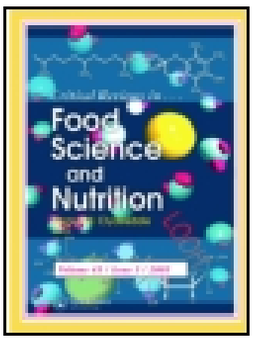

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LIFESTYLE GENOMICS AND THE METABOLIC SYNDROME: A REVIEW OF GENETIC VARIANTS THAT INFLUENCE RESPONSE TO DIET AND EXERCISE INTERVENTIONS

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ABSTRACT

Metabolic syndrome (MetS) comprises a cluster of risk factors that includes central obesity, dyslipidemia, impaired glucose homeostasis and hypertension. Individuals with MetS have elevated risk of type 2 diabetes and cardiovascular disease; thus placing significant burdens on social and healthcare systems. Lifestyle interventions (comprised of diet, exercise or a combination of both) are routinely recommended as the first line of treatment for MetS. Only a proportion of people respond, and it has been assumed that psychological and social aspects primarily account for these differences. However, the etiology of MetS is multifactorial and stems, in part, on a person's genetic make-up. Numerous single nucleotide polymorphisms (SNPs) are associated with the various components of MetS, and several of these SNPs have been shown to modify a person's response to lifestyle interventions. Consequently, genetic variants can influence the extent to which a person responds to changes in diet and/or exercise. The goal of this review is to highlight SNPs reported to influence the magnitude of change in body weight, dyslipidemia, glucose homeostasis and blood pressure during lifestyle interventions aimed at improving MetS components. Knowledge regarding these genetic variants and their ability to modulate a person's response will provide additional context for improving the effectiveness of personalized lifestyle interventions that aim to reduce the risks associated with MetS.

KEY WORDS: Diet-Gene Interaction, Exercise-Gene Interaction, Lifestyle Intervention, Metabolic Syndrome, Single Nucleotide Polymorphism

BACKGROUND

Metabolic syndrome (MetS) refers to a cluster of conditions – central obesity, dyslipidemia, impaired glucose homeostasis and hypertension – that increase the risk of developing type-2 diabetes (T2D) and cardiovascular disease (CVD) (Kelly et al. 2008). The International Diabetes Foundation estimates that a quarter of the adult population worldwide suffers from MetS (IDF Worldwide Definition of the Metabolic Syndrome | International Diabetes Federation 2005), and the impact of MetS continues to escalate alongside the rising prevalence of urbanization and sedentarism (Kaur and Jaspinder 2014). While pharmaceuticals are widely prescribed to treat the individual components of MetS, changes in lifestyle habits (i.e., diet and exercise) have beneficial effects and represent the cornerstone of all treatments (Bassi et al. 2014).

Lifestyle interventions are not standardized in any way and can range from brief counselling and education about healthy food choices, to structured programs spanning weeks to months to achieve changes in diet and exercise habits. Numerous diet interventions to reduce MetS have been proposed, and include hypocaloric, low-fat, high protein, and Mediterranean diets – all of which typically target metabolic improvements through weight loss or changes in diet quality (Garcia et al. 2016; Leiter et al. 2011). Similarly, increased physical activity (in particular aerobic exercise) has also been shown to improve dyslipidemia and insulin sensitivity, as well as promote weight loss (Leiter et al. 2011). Interventions that encompass changes in both diet and exercise habits (i.e., hereon referred to as lifestyle interventions) are thought to have greater efficacy because the benefits of a combined approach may be larger than those achieved by either alone (Delahanty et al. 2012; Lindström et al. 2003). Despite the fact lifestyle interventions to prevent or manage MetS are commonly prescribed, not everyone responds to them in the same manner (Melanson et al. 2013; Bouchard et al. 2012). The

etiology of MetS is multifactorial and these varying responses are attributed, in part, to underlying genetic differences.

The heritability of MetS has been estimated to range from 20-60%, suggesting that genetics plays an important role in the pathogenesis of this condition (Khan et al. 2015; Stankakova and Laakso 2014). The genetic basis of MetS has been investigated in family studies (van Dongen et al. 2013), twin studies (van Dongen et al. 2013), candidate gene association studies (Roche et al. 2005), and genome-wide association studies (GWAS) (Brown and Walker 2016). To date, GWAS have identified approximately 60 genetic variants associated with obesity, 90 with hypertension, 160 with dyslipidemia, 90 with glucose homeostasis, and 30 with MetS as a whole (Brown and Walker 2016). Collectively, these past genetic investigations have established a catalogue of candidate genes to consider in gene-lifestyle studies related to MetS, and whether they can influence a person's response to diet and/or exercise interventions.

While we acknowledge that the underlying genetic architecture associated with MetS may encompass common and rare genetic variants, copy number variation and epigenetic mechanisms, the vast majority of research to date has focused on common single nucleotide polymorphisms (SNPs). Thus, the goal of this review is to highlight research showing that SNPs can modulate a person's response to lifestyle interventions. Although the functional outcome of most SNPs remains poorly understood, this review also discusses potential mechanisms by which these genetic variants may be associated with MetS components. The research outlined in this timely review supports the notion that tailoring lifestyle interventions based on a person's genetic makeup may help to achieve greater clinical improvements in MetS components.

1. Central Obesity

Body weight is a complex trait that is influenced by genetic, environmental, psychological, and physiological factors (Mutch and Clément 2006). Obesity, which is commonly defined as having a body mass index (BMI) ≥ 30 kg/m^2, stems from a chronic positive energy balance that leads to excess fat accumulation (Mutch and Clément 2006). Moreover, central fat accumulation (i.e., visceral adipose tissue), which is typically approximated by measuring waist circumference (>102 cm in men and >88 cm in women), is associated with many pathologies and promotes insulin resistance (Shulman et al. 2000). Establishing efficacious lifestyle strategies to combat the obesity epidemic is therefore of the utmost importance for the prevention and treatment of MetS.

