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Genetic Profiling for Weight Loss: Potential Candidate Genes

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Abstract

Background: Genome wide association studies have provided valuable information pertaining to a potential link between certain genetic polymorphisms and the prevalence of obesity. These findings have led to the assessment of obesity-related genes in relation to health outcomes after participation in a weight loss intervention. Few studies to date have taken these findings one-step further regarding use of these genes as part of a genetic profile to dictate dietary prescription for optimization of weight loss and health outcomes. The purpose of this review to explain how genetic profiling may be useful within a weight loss intervention to promote weight loss and improved health outcomes, and identify potential candidate genes for use in genetic profiling. Methods: A literature search was conducted using PubMed Central since this search engine's primary focus is within the biomedical discipline, including literature from MEDLINE, life science journals, and related online books.

Results and conclusions: To date, candidate genes selected within weight loss interventions utilizing a genetic profile are relatively inconsistent. One investigation demonstrated clear, significant results in favor of dietary prescription based on the profile used and thus warrants further investigation with use of the candidate genes selected. This genetic profile is further supported by investigations assessing each candidate gene in relation to health outcomes from weight loss interventions. Therefore, weight loss interventions genotyping for FABP2 (rs1799883), PPARG2 (rs1801282), ADRB3 (rs4994C3), and ADRB2 (rs1042713 and rs1042714) together to dictate dietary intervention, while including an exercise component, may be useful in optimizing success from participation in a weight loss intervention.

Keywords: Genetic profiling; Nutrigenetics; Weight loss; Obesity

Introduction

Originally, the onset of obesity was considered as solely credited to a positive energy balance such that energy intake exceeded energy expenditure of basal metabolic needs, thermic effect of food, lifestyle and physical activity. Currently, obesity is attributed to an interaction among multiple components, including physiological, metabolic, behavioral, social, and genetic factors [1]. Attention to genetic factors as a cause of the obesity epidemic has gained recent attention as of late and may be associated with the start of genome-wide association studies (GWAS). With use of GWAS, identification of countless candidate genes associated with BMI classification of obesity and unfavorable body fat distribution has been identified [2-5]. Furthermore, various polymorphisms associated with these candidate genes have been linked to metabolic pathways related to the thermic effect of food, fat oxidation, and basal metabolic rate [6]. Thus, these findings have initiated research within the area of nutrigenetics. Nutrigenetics, also commonly referred to as genetic profiling, pertains to the influence of genotype on the response to caloric restriction within a weight loss program [6]. The purpose of this literature review is to explain how genetic profiling may be useful within a weight loss intervention to promote weight loss success and improved health outcomes, and to identify potential candidate genes for use in the profile.

Genetic profiling (Nutrigenetics)

The concept of genetic profiling to classify or predict clinical outcomes and disease states is used frequently with microarray analyses in oncology [7]. Within a clinical setting, genotypes associated with metabolism, transport of nutrients, removal of toxins, and protection from antioxidants are analyzed to determine a pattern of baseline genetic variation [8]. Determining baseline variation in candidate genes provides insight regarding clinical intervention, diet, and exercise [8]. This practice is relatively new in the arena of weight loss. With countless genes revealed as associated with obesity, the challenge is determining which candidate genes and polymorphisms are most effective in relation to predicting dietary prescription to induce weight loss and improve health outcomes. To date, few studies have assessed a specific genetic profile in relation to dietary intervention while participating in a weight loss intervention [7-9].

In a retrospective analysis conducted by Mutch et al. [7], a smaller sample size from a larger European multicenter study, the Nutrient-Gene Interactions in Human Obesity-Implications for Dietary Guidelines Trial (NUGENOB; www.nugenob.org), was assessed in regards to baseline genotype and response to the weight loss intervention. Specifics of the NUGENOB trial are described earlier (www.nugenob.org). Briefly, the dietary intervention in the NUGENOB intervention consisted of a 600 kcal deficit with participants randomized into either a low fat, high carbohydrate (CHO) diet (20-25% kcal fat, 60-65% kcal CHO, 15% kcal protein) or a moderate fat, low CHO diet (40-45% kcal fat, 40-45% kcal CHO, 15% kcal protein). Mutch et al. selected 53 participants from the NUGENOB trial who were closely matched in baseline characteristics [7]. This smaller sample of participants were then classified as responders or non-responders based on their success in the NUGENOB intervention. Responders exhibited an 8-10 kg weight loss by the end of the intervention, whereas non-responders exhibited less than four kg weight loss. Genotype was determined from

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microarray analysis of adipose biopsies collected at the start of the study. The following candidate genes were identified as having significantly different allele patterns between responders and non-responders at baseline: transmembrane protein 132A (TMEM132A), quinolinate phosphoribosyltransferase (QPRT), claudin 5 (CLDN5), prostaglandin D2 synthase (PTGDS), endothelial cell adhesion molecule (ESAM), fibromodulin (FMOD), family with sequence similarity 69 B (FAM69B), interferon alpha-inducible protein 27 (IF127) [7]. Taken together, these findings suggest that the identified candidate genes are associated with success in the aforementioned weight loss intervention [7].

Similarly, Dopler-Nelson et al. [9] retrospectively categorized participants to their dietary intervention groups, i.e. true match to diet or false match to diet, via baseline genotype in a smaller sample from a large, 12-month, randomized controlled trial, The AtoZ Weight Loss Trial [10]. Specifics of the AtoZ weight loss trial are described elsewhere [10]. In short, the following diets were included in the AtoZ trial: Atkins (<20 g/d CHO x 2-3 months, then ≤50 g/d CHO), Zone (40% kcal CHO, 30% kcal fat, 30% kcal protein), LEARN (55-60% kcal CHO, <10% kcal saturated fat), Ornish (≤10% kcal fat) [10]. Dopler-Nelson et al. contacted all participants in the AtoZ Weight Loss Trial regarding retrospective genetic analysis. Of all 311 participants contacted, 141 individuals participated in the retrospective genetic profiling study [9]. Genotyping was determined via buccal cheek swabs to assess genetic variants among the following four candidate genes: fatty acid binding protein (FABP2, rs1799883), peroxisome-proliferator activated-receptor gamma 2 (PPARG2, rs1801282), beta-3 adrenergic receptor (ADRB3, rs4994C3), beta-2 adrenergic receptor (ADRB2, rs1042713 and rs1042714). Findings determined that individuals who were truly matched to their dietary intervention based on genotype experienced 5.3 percent loss in body weight (BW) over 12-months versus 2.3 percent BW in false matches ($p<0.005$) [9]. True matches to the programs lowest in CHO (Atkins) and fat (Ornish) experienced 6.8% total weight loss in comparison to 1.4% in false matches. Additionally, positive blood lipid changes were demonstrated in favor of those who were true genotype matches [9].

