors implicated in adipogenesis

The last group of genes acting in connection with peripheral regulation of energy expenditure comprises the

Table 1. Multivariate conditional logistic regression model of risk factors for childhood obesity (modified from Ochoa *et al.*[42])

	OR	95% CI	P
Family obesity	4·46	2·21, 9·00	<0·01
Physical activity (for each MET-hour per week)	0·94	0·92, 0·96	<0·01
TV watching (for each hour per week)	1·07	1·00, 1·14	0·03
Soft drinks (for each additional serving per d)	1·49	1·07, 2·06	0·02

MET, energy expended during each specific activity: RMR; TV, television.

transcription factors leading to adipogenesis and adipocyte differentiation. The key factors are the PPARγ, particularly the adipose-specific isoform PPARγ2[37,38]. In a meta-analysis examining the Pro12Ala polymorphism in 19 136 subjects a positive association with BMI has been found[3]. The frequency of the Ala allele, similar to other Caucasian populations, has been found to be higher in obese subjects (allelic frequency 0·13) than in controls (allelic frequency 0·08), suggesting that this polymorphism is associated with obesity[19,39]. There is also information on the functional role of PPARγ gene variants: some chimeric proteins appear to have a reduced activity[40].

Gene–environment interactions in relation to obesity phenotypes

Commonly, an obese individual will have inherited minor functional mutations or gene variants in genes coding for key proteins involved in the regulation of body weight[41]. These combined genetic effects account for the biological diversity, and in their absence all organisms would respond in a virtually identical manner to the same environmental challenge. However, obesity development also depends on family and lifestyle influences, as shown in Table 1[42]. Thus, the interaction between functional gene polymorphisms and environmental factors may play a substantial role in the risk of developing obesity[43].

Research into gene–environment interactions suggests that the interplay between genotype and environment deviates from the additive or multiplicative effects of these two factors (the underlying model needs to be specified to appraise the nature of the interaction). This outcome could be a result of chance alone, which highlights the importance of confirmatory findings, but an absence of interaction could also simply reflect the lack of statistical power (i.e. sample size) of the study to detect such an effect[3]. Genotype–environment interactions arise when the response of a phenotype (e.g. body weight) to environmental changes (e.g. overfeeding) depends on the individual's genetic background. Most of the genetic epidemiology studies on human obesity have assumed the absence of genotype–environment interactions simply because of the difficulties in assessing such interactive effects in quantitative genetic models[3].

There are several plausible scenarios for the interaction between genetic and environmental factors. A higher obesity risk (represented by a quantitative trait BMI) will
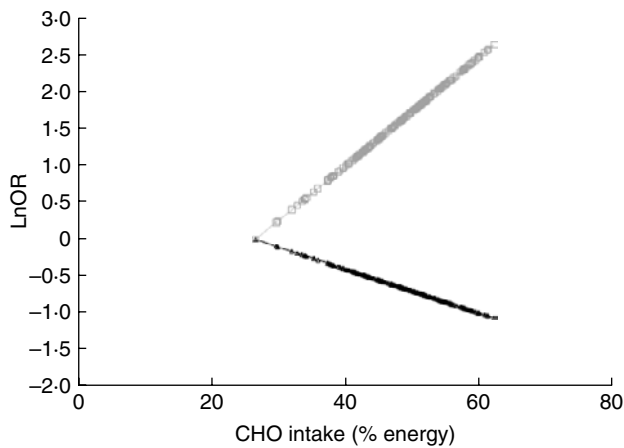
Fig. 1. Obesity risk linked to the single-nucleotide polymorphism Gln27Glu of the β-adrenoceptor 2 gene depends on carbohydrate (CHO) consumption. Natural logarithms of the OR (LnOR) of being obese for women with (□) and without (▲) the polymorphism (logistic regression model) according to the intake of CHO (% energy) and adjusting for age and physical activity during leisure time (metabolic equivalent-hours/week). For interaction, $P=0.056$. (From Martínez *et al.*[44].)

