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# Paving the Way for Personalised Behaviourally based Prevention of Obesity: Systematic Search of the Literature

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## ABSTRACT

*We have identified in the literature variants in 64 genes that may be involved in gene-obesity-behaviour interactions. Personalisation of behaviourally based preventive approaches against obesity seems feasible, however obesity genomics is still in the discovery phase of translational research and abundant replication studies are needed before these largely pioneering findings can be extended to practice and population impact. Automation of search algorithms and development of more efficient tools for knowledge synthesis of genomic research into gene-obesity-behaviour interactions might facilitate the advent of widely available personalised prevention approaches. Our future efforts shall therefore concentrate on developing such tools, as well as a research repository dedicated to the use of public health genomics for obesity control.*

**Key words:** *obesity, genomics, single nucleotide polymorphism, health behaviour, public health, translational research*

## Introduction

Efforts aimed at primary and secondary prevention of cardiovascular disease, the major killer of contemporary adult populations<sup>1–3</sup>, largely rely on modification of risk behaviours related to smoking, physical activity, dietary intake, and alcohol consumption<sup>4,5</sup>. Control of obesity and hypertension, the interim risk states between health and disease, constitute another large part of preventive ventures.

In the public health that increasingly turns its attention toward genomics, the major challenge is to understand the role of genetic variants in susceptibility to chronic diseases and associated risk factors<sup>6</sup>. This has required characterising the nature of gene variation, assembling an extensive catalogue of single nucleotide polymorphisms (single base-pair mutations that occur at a specific site in the DNA sequence, SNPs) in candidate genes, and performing association studies and other gene mapping studies.

A step further, we need to incorporate findings from genomics into clinical and public health interventions. Beyond associations studied in classical epidemiology – those of behavioural risk factors and obesity phenotype<sup>7</sup>

– as well as beyond the major genes that play a deciding role in monogenic obesity, such as is leptin deficiency for example, we were interested in SNPs – primary genetic information and primary variants where the genetic predisposition could be discovered – and their role in developing common obesity<sup>8</sup>. No single SNP will cause a complex trait; however, in a gene-environment interaction, a combination of variants exposed to what is often called 'obesogenic' environment will increase the relative risk that an individual develops the trait.

The extent to which this process is mediated by associations between particular SNPs and behavioural risk factors for overweight or obesity may determine opportunities for novel, personalised preventive interventions. Currently most effective interventions combine nutrition education and exercise counselling with behavioural strategies to improve a person's ability to lose weight<sup>9,10</sup>. In other words, current interventions require that all people work on both sides of the intake-expenditure energy equation. Such one-size-fits-all approach has not reaped much success in controlling the burden of obesity. Alternatively, personalised prevention strategies might

be able to identify people who are more likely to benefit from focusing on one or the other side of the energy equation, as well as people who are more likely to lose weight in response to certain macronutrient diet compositions (e.g., low-fat or low-carbohydrate diet).

## Objectives

In the informational abundance of over 10 million human SNPs that are currently listed in publicly accessible databases<sup>11</sup>, we aimed to identify SNPs that are linked both with increased body weight and behavioural risk factors for this trait, thus holding promise for future design of personalised behaviourally based preventive interventions to reduce obesity.

## Methods

In the initial search, the results of which have previously been communicated<sup>12</sup>, we searched the Cochrane Database of Systematic Reviews, MEDLINE, INSPEC, Current Contents, and Cochrane Controlled Trials Register for abstracts of surveys published to December 2008 in any language, which had examined the associations between any SNPs and behaviours implicated in the aetiology of human obesity, namely physical activity, smoking, diet, alcohol consumption, and psychological stress. Two researchers checked all abstracts for eligibility and we included in both the previous and the current report only those articles that found significant associations between identified SNPs and one or more behaviours of interest. Animal studies were excluded.

For this report, we expanded the search to December 2009 using HuGE Navigator, an integrated knowledge base on human genome epidemiology<sup>13</sup>. HuGE Navigator is updated weekly from PubMed by means of an automatic literature screening program. A genetic epidemiologist selects abstracts that meet inclusion criteria and indexes them by gene, category, and study type. We searched HuGE Navigator's Phenopedia for gene-environment interaction articles with obesity and behaviours of interest as search terms.

## Results

Our initial search returned 77 abstracts of which 18 were deemed eligible for inclusion (Tables 1 and 2). The HuGE Navigator search returned all but one abstracts identified in the initial search<sup>14</sup>, as well as 45 additional articles eligible for inclusion (Table 3). In total, gene-obesity-behaviour interactions were reported for 46 genes.

In one article, where 26 SNPs on the fat mass and obesity associated (FTO) gene were found to be associated with body mass index (BMI), two variants – rs1477196 and rs1861868 – were only associated with obesity in people with low levels of physical activity. No association between these two variants and BMI was found among people with above-average physical activity scores.