In addition to the retrospective analyses, Arkadianos et al. [8] conducted the only investigation to our knowledge where participants were matched prospectively to a dietary intervention based on genotype at baseline. Ninety-three patients from the Dr. Arkadianos Clinic participated in an intervention approximately 11-months in length [8]. All participants followed a low saturated fat, low glycemic index, Mediterranean-style diet. With typical macronutrient distribution range of the Mediterranean diet consisting of approximately 38% kcal CHO, 46% kcal fat, and 16% kcal protein [11]. Fifty obese (22 female, 28 male, average BMI 32 kg/m^2) participants, aged approximately 45 years old, included specific alterations in their dietary prescription based on genetics variants within the candidate gene of interest (nutrigenetic group), whereas 43 participants (18 female, 25 male, average BMI 32 kg/m^2) simply followed the prescribed diet (control group). Participants attended regular appointments with their physician at the clinic where BW was measured and a fasting blood sample was collected at baseline and completion [8]. Genotyping was determined by Buccal cheek swabs. The following variants among candidate genes were of interest: 5,10-methylenetetrahydrofolate reductase (MTHFR, rs1801131, 677C>T), 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR, 66A>G), 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR, 275A>G), cystathione-beta-synthase (CBS, 699C>T); glutathione s-transferase MI (GSTMI, deletion), glutathione s-transferase theta 1 (GSTT1, deletion), glutathione s-transferase pi (GSTP1, 313A>G, 341C>T); SOD2 (-28C>T), SOD3 (760C>G), nitric oxide synthase (NOS3, 894G>T); vitamin D receptor (VDR, CTaqIT, TBsmIC, TFokIC), collagen type 1 alpha 1 (COLIA, G SpI T); tumor necrosis factor alpha (TNFalpha, -308G>A), interleukin 6 (IL6, 1595C>G), nitric oxide synthase 3 (NOS3, 894G>T); cholesteryl ester transfer protein (CETP, 279G>A), lipoprotein lipase (LPL, 1595C>G), apolipoprotein C-3 (APOC3, 3175C>G); angiontensin I convertin enzyme (ACE, INS/DEL), peroxisome-proliferator activated-receptor gamma 2 (PPARG2, Pro12Ala) [8]. Upon completion of the study change in BMI between approximately three to ten months of the intervention was not significant; however, after about ten months, BMI decreased 5.6% (1.93 kg/m^2) in the nutrigenetic group versus a 2.2% gain (0.51 kg/m^2) in the control group ($p<0.023$). After 90 days, among the participants with pre-diabetes, 57% of individuals in the nutrigenetic group and 25% of individuals in the control group demonstrated a significant reduction in fasting blood glucose ($p<0.046$). Findings suggest use of genetic profiling to optimize dietary intervention may promote weight loss and maintenance in comparison to random assignment to a diet for weight loss. Additionally, patients with pre-diabetes experienced improved insulin sensitivity when genetically matched to a diet for weight loss [8].

To date, the only nutrigenetic studies conducted are inconsistent among selected candidate genes. Furthermore, while potential genes have been identified among these studies, the investigation conducted by Dopler-Nelson et al. [9] utilized the most practical intervention and genetic profile while demonstrating clear, significant effects. Therefore the five candidate genes of interest within this investigation, FABP2 (rs1799883), PPARG2 (rs1801282), ADRB3 (rs4994C3), ADRB2, (rs1042713 and rs1042714), provide promise for future use as a determinant for dietary prescription to promote weight loss and improved health outcomes. See Table 1 for details of nutrigenetic studies.

Potential candidate genes to include in a genetic profile for weight loss

FABP2 (rs1799883)

Association with obesity: Intestinal fatty acid binding protein 2 (FABP2) is a protein located in the cytosol of intestinal epithelial cells and is associated with long-chain fatty acid metabolism [12]. At rs1799883 a transition occurs at codon 54 resulting in replacement of alanine (Ala) with threonine (Thr) [13]. The wild-type allele pattern for FABP2 is Ala/Ala, whereas the mutant-type is Ala/Thr or Thr/Thr. In most populations, the allelic frequency of Thr at codon 54 is 30% [13].

Among the investigations assessing FABP2 genotype in overweight and obese individuals [13,14], and obese individuals in comparison to normal weight individuals [15], evidence suggests that overweight and obese individuals are more likely to contain the mutant-type allele patterns of FABP2 at rs1799883. Consequently, the mutant-type allele patterns have demonstrated an association with markers of insulin resistance and an unfavorable blood lipid profile [13-15].

Weight loss interventions: Considering the aforementioned association, weight loss interventions have been conducted in relation to baseline genotype of FABP2 rs1799883 [16-20]. In a two-month randomized, clinical trial conducted by de Luis et al. [19], 204 apparently healthy, obese (average BMI 34.3 ± 4.8 kg/m^2) men and women (50 males and 154 females), with an average age of 46.5 ± 15.7 years, were randomly assigned to either a hypocaloric lower fat diet (1500 kcal/d,

Study	Candidate Genes	Design	Methods	Results
Mutch et al. [7]	TMEM132A QPRT CLDN5 PTGDS ESAM FMOD FAM69B IF127	• 10 weeks • 53 participants from NUGENOB study • Males and females • Retrospective genotype matching based on weight loss ○ responder: 8-12 kg wt loss ○ non-responder: <4 kg wt loss	• Randomly assigned to hypocaloric diet (~600 kcal deficit): ○ low fat, high CHO diet: 20-25% kcal fat, 60-65% kcal CHO, 15% kcal protein ○ moderate fat, low CHO diet: 40-45% kcal fat, 40-45% kcal CHO, 15% kcal protein • 3-day weighed food log at 0 and 10 wks • One day weighed food log at 2,5,7 wks • Weekly contact with RD • No exercise component	• Candidate genes significantly increased in non-responders –vs- responders • Responders to weight loss had less expression of candidate genes • No difference between weight loss outcomes and diet intervention
Dopler-Nelson et al. [9]	FABP2 (rs1799883) PPARG (rs1801282) ADRB3 (rs4994C3) ADRB2 (rs1042713 and rs1042714R)	• 12 months • 141 participants from AtoZ weight loss trial • Retrospective genotype matching ○ true or false match to diet group based on genotype	• Randomly assigned to diet group: ○ Atkins (≤ 20 g/d CHO for 2-3 mo, then ≤50 g/d CHO ○ Zone (40% kcal CHO, 30% kcal fat, 30% kcal protein) ○ LEARN (55-60% kcal CHO, <10% kcal sat fat) ○ Ornish (≤10% kcal fat) • Weekly meeting RD x 2 mo, then random follow-up between 2-12 mo • Random 3-day food recalls via NDSR • BW, body composition, WC, HC, BP, fasting insulin and BG, blood lipid profile measured at 0,2,6,12 mo • Exercise was encouraged	• BW reduction, true match versus false match (p=0.005) • True matches to lowest CHO (Atkins) and fat (Ornish) diets had greatest weight loss (p=0.03)
Arkadianos et al. [8]	ACE INS/DEL APOC3 3175C>G CBS 699C>T CETP 279G>A COLIA1 GSpIT GSTMI GSTP1 313A>G, 341C>T GSTT1 IL61595C>G MTRR 66A>G MTHFR 1298A>C, 677C>T MTR 275A>G NOS3 894G>T PPARG Pro12Ala SOD2 -28C>T SOD3 760C>G TNFalpha -308G>A VDR CTaqIT, TBsmIC, TFokIC	• 10 month, blinded, RCT • 50 participants in nutrigenetic group ○ 22 female, 28 male • 43 participants in control group ○ 18 female, 25 male • Prospective genotype matching to diet ○ specific alterations in dietary Rx based on variations in candidate genes • Physicians blinded to treatment groups	• Control group followed low-glycemic index, Mediterranean style diet ○ 38% kcal CHO, 46% kcal fat, 16% kcal protein • Nutrigenetic group followed same diet with alterations pending genotype • Regular clinical visits for all pts • BW measured and fasting blood sample collected at baseline and completion • Home exercise routines provided	• 5.6% reduction in BMI (1.93 kg/m^2) in nutrigenetic group versus 2.2% gain (0.51 kg/m^2) in control group (p<0.023) • 57% of pts in nutrigenetic group with pre-diabetes had reduced BG versus 25% in control group (p<0.046)
CHO: Carbohydrate; RD: Registered Dietitian; RCT: Randomized Controlled Trial; wks: Weeks; mo: Months; pts: Patients; Rx: Prescription; BG: Blood Glucose				

Table 1: Nutrigenetic studies.