Table 2. Obesity risk linked to the Pro12Ala polymorphism of the *PPARγ2* gene depends on carbohydrate (CHO) consumption (from Marti *et al.*[39])

	Crude		Adjusted	
	OR	*P*	OR	*P*
Low CHO (<49% total energy)	0·50	0·19	0·46	0·2
High CHO (>49% total energy)	4·78	0·045	5·12	0·05

Table 3. Obesity risk linked to the single-nucleotide polymorphism Trp64Arg of the β-adrenoceptor 3 (*ADRB3*) gene depends on physical activity (PA) levels (from Marti *et al.*[49])

	Trp64	Arg64
Cases:control		
Low PA (M/S<0·5)	1·84	5·5
High PA (M/S>0·5)	0·23	0·20
OR		
Low PA	1·(reference)*	2·98*
High PA	0·13*	0·11*

For interaction recreational activity × *ADRB3* mutation, $P=0.06$.
M/S, metabolic equivalent-hours per week: time spent sitting down during leisure time.
*0·13 $\xrightarrow{\times 7}$ 1 (reference) $\xrightarrow{\times 3}$ 2·98 $\xleftarrow{\times 27}$ 0·11.

arise from the presence of obesity-related gene variants and environmental influences (i.e. high consumption of carbohydrates (CHO), low levels of physical activity) for a population carrying a given polymorphism. Indeed, individuals inherit a number of gene variants in key loci, but they also make specific lifestyle choices (e.g. low-fat *v.* high-fat diets, high *v.* low levels of physical activity etc.) that affect weight gain. Thus, while environmental factors may be changed in the short term, genetic factors cannot, but they might interplay.

The gene–environment relationship is a key issue not only in understanding the pathogenesis of multifactorial diseases, but also in designing appropriate treatments (i.e. 'personalised nutrition'). It is possible to investigate gene–lifestyle interactions in human obesity using either intervention or epidemiological observational studies relating to the influence of the whole genome or specific gene variants. The remainder of the paper will review some examples of gene–lifestyle interactions relating to the diet and physical activity of obese subjects.

Gene variants, carbohydrate consumption and obesity risk

Few attempts have been made to examine the influence of gene–diet interactions on obesity-related phenotypes. A case–control design with selected criteria for inclusion (BMI >30 kg/m^2 for cases and BMI <25 kg/m^2 for controls) has found a significant interaction between obesity risk and high levels of CHO consumption (>49% total energy) for carriers of the Glu allele of the *ADRB2* gene[44]. Obesity incidence was not found to be directly affected by the polymorphism (OR 1·40, $P=0.246$), but using a multivariate logistic model after adjustment for confounding factors and/or effect modifiers a marginally-significant interaction between the single-nucleotide

polymorphism and CHO intake was found among women. This finding suggests that a dietary intake higher than the median CHO consumption (>49% total energy) produces an increased obesity risk in those women carrying the Glu27 allele (OR 2·56, $P=0.051$) when adjusted for age and physical activity. A second model, using CHO:fat instead of the percentage energy derived from CHO, supports these results; a CHO intake:fat intake of >1·77 was found to be associated with a higher risk of obesity (OR 3·21, $P<0.02$) in women with the *ADRB2* gene polymorphism. The natural logarithms of the OR of being obese for women with and without the polymorphism according to the intake of CHO were found to be marginally significant for women with the polymorphism (*b* 0·074, $P=0.056$), using the lower level of intake as the reference and adjusting for age and physical activity (Fig. 1). Among female subjects bearing the Glu27 polymorphism an association between high CHO intake and higher insulin levels ($P<0.03$) was found, which may contribute to the greater likelihood of an onset of obesity among these subjects. The fact that some studies have shown that a polymorphism on the *ADRB2* gene adversely reduces fat oxidation[45], which may consequently be associated with hyperlipidaemia, insulin resistance and hyperinsulinaemia, also helps to explain that carriers of the Glu27 allele may show an impaired response after high CHO intake, leading to obesity.