Investigating the influence of genetics, which is thought to explain 50-80% of the variation in BMI within the general population (Hinney et al. 2010; Bouchard et al. 1990), on the magnitude of weight loss in response to lifestyle interventions will aid in the development of effective personalized treatment strategies. In support of this idea, the following paragraphs highlight reported associations between SNPs in various genes and weight loss outcomes during lifestyle interventions. Although upwards of 60 SNPs in many genes have been associated with obesity (Brown and Walker 2016), this review will emphasize research related to four genes due to their prevalence in published literature and relevance to central obesity.

1.1. Fat Mass and Obesity-Associated Gene

One of the first GWAS to identify genetic variants associated with obesity-related traits reported a strong association between the fat mass and obesity-associated gene (*FTO*) region on chromosome 16 with BMI, waist circumference and weight (Scuteri et al. 2007). Subsequent molecular investigations revealed that the *FTO* gene encodes for a FE (II) and 2-oxoglutarate dependent DNA/RNA methylase; however, the precise molecular link(s) between FTO methylase activity and body weight requires further

elucidation. Individuals homozygous for the A "risk" allele in the rs9939609 (T/A) SNP weigh ~3 kg more and have a 1.7-fold increased risk of being obese compared to people with the AT or TT genotypes (Frayling et al. 2007). This association has been replicated in numerous studies and in many different ethnicities (Tung et al. 2014). A meta-analysis of 14 studies revealed that this SNP is also associated with a small, but statistically significant, increased risk for developing MetS (Wang et al. 2012). Numerous lifestyle interventions have been carried out to investigate associations between rs9939609 and a person's response to diet and exercise; however, the studies presented below show that the results to-date remain equivocal.

A few studies reported that individuals with the A-allele experienced a different response to a lifestyle intervention compared to TT homozygotes (Woehning et al. 2012; Razquin et al. 2010; Huang et al. 2014). For example, a 3-year intervention in 776 individuals with CVD from Spain compared body weight changes with two Mediterranean diets (one supplemented with nuts, the other with virgin olive oil) to that seen with a low-fat diet. AA-carriers had the highest BMI at baseline, but experienced the lowest body weight gains in response to the Mediterranean diets compared to TT homozygotes (Razquin et al. 2010). In the The Preventing Overweight Using Novel Dietary Strategies **(**POUNDS LOST) trial , the interactions between rs9939609 and protein intake, appetite, and food consumption were investigated in overweight adults (Huang et al. 2014). Briefly, the POUNDS LOST trial was a 2-year long RCT in 811 adults with overweight and obesity who were assigned to one of four low calorie (750 kcal/d deficit) diet interventions that varied in macronutrient content (Sacks et al. 2009). The authors reported that A-allele carriers (i.e., AT + AA) who consumed a hypocaloric, high-protein diet exhibited fewer food cravings and reduced appetite compared to people carrying the TT-genotype; however, no effect of genotype on the extent of weight loss was observed (Huang et al. 2014).

Not all studies have suggested a modifying effect of rs9939609 on lifestyle-induced changes in body weight. For example, a recently published systematic review and meta-analysis of randomized controlled trials (RCTs) examined the effect of rs9939609 on various measures of adiposity (e.g., BMI, body weight, or waist circumference) in overweight and obese adults (Livingstone et al. 2016). Based on 8 eligible RCTs comprising approximately 10 000 adults, Livingstone *et al.* reported that rs9939609 was not associated with differences in weight loss in response to lifestyle interventions.

While most investigations in the area have focused on the effect of rs9939609 on body weight, it is notable that the most consistent findings are related to the effects of this SNP on appetite. Indeed, evidence-to-date suggests that carriers of the *FTO* risk allele have greater food intake and reduced satiety compared to those carrying the common allele, with no impact on energy expenditure (Speakman 2015). Therefore, incorporating the rs9939609 SNP into behavioural weight management programmes that emphasize reductions in daily caloric intake may serve as an additional motivator for weight loss in people carrying the *FTO* risk allele.

1.2. Melanocortin-4 Receptor

The melanocortin-4 receptor (*MC4R*) gene is involved in appetite and satiety regulation in the hypothalamus (Martínez and Milagro 2015). Multiple SNPs in *MC4R* have been associated with obesity risk and a potential role in fat deposition, with the rs17782313 (T/C) SNP showing the strongest association (Loos et al. 2008). Haupt *et al*. investigated whether rs17782313 was associated with weight loss and changes in fat deposition during a 9-month lifestyle intervention (3 hours of exercise/week, reduced caloric intake to < 30% fat, < 10% saturated fat and increased fiber) in 242 adults with a BMI ≥ 27 kg/m^2 or diagnosed with T2D (Haupt et al. 2009). The C-allele was associated with higher BMI, body weight, total fat, and non-visceral fat tissue mass compared to TT homozygotes; however, there was no influence on changes in weight loss or fat deposition during the intervention (Haupt et al. 2009).