27% kcal fat, 52% kcal CHO, 20% kcal protein) or a hypocaloric lower CHO diet (1507 kcal/d, 36% kcal fat, 38% kcal CHO, 26% kcal protein). Aerobic exercise consisting of 60 minutes per day, three days per week was encouraged. Three-day food records were collected at baseline and two-months to determine dietary compliance. Anthropometric measurements and fasting blood samples were collected at baseline and two months. Overall, from baseline to two months all participants experienced significant loss in body weight (BW) and fat mass (FM) ($p<0.05$). Regardless of diet group, a significant reduction in cholesterol, TG, insulin, and leptin was demonstrated in the wild-type allele pattern, with no significant changes in mutant-type allele pattern. However, participants with the mutant-type allele pattern who followed the lower CHO diet experienced a significant reduction in FM in comparison to the wild-type allele pattern ($p<0.05$) [19].

Similarly, Martinez-Lopez et al. [20] conducted a two-month weight loss intervention utilizing a hypocaloric, moderate CHO and fat diet (1000 kcal/d for women, 1200 kcal/d for men, with 30% kcal from fat, 55% kcal CHO, 15% kcal protein) in 109 overweight and obese (BMI >25 kg/m^2) men and women (20 male, 89 female), with mean age of 38.6 ± 11.3 years. Additionally, participants were instructed to consume less than 200 mg dietary cholesterol per day, 25 grams per day of fiber and two grams per day from plant stanols/sterols. Exercise was not included in this intervention. To assess dietary compliance, an RD collected 24-hour dietary recalls at baseline, one month, and two months. Anthropometric measurements and blood samples were collected at baseline, one month, and two months. Significant

reductions in BW, BMI, body fat percentage (BF%), waist circumference (WC), waist-to-hip ratio (WHR), systolic blood pressure, fasting glucose, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and insulin was exhibited in all participants at completion ($p<0.05$). Additionally, a significantly greater reduction in BW, BMI, WC, WHR, and C-reactive protein was demonstrated in individuals with the mutant-type allele patterns ($p<0.05$) [20].

Along with this, de Luis et al. [16,18] conducted two, three-month weight loss investigations testing varying fat content within the dietary interventions. In the first investigation, 111 obese participants, with average BMI of 30.7 ± 7.1 kg/m^2 and an average age of 49.7 ± 10.1 years, consumed a diet consisting of 1459 kcal/d, with 34.4% kcal fat, 45.7% kcal CHO, 19.9% kcal protein. Fat content was further divided into 21.8% kcal from saturated fat, 55.5% from monounsaturated fats (MUFA), and 22.7% from polyunsaturated fats (PUFA) (seven grams per day omega-6 fatty acids and two grams per day omega-3 fatty acids) [16]. Two to three hours of walking per week was encouraged as aerobic exercise. Dietary intake was assessed via three-day food records at baseline and three months, and weekly dietary monitoring by an RD via phone call. Anthropometric measurements and blood samples were collected at baseline and three months. All in all a significant decrease in BW, BMI, fat free mass (FFM) and systolic blood pressure were demonstrated in all participants from baseline to three months, with the mutant-type allele patterns exhibiting greater reductions in BMI, BW, FFM, FM, and WC in comparison to individuals with the wild-type allele pattern ($p<0.05$). Interestingly only individuals with the mutant-type allele patterns demonstrated significant decrease in total cholesterol, LDL, insulin and HOMA after three months ($p<0.05$) [16].

In the second investigation, 122 apparently healthy, obese (average BMI 37.4 ± 6.1 kg/m^2, average age 47.8 ± 11.9 years) males and females were assessed [18]. The dietary protocol was slightly different from the aforementioned protocol such that higher amounts of MUFAs were included as opposed to PUFAs. The diet was composed of 1342 kcal/d, 34.1% kcal fat, 46.6% kcal CHO, 19.2% kcal protein. Fat content was further divided into 21.7% kcal from saturated fat, 67.5% kcal as MUFA and 10.8% kcal PUFA. Three-day food records were collected at baseline and three months to determine dietary compliance. Exercise and measurement protocols were identical to the previously mentioned trial [16]. In this trial all participants demonstrated a significant decrease in BW, BMI, and WC ($p<0.05$). In contrast to the previously mentioned investigation, individuals with the wild-type allele pattern demonstrated significant reduction in FM, along with fasting insulin and leptin levels ($p<0.05$) [18].

Finally, in another three-month weight loss intervention conducted by de Luis et al. [17], 69 apparently healthy, obese participants (average BMI 34.1 ± 5.1 kg/m^2), with an average age of 45.5 ± 16.6 years, consumed a hypocaloric diet consisting of 1520 kcal/d, 25% kcal fat, 52% kcal CHO, 23% kcal protein. Aerobic exercise was encouraged for 60 minutes at least three days per week. Three-day food records were collected at baseline and three-months to determine dietary compliance. Anthropometric measurements, blood sample, and maximal oxygen consumption was measured at baseline and three months. All participants demonstrated a significant reduction in BW, BMI, WC, and increase in oxygen consumption between baseline and three months ($p<0.05$). Individuals with the wild-type allele pattern demonstrated a greater decrease in FM, LDL and leptin levels in comparison to those with the mutant-type allele pattern ($p<0.05$). However, individuals with the mutant-type allele pattern demonstrated more significant reduction in fasting glucose at three months ($p<0.05$) [17].

Overall, health outcomes from weight loss interventions in relation to FABP2 rs1799883 genotype have been variable. Among the two-month weight loss interventions [19,20], de Luis et al. [19] demonstrated greater reductions in biochemical markers related to lipid and CHO metabolism in carriers of the wild-type allele pattern regardless of dietary intervention, yet greater reductions in FM in individuals with the mutant-type allele pattern following the lower CHO diet. In contrast Martinez-Lopez et al. [20] demonstrated favorable outcomes in anthropometrics in individuals carrying the mutant-type allele pattern, but biochemical changes were not significantly different between genotypes. In the three-month weight loss interventions [16-18], varying responses in relation to genotype were demonstrated pending on the type of fat included in the diet, MUFA versus PUFA. Additionally, when specific fat content was not controlled, individuals with the mutant-type allele pattern demonstrated improvements in fasting glucose, whereas those with the wild-type allele pattern experienced greater improvements in LDL cholesterol, FM, and fasting leptin levels while following a lower fat, moderate CHO diet [17]. See Table 2 for details of weight loss interventions.