Interestingly, a series of research papers has been devoted to the interplay between the polymorphism Pro12Ala of the *PPARγ2* gene and dietary patterns in relation to obesity phenotypes[3]. *In vivo* ligands for

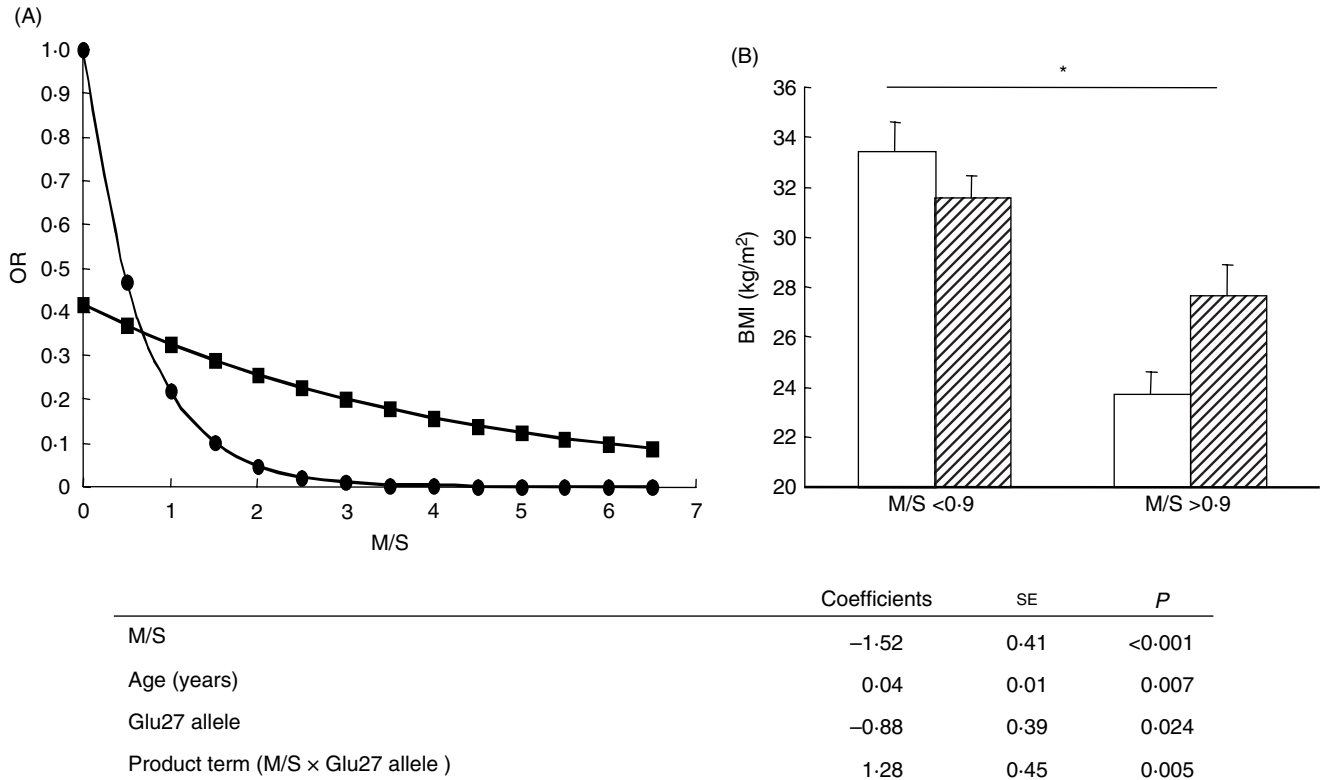|	Coefficients	SE	P
M/S	−1·52	0·41	<0·001
Age (years)	0·04	0·01	0·007
Glu27 allele	−0·88	0·39	0·024
Product term (M/S × Glu27 allele)	1·28	0·45	0·005

Fig. 2. Obesity risk linked to the single-nucleotide polymorphism Gln27Glu of the β-adrenoceptor 2 gene depends on physical activity levels. (A) The change in the magnitude of the association between the Gln27 allele (●, Gln27; ■, Glu27) and the obesity risk is dependent on the exposure to physical activity (metabolic equivalent-hours per week:time spent sitting down during leisure time; M/S). (B) Average BMI for subjects with (///) and without (□) the Glu27 polymorphism. Values are means with their standard errors represented by vertical bars. The table shows coefficients obtained with the multivariate logistic regression model using obesity (BMI>30 kg/m^2) as the outcome and represent the independent effects for recreational energy expenditure (M/S), age and the Glu27 polymorphism and a product term assessing the effect modification of the polymorphism by M/S. (From Corbalán *et al.*[50].)