Variants in the *MC4R* gene were recently associated with weight loss response in participants from the Diabetes Prevention Program (DPP). Briefly, the goal of the DPP was to investigate if a lifestyle intervention could prevent the onset of T2D compared to pharmacological treatment (Knowler et al. 2002). Over 3 000 overweight and obese adults with elevated blood glucose levels were randomly assigned to a lifestyle intervention group (low-fat hypocaloric diet and 150 min/week of moderate physical activity), a metformin group, or a placebo control group. Seven SNPs in the *MC4R* gene were significantly associated with weight loss response to the lifestyle intervention in either the short-term (i.e., 6 months) or long-term (i.e., 2 years); however, only the rs1943218 (T/C) SNP was found to consistently influence weight change (Pan et al. 2013). Specifically, TT homozygotes for rs1943218 showed a greater amount of short and long-term weight loss compared to individuals with the CC and CT genotypes; however, these associations were only nominally significant. SNPs in *MC4R* have also been associated with weight loss maintenance in another lifestyle intervention study. Reinehr *et al.* examined whether SNPs in the coding region of *MC4R*, which were previously shown to reduce MC4R receptor activity, were associated with weight loss maintenance in children in response to a year-long lifestyle intervention comprising physical activity, nutrition education, and behavioral therapy (Reinehr et al. 2009). While no differences in weight loss were reported, children carrying SNPs that reduce MC4R activity were unable to maintain weight loss to the same extent as the control group. Collectively, the aforementioned studies suggest that SNPs in *MC4R* may be associated with multiple aspects of body weight regulation, including overall body weight, weight loss response, and/or weight loss maintenance.

Given the role of MC4R as a critical regulator of energy homeostasis, it is not unexpected that interventions that influence the balance between energy intake and energy expenditure would be modified by SNPs in this gene. Most of the mutations identified to date in the *MC4R* gene have been found to influence MC4R protein translation, translocation, or ligand binding (Tao 2010); thus favoring a positive energy balance. Therefore, personalized lifestyle interventions should place a greater emphasis

on promoting increased energy expenditure to circumvent a genetic predisposition for reduced MC4R activity.

1.3. Peroxisome Proliferator-Activated Receptor Gamma 2

The peroxisome proliferator-activated receptor gamma 2 (*PPARγ2*) gene is an important nuclear hormone receptor that is highly expressed in adipose tissue and plays a central role in the regulation of adipogenesis and fat metabolism (Sharma and Staels 2007). Considerable evidence shows that essential polyunsaturated fatty acids and their derivatives are natural ligands for *PPARγ2* (Grygiel-Górniak 2014), suggesting a potential link between dietary fat quality and transcriptional activity. The rs1801282 (C/G) SNP in *PPARγ2* – also known as Pro12Ala – has been associated with differences in weight loss in response to lifestyle interventions (Garaulet et al. 2011; Lindi et al. 2002). Interestingly, the *PPARγ2 Ala* allele was associated with a general reduction in PPARγ transcriptional activity due to a lower DNA binding affinity compared to the *Pro* allele (Deeb et al. 1998).

Associations between weight loss, dietary fat intake and rs1801282 were identified in a Spanish cohort of 1 465 individuals after a calorie reduced (600 kcal/d deficit), Mediterranean diet intervention coupled with moderate intensity physical activity 3 times/week (Garaulet et al. 2011). When participants were grouped according to dietary fat intake, individuals carrying the G-allele (i.e., GG or GC) tended to have a higher percentage of total weight loss when consuming a low fat diet compared to CC carriers. In contrast, individuals carrying the G-allele who had a high fat intake had significantly less weight loss than CC carriers. This relationship between fat intake and genotype was also reported in participants from the Finnish Diabetes Prevention Study (DPS), where G-allele carriers who consumed a low fat/high fibre diet experienced greater weight loss over the 3-year intervention compared to individuals with the CC-genotype (Lindi et al. 2002). Together, these results suggest a potential interaction between dietary fat intake, weight loss, and *PPARγ2* genotype.

Other reports have shown an interaction between rs1801282 and weight loss, irrespective of diet macronutrient composition. Specifically, adults with the CC-genotype who participated in a 6-week calorie-reduced diet intervention (500 kcal/d deficit) had a greater BMI and waist circumference at baseline, lost more weight and body fat during the intervention, and were able to better maintain weight loss post-intervention (Vogels et al. 2005).

In contrast, neither Matsuo *et al*. nor Goyenechea *et al*. found an association between rs1801282 and response to a weight loss intervention. Specifically, Matsuo *et al*. reported no association between *PPARγ2* SNPs (including rs1801282) and the magnitude of weight loss in response to a 14-week hypocaloric intervention (1 200 kcal/d) in Japanese women with a BMI ≥ 25 kg/m^2 (Matsuo et al. 2009). Similarly, Goyenechea *et al*. found no association between rs1801282 and weight loss following a 10-week hypocaloric intervention (500 kcal deficit/d) in Spanish adults with obesity (Goyenechea et al. 2006). Taken together, rs1801282 is of potential interest as a modifier of response to a lifestyle intervention, but further replication of promising initial findings is necessary.

Future studies examining the impact of *PPARγ2* SNPs on obesity should account for dietary fat quality. Indeed, diets rich in polyunsaturated fats, such as the Mediterranean diet, will provide more natural ligands compared the typical Western diet that is rich in saturated fats. It is therefore possible that providing personalized advice that favors an increase in the amount of natural ligands in the diet could lead to a longer and more sustained activation of PPARγ that counteracts the effect of SNPs that lower its DNA binding affinity.

1.4. Adrenoceptor Beta 3

Since it was first reported over 20 years ago, the rs4994 (T/C) SNP in the adrenoceptor beta 3 (*ADRB3*) gene (also known as Trp64Arg) has repeatedly been associated with obesity (Kurokawa 2011). The *ADRB3* gene is a member of the adrenergic receptor family, which plays an important role in the

regulation of energy homeostasis and thermogenesis in adipose tissue (Kurokawa et al. 2008). Reports in multiple populations have shown that carrying the C-allele (i.e., CC + CT) is associated with less weight loss after a lifestyle intervention compared to those with the TT-genotype (Tchernof et al. 2000; Sakane et al. 2016). For example, postmenopausal women with the CC or CT genotype experienced less visceral adipose tissue weight loss compared to TT homozygotes following a 13-month hypocaloric (1200 kcal/d) diet intervention (Tchernof et al. 2000). Sakane *et al.* also reported an association between rs4994 and weight loss in adults participating in the Japanese Diabetes Prevention Program (Sakane et al. 2016). Specifically, individuals with the CC or CT genotype lost significantly less weight during the lifestyle intervention than those carrying the TT-genotype. Despite these reports demonstrating an association between rs4994 and weight loss, the role of this SNP remains disputable. Indeed, several studies have found no association between this SNP and weight loss following exercise (Tahara et al. 2010) or a combination of diet and exercise (Kuriyama et al. 2008; Saliba et al. 2014).