Use in genetic profiling for weight loss: Considering these findings, one may conclude that differences in FABP2 rs1799883 genotype elicit different responses to weight loss interventions. Therefore, when considering dietary prescription to optimize weight loss, evidence supports a lower CHO, moderate fat, and adequate protein diet to improve markers of body composition in overweight and obese individuals carrying the mutant-type allele patterns [16,19,20]. Furthermore, a moderate CHO, lower fat, and adequate protein diet may be helpful for individuals with the wild-type allele pattern to improve body composition and fasting blood lipid levels [17].

PPARG2 (rs1801282)

Association with obesity: Peroxisome proliferator-activated receptor gamma-2 (PPARG2) is an isoform of the peroxisome proliferator-activated receptor gamma gene and consists of an additional 28 amino acids at its amino terminus [21]. PPARG2 is primarily located in adipocytes and plays an important role in adipocyte differentiation [22-24]. A missense mutation in PPARG2 occurs at codon 12 of exon B in rs1801282 and consists of a transition of alanine (Ala) for proline (Pro) [24]. The wild-type allele pattern for PPARG2 is Pro/Pro, whereas the mutant-type is Pro/Ala or Ala/Ala. In contrast to FABP2 rs1799883, the allelic frequency of Ala varies among populations; for example, the frequency among Caucasians is about 11%, whereas the frequency among Asians is about 9% [25,26].

Findings are mixed in terms of PPARG2 allele patterns and weight status, where some investigations have demonstrated strong associations among the mutant-type allele patterns and more favorable body composition, blood lipid profile, and insulin sensitivity in normal-weight, middle-aged and elderly men and women [21,24], but the majority of investigations have demonstrated the opposite [25-28]. Interestingly, in an investigation comparing overweight/obese individuals to normal weight individuals, those with the mutant-type allele patterns, regardless of weight status, demonstrated higher BW and unfavorable body composition [27]. Additionally, in post-menopausal women, when comparing normal weight to overweight/obese individuals, overweight/obese women with the mutant-type allele patterns demonstrated significantly higher levels of total cholesterol, LDL cholesterol, and TGs [28]. Moreover, findings from a longitudinal, retrospective study suggests the mutant-type allele patterns in PPARG2

Study	Design	Dietary and Exercise Intervention	Methods	Results
FABP2 (rs1799883)				
de Luis et al. [19]	• 2 months • 204 obese, AH adults ○ 50 males and 154 females • Randomized into diet groups	• Low fat diet: 1500 kcal/d, 52% kcal CHO, 27% kcal fat, 20% kcal protein • Low CHO diet: 1507 kcal/d, 38% kcal CHO, 36% kcal fat, 26% kcal protein • Aerobic exercise encouraged (walking), 60 min x 3x/wk	• Measures at 0, 2 mo: REE, WC, HC, BW, BP, BG, fasting insulin, CRP, blood lipid profile, adipocytokines • Dietary data collected at 0 and 8 wks via 3-day food records	• All participants: weight loss and fat mass loss at 2 mo (p<0.05) • Mutant-type: reduced fat mass with lower CHO diet (p<0.05) • Wild-type: reduced cholesterol, TG, insulin, and leptin for both diets (p<0.05)
Martinez-Lopez et al. [20]	• 2 months • 109 overweight and obese, AH adults • 20 male, 89 female	• 1000 kcal/d for women, 1200 kcal/d for men • 55% kcal CHO, 30% kcal fat, 15% kcal protein • Lipid breakdown: <7% kcal sat fat, 10-15% PUFA, 10% PUFA, <200 mg/d dietary cholesterol, 2 g/d from plant stanols/sterols • 25 g/d fiber • No exercise intervention	• Measures at 0, 1, 2 mo: BW, BF%, WC, HC, RMR, BP, BG, insulin, blood lipid profile, CRP • Dietary data collected at 0, 1, 2 mo via 24-hr dietary recall	• All participants: reduction in BW. BMI BF%, WC, WHR, SBP, BG, insulin, and blood lipids at 2 mo (p<0.05) • Mutant-type: greater reductions in BW, BMI, WC, WHR, and CRP (p<0.05)
de Luis et al. [17]	• 3 months • 69 obese, AH adults	• 1520 kcal/d, 52% kcal CHO, 25% kcal fat, 23% kcal protein • Aerobic exercise encouraged, 60 min at least 3x/wk	• Measures at 0, 3 mo: REE, WC, HC, BW, BP, BG, fasting insulin, CRP, blood lipid profile, adipocytokines, oxygen consumption • Dietary data collected at 0, 3 mo via 3-day food records	• All participants: decrease in BMI, BW, WC, and increase in oxygen consumption at 3 mo (p<0.05) • Mutant-type: reduction in BG at 3 mo (p<0.05) • Wild-type: reduction in FM, LDL, and leptin at 3 mo (p<0.05)
de Luis et al. [16]	• 3 months • 111 obese, AH adults	• 1459 kcal/d, 45.7% kcal CHO, 34.4% kcal fat, 19.9% kcal protein • Lipid breakdown: 21.8% sat fat, 55.5% MUFA, 22.7% PUFA (7 g/d n-6 FA, 2 g/d n-3 FA) • Walking only for 2-3 hr/wk	• Measures at 0, 3 mo: BW, FFM, FM, BP, BG, HbA1c, insulin, blood lipids, adipocytokines • Dietary data collected at 0, 3 mo via 3-day food records • Weekly dietary monitoring by RD via phone call	• All participants: reduction in BMI, BW, FFM, WC, SBP (p<0.05) • Mutant-type: ○ reduction in BMI, BW, FFM, FM, WC at 3 mo (p<0.05) ○ reduction in in total cholesterol, LDL, insulin, and HOMA at 3 mo(p<0.05)
de Luis et al. [18]	• 3 months • 122 obese, AH adults	• 1342 kcal/d, 46.6% kcal CHO, 34.1% kcal lipids, 19.2% kcal protein • Lipid breakdown: 21.7% sat fat, 67.5% MUFA, 10.8% PUFA • Walking only for 2-3 hr/wk	• Measures at 0, 3 mo: BW, FFM and FM via BIA, WC, HC, BP, BG, insulin, blood lipids, CRP, adipocytokines • Dietary data collected at 0, 3 mo via 3-day food records	• All participants: reduction in BMI, BW, WC at 3 mo (p<0.05) • Wild-type: reduction in FM, insulin, and leptin at 3 mo (p<0.05)
PPARG (rs1801282)				
Curti et al. [34]	• 9 months • 134 adults with pre-diabetes or metabolic syndrome	• Medication Group: 850 mg metformin 2x/d, lifestyle intervention • Lifestyle Group: ○ 16-session curriculum covering diet, exercise, and behavior modification. ○ Individual meetings weekly x 8 mo, then monthly thereafter. ○ Low-fat, hypocaloric diet ○ 150 min/wk of physical activity. • Dietary Rx for both groups: 500-1000 kcal/d deficit, 55% kcal CHO, <30% kcal fat, 8-10% kcal sat fat, ~ 15% kcal protein, <300 mg/d cholesterol	• Measures at 0, 9 mo: BW, BMI, WC, BP, CRP, BG, insulin, blood lipids • Dietary data collected at 0, 9 mo via 24-hr dietary recall • Physical activity measured at 0, 9 mo via IPAQ	• All participants: reduced BW (p<0.001), WC (p=0.01), BG (p=0.041), insulin (p<0.001), apolipoprotein B (p<0.001), and increased HDL (p<0.001) at 9 mo • Mutant-type: reduced BP at 9 mo (p<0.001)
Franks et al. [31]	• 12 months • 3,234 obese men and women with pre-diabetes • Participants from the U.S. Diabetes Prevention Program • Randomized into a control group, medication group, lifestyle group	• Consistent with Curti and colleagues (see above)	• Measures at 0, 12 mo: BW, WC, FM • Dietary intake was measured at 0,12 mo via a food frequency questionnaire	• Mutant-type, medication group: reduced BW at 12 mo (p=0.01) • Mutant-type, lifestyle group: reduced BW at 12 mo (p=0.04)