Another article indicated that alcohol consumption may play a protective mediating role in one variant's impact on glucose metabolism: in men, carriers of 14672C>G in the promoter region of hormone-sensitive lipase locus (LIPE) who did not drink alcohol had higher glucose levels

**TABLE 1**  
SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) (IDENTIFIED IN THE INITIAL SEARCH) WHICH SEEM TO BE INVOLVED IN THE PATHOPHYSIOLOGY OF OBESITY AND LINKED WITH RISK BEHAVIOURS (PHYSICAL ACTIVITY, ALCOHOL CONSUMPTION, AND CONTROL OF APPETITE)

People	SNP	Phenotype associations
704 healthy Old order Amish people [Arch Intern Med 168 (2008), 1791–7]	rs1477196 and rs1861868 on fat mass and obesity associated (FTO) gene	Associated with body mass index in people with low physical activity scores (adjusted for age and sex)
Population of mostly overweight and obese 373 men and 361 woman [Clin Genet 65 (2004), 93–100]	14672C>G in promoter region of hormone-sensitive lipase locus (LIPE) gene	In women, LIPE 14672G was associated with significantly higher total cholesterol, LDL-cholesterol and apoE; in men, carriers who don't drink alcohol have higher glucose levels than non-carriers
1,058 cases and 1,102 controls [Cancer Epidemiol Biomarkers Prev 15 (2006), 811–5]	Ser(326)Cys and 11657A/G in Oxodeoxyguanosine (OGG1) gene	Ser(326)Cys associated with breast cancer risk among moderate alcohol drinkers 11657A/G associated with BMI>25
First: 93 cases 469 controls; Second: 564 cases 562 controls; Third: 394 cases 958 controls [Human Molecular Genetics 16 (2007), 3017–26]	rs2293855 in myotubularin-related protein 9 (MTMR9) gene	MTMR9 mRNA levels increased after fasting and decreased after high-fat diet – regulation of hypothalamic neuropeptides and thus possibly control of appetite
Sample of 218 obese Finnish sibling pairs; independent samples of 837 cases and 968 controls [J Clin Invest 112 (2003), 1762–72]	SNP haplotype of the SLC6A14 gene	Evidence of linkage emerged mainly from the obese male sib pairs, suggesting a gender-specific effect for the underlying gene
2455 white female twins [Obesity (Silver Spring) 15 (2007), 5–9]	A tagging SNP/tSNP, Ala484Thr (rs7498665) in the region encompassing the human SH2-B gene	Ala484Thr (minor allele frequency 0.38) was associated with serum leptin, total fat, waist circumference, and body weight

**TABLE 2**  
SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) (IDENTIFIED IN THE INITIAL SEARCH) WHICH SEEM TO BE INVOLVED IN THE PATHOPHYSIOLOGY OF OBESITY AND LINKED WITH RISK BEHAVIOURS (DIET)

People	SNP	Phenotype associations
1680 middle-aged Dutch women [Plos ONE 3 (2008), e1405]	rs2272382, rs227283, and rs1528133 in the TUB gene	Eating behaviour associated with body composition and macronutrient intake
451 obese participants [Horm Metab Res 39 (2007), 395–7]	P129T polymorphism in fatty acid amide hydrolase (member of the endocannabinoid (ECS) system)	After six weeks of low fat diet, carriers had a significantly greater decrease in total cholesterol and triglycerides, compared with wild type
1,073 men and 1,207 women in the Framingham offspring study [J Mol Med 82 (2007), 119–28]	APOA5-1131T>C polymorphism	Modulates the effect of fat intake on BMI and risk for overweight or obesity
214 overweight women from Korea [Metabolism 55 (2006), 578–86]	Haplotype 1 (ht1) (CGTACC) on the uncoupling protein 3 (UCP-3) gene	After one month of low-energy diet, associated with greater reduction in body weight, BMI, body fat mass; but not with body fat free mass
453 overweight women from Korea [Biochem Biophys Res Commun 335 (2005), 624–30]	A-3826G, A-1766G, and Ala64Thr (G+1068A) on UCP-1 gene	After one month of very low calorie diet, ht3[GAG] associated with faster reduction in waist-to-hip ratio and body fat mass
249 non-diabetic overweight or obese people from Korea [Int J Obes (Lond) 30 (2006), 1702–8]	276G>T at adiponectin (ADIPOQ) gene	Modifies response to low calorie diet
300 patients randomised to two diet groups over 3 to 12 months [Proc Nutr Soc 61 (2002), 427–34]	Various SNPs on several genes	Interactions with metabolic response to Mediterranean/low fat diet or Western type diet
30 men and 29 women [J Nutr 138 (2008), 1609–14]	-11377 C>G at the adiponectin gene	C/C homozygous men had a greater decrease in the steady-state plasma glucose concentrations when changing from SFA-rich to MUFA-rich diet
458 overweight women [Biochem Biophys Res Commun 359 (2007), 451–6]	10 polymorphisms in uncoupling protein UCP-2 and UCP-3	Modified response to a one-month very-low calorie diet regimen
651 people of Japanese ethnicity (274 Hawaiian Americans and 377 native Japanese people) [Obesity (Silver Spring) 16 (2008), 1463–6]	rs235326 in the gene encoding human integrin beta 2 subunit (ITGB2)	In Hawaiian Americans (whose diet has become »westernized«): compared with C carriers, TT homozygotes were 3.29-times more likely to be obese; no such association was found among people living in Japan
1,357 obese adults and children from France [Obes Res 11 (2003), 1163–7]	79-bp T-to-C on the 3' region of the diacylglycerol acyltransferase (DGAT) encoding gene	Not associated with obesity-related phenotypes in this study, although a positive association has been reported in Turkish women
People living in affluent societies in several parts of Asia and Pacific islands [Biochem Biophys Res Commun 295 (2002), 207–22]	Thrifty SNPs encoding FABP <sup>n</sup> , MTP, CAL10, beta 3AR, apo-E, UCP2, UCP3-p, PPARgamma2 and LEPR	Differences in these SNPs between Mongoloids and Caucasoids may have been caused by natural selection depending on the types of agricultures practiced in different regions and consequently diet