PPARγ2 are thought to include a variety of fatty acids according to their chain length or extent of saturation. An inverse interaction between dietary polyunsaturated fat: saturated fat and BMI among 12Ala carriers was found, the mean BMI being greater in Ala carriers than in Pro/Pro homozygotes when polyunsaturated fat:saturated fat is low. In a population of women of larger body size the intake of saturated fat was found to be directly associated with increased BMI in carriers and non-carriers of the 12Ala variant, whereas the intake of monounsaturated fat was shown to be inversely associated with BMI only in 12Ala carriers of the PPARγ2 polymorphism[46].
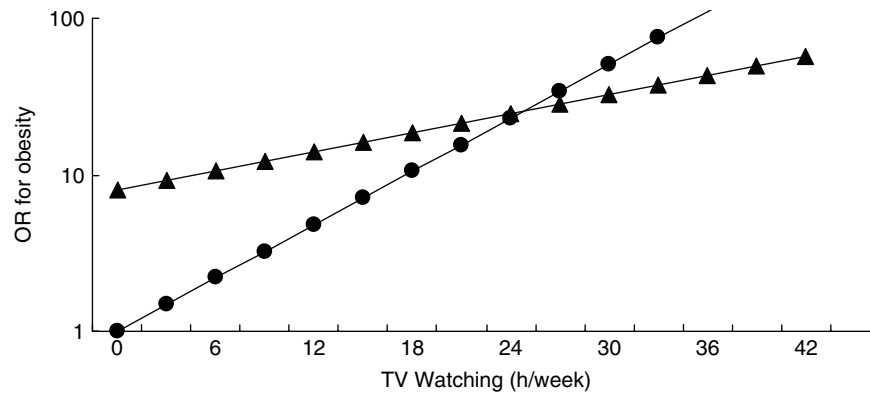
A case–control study has reported a higher risk of obesity for carriers of the 12Ala variant with increasing intake of arachidonic acid[47], whereas the author's group has found an increased obesity risk for carriers of the 12Ala allele when consuming >49% total energy from CHO (Table 2)[39].

Gene variants, physical activity levels and obesity risk

To estimate physical activity levels face-to-face interviews were conducted with volunteers and validated questionnaires relating to their participation (number of hours per week) in different sports, exercises or physical activities (using the compendium of physical activities[48]) were completed. The amount and intensity of leisure time were quantified by assigning metabolic equivalents (energy expended during each specific activity:RMR) to each activity[42,49].

In a case–control study that assessed the role of the Trp64Arg mutation of the *ADRB3* gene on the risk of developing obesity it was found that the effect of the *ADRB3* mutation on obesity risk changes depending on the recreational physical activity levels[49]. The metabolic equivalent-hours/week:time spent sitting down during leisure time (M/S) was used to estimate recreational energy expenditure. An effect modification across recreational physical activity strata was apparent, and a univariate OR of 2·98 (95% CI 1·00, 8·56) was found within the sedentary group (low physical activity; M/S<0·5) whereas no increment in risk was apparent for active subjects (high physical activity; M/S>0·5). When the association between the risk of obesity and the Trp64Arg mutation was adjusted for gender and age using multivariate logistic regression models and introducing a product-term (age × *ADRB3* mutation), a borderline significant interaction (P=0·06) between recreational activity and the *ADRB3* mutation was demonstrated (Table 3). Thus, carriers of the Trp64Arg mutation with low levels of

Fig. 3. Obesity risk linked to the single-nucleotide polymorphism Gln27Glu of the β-adrenoceptor 2 gene depends on the time spent watching television (TV) in Spanish children and adolescents aged 5–18 years with a BMI of >97th percentile of the Spanish BMI reference data for age and gender[52]. MET, energy expended during each specific activity: RMR; (▲), Carriers; (●), non-carriers. (From Ochoa *et al.*[51].)

Girls	OR	95 % CI	*P*
Gln27Glu genotype	7·92	1·89, 33·2	0·005
Physical activity (MET-hours per week)	0·92	0·88, 0·96	<0·001
TV watching (h/week)	1·14	1·05, 1·24	0·003
Interaction term (product Gln27Glu × TV watching)	0·92	0·85, 0·99	0·023

physical activity have the highest risk of obesity after adjustment for age and gender.