Lindi et al. [29]	• 36 months • 490 overweight and obese adults with pre-diabetes ○ 161 men, 329 women • Participants from Finnish Diabetes Prevention Study • Multicenter, RCT • Randomized into control or intervention group	• Individuals met with an RD for dietary counseling 7 times within the first year and every 3 months thereafter until completion of the study • Specific dietary goals included consuming <30% kcal from fat, <10% kcal sat fat, and 15 g fiber/1000 kcal consumed • 30 min/d exercise was encouraged	• Measures at 0, 36 months: BW, BMI, WC, HC, BG, and insulin • Dietary data was collected 4x/yr via 3-day food records	• Mutant-type, control group: at 36 mo, Ala/Ala had greater chance of developing type 2 DM versus wild-type ($p<0.05$) • Mutant-type, Intervention group: ○ Higher risk of developing type 2 DM in Ala/Ala versus wild-type allele ($p>0.05$) ○ Reduced BW at 36 mo in Ala/Ala versus wild-type ($p=0.043$) ○ Greater reduction in BW at 36 mo in Ala/Pro versus wild-type ($p>0.05$)
Nicklas et al. [36]	• 18 months ○ 6 mo intervention ○ 12 mo maintenance • 70 obese, AH, postmenopausal women	• 6 month weight loss intervention: ○ weekly group meetings with RD for dietary instruction, education, counseling ○ goal to reduce total caloric intake 250-350 kcal/d ○ Supervised walking 1 d/wk at 50-60% HRR, unsupervised walking 2 d/wk • 12 month maintenance: met with RD bi-weekly for the first 6 mo, no meetings during the last 6 mo	• Measures at 0, 6 mo: BW, body composition via DXA, maximal oxygen uptake, RMR via indirect calorimetry, BG, insulin	• Mutant-type: reduced BW, BG, and insulin at 6 mo ($p<0.001$)
Garaulet et al. [35]	• 1465 overweight and obese, AH men and women • Length of study individualized pending time to reach goal weight ○ Goal weight determined considering a weight loss of 0.5-1.0 kg/wk	• 600 kcal deficit based on calculated energy needs via the Harris-Benedict Equation (included activity factors) • Resulted in about 1200-1800 kcal diet for women and 1500-2000 kcal diet for men • 50% kcal CHO, 35% kcal fat (< 10% sat fat, 20% MUFA), 15-20% kcal protein • Exercise: 10,000 steps/d and at least 30 minutes of moderate-intensity exercise	• Measures at 0, completion: BW, body composition via BIA, WC, HC, BP, blood lipid profile, BG, and insulin • Dietary data was collected at 0, completion via 24-hr recall	• Mutant-type: greater percentage of weight loss from 0 when consuming lower fat diet ($p=0.286$) • Wild-type: greater percentage of weight loss from 0 when consuming a higher fat diet ($p=0.037$)
ADRB3 (rs4994)				
Rawson et al. [12]	• 34 obese, AH, postmenopausal women • Length of study individualized, based on Metropolitan Life Insurance Tables ○ Average length of study 13.5 ± 2.6 months	• 1200 kcal/d, 55% kcal CHO, <30% kcal fat, <7% kcal sat fat, ~ 15% kcal protein, <200 mg/d cholesterol • No exercise intervention	• Measures at 0, completion: BW, body composition, RMR, TEE, TEF via doubly labeled water technique	• All participants: reduced body mass, BMI, BF%, FFM, and FM ($p<0.05$) at completion • No difference between genotypes
Shiwaku et al. [43]	• 3 months • 76 normal and overweight, AH women • Behavioral weight loss intervention	• Individualized dietary counseling promoting caloric restriction from baseline intake • Group sessions emphasizing implementation of healthy lifestyle habits • 7000 steps/d	• Measures at 0, 3 months: BW, BP, WC, HC, tricep skinfolds, body composition via BIA, blood lipids • Dietary compliance measured via food frequency questionnaires • Exercise compliance measured via physical activity questionnaire	• All participants: exhibited significant reductions in BW, BP, EC, HC, tricep skinfold, LDL, LDL to HDL ratio, and phospholipids upon completion ($p<0.05$), with no difference between genotypes
Tahara et al. [44]	• 3 months • 57 overweight and obese, AH men • Behavioral weight loss intervention	• At least one individualized dietary counseling session with RD promoting caloric restriction from baseline dietary intake • Three group sessions (baseline, mid-point, completion) emphasizing implementation of healthy lifestyle habits • 10,000 steps/d	• Measures weekly: BW and WC • Questionnaires to assess dietary and exercise compliance completed at 3 mo	• All participants: reduced BW, WC ($p<0.05$) at 3 mo • No difference between genotypes