than non-carriers, but there were no differences among people who do drink alcohol. In the oxodeoxyguanosine (OGG1) gene, variant Ser(326)Cys was found to be associated with the risk for breast cancer, but only among moderate alcohol drinkers, while another variant in the same gene – 11657A/G – was associated with increased body weight.

Variants in the myotubularin-related protein 9 (MTMR9) gene, SLC6A14 gene, and SH2-B gene showed the potential to affect control of appetite.

A number of articles implicated various SNPs, located on several genes, in changing carriers' response to diet. In the TUB gene, for example, AG heterozygote and AA homozygote of the rs2272382 derived less energy from

fat, and both were associated with increased energy intake from carbohydrates. Both rs22728133 and rs1528133 were also associated with higher glycaemic load in the diet, which was higher than glycaemic load among the wild types. Concerning the APO gene, among people with APOA5-1131T (major allele) the BMI increased with higher fat intake; however, in APOA5-1131C (minor allele) no increase was seen in BMI with increased fat consumption. Carriers of APOA5-1131C minor allele had a lower risk for overweight and obesity, but not when fat intake was low.

UCP-3 was exposed as an anti-thrifty gene that dissipates energy as heat and prevents obesity, while variants in the adiponectin gene had an impact on insulin resis-

TABLE 3

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) (IDENTIFIED IN THE HUGENAVIGATOR SEARCH) WHICH SEEM TO BE INVOLVED IN THE PATHOPHYSIOLOGY OF OBESITY AND LINKED WITH RISK BEHAVIOURS (PHYSICAL ACTIVITY, DIET, AND MIXED INTERVENTIONS)

People	SNP	Phenotype associations
Physical activity		
604 Caucasian individuals (aged 40–65 yr) [J Clin Endocrinol Metab 86 (2001) 5881–7]	Gly16Arg in the beta(2) – adrenergic receptor (BAR-2) gene	Women carriers of the Arg16Arg genotype had lower fasting plasma NEFAs (nonesterified fatty acid) ( $P < 0.01$ ) and greater suppression of NEFAs ( $P < 0.01$ ) after an oral glucose load than women bearing the Gly16 allele. After adjustment for confounding by age, smoking, and BMI, the effect of the Arg16Arg genotype on the suppression of NEFA levels was modified by physical activity level ( $P$ for interaction $< 0.05$ )
FTO variant rs1121980 was genotyped in 20,374 participants (39–79 y of age) from the EPIC and Nutrition-Norfolk Study [Am J Clin Nutr 90 (2009) 425–8]	rs1121980 in the FTO	Physical activity attenuates the effect of the FTO rs1121980 genotype on BMI and WC
Two European prospective population-based cohorts of 4,762 Finnish adolescents (NFBC 1986) and 3,167 French adults (D.E.S.I.R.) [J Mol Med 87 (2009) 537–46]	rs1421085 and rs17782313 in FTO and MC4R	The combined effects of common polymorphisms in FTO and MC4R are additive, predictive of obesity, and may be influenced by interactions with physical activity levels and gender
862 subjects from the Quebec Family Study [Hum Genomics 3 (2009) 157–68]	LIPE C-60G polymorphism	In women, no evidence of a gene-physical activity interaction was observed, except for subcutaneous abdominal fat ( $P = 0.05$ ). Between physical activity and body fat in men are dependent on the LIPE C-60G
737 Korean children and 732 adults [Obesity (Silver Spring) 17 (2009) 355–62]	(UCP)2 and UCP3; UCP2-866G>A, UCP2Ala55Val, and UCP3-55C>T	UCP3-55CC carriers had higher BMI values than UCP3-55T carriers. Low physical activity may aggravate the susceptibility to overweight in UCP2-866GG and UCP3-55CC carriers
1306 participants enrolled in the JingNing population study [J Hypertens 26 (2008) 2161–7]	ADRA2B D/I polymorphism	ADRA2B D allele is associated with a favourable anthropometric and metabolic profile in Chinese population, especially in physically less active participants
3,856 type 2 diabetic case subjects and 4,861 normal glucose-tolerant control subjects [Diabetes 57 (2008) 95–101]	rs9939609 in the FTO	Low physical activity seems to accentuate the effect of FTO rs9939609 on body fat accumulation
Sample of 14,716 African Americans (AAs) and whites from the ARIC [Int J Obes (Lond) 31 (2007) 919–26]	GNB3 825C>T in the GNB3 gene	The variation within the GNB3 gene may interact with physical activity level to influence obesity status
A population-based study comprising 899 women and 902 men aged between 30 and 75 years in Vara, Sweden [Diabetologia 49 (2006) 496–500]	PPARGC1A GLy482Ser	The risk of obesity associated with 482Ser is evident only in physically inactive elderly male subjects. Whenever possible, the level of physical activity should be addressed in future studies on disease risk associated with PPARGC1A Gly482Ser
157 obese subjects (BMI $> \text{or} = 30$ ) and 150 controls (BMI $< 25$ ) [Ann Nutr Metab 49 (2005) 183–8]	UCP3 –55C>T polymorphism	UCP3 –55C>T polymorphism carriers have apparently a lower risk of obesity when taking into consideration recreational energy expenditure. Interestingly, this inverse beneficial association may only occur in people with a high level of physical activity
Diet		
108 subjects who underwent an 8-day modified medical fasting treatment [Ann Nutr Metab 54 (2009) 184–8]	GNB3 C825T polymorphism	Pronounced mental discomfort during fasting in 825T allele carriers might partly explain their increased risk for obesity
180 Spanish volunteers (BMI: 31.4+/-3.2 kg/m <sup>2</sup> ) [Horm Metab Res 41 (2009) 55–61]	rs17300539 (11391 G/A) in the adiponectin gene	A allele confers protection from weight regain after a low-calorie diet, and the effect is particularly evident 32–60 weeks after the dietary intervention, when improvement in GG subjects had disappeared
Detailed dietary report information on FTO variation and dietary intake [Am J Clin Nutr 88 (2008) 971–8]	rs9939609 in the FTO	Persons carrying minor variants at rs9939609 were consuming more fat and total energy than were those not carrying such variants