Although it is difficult to reconcile discrepant findings in the literature, it is notable that the TT-genotype (or Trp64 genotype) was reported to have a higher responsiveness (i.e., lipolysis) to a selective human beta3-adrenergic receptor agonist compared to CT and TT genotypes in human omental adipocytes (Corbalán et al. 2002). Interestingly, responsiveness to lipolytic adrenergic stimulation is known to vary greatly between adipose tissue depots and in a sex-specific manner (White and Tchoukalova 2014). Thus conflicting results may be explained by differences in the sex-makeup or the type of obesity (gynoid versus android) in different study cohorts. Future lifestyle intervention studies in which the effects of *ADRB3* SNPs on weight loss are investigated should therefore account for sex-specific differences in body fat distribution to avoid this potential confounder.

2. Dyslipidemia

Elevated triglyceride and reduced high-density lipoprotein cholesterol (HDL-C) levels constitutes two major risk factors for MetS. Twin studies suggest that the heritability of triglycerides and HDL-C ranges between 60-80% (Heller et al. 1993; Austin et al. 1987). Genome-wide screening of more than 100 000 individuals of European descent revealed 95 genetic loci that explained 25-30% of the variability in blood lipids (Teslovich et al. 2010); however, only a few of these SNPs have been investigated in relation to lifestyle interventions. Understanding the contribution of SNPs to the variable responses in lipid levels observed between people during lifestyle interventions may help to develop more effective approaches to improve lipid profiles. While SNPs in the apolipoprotein A-V gene are the most extensively studied in conjunction with lifestyle interventions, variants in other genes also show potential as modifiers of response and will be briefly discussed.

2.1. Apolipoprotein A-V

The apolipoprotein A-V (*APOA5*) gene was first reported to play a key role in hepatic lipoprotein synthesis and hypertriglyceridemia. Additional research has shown that APOA5 is able to stimulate lipoprotein lipase-mediated triglyceride hydrolysis and to participate in hepatic clearance of remnant lipoproteins (Guardiola and Ribalta 2017). Although several SNPs in *APOA5* have been associated with blood lipids, the rs662799 (T/C) SNP in particular has been investigated in lifestyle interventions targeting improvements in blood lipid profiles (Guionnet 2008). The majority of studies have shown that this SNP influences triglyceride and HDL-C levels in response to lifestyle interventions. For example, an investigation in 283 Korean men with elevated triglyceride levels found an interaction between *APOA5* genotype, lifestyle, and changes in triglyceride and HDL-C levels (Jang et al. 2010). Specifically, when participants with moderately elevated triglyceride levels (2.26-7.90 mmol/L) replaced 1/3 of refined rice with legumes, increased vegetable intake, and incorporated regular walking (30 minutes/d), those with

the TT-genotype showed greater improvements in serum triglycerides and HDL-C levels compared to those with the CC or CT genotypes.

In contrast, another study in 357 Caucasian pediatric/adolescents with obesity who participated in a 30-day lifestyle intervention comprised of a caloric deficit and 120 minutes of daily endurance exercise found that C-allele carriers experienced a ~32% reduction in plasma triglycerides with the intervention compared to the ~20% reduction observed in TT homozygotes (Zlatohlavek et al. 2012). This same study also reported a similar finding with another SNP in *APOA5* (rs3135506). It is not clear why the genotype response between the two aforementioned studies differed; however, they both suggest that genetic variation in *APOA5* is associated with changes in circulating triglyceride levels.

A two-year RCT secondary to the POUNDS LOST trial focused on interactions between another SNP in *APOA5* (rs964184; C/G) and blood lipid levels in participants randomly assigned to diet groups that differed in macronutrient content (Zhang et al. 2012). Overall, adults who were overweight and obese (n=734; BMI of 25-40 kg/m^2) and carried the G-allele (i.e., GG + GC) experienced greater improvements in blood lipid profiles compared to those with the CC-genotype. G-allele carriers in the high-fat diet group (40% of total calories from fat) showed greater improvements in HDL-C, while those in the low-fat diet group (20% of total calories from fat) experienced significantly greater reductions in total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Zhang et al. 2012). Collectively, these studies suggest that various SNPs in the *APOA5* gene may modify triglycerides and/or HDL-C levels during lifestyle interventions; however, further work is necessary to identify the causative SNP in this genomic region.

While the functional consequences of *APOA5* genetic variants remain poorly defined, interesting work by Cui et al. suggests that SNPs in *APOA5* may influence promoter activity, either directly or through high linkage disequilibrium with a functional variant (Cui et al. 2014). These authors reported

that the rs2266788 SNP (which is in high linkage disequilibrium with the above-mentioned rs662799) modifies the mIR-3201 binding site in the *APOA5* promoter region, extending mRNA half-life. It is therefore plausible that discrepant findings from past lifestyle intervention studies may be explained by certain SNPs affecting *APOA5* expression levels and, consequently, triglyceride clearance, while other SNPs do not.