Bea et al. [45]	• 12 months • 148 normal weight and overweight/obese, AH postmenopausal women • Secondary analysis from a block randomized resistance training trial ○ 320 sedentary individuals randomized into exercise or control group	• No dietary intervention • High-intensity resistance training and moderate impact weight-bearing exercise • 75 min x 3 d/wk • 2 x 6-8 repetitions at 70-80% 1RM • 1RM measured and adjusted every 6-8 weeks	• Measures at 0, 12 months: body composition via DXA	• All participants: increase in lean soft tissue (p<0.05) • No significant differences between genotype
Phares et al. [47]	• 6 months • 70 overweight, AH, men (29) and women (41)	• No caloric restriction • 55% kcal CHO, 30% kcal fat, 15% kcal protein • Endurance exercise 3 d/wk ○ progressed in intensity (50-70% Vo2 max) and time (20-40 min) x 10 wks ○ then participants trained for 40 min at 70% Vo2max for remaining 14 weeks • Walking for 45-60 min/d x 1 d/wk during last 14 wks	• Measures at 0, 6 months: Body composition via DXA, Vo2 max, oral glucose tolerance test • Dietary compliance measured with food records collected at 0, 2, 4, 6 mo	• All participants: reduced BF%, % trunk fat, and FM (p<0.05) at 6 mo • Mutant-type: greater reduction in BF% (p=0.027), % trunk fat (p=0.03), FM (p=0.037) at 6 mo
Lee et al. [48]	• 3 months • 80 overweight, AH women	• Individualized, weekly, dietary counseling with RD emphasizing reduction of intake from baseline • 60 min supervised, moderate-intensity, aerobic exercise weekly • 10,000 steps/d	• Measures at 0, 3 months: BW, WC, BF% via brozek equation, tricep and subscapular skinfold thickness, blood lipids • Dietary compliance measured via 2-day food records at 0, 3 months	• All participants: reduced BW, BMI, BF%, WC, and total cholesterol (p<0.01) at 3 mo • Wild-type: ○ reductions in HDL (p<0.05), LDL (p<0.05), TG (p<0.01) ○ greater reductions in BW, BMI (p<0.01)
de Luis et al. [49]	• 3 months • 260 obese, AH, men (55) and women (166) • Randomized into diet group differing in fat content	• MUFA diet: ○ 1342 kcal/d ○ 46.6% kcal CHO, 34.1% kcal fat, 19.2% kcal protein ○ 21.7% sat fat, 67.5% MUFA, 10.8% PUFA • PUFA diet: ○ 1459 kcal/d ○ 45.7% kcal CHO, 34.4% kcal fat, 19.9% kcal protein ○ 21.8% sat fat, 55.5% MUFA, 22.7% PUFA • 60 min/d aerobic activity, 3 d/wk	• Measures at 0, 3 months: BW, BP, body composition via BIA, BG, insulin, blood lipids • Dietary compliance via 3-day food records collected at 0, 3 months	• All participants: reduced BW, BMI, FM, and WC at 3 mo (p<0.05) • Mutant-type, MUFA: ○ greater reduction in WC (p>0.05) versus wild • Wild-type, MUFA: ○ greater reduction in BMI (p<0.05) versus mutant • Mutant-type, PUFA: ○ greater reductions in BW, WC, insulin versus wild (p<0.05) • Wild-type, PUFA: ○ reduced BG, insulin, TC, LDL, TG (p<0.05) ○ greater reductions in BMI, FM, WHR, HOMA versus mutant (p<0.05)
ADRB2 (rs1042713)				
Saliba et al. [61]	• 7 weeks • 109 obese, AH women	• Individual diet Rx with 600 kcal deficit • 3 individual dietary counseling sessions and 2 group sessions • One group session providing information on how to increase physical activity from baseline	• Measures at 0, 7 weeks: BW	• No significant differences among allele patterns and weight loss outcomes
Ruiz et al. [62]	• 3 months • 78 obese, AH women	• Individualized dietary prescription with 600 kcal deficit • Weekly dietary counseling sessions with RD	• Weekly Measures: BW • Measures at 0, 3 months: BW, body composition via DXA, WC, RMR • Dietary compliance measured via 3-day food records at 0, 3 months, and 1-day food records at weeks 2, 5, 7	• No significant differences among allele patterns and weight loss outcomes

Verhoef et al. [63]	• 5 months • 150 overweight and obese, AH men (39) and women (111)	• Very low calorie diet x 2 mo followed by instruction to maintain BW for last 3 months • Diet was provided and consisted of 50 g CHO/d, 7 g fat/d, 52 g protein/d	• Measures at 0, 2, 5 months: BW, WC, HC, and body composition via BOD POD	• All participants: reduced BW, BMI, FM, percent FM, WC, HC at 5 mo ($p<0.001$) • No significant differences among allele patterns and weight loss outcomes
ADRB2 (rs1042714)				
Saliba et al. [61]	See above	See above	See above	• No significant differences among allele patterns and weight loss outcomes
Bea et al. [45]	See above	See above	See above	• Mutant-type: increase in lean soft tissue in exercise group versus control ($p<0.05$) • Wild-type: no change in lean soft tissue in exercise group
Ruiz et al. [62]	See above	See above	See above	• Mutant-type: greater reduction in BW ($p=0.002$) and LM at 3 mo ($p=0.001$)
Rauhio et al. [59]	• 12-months • 62 obese, AH, postmenopausal women	• 700 kcal/d x 3 mo, with weekly dietary counseling with RD • 9 mo weight maintenance period • Daily physical activity log recording activity type, duration, and perceived intensity	• Measures at 0, 3, 12 mo: BW, WC, body composition via DXA	• All participants: lost weight with favorable change in body composition • Wild-type: reduced gynoid fat percentage at 3 mo ($p<0.03$)

AH: Apparently Healthy; min: Minutes; x/wk: Times per Week; mo: Months; REE: Resting Energy Expenditure; WC: Waist Circumference; HC: Hip Circumference; BW: Body Weight; BP: Blood Pressure; BG: Blood Glucose, Fasting Insulin; CRP: c-Reactive Protein; wks: Weeks; BF%: Body Fat Percentage; SBP: Systolic Blood Pressure; WHR: Waist to Hip Ratio; hr/wk: Hours per Week; FM: Fat Mass; FFM: Fat Free Mass; BIA: Bioelectrical Impedance; DM: Diabetes Mellitus; IPAQ: International Physical Activity Questionnaire; HRR: Heart Rate Reserve; DXA: dual X-ray Absorptiometry; RMR: Resting Metabolic Rate; TEE: Total Energy Expenditure; TEF: Thermic Effect of Food; 1RM: One Repetition Maximum; LM: Lean Mass

Table 2: Weight loss interventions.

rs1801282 may serve as a predictor for weight gain, regardless of baseline weight status, throughout the life cycle. These findings support increased susceptibility to overweight/obese weight status, adverse body composition, and abnormal blood lipid profiles in individuals carrying a mutant-type allele pattern of PPARG2 rs1801282; thus further research assessing PPARG2 genotype in relation to success in a weight loss intervention is warranted.

Weight loss interventions: In lieu of the aforementioned findings, few investigations have assessed the association between baseline PPARG2 rs1801282 genotype and response to weight loss interventions. In an investigation conducted by Lindi et al. [29], 490 overweight/obese men and women (average BMI 31.1 ± 4.6 kg/m^2, aged 40-68 years old) with pre-diabetes were assessed for baseline PPARG2 rs1801282 genotype in relation to health outcomes after participating in the Finnish Diabetes Prevention Study [30]. Briefly, participants were randomized into a control group or lifestyle intervention group. In the intervention group, regarding the dietary component, individuals were instructed to consume less than 30% calories from fat, less than 10% calories from saturated fat and 15 grams of fiber per 1000 kcals, with no specific instruction regarding total caloric intake, and macronutrient range for CHO and protein. Participants met with an RD for dietary education/counseling seven times within the first year and every three months over the last two years. Additionally, 30 minutes of exercise per day was encouraged [30]. Dietary data from three-day food records, anthropometric measurements, and blood sample for biochemical data was collected at baseline and at three years.

At three years, within the control group, participants homozygous for Ala allele (a mutant-type allele pattern) had significantly greater chance of developing type 2 diabetes, a 2.36 fold odds ratio, in comparison to individuals with the wild-type allele pattern [29]. In the intervention group, individuals with the Ala allele did not demonstrate a significant association with increased risk of type 2 diabetes; however the risk of developing type 2 diabetes was still higher in individuals homozygous for Ala in comparison to those with the wild-type allele pattern. Moreover, within the intervention group, individuals homozygous for the Ala allele experienced a significant reduction in body weight in comparison to those with the wild-type allele pattern ($p=0.043$). While not statistically significant, individuals with the other mutant-type allele pattern, heterozygotes for Ala, also exhibited greater reduction in body weight in comparison to individuals with the wild-type allele pattern [29].