The association between the 27Glu polymorphism and obesity risk has been estimated using multivariate logistic regression[50]. An effect modification (interaction) on the risk of obesity linked to the 27Glu polymorphism by the level of recreational energy expenditure (M/S) was derived after adjustment for age. A significant interaction (product term M/S × 27Glu allele; *P*=0·005) between recreational energy expenditure and the 27Glu allele was demonstrated (Fig. 2). The mean BMI of the two groups was compared on the basis of energy expenditure using the 75th percentile of energy expenditure during leisure time as a cut-off (M/S 0·9). Interestingly, a significant interaction was found in the linear model between the Glu27 allele and the M/S (*P*=0·003). Women who were more active in their leisure time (M/S>0·9) and were carriers of the 27Glu allele had a higher BMI compared with non-carriers. The data demonstrate that obese women who are carriers of the 27Glu allele do not benefit equally from physical activity compared with non-carriers. Such individuals may be more resistant to losing weight when they participate in higher physical activity levels.

Physical activity in children and adolescents seems to be declining, while their time spent in sedentary activities such as television (TV) watching is increasing. Time spent watching TV replaces more vigorous activities and increases the likelihood of children adopting unhealthy food habits, thus it is a risk factor for obesity. This change in activity may explain why TV viewing is a

significant predictor of BMI and overweight in childhood and has been validated as a good index of sedentary behaviour.

A matched case–control study was conducted to assess the interaction between the Gln27Glu polymorphism of the *ADRB2* and TV viewing (as a proxy for sedentary lifestyles) in relation to obesity in a group of Spanish children and adolescents[51]. The study population comprised 330 Spanish children and adolescents. Cases (*n* 165) were subjects aged 5–18 years with a BMI of >97th percentile of the Spanish BMI reference data for age and gender[52]. Using logistic regression analysis it was found that the Glu27Glu genotype of the *ADRB2* gene was not associated with obesity in boys in the fully-adjusted model. However, female subjects carriers of the 27Glu allele (twenty-five homozygous Glu27Glu and ninety-three heterozygous: Glu27Gln) were found to have a significantly higher risk of obesity (OR 1·95 (95 % CI 1·02, 3·70)) in the completely-adjusted model. When the OR for obesity for girls were calculated for the presence of the 27Glu allele in homozygotes, the values were higher (OR 2·83 (95 % CI 1·12, 7·19). In the fully-adjusted model when physical activity (metabolic equivalent-hours per week) and the usual time spent in watching TV were also taken into account and introduced in the model the adjusted OR for obesity linked to the genotype Glu27Glu in the female population rose to 4·84 (95 % CI 1·37, 17·10).

An effect modification (interaction) on obesity risk linked to the Gln27Glu polymorphism of the *ADRB2* gene by the number of hours spent watching TV (*P*=0·023) was

observed after adjustment for physical activity (Fig. 3). In order to calculate different OR for sedentary and non-sedentary subjects the female population was subdivided using the median of the number of hours spent watching TV (12·5 h/week). In homozygous subjects for the wild-type genotype the risk of obesity was found to increase seven times for sedentary girls (i.e. they spent >12·5 h/week watching TV; OR 7·27 (95 % CI 1·42, 37·13)) as compared with non-sedentary girls (<12·5 h/week watching TV). Surprisingly, among subjects who were 27Glu carriers even girls with a low level of TV watching (<12·5 h/week) were found to have a high obesity risk (OR 4·60 (95 % CI 1·01, 20·02)), which was not very different from the OR values for sedentary girls (>12·5 h/week watching TV; OR 6·05 (95 % CI 1·31, 27·71)). These results suggest that carriers of the 27Glu allele of the *ADRB2* gene may not benefit from a reduction in sedentary behaviour as much as the subjects who do not carry the polymorphism.

Conclusion

There is now evidence to indicate that most of the susceptibility genes for obesity do not have a main aetiological role, but it is likely that they act as effect modifiers to environmental factors such as diet or physical activity. This finding implies that lifestyle factors should be investigated in genetics studies and that genetic factors should be determined in dietary interventions and in clinical trials. Thus, it is crucial to take into consideration gene–environmental interactions when designing programmes for both obesity prevention and treatment.

Acknowledgments

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