2.2. Apolipoprotein E

The apolipoprotein E (*APOE*) gene was previously associated with triglyceride levels in a GWAS (Kristiansson et al. 2012). APOE is involved in the regulation of lipoprotein metabolism, including that of HDL-C, and is well-associated with plasma lipid levels (Eichner et al. 2002). Briefly, three *APOE* isoforms encoded by the ε2/ε3/ε4 haplotype exist, with the ε3 isoform being the most common. Compared to ε3, the ε2 isoform was reported to decrease cholesterol levels and increases triglycerides, while the ε4 isoform increased both (Povel et al. 2011). A small, randomized crossover intervention study (n=28) compared the intake of whole grain wheat sourdough to refined white bread on serum lipids in individuals stratified according to CVD risk and their *APOE* genotype (Tucker et al. 2010). The authors reported that participants classified as 'high risk' for CVD and who carried the ε3/ε3 genotype showed increased triglyceride and a higher triglyceride:HDL-C ratio following the consumption of whole grain wheat sourdough bread compared to those with ε2/ε3 and ε3/ε4 genotypes. Although this study was limited by its small sample size, it is noteworthy due to its crossover design and high compliance regarding the consumption of bread products. Interestingly, the results of this study suggest that consumption of whole grains, which are typically associated with improvements in CVD risk, may be detrimental in at-risk individuals carrying the common *APOE* genotype. However, given the small sample size of this study, further investigations are necessary before implementing personalized dietary advice in relation to whole grain consumption.

2.3 Transcription Factor 7 Like 2

The transcription factor 7 like 2 (*TCF7L2*) gene has recently been shown to influence blood lipids (Perez-Martinez et al. 2012). Corella *et al.* examined associations between the rs7903146 (C/T) SNP in *TCF7L2* and total cholesterol, LDL-C, and triglyceride levels during a lifestyle intervention (Corella et al. 2013). Specifically, 7 018 participants with T2D and high CVD risk from Spain were randomly assigned to either a Mediterranean diet with extra-virgin olive oil group, a Mediterranean diet with mixed nuts group, or a control group (Corella et al. 2013). When adherence to the Mediterranean diet was low, participants with the TT-genotype showed higher total cholesterol, LDL-C, and triglyceride levels compared to individuals carrying the C-allele. However, when adherence to the diet was high, no difference was observed. These findings suggest that adopting the Mediterranean diet may offer some protection from high blood lipid levels to individuals with the TT-genotype in rs7903146. However, given the relative novelty of this relationship, further investigations are necessary to unravel the mechanism of action

2.4 Other SNPs Associated with the Lipid Response to Lifestyle Interventions

Many other SNPs in various genes have been studied as modifiers of response to lifestyle interventions. For example, 82 SNPs studied in 3 561 individuals with overweight and obesity and T2D were investigated in the Look AHEAD trial (Huggins et al. 2013). This trial was comprised of a year-long 7% weight loss goal by means of calorie restriction and increased physical activity (200 min/week) in comparison to a control group who only received general diabetes support sessions. The authors identified 12 SNPs that were associated with increases in HDL-C and 6 SNPs associated with reductions in triglycerides in response to the lifestyle intervention. For example, carrying the A-allele in either rs8034802 (T/A) in *LIPC,* rs3764261 (C/A) in *CETP,* or rs1535 (A/G) in *FADS2* was associated with increased HDL-C. Additionally, carrying the minor allele in rs693 (G/A) in *APOB,* rs4082919 (C/A) in *PGS1*,

or rs8034802 (T/A) in *LIPC* was associated with reduced triglyceride levels after the lifestyle intervention. An interesting next step would be to explore whether a genetic risk score (GRS) that comprises all of these various SNPs serves as a stronger predictor of changes in blood lipids than any of the SNPs individually. A recent study examined if providing patients at intermediate risk of coronary heart disease with a GRS in addition to a conventional risk assessment led to greater changes in blood lipids and lifestyle habits (dietary fat intake, physical activity) compared to patients who received only a conventional risk assessment (Kullo et al. 2016). The results revealed that patients who received a GRS showed greater reductions in LDL-C after 6 months compared to controls. Therefore, providing people with a GRS in the context of a lifestyle intervention that targets blood lipids may provide an additional impetus to adopt healthier behaviours.

3. Glucose Homeostasis

Glucose homeostasis is an important aspect of metabolic health and is considered a core component of MetS (Roberts et al. 2013). When fasting glucose levels increase above 6.1 mmol/L, this augments the risk of developing insulin resistance (Norris and Rich 2012). Numerous GWAS have been conducted to determine the genetic contribution to glucose homeostasis, and these studies have revealed that common glycemic traits (e.g., glucose and insulin) are strongly heritable (Brown and Walker 2016; Dupuis et al. 2010). A recent review by Mohlke and Boehnke indicated that 137 loci have been associated with T2D and various glycemic traits (Mohlke and Boehnke 2015); however, only a small number of these loci have been examined for their role in modifying a person's glycemic response to a lifestyle intervention. The following section highlights specific gene-lifestyle interactions that have been examined in three large-scale cohort studies that investigated T2D prevention.

3.1 Phosphoinositide-3-Kinase

The phosphoinositide-3-kinase (*PI3K*) gene has an important regulatory role in insulin signaling and glucose homeostasis. Genetic variation in *PI3K* was examined in participants from the Finnish DPS to assess its capacity to modify glycemic responses following a one-year lifestyle intervention (Laukkanen et al. 2004). Briefly, the DPS trial consisted of a one-year lifestyle intervention followed by a two-year maintenance period in individuals who were overweight with impaired glucose tolerance. The participants were randomly assigned to a control group (i.e., diabetes support and education) or an intensive weight-loss intervention group (i.e., personalized nutritional counselling and physical activity). The rs3730089 (G/A) SNP in the *PI3K* gene influenced the reduction in blood glucose levels in response to an oral glucose challenge. Specifically, G-allele carriers in the intervention group showed greater reductions in 2-hr glucose levels compared to homozygotes for the minor A-allele (i.e., AA-genotype). No effect of this SNP on blood glucose was observed in subjects in the control group. Exercise is known to enhance insulin-stimulated glucose uptake into skeletal muscle by promoting increased GLUT4 translocation to the sarcolemma. PI3K plays a critical role in insulin-mediated GLUT4 translocation; however, how rs3730089 influences PI3K function is unclear at this time. Examining if rs3730089 influences *PI3K* mRNA levels or the interaction between PI3K and insulin receptor substrate, for example, will provide important molecular clues to better understand this gene-exercise interaction.

3.2 Transcription Factor 7 Like 2

TCF7L2 is a transcription factor that plays a critical role in the Wnt signaling pathway to influence incretin-induced insulin secretion from the pancreas (Jin 2016). Florez and colleagues explored the relationship between insulin secretion/sensitivity and SNPs in *TCF7L2* in participants from the DPP (Florez et al. 2006). The authors reported that TT homozygotes for two SNPs in *TCF7L2*, rs12255372 (G/T) and rs7903146 (C/T), had lower insulin secretion and higher insulin sensitivity at baseline compared to the major allele carriers of either SNP. However, genotype-related differences in insulin

secretion were no longer observed in participants after the lifestyle intervention. This suggests the influence of genetic variants in the *TCF7L2* on insulin secretion may be greater in unhealthy individuals compared to healthy individuals. Interestingly, these results may be explained by differences in *TCF7L2* gene expression. Elegant functional studies by Lyssenko and colleagues demonstrated that the aforementioned SNPs influence *TCF7L2* gene expression in human islets, with carriers of the TT-genotype showing higher *TCF7L2* expression (Lyssenko et al. 2007). Moreover, a recent study found that a six-month exercise intervention caused increased methylation in *TCF7L2* and reduced *TCF7L2* gene expression in adipose tissue (Rönn et al. 2013). Thus it is plausible that the normalization in insulin secretion in carriers of the "risk" genotypes compared to common genotypes after the lifestyle intervention may stem from greater reductions in *TCF7L2* gene expression. Future studies examining the methylation status of *TCF7L2* and the corresponding impact on gene expression in a genotype-specific manner will be particularly enlightening.

3.3 Insulin Receptor Substrate 1

The insulin receptor substrate 1 (*IRS1*) gene encodes a protein that plays a key role in the propagation of insulin signaling (Kovacs et al. 2003). A common variant, rs2943641 (C/T), located upstream of the *IRS1* gene was found to be associated with insulin resistance and hyperinsulenia, with carriers of the C-allele having an increased relative risk of T2D (Rung et al. 2009). Interestingly, the C-allele was also reported by the same authors to be associated with reduced IRS1 protein expression and lower PI3K activity. Qi *et al* investigated if rs294361 modified the effects of weight-loss diets on insulin resistance in participants from the POUNDS LOST trial (Qi et al. 2011). After 6-months, individuals carrying the "at-risk" CC-genotype and who consumed a diet high in carbohydrates (65% energy from carbohydrate) showed greater reductions in insulin levels and insulin resistance (according to HOMA-IR) compared to T-allele carriers; however, the opposite genotype effect was seen in individuals consuming

a low-carbohydrate diet (~35% carbohydrates). A potential explanation for the opposite genetic effects may be related to the varying macronutrient composition of the low and high carbohydrate diets. Indeed, the low carbohydrate diet contained twice as much fat as the high carbohydrate diet (20% vs. 40% energy from fat). High-fat diets impair insulin signaling by decreasing IRS1 and PI3K activity (Hansen et al. 1998); thus it is possible that the opposite genotype effects seen in the low carbohydrate diet may be related to fat content. Future studies examining the modifying role of rs294361 should consider taking skeletal muscle biopsies to study the phosphorylation status of IRS1 in a genotype-specific manner. Moreover, incorporating this SNP into personalized lifestyle interventions should consider not only the carbohydrate content of the diet, but also fat content.

3.4 Other SNPs Associated with the Glucose Response Following Lifestyle Interventions

SNPs in other genes have been studied using the same large-scale cohorts described in the preceding sections. The rs2070895 (G/A) SNP in *LIPC*, a gene that encodes a hepatic lipase that regulates lipoprotein metabolism, was investigated for its potential to modify risk of T2D in participants from the Finnish DPS (Todorova et al. 2004). High hepatic lipase activity was previously associated with low HDL-C levels; therefore, a lower lipase activity would favor an improvement in lipid profiles. Within the lifestyle intervention group, subjects with the major GG-genotype in *LIPC* were found to be more likely to develop T2D (13% of individuals) after three years compared to A-allele carriers (1% of individuals). By using changes in circulating HDL-C levels as a proxy for hepatic lipase activity, the authors speculated that the genotype effect may stem from alterations in hepatic lipase activity, with carriers of the "at risk" G allele showing smaller changes in HDL-C levels compared to C-allele carriers.

Another study used a subset of participants from the Finnish DPS to examine associations between glucose tolerance and T2D development with an insertion/deletion (I/D) polymorphism (12Glu9) in the α2 β-adrenergic receptor gene (*ADRA2B*). This SNP was previously reported to be

associated with alterations in key metabolic processes, including a reduction in basal metabolic rate in individuals with obesity (Siitonen et al. 2004). In the control group, individuals with the D/D genotype (Glu9/9) had an increased risk of T2D and reduced acute insulin response compared to subjects with the I/I genotype (Siitonen et al. 2004). Interestingly, these genotype differences were not observed in the lifestyle intervention group, most probably due to significant weight loss reducing the demand for insulin production. This suggests that a lifestyle intervention targeting weight loss may overcome these genetic differences; however, the impact of this genetic variant should be considered when weight loss is not the goal.

A potential association was found between insulin sensitivity/secretion and the rs1044498 (A/C) SNP, also known as K121Q, in the ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (*ENPP1*) gene in participants from the DPP (Moore et al. 2009). This gene encodes a membrane glycoprotein that regulates insulin signaling, and has been shown to modify the severity of insulin resistance (Moore et al. 2009). Within the placebo group, carriers of the C-allele for rs1044498 had an increased incidence of T2D at baseline and over the 4-year follow-up period, but this genetic association was not observed in individuals in the lifestyle modification group. However, the authors were unable to conclude if the increased risk in C-allele carriers was due to reduced insulin sensitivity or secretion once they adjusted for confounding variables. This suggests that further investigations are necessary to elucidate the potential role of rs1044498 as a mediator of T2D risk and/or response to a lifestyle intervention.

Finally, a 2016 study explored whether a genetic risk score (GRS) corresponding to 31 SNPs previously associated with T2D could predict changes in insulin resistance and beta-cell function in subjects from the POUNDS LOST trial (Huang et al. 2016). An interaction was identified between the GRS and dietary protein for various markers. Specifically, individuals with a lower GRS showed a greater

decrease in fasting insulin, HOMA-IR, and other measures of insulin resistance when consuming a low-protein weight-loss diet (15% protein), compared to the high GRS group. In contrast, the opposite genetic effect was observed in the high-protein weight-loss diet group. This genetic effect was only seen with dietary protein, as no associations with dietary carbohydrate and fat intake were reported by the authors. However, the precise mechanism of action to explain these dietary protein / genetic results is difficult to tease apart due to the fact that the GRS comprised 31 different genes associated with various canonical pathways.

Collectively, these various clinical investigations have provided the first glimpses of how genotype-lifestyle interactions could influence glucose homeostasis and, more importantly, the potential risk of insulin resistance and T2D. Although this area of investigation remains in its infancy, the aforementioned studies provide some initial clues as to the functional impact of various SNPs associated with T2D risk and their ability to modify an individual's response to a lifestyle intervention. Such insights will help guide the development of more efficacious personalized lifestyle interventions that aim to prevent the development of T2D.

4. Blood pressure

Hypertension, which is defined as having a systolic/diastolic blood pressure (BP) greater than 140/90 mmHg, is a component of MetS. Moreover, hypertension is also a significant risk factor for the development of CVD (Mulè et al. 2014). The heritability of BP traits has been estimated to lie between 30-60% (Shih and O'Connor 2008). A recent GWAS of more than 200 000 individuals identified 66 SNPs associated with BP control (Ehret et al. 2016); however, only a small number of these variants have been examined for their effects as modifiers of lifestyle interventions. SNPs in the renin-angiotensin-aldosterone system (RAAS) are of primary interest due to its central role in BP regulation (Ge et al. 2007). In particular, the angiotensin I-converting enzyme (*ACE*) gene has been investigated for its

association with BP response to lifestyle interventions. Consequently, this section will focus on the *ACE* gene; however, we anticipate that other SNPs in other genes will be shown to influence changes in BP in future lifestyle intervention studies.

The rs4646994 insertion/deletion (I/D) SNP in the *ACE* gene exists as three possible genotypes (I/I, I/D, or D/D), and has been explored for its role in mediating salt-sensitive hypertension (de Carvalho et al. 2016). Salt sensitivity can be defined as experiencing a 5-10% increase in systolic BP (equivalent to 5 mmHg) in response to a change in dietary salt (NaCl) consumption (Felder et al. 2013). A study conducted in a Spanish cohort of 71 otherwise healthy hypertensive adults examined the association between rs4646994 and BP response to salt consumption (Poch et al. 2001). In this single-blinded, placebo-controlled crossover study, individuals participated in a low salt intervention for one week (50 mmol of Na/d) followed by a high-salt intervention for the second week (260 mmol /day Na). The authors found that I/I homozygotes had a greater increase in BP in response to high-salt intake compared to the D/D or I/D genotypes, suggesting this particular genotype has a higher susceptibility to salt-associated hypertension. This finding aligns with those from independent studies showing that participants with the I/I genotype had significantly higher BP when consuming a high-salt diet compared to both I/D and D/D genotypes (Giner et al. 2000; Hiraga et al. 1996). Based on these intervention studies, the I/I genotype appears to confer a greater risk for salt-sensitive hypertension. Therefore, lifestyle interventions promoting a reduction in salt intake should be particularly effective in individuals carrying this salt-sensitive genotype.

The effects of variants in the *ACE* gene on BP response have also been investigated in the context of exercise-based interventions (Jones et al. 2002). However, due to the variability in type, duration, and intensity of exercise in various studies, the role of rs4646994 as a mediator of exercise-induced changes in BP remains equivocal. For example, the effects of a single bout of aerobic exercise

on BP was examined in 47 Caucasian men with stage one hypertension after low-intensity (40 min at 40% of maximal oxygen consumption), moderate intensity (40 min at 60% maximal oxygen consumption), and seated rest (control) on a cycle ergometer (Blanchard et al. 2006). The authors reported that the D/D genotype had lower systolic BP after the low-intensity cycling compared to I/I or I/D genotypes, while there were no difference in systolic BP amongst genotypes after moderate intensity cycling or in diastolic BP at any intensity (Blanchard et al. 2006). In contrast, a more recent study explored the association between an acute bout of exercise in 34 men and women in a randomized crossover trial (Goessler et al. 2015) consisting of an exercise session (45 min of moderate intensity walking at 60-75% of maximal heart rate) and a control session. Participants with at least one insertion allele (I/I or I/D) had lower systolic and diastolic BP for five hours after the walking intervention, compared to the sedentary control intervention. No effect of walking on BP was seen in individuals carrying the D/D genotype.

As these aforementioned studies consisted of acute exercise interventions, it is also necessary to consider the impact of rs4646994 on BP following prolonged and/or continuous exercise. The relationship between *ACE* genotype and BP was investigated in 68 young, otherwise healthy, pre-menopausal women during a 12-week exercise intervention (60% of maximal heart rate achieved by 30 min of walking and one set of resistance training, 2-3 times/week) (Kim 2009). After the exercise intervention, individuals carrying the I/I genotype experienced greater decreases in diastolic BP compared to the D/D genotype. In contrast, a trial of similar duration conducted in a cohort of 64 elderly hypertensive women assigned to a whole-body resistance training program (3 times/week) found no evidence of a modifying effect for rs4646994 on exercise-induced changes in BP (Mota et al. 2013). An important limitation to consider in all of these exercise studies is that dietary habits were not strictly controlled for. This is an important confounder, as the balance between dietary intake of vitamins and minerals such as sodium, potassium, and vitamin D have integral roles on the regulation of BP

(Drenjančević-Perić et al. 2011; Plum and DeLuca 2010). A future step in this area would be to examine the associations between SNPs in *ACE* and other parameters of RAAS function, such as plasma renin and angiotensin levels, while also controlling more thoroughly for dietary habits.

Conclusion

The current review has highlighted the potential role of SNPs as modifiers of response to lifestyle interventions aimed at improving the various components of MetS (**Figure 1**). The majority of research thus far has investigated lifestyle-gene associations in relation to individual MetS components, and identified numerous SNPs that can influence a person's response to diet and/or exercise interventions in regard to weight loss, improvements in insulin sensitivity and lipid profiles, and blood pressure. It is anticipated that through studies such as the ones outlined in the current review, a panel of SNPs associated with the individual MetS components will be identified and eventually used to establish a GRS to assist physicians, kinesiologists, and registered dietitians develop personalized diet and exercise interventions to improve patient outcomes (**Figure 1**). However, further replication of promising gene-lifestyle interactions and a greater understanding of the functional consequences of individual SNPs are necessary before the widespread implementation of lifestyle interventions for MetS based on personalized genetic information. Moreover, it will be necessary to explore how knowledge of lifestyle-gene associations is best implemented into clinical practice in order to ensure that both health care professionals and patients are adequately educated to effectively use genetic information to improve health outcomes.

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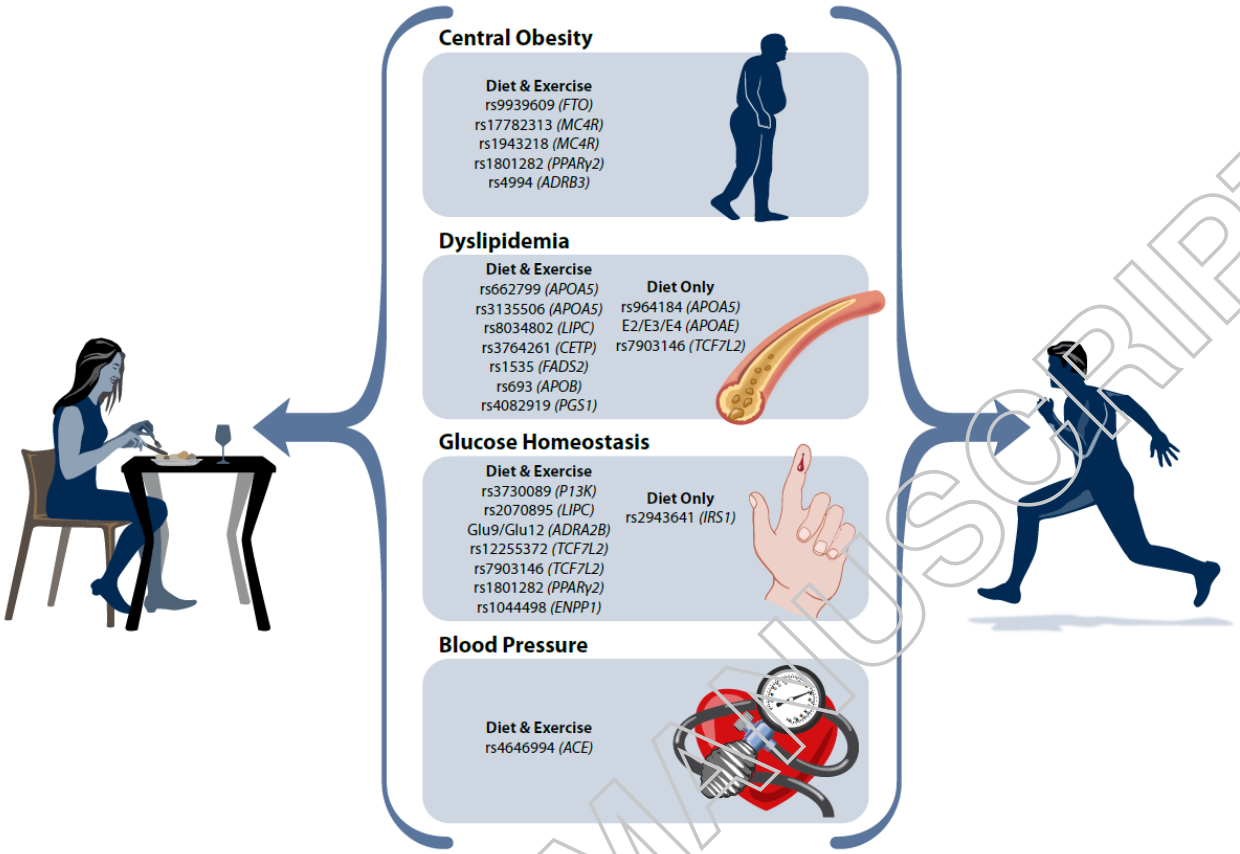

Figure 1. Genetic variants reported to influence a person's response to lifestyle interventions. Single nucleotide polymorphisms (SNPs, identified with unique rs numbers) that have been shown in the literature to influence response to lifestyle interventions targeting the individual components of Metabolic Syndrome are indicated within defined boxes. In most instances, SNP effects have been shown to influence a person's outcome to a combined diet and physical activity lifestyle intervention; however, some SNPs have also been found to influence response to diet interventions alone.