Along with this investigation Franks et al. [31] demonstrated similar findings in the Diabetes Prevention Program conducted in the United States. The U.S Diabetes Prevention Program was a multi-centered, randomized controlled trial [32]. The present investigation reports on data collected in one year of the program in 3,234 obese (average BMI 34.1 kg/m^2, average age of 51 years) men and women with pre-diabetes. Briefly, participants were randomized to a control group, a medication group, and a lifestyle intervention. The medication group received 850 mg twice daily of metformin along with annual individual meetings emphasizing consumption of healthy diet and participation in a regular exercise program. Details of this intervention group were described earlier [32]. The lifestyle intervention included a 16-session curriculum covering diet, exercise, and behavior modification. The curriculum included individual meetings with study personnel for the first 24 weeks, with monthly sessions thereafter for the remainder of the study. Participation in 150 min of physical activity per week was prescribed. Further, in both groups dietary prescription was based on the National Cholesterol Education Program step 1 diet (500-1000 kcal/d reduction, 55% kcal CHO, <30% kcal fat with 8-10% kcal from saturated fat, ~15% kcal protein, and <300 mg/d cholesterol) [33]. Consistent with previously mentioned findings, individuals with mutant-type allele pattern demonstrated significantly greater reduction in body weight in the drug group ($p=0.01$) and lifestyle intervention ($p=0.04$) in comparison to individuals with the wild-type allele pattern [31].

Similarly, Curti et al. [34] assessed baseline genotype of PPARG2 rs1801282 along with FTO rs9939609 and PPARG ApoA1 -75G/A in a 9-month weight loss intervention in 18-80 year old, apparently healthy, overweight/obese (BMI 30.4 ± 0.48 kg/m^2) males and females. Dietary and exercise intervention was consisted with the lifestyle intervention implemented by Franks et al. [31]. At baseline and nine months, BW, BMI, blood pressure, WC, and blood samples were collected. Additionally, 24-hour food recalls were collected to determine dietary compliance, and physical activity was assessed with the International Physical Activity Questionnaire. Regarding PPARG2 rs1801282 genotype, outcomes demonstrate a significant reduction in blood pressure favoring the mutant-type allele patterns ($p<0.001$). All participants experienced a significant reduction in BW ($p<0.001$), WC ($p=0.01$), fasting blood glucose ($p=0.041$), fasting insulin ($p<0.001$), apolipoprotein B ($p<0.001$), and increased HDL ($p<0.001$) [34].

In addition, Garaulet et al. [35] included 1465 apparently healthy, overweight/obese (BMI 25-40 kg/m^2), males and females, aged 20-65 years old in their weight loss intervention. Length of the study was individualized depending on how long it took each participant to reach goal weight. Individual goal weight was determined considering a weight loss of 0.5-1 kg per week. The Harris-Benedict Equation was used to calculate energy needs, and then 600 kcals were deducted from the predicted energy needs to promote weight loss. In addition, participants were instructed to consume 50% of their kcal from CHO, 35% kcal fat (<10% kcal saturated fat, 20% MUFA), and 15-20% kcal protein. Overall this resulted in a 1200-1800 kcal diet for women and 1500-2000 kcal diet for men. Participants met with an RD weekly for group education sessions. The exercise intervention included 10,000 steps per day along with daily physical activity of moderate-intensity for 30 minutes or more. Dietary data was collected via 24-hour diet recalls; BW, body composition via bioelectrical impedance, WC, HC, and blood pressure were measured at start and finish of each individual's study time. Overall, a significant interaction between heterozygous carriers of the mutant-type allele pattern was demonstrated between fat intake and weight loss ($p<0.001$). When consuming a lower fat diet, individuals with the mutant-type allele patterns demonstrated greater percentage of weight loss from baseline in comparison to those with the wild-type allele pattern ($p=0.286$); additionally, when consuming a higher fat diet, those with the mutant-type pattern demonstrated less weight loss from baseline in comparison to individuals with the wild-type pattern ($p=0.037$) [35].

Finally, Nicklas et al. [36] conducted an 18 month trial, including six months of weight loss intervention followed by 12 months of follow up in 70 postmenopausal (average age 61 years old), apparently healthy, obese (average BMI ~31 kg/m^2) women. For the six-month weight loss intervention, participants were instructed to reduce caloric intake by 250-350 kcal/d, with no specific instruction regarding macronutrient distribution. In addition, participants attended weekly group meetings with an RD for dietary instruction, education, and counseling. Along with the dietary component, the exercise component included walking on a treadmill at 50-60% measured heart rate reserve one day per week in the investigator's laboratory, and walking two days per week outside of the lab. Measures at baseline and six months include the following: BW, body composition via DXA scan, maximal oxygen uptake, resting metabolic rate via indirect calorimetry, and blood sample. Of all the measures collected, significant reductions from baseline to six months were only exhibited in BW, fasting glucose, and insulin favoring individuals with the wild-type allele pattern ($p<0.001$). Individuals with the mutant-type allele pattern also demonstrated significant reduction in fat oxidation [36].

As for the 12-month follow up portion of the study, for the first six months of this time participants attended group sessions with an RD bi-weekly to discuss healthy lifestyle change. Participants were encouraged to continue progress for the last six months and return for BW measurements after six months [36]. Upon completion of the12 month maintenance period, incidence of weight regain was significantly higher in women with the mutant-type allele pattern ($p<0.01$) [36].

Among all weight loss interventions conducted, the majority of evidence supports greater reductions in BW, improvements in body composition, and improvements in fasting blood glucose in individuals with the mutant-type allele pattern [29,31,34,35]. In contrast, Nicklas et al. [36] demonstrated significant reduction in BW, fasting blood glucose, and insulin levels favoring individuals with the mutant-type allele pattern. Differences in health outcomes regarding genotype may be attributed to length of intervention and/or degree of caloric restriction, suggesting individuals with the wild-type allele pattern may improve health outcomes in a shorter period of time with less caloric restriction, whereas those with the mutant-type allele pattern may require longer interventions with a more intense dietary protocol.

Use in genetic profiling for weight loss: The role of PPARG2 in adipocyte differentiation and fat metabolism is supported by significant associations demonstrated between baseline genotype and degree of obesity, body composition, and blood lipid profile in overweight/obese individuals [25-28]. Regarding use of PPARG2 rs1801282 as a predictor for dietary intervention to promote weight loss and improve markers of health, evidence supports implementation of a hypocaloric, lower-fat diet, moderate CHO and protein diet specifically in individuals carrying the mutant-type allele pattern. Therefore, preliminary evidence supports the use of baseline PPARG2 rs1801282 genotype to optimize dietary prescription within a weight loss program [29,31,34,35].

ADRB3 (rs4994)

Association with obesity: Beta-3-adrenergic receptor (ADRB3) is located primarily in adipocytes and plays a role in lipid metabolism and thermogenesis [37,38]. A missense mutation in rs4994 at codon 64 results in the replacement of tryptophan for arginine [38]. The wild-type allele pattern of ADRB3 is homozygous for tryptophan, Trp/Trp, whereas the mutant-type allele patterns include arginine and can be homozygous, Arg/Arg, or heterozygous, Trp/Arg.