Cohort of 1,721 Caucasian men and women with a BMI of 25kg/m(2) or more [Mol Genet Metab 95 (2008) 188–91]	CB1, NPY, 420C>G polymorphisms in the resistin gene	Genetic polymorphisms associated with obesity may become relevant only under the condition of a low calorie diet
Population-based sample of Caribbean-origin Hispanics (n = 920, aged 45–74 y) [Nutr 138 (2008) 1852–8]	rs894160 (11482G>A) in the PLIN gene	In subjects with higher complex carbohydrate intake, the minor allele was protective against obesity, whereas in subjects with lower carbohydrate intake, the minor allele was associated with increased obesity
204 obese people [Diabetes Res Clin Pract 82 (2008) 113–8]	FABP2	Weight loss is associated with different changes, depending on the FABP genotype with both hypocaloric diets tested
78 obese people [Ann Nutr Metab 52 (2008) 209–14]	Lys656Asn polymorphism in the LEPR gene	In wild type patients, the changes in serum leptin concentration due to 2 months' intervention with low fat are higher than with a low carbohydrate diet
107 obese people (body mass index >30) [Horm Metab Res 40 (2008) 214–8]	-55CT polymorphism of the UCP3 gene	Patients with -55CC genotype have a significant decrease in leptin, interleukin 6, BMI, weight, fat mass, systolic blood pressure, LDL cholesterol, waist circumference, waist-to-hip ratio weight, fat mass, and systolic blood pressure, in response to a hypocaloric diet
29 obese and 45 non-obese people 18–40 years old [Behav Neurosci 121 (2007) 877–86]	DRD2 and DAT1	Energy intake was greater for individuals high in food reinforcement and greatest in those high in food reinforcement with the TaqI A1 allele
Healthy Japanese men, n=295 [J Epidemiol 15 (2005) 203–10]	ADRB3 Trp64Arg	High energy intake interacts with the polymorphism and leads to a significant increase in risk of obesity. The Trp64Arg polymorphism of ADRB3 warrants consideration, along with other polymorphisms involved in the development of obesity, for tailor-made prevention of obesity
85 healthy Japanese men [Metabolism 56 (2007) 925–30]	Asp358Ala (T/G) polymorphism in the interleukin 6 receptor (IL6R) gene	Dietary energy intake modifies the association between gene and waist circumference
Selected obese women – diet responsive (n=74) and diet-resistant (n=67) [Obesity (Silver Spring) 15 (2007) 1068–75]	Two PPARgamma SNPs, Pro(12)Ala and C1431T, and eight polymorphisms across the ACSL5 gene	The PPARgamma Pro(12)Ala single nucleotide polymorphism was associated with diet resistance (odds ratio = 3.48, 95% confidence interval = 1.41 to 8.56, p = 0.03) after the first 6 weeks of a 900-kcal formula diet (low calorie)
67 volunteers in the 10 week low-energy diet program, followed by a 1-year weight-loss maintenance [Br J Nutr 96 (2006) 965–72]	-174G>C from IL-6 and PPAR-gamma2 Pro12Ala variants	The present study demonstrates that the C allele of the -174G>C polymorphism gives protection against regain of weight lost. Moreover, the presence of the Ala allele of the PPARgamma-2 together with the C allele strengthens this protection
351 French-Canadians, 40 overweight subjects and 4 controls [J Mol Med 85 (2007) 129–37]	CPT1	Indices of obesity might be modulated by an interaction between CPT1 variants and fat intake
549 adult obese women recruited from eight European centres [Eur J Nutr 45 (2006) 454–62]	42 polymorphisms in 26 candidate genes	The test of interaction between fibre intake and the -514 C > T polymorphism of the hepatic lipase gene (LIPC) was significant; the -11377G > C polymorphism of the adiponectin gene (ADIPOQ) and the -681 C > G polymorphism of the PPARG3 gene might interact with the percentage of energy derived from fat in the diet, for the development of obesity
60 obese women exposed to short-term and long-term hypocaloric diets, varying in macronutrients [Nutr Hosp 21 (2006) 317–31]	PPARgamma2 and beta2 – adrenergic receptor genes	Intake of dietary fats and saturated fatty acids should be controlled in Pro12Pro/Gln27Gln and Pro12Pro/Gln27Glu, and complex CHO and MUFA in Pro12Pro/Glu27Glu. In Pro12Ala/Gln27Glu, AGPI intake can result in greater body weight loss
14-week calorie restriction diet in 95 middle-aged, Japanese women (BMI >/=25 kg/m2) [Obesity (Silver Spring) 17 (2009) 1924–31]	rs2959272, rs1386835, rs709158, rs1175540, rs1175544, and rs1797912 in the PPARG gene	Body weight decreased significantly (-7.7+/-3.1 kg; -11.3+/-4.4%). All six SNPs were found to be associated with the weight reduction, with rs1175544 having the strongest association

Non-diabetic/overweight-obese Koreans (n=177) [J Int Obes (Lond) 30 (2006) 1601–8]	6209T>C, 10076C>G, 10171A>T, 11482G>A, 13042A>G, 13048C>T and 14995A>T in perilipin (PLIN) – a class of protein-coating lipid droplets in adipocytes	Subjects with nCA/nCA haplotypes at SNPs 10076C>G/10171A>T showed greater reduction in FFA levels than those with CA/CA haplotype after a 12-week calorie restriction (–300kcal/day) program
606 hyperlipaemic and overweight men [Clin Genet 68 (2005) 152–4]	Several SNPs (wildtype and carriers of the –1131T>C polymorphism) in the Apolipoprotein A5 gene	Reduction of BMI was significantly higher in C allele carriers after a short-term dietary fat restriction
150 obese patients at baseline and 48 patients who completed the dietary follow-up; randomised trial with 1-year low energy diet [J Clin Endocrinol Metab 90 (2005) 5121–6]	Minor A-allele at the PLIN 11482G>A polymorphism	PLIN11482A carriers were resistant to weight loss
224 overweight-obese subjects with coronary artery disease (CAD) or metabolic syndrome [Int J Obes Relat Metab Disord 28 (2004) 434–41]	Participants subdivided into 4 categories: (TT-CC, n=73); (TT-CT/TT, n=90); (TA/AA-CC, n=29); (TA/AA-CT/TT, n=32) according to status on beta3-AR and UCP3	After a –300 kcal/day mild weight reduction program for 12 weeks, the beneficial effects on body fat distribution and glycemic control were greatest in the 'wild-type' group and smallest in 'both variants' group. In addition, these effects were less beneficial in carriers with beta3-AR gene variant than with UCP3 gene promoter variant
EPIC-Heidelberg: 154 subjects with a body mass index > 35 kg/m(2) and 154 age- and sex-matched normal-weight controls; dietary fatty acid intake assessed by food frequency questionnaire [Eur J Nutr 41 (2002) 210–21]	PPARA, PPARG2, UCP1, UCP2, UCP3, BAR-2, APM1, leptin, SORBS1, HSL, and TNFA	Gene-diet interactions suggest that the allelic variants of candidate genes (leptin, TNFA, PPARG2) might strongly affect diet-related obesity risk
61 women with the APOE 2/3 and APOE 3/3 genotype (APOE4-) and 18 women with the APOE 3/4 genotype (APOE4+) [Metabolism 51 (2002) 853–8]	Apolipoprotein E (APOE)	It may be prudent to genotype older women before initiating low-fat diet therapy, as those with the APOE4 allele benefit the most, while the lipid profile could worsen in women without the APOE4 allele after a low-fat, low-cholesterol diet over 10 weeks
170 Caucasian participants [Arch Med Res 40 (2009) 306–10]	Lys109Arg in the leptin receptor gene (LEPR)	The Arg allele carriers of the Lys109Arg LEPR gene polymorphism were associated with an increased proinflammatory state and stress condition at baseline. These obesity-related markers were importantly decreased after an 8-week energy-restricted (hypocaloric) diet (–30% E) diet
Low-fat vegan diet or a diet for 74 weeks among 93 adults with type 2 diabetes [Nutrition 25 (2009) 58–65]	A1A1 and A1A2 in the D2 dopamine receptor	Among whites in the vegan group, A1(+) individuals reduced fat intake (P = 0.04) and A1c (P = 0.01) significantly less than did A1(–) individuals
131 obese individuals (body mass index >30) [Horm Metab Res 41 (2009) 62–6]	–55CT polymorphism in the UCP3 gene	Carriers of the T variant experienced decreases in BMI, weight, and fat mass on two different hypocaloric diets, without statistical changes in biochemical parameters
363 subjects with impaired fasting glucose (IFG) or newly diagnosed type 2 diabetes followed a dietary intervention and regular walking for 12 weeks without any medication [Diabetes Care 32 (2009) 552–8]	ADIPOQ	ADIPOQ genetic variants can affect circulating adiponectin levels and insulin resistance indexes in subjects with IFG or newly diagnosed type 2 diabetes in response to dietary intervention
Mixed interventions		
507 overweight individuals randomised to intensified diet and physical activity group or a conventional care control group [BMC Med Genet 10 (2009) 94]	rs659366, rs653529, rs15763, and rs1726745; rs659366-G, rs653529-A, rs15763-G and rs1726745-A in the UCP2 and UCP3	Genetic variation in the UCP2-UCP3 gene cluster may act as a modifier increasing serum lipid levels and indices of abdominal obesity, and may thereby also contribute to the metabolic aberrations observed in obesity and type 2 diabetes

120 obese Japanese women and 146 healthy age-matched controls; diet and exercise therapy for 6 months [Metabolism 55 (2006) 819–24]	Angiotensinogen (AGT) Met235Thr polymorphism (M235T)	The T/T genotype of the AGT M235T gene polymorphism was positively related to visceral obesity and hyperinsulinemia
67 obese (body mass index >30) nondiabetic outpatients [Arch Med Res 37 (2006) 854–9]	Lys656Asn polymorphism in the leptin receptor gene	Patients with Asn656 allele of LEPR gene have a different response to a lifestyle modification program than wild-type patients, and Lys656Lys patients have a significant decrease in weight, BMI, fat mass, waist circumference, systolic blood pressure and leptin levels
69 obese (body mass index > 30) nondiabetic outpatients [Ann Nutr Metab 50 (2006) 354–60]	Thr54 polymorphism in the FABP2 gene	Carriers of the Thr54 allele have a different response to a lifestyle modification (Mediterranean hypocaloric diet and exercise) than wild-type obese subjects, with a significant decrease of systolic blood pressure and glucose levels in Thr54 carriers and a significant decrease in fat mass, low-density lipoprotein cholesterol, and leptin in wild-type patients
76 perimenopausal women with no clinical symptoms; 3-month behavioural intervention study using a combination of diet and exercise programs [Int J Obes Relat Metab Disord 27 (2003) 1028–36]	Trp64Arg mutation in the beta(3)-adrenergic receptor (beta(3)AR) gene	The mutation is associated with difficulty in losing weight through behavioural intervention, although it is not related to obesity-related phenotypes and resting energy expenditure before the intervention
69 obese non diabetic outpatients [Med Clin (Barc) 129 (2007) 401–4]	G308A variant in the tumor necrosis factor alpha (TNF-alpha) gene	Carriers of G308G variant of TNF-alpha gene have a better metabolic response (to a 3-month of lifestyle modification program that included a hypocaloric diet 1,520 kcal) than A308 obes
Randomised controlled trial of 3,548 high-risk individuals from 27 participating centres throughout the USA [Diabetologia 51 (2008) 2214–23]	rs9939609 in the FTO gene and rs7566605 in the INSIG2 gene	Within the DPP study population, common variants in FTO and INSIG2 are nominally associated with quantitative measures of obesity, directly and possibly by interacting with metformin or lifestyle intervention
151 subjects participating in a lifestyle intervention program to prevent diabetes [Exp Clin Endocrinol Diabetes 117 (2009) 194–7]	rs8050136 in FTO	Increased body weight in carriers of the risk allele of FTO SNP rs8050136 is a consequence of increased food intake, but not of impaired energy expenditure

tance. In the initial report of the RIVAGE study, some SNPs showed interactions with a metabolic response to diet (through ApoE and LDL-cholesterol and triacylglycerols, apoA-IV and LDL cholesterol, MTP and LDL-cholesterol, intestinal fatty acid-binding protein, and triacylglycerols).

Ethnic specific and region specific responses, possibly related to diet, were shown to be mediated by several SNPs in the human integrin beta 2 subunit (ITGB2) gene, the diacylglycerol acyltransferase (DGAT) gene, as well as thrifty genes FABP<sup>2</sup>, MTP, CAL10, beta 3AR, apo-E, UCP2, UCP3-p, PPARgamma2, and LEPR.

None of the abstracts reported on a link between any SNPs and smoking, whereas psychological stress was only mentioned in one article, where it was reported to have been reduced following an 8-week hypocaloric diet.

Studies identified through HuGE Navigator fell in one of three categories, where SNPs were linked with increased body weight and either physical activity, diet characteristics, or some type of a mixed intervention aimed at reducing body weight, which invariably combined modification of both physical activity and dietary habits.

Physical activity extended an exacerbated protective effect on body weight or metabolic events when coupled with several polymorphisms in the BAR-2, FTO, MC4R,

LIPE, GNB3, UCP3, and the PPARG gene. An exception was the ADRA2B gene where, in a Chinese population, the D allele conferred a favourable anthropometric and metabolic profile, especially when combined with lower levels of physical activity.

Some studies found gene-obesity-diet interactions. Carriers of GNB3 C825T seem to feel mental discomfort when fasting, which may explain their increased susceptibility towards increased body weight. The 11391/A allele in the adiponectin gene may protect from weight regain after a low-calorie dietary intervention. A low-calorie diet also seems to be a good choice for carriers of CB1, NPY, 420C>G polymorphisms in the resistin gene: allele carriers had a better response to the dietary regimen in terms of weight loss and metabolic changes, when compared to wild type participants.

In one study, a minor allele in the rs894160 on the PLIN gene was associated with additional weight gain, but only combined with low intake of carbohydrates; when coupled with higher intake of complex carbohydrates, the allele seems to have played a protective role against obesity. Another study found that both carriers of wild type and mutant alleles on the Lys656Asn locus in the LEPR gene lost weight in response to a low-fat, as well as a low-carbohydrate diet. However, only wild type



carriers had lower leptin concentrations, which was seen with both tested diets.

A hypocaloric diet seems to work well for people with the -55CT polymorphism of the UCP3 gene, whereas having the PPARgamma Pro(12)Ala SNP may confer resistance to a low-calorie diet. On the contrary, the C allele of the PPARgamma-2-174G>C SNP seems to protect against regain of lost weight, and this effect is further strengthened by the presence of the Ala allele of the PPARgamma-2. Another study found that some CPT1 variants may modify body weight response to fat intake.

Several genotype-by-nutrient interactions were confirmed in a study of 549 obese European women. Although the study tested 42 polymorphisms in 26 candidate genes, the only tests that yielded statistical significance were for the interaction between fiber intake and the -514 C > T polymorphism of the LIPC gene, as well as those for fat intake and -11377G > C polymorphism of the ADIPOQ gene and the -681 C > G polymorphism of the PPARG3 gene.

Carriers of the minor allele PLIN11482A showed resistance to weight loss after a 1-year low-energy dietary program. Women with APOE4 allele benefit the most from a low-fat, low-cholesterol diet, whereas the lipid profile could worsen in women without the APOE4 allele.

Finally, response to complex interventions that include advice on both diet and physical activity may be hampered or facilitated by various SNPs in the UCP2, UCP3, AGT, LEPR, FABP2, beta(3)AR, TNF-alpha, FTO, and INSIG2 genes.

## Discussion

We have identified in the literature a number of SNPs that may be associated with increased risk for overweight or obesity and also with behavioural risk factors for these traits. With the advent of personalised health care, results of SNP genotyping are likely to start guiding personalised prevention of complex diseases in the near future.

Personalised prevention of obesity may develop two-fold: as behaviourally based or pharmacogenomic approaches. Based on our findings, it is imaginable that, for example, carriers of rs1477196 and rs1861868 in the FTO gene would need to be advised to make sure they kept physically active above levels recommended for the general population, as this may protect them from excess weight. Carriers of P129T polymorphism in fatty acid amide hydrolase and carriers of APOA5-1131T>C polymorphism may need to be advised to opt for low-fat diets, whereas low-energy diets may prove a better choice for carriers of ht1 on the UCP-3 gene, carriers of A-3826G, A-1766G, and G+1068A on the UCP-1 gene, and carriers of 276G>T at the ADIPOQ gene. APOA5-1131T>C polymorphism is of particular interest and preventive potential, due to its high prevalence of 13% in the studied population.

These and most probably other SNPs hold promise for future design of personalised behaviourally based inter-

ventions for preventing obesity. However, we are still in the discovery phase of genomics obesity research<sup>15</sup>. Most of the gene-environment-behaviour interactions explored in this paper have only been tested in a single study. Moreover, studies are often poorly described and lack methodological detail necessary for critical appraisal; samples are often small, include healthy volunteers, or no information is given on the selection process; analysis frequently fails to account for multiple testing, and only some studies report the proportion of variance explained by any given gene variant. Indeed, more than half of the obesity related genes in the HuGE Navigator's Phenopedia have only been implicated in a single study thus far. It is likely that many of these associations may be rejected in future replication studies.

We believe now is the time to help obesity genomics on the long road towards effective clinical and public health interventions, not least by developing reporting standards – which are lacking for this field of research. This gap has been somewhat filled while our paper was under review<sup>16</sup>. Some of the included studies reported sufficient information on markers (including i.e. rs code for SNP markers, which are widely accepted unique SNP identifiers), while some reported SNP or other descriptions in a non-standardised way. Results were not always clearly stated, especially in the articles covering gene-obesity-diet interactions.

These issues made us consider and investigate the feasibility of using some of the existing standards. Although a number of relevant attempts have been made, including the GO ontology and several applications that use the XML language, we could not identify any applications that could fit the available data from the included studies, which are commonly reporting a simple association of a genetic marker with some phenotypic trait or a disease.

Given the already large number of studies reporting on gene-obesity-behaviour interactions, an enormous potential for similar future work, as well as the relevance of this line of research for population health, it would seem prudent to consider developing a specific reporting standard for these studies. At the very least, following the reporting practice developed for other study designs (e.g. CONSORT for clinical trials), we would argue in favour of stating the study design as part of the title, as well as introducing a structured abstract that would include the information on a unique SNP identifier (rs code), effect allele, physical SNP location (usually defined as the number of base pairs from the chromosome start), chromosome, gene name, analysed trait, information on possible effect modifiers (i.e., adjustment for age and sex, other confounders, multivariate methods), proportion of variance, and other information. The application and use of such structured reporting format would likely enable creation of more informative, perhaps even entirely computer-generated summary reports. Establishing a vocabulary consensus in describing elements of study and data, for the purpose of annotation and integration, would also be a valuable contribution to the field.

As we contemplate what effects genetic testing, once widely available, might have on people's motivation to lose weight or the public's readiness to accept the new realities or, indeed, what new types of obesity might soon become definable in the disease categorisation of the genomic era, some improvement in the scientific communication to help us get there faster seems advisable. This seems in tune with views of others previously expressed in this journal<sup>17</sup>.

### Strengths and limitations

We have conducted a comprehensive search across multiple databases and present in one place current state of the evidence relevant to the development of future behaviourally based obesity prevention strategies. However, we did not hand search the references in the included articles and it is possible that some published studies escaped our search strategy. Furthermore, we did not perform a formal assessment of the quality of the included studies, as we felt this was beyond the scope of the paper. Finally, we have not attempted to synthesise the findings at this stage, due to the heterogeneity of the included studies.

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### Conclusions

Personalisation of behaviourally based preventive approaches against obesity seems feasible in the near future. Automation of search algorithms, as well as development of more efficient tools for knowledge synthesis of genomic research into gene-obesity-behaviour interactions might facilitate the advent of widely available personalised prevention strategies. As a small step forward, we propose that structured standards of reporting specific to the field be developed as soon as possible, so as not to unnecessarily delay translation of these burgeoning findings into clinical and public health practice. In addition, our future efforts shall concentrate on developing a research repository dedicated to the use of public health genomics for obesity control.

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### UTIRANJE PUTA ZA PERSONALIZIRANU PONAŠAJNU PREVENCIJU PRETILOSTI: SUSTAVNA PRETRAGA LITERATURE

### SAŽETAK

Cilj ovog rada bio je identificirati polimorfizme jednog nukleotida (SNP, od engl. single nucleotide polymorphism) koji bi mogli odrediti interindividualne razlike u odgovoru, u smislu promjene tjelesne težine, na pojedine ponašajne čimbenike rizika za prekomjernu debljinu ili pretilost, stoga otvarajući mogućnosti za personalizirane ponašajne preventivne intervencije. U bibliografskim bazama, bez jezičnih restrikcija, identificirali smo radove koji su izvještavali o

povezanosti pojedinih SNP-ova s prekomjernom debljinom ili pretilošću kao i s ponašajnim rizičnim čimbenicima za razvoj ovih značajki. Identificirali smo 64 genske varijante koje bi mogle biti uključene u interakcije gen-pretilost-ponašanje. Temeljem ovih rezultata moguće je zamisliti razvoj personaliziranog savjetovanja o promjeni životnih navika, s ciljem smanjena tjelesne težine, međutim genomika pretilosti još je u ranoj translacijskoj fazi; potrebna je replikacija rezultata u brojnim budućim istraživanjima prije no što ovi u velikoj mjeri pionirski rezultati unaprijede kliničku i javnozdravstvenu praksu. U kvaliteti istraživanja kao i izvještavanja o njima ima mnogo prostora za poboljšanja. Zaključujemo da je personalizacija ponašajnih preventivnih intervencija protiv pretilosti izvediva no automatizacija pretraživačkih algoritama i razvoj učinkovitijih metoda sinteze znanja generiranih u genomskim istraživanjima mogli bi ubrzati translaciju prema širokoj dostupnosti personaliziranih preventivnih pristupa. Naša će buduća nastojanja stoga uključivati razvoj takvih metoda i oruđa, kao i razvoj repozitorija istraživanja posvećenog uporabi javnozdravstvene genomike u kontroli pretilosti.