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Single nucleotide polymorphisms and health behaviours related to obesity–trawling the evidence in the prospect of personalised prevention

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Abstract. Efforts aimed at primary and secondary prevention of cardiovascular diseases, the major killer of contemporary adult populations, largely rely on modification of risk behaviours related to smoking, physical activity, dietary intake, and alcohol consumption, and also control of obesity and hypertension, the interim risk states between health and disease. We propose that the extent to which the gene x ‘'obesogenic' environment interaction depends on associations between particular single nucleotide polymorphisms (SNPs) and behavioural risk factors for overweight or obesity determines opportunities for novel, personalised preventive interventions. We systematically searched for SNPs that might be of interest for this postulate and we present various SNPs that have been shown to be associated with overweight or obesity and behavioural risk factors for developing

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these traits, and thus hold promise for future design of personalised preventive interventions.

Keywords. cardiovascular diseases, obesity, genomics, single nucleotide polymorphism, health behaviour

Introduction

Efforts aimed at primary and secondary prevention of cardiovascular diseases, the major killer of contemporary adult populations [1-3], largely rely on modification of risk behaviours related to smoking, physical activity, dietary intake, and alcohol consumption [4, 5]. 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, a major challenge is to understand the role of genetic variants in susceptibility to chronic diseases and associated risk factors [6]. 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 and other gene mapping studies.

A step further, we need to incorporate findings from genomics in real life interventions. Beyond associations studied in classical epidemiology–those of behavioural risk factors and obesity phenotype [7]–or even 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 variants where the genetic predisposition could be discovered–and their role in developing common obesity [8]. No single SNP will cause a complex trait; however, in a gene x 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.

We propose that the extent to which this process is mediated by associations between particular SNPs and behavioural risk factors for overweight or obesity determines opportunities for novel, personalised preventive interventions. In the informational abundance of over 10 million human SNPs that are currently listed in publicly accessible data bases [9], we aimed to identify SNPs that might be of interest for this postulate–that is which are linked with both obesity and behavioural risk factors.

1. Material and methods

We searched CDSR, MEDLINE, INSPEC, CC, and CCTR for surveys in any language that examined the associations between any SNPs and behaviours implicated in the aetiology of human obesity, namely physical activity, smoking, diet, and alcohol consumption. Two researchers checked all abstracts for eligibility and we included in this report only those articles that found significant associations between identified SNPs and one or more behaviours of interest. Animal studies were excluded.

2. Results

Our initial search returned 77 abstracts of which 18 were deemed eligible for inclusion (Tables 1 and 2). 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 [10]. 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 promoter region of hormone-sensitive lipase locus (LIPE) who don't drink alcohol had higher glucose levels than non-carriers, but there were no differences among people who do drink alcohol [11]. 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 [12].

Variants in the myotublarin-related protein 9 (MTMR9) gene, SLC6A14 gene, and SH2-B gene showed the potential to affect control of appetite [13-15].

A number of articles implicated various SNPs, located on several genes, in changing carriers' response to diet [16-24]. 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 [16]. Both rs22728133 and rs1528133 were also associated with higher glycaemic load in the diet,

Table 1. SNPs incriminated 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 [10]	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 [11]	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 [12]	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 [13]	rs2293855 in myotublarin-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 [14]	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 [15]	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

which was higher than glycaemic load among the wild types. Concerning the APO gene [18], 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 [19], while variants in the adiponectin gene had an impact on insulin resistance [21]. In the initial report of the RIVAGE study, some SNPs showed interactions with the 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) [22].

Lastly, 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", MTP, CAL10, beta 3AR, apo-E, UCP2, UCP3-p, PPARgama2, and LEPR [26-28].

3. Conclusion

We have identified in the literature a number of SNPs that are associated with increased risk for overweight or obesity and also with behavioural risk factors for these traits. These and most probably many other SNPs hold promise for future design of personalised interventions for prevention of cardiovascular diseases.

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Table 2. SNPs incriminated in the pathophysiology of obesity and linked with risk behaviours (diet)

People	**SNP**	**Phenotype associations**
1680 middle-aged Dutch women [16]	rs2272382, rs227283, and rs1528133 in the TUB gene	Eating behaviour associated with body composition and macronutrient intake
451 obese participants [17]	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 [18]	APOA5-1131T>C polymorphism (present in 13% of the studied population)	Modulates the effect of fat intake on BMI and risk for overweight or obesity
214 overweight women from Korea [19]	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 [20]	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[21]	276G>T at adiponectin (ADIPOQ) gene	Modifies response to low calorie diet
300 patients randomised to two diet groups over 3 to 12 months [22]	Various SNPs on several genes (see text)	Interactions with metabolic response to Mediterranean/low fat diet or Western type diet
30 men and 29 women [23]	-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 [24]	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) [25]	rs235326 in the gene encoding human integrin beta 2 subunit (ITGB2)	In Hawaiian Americans (whose diet has become "westernised"): 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	79-bp T-to-C on the	Not associated with

and children from France [26]	3’ region of the diacylglycerol acyltransferase (DGAT) encoding gene	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 [27]	Thrifty SNPs encoding FABP”, MTP, CAL10, beta 3AR, apo-E, UCP2, UCP3-p, PPARgama2 and LEPR	Differences in these SNPs between Mongoloids and Caucasoids may have been caused by natural selection depending on the types of agricultures practised in different regions and consequently diet

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