In a quantitative meta-analysis conducted in over 9000 participants across diverse populations, regardless of weight classification, heterozygous carriers of the mutant-type allele pattern exhibited a significantly greater BMI in comparison to individuals with the wild-type allele pattern [38]. Along with this, more recent investigations comparing normal weight to overweight/obese males and females have also demonstrated increased BF%, visceral adipose tissue (VAT), WC, WHR, decreased HDL levels, and impaired glucose tolerance in carriers of the mutant-type allele patterns [39-41]. Furthermore, in premenopausal obese and normal weight women, individuals with the mutant-type allele pattern exhibited significantly higher fasting BG, total cholesterol, TG, and lower HDL in comparison to obese individuals with the wild-type allele pattern [42]. Interestingly, no significant differences for body composition, fat distribution, blood pressure, fasting BG, insulin, and blood lipid levels were demonstrated between genotype in normal weight women [42]. Considering this evidence, along with ADRB3's role in lipid metabolism, research is warranted assessing health outcomes from a weight loss intervention in relation to ADRB3 rs4994 genotype.

Weight loss interventions: Multiple investigations have assessed baseline ADRB3 rs4994 genotype in relation to health outcomes after participation in a weight loss intervention and have found mixed results. In an investigation conducted by Rawson et al. [12], 34 obese (BMI >30 kg/m^2), postmenopausal (average age 57 years), Caucasian women were prescribed a 1200 kcal diet based on the step two diet plan from the National Cholesterol Education Program (500-1000 kcal/d reduction, 55% kcal CHO, <30% kcal fat with <7% kcal from saturated fat, ~15% kcal protein, and <200 mg/d cholesterol) [33]. An exercise component was not included in this intervention. Length of study was dependent on how long it took each participant to reach her goal weight, which was based on the Metropolitan Life Insurance Tables. Average length of study for participants was approximately 13.5 months. Measures from baseline to completion of the study included BW and body composition via doubly labeled water technique. Interestingly, all participants experienced a significant reduction in body mass, BMI, BF%, FFM, and FM from baseline to completion ($p<0.05$), with no genotype x time interactions observed [12].

Along with Rawson et al. findings, Shiwaku et al. [43] also did not find significant differences in health outcomes between ADRB3 rs4994 genotype after participation in a weight loss intervention. Seventy-six apparently healthy, normal and overweight (BMI >21 kg/m^2) Japanese women aged 35-69 years old participated in a three-month weight loss program that included individualized dietary counseling promoting caloric restriction from baseline dietary intake, with no specific prescription regarding macronutrient intake. The exercise component of the program consisted of 7000 steps per day measured with a pedometer. Additionally, participants attended supportive group therapy sessions with study personnel emphasizing implementation of healthy lifestyle habits [43]. Body composition measurements, BW, and a blood sample were collected at baseline and three months. Overall, all participants exhibited significant reductions in WC, HC, triceps skinfold measurement, blood pressure, BW, HDL LDL to HDL ratio, and phospholipids from baseline to completion of the study ($p<0.05$), with no significant differences in outcomes exhibited between ADRB3 rs4994 genotype [43].

Similarly, Tahara et al. [44] conducted a three-month behavioral weight loss intervention in 57 apparently healthy, normal and overweight/obese Japanese men (BMI >23 kg/m^2), with an average age of 48 years old. The dietary intervention consisted of individual meeting(s) with an RD at least once during the study for dietary counseling to promote consumption of a healthier, lower calorie diet in comparison to baseline diet, with no specific prescription regarding macronutrient intake. Additionally, the exercise intervention included 10,000 steps per day measured with a pedometer. Participants also attended three group meetings (baseline, mid-point, and completion of the study) emphasizing healthy lifestyle habits. In order to determine compliance with the diet and exercise interventions, a battery of questionnaires was provided at completion of the study. Additionally, BW and WC were measured once per week throughout the duration of the study. While all participants experienced significant reductions in anthropometric measures from baseline to three-months ($p<0.05$), no significant differences were identified between ADRB3 rs4994 genotype [44].

Furthermore, Bea et al. [45] retrospectively assessed baseline genotype of three common mutations of beta-adrenergic receptor (ADRB2, ADRA2B, ADRB3) in response to health outcomes from a block-randomized controlled lifestyle intervention [46]. This intervention is different from previously mentioned trials [12,43,44] such that there was no dietary component within the weight loss intervention, solely an exercise component. This secondary analysis included 148 apparently healthy, normal and overweight/obese (BMI >21 kg/m^2) postmenopausal women, with an average age of 56 years. The lifestyle intervention was 12-months in length, where participants were randomized at baseline to an exercise group or control group. Dietary intervention was not included in this investigation. The exercise intervention consisted of high-intensity resistance training and moderate impact weight-bearing exercise for 75 minutes, three days per week. Individuals completed two sets of six to eight repetitions at 70-80% one repetition maximum (1 RM). Participant's 1 RM was adjusted every six to eight weeks as strength improved. Body composition was measured via DXA at baseline and 12 months. Regarding ADRB3 rs4994 polymorphism, as reported in previous studies with dietary and/or lifestyle interventions, no significant differences were exhibited between ADRB3 rs4994 genotype and changes in body composition from baseline to 12 months. Additionally, all ADRB3 rs4994 genotypes lost significant and equivalent BF% ($p<0.05$) [45].

In contrast to the previously mentioned studies demonstrating no significant differences between ADRB3 rs4994 genotype after participating in a weight loss intervention [12,43-45], some investigations have found significant differences between genotype [47-49]. Phares et al. [47] conducted a six-month weight loss intervention within 70 apparently healthy, overweight (average BMI 28 kg/m^2), Caucasian men and women (29 men, 41 women), aged 50-75 years old. The dietary intervention was not hypocaloric, but included a macronutrient distribution range as recommended by the American Heart Association (55% kcal CHO, 30% kcal fat, 15% kcal protein). The exercise intervention consisted of endurance exercise three days per week and progressed in intensity and duration for the first ten weeks of the trial, i.e. 50-70% individual VO2max and 20-40 minutes. For the last 14 weeks, participants trained at 70% VO2max for 40 minutes and also included 45-60 minutes of walking on one day during the weekend. Dietary compliance was measured from three-day food records collected at baseline, two, four and six months. Measures at baseline included blood sample for genotyping, maximal oxygen consumption via stress test, oral glucose tolerance test, and body composition via DXA scan. At six months, body composition was measured once more. While all participants exhibited a significant reduction in BF%, FM, and percent trunk mass from baseline to six months, individuals with the mutant-type allele pattern demonstrated greater reduction in BF% ($p=0.027$), FM ($p=0.037$), and percent trunk fat ($p=0.03$) in comparison to individuals with the wild-type allele pattern [47].

In a three-month weight loss intervention conducted by Lee et al. [48], 80 apparently healthy, overweight (BMI 25-30 kg/m^2), Japanese women, aged 40-69 years old, attended weekly dietary counseling sessions with an RD regarding reduction of baseline energy intake, with no specific prescription for macronutrients. In addition, participants completed 60 minutes of supervised, moderate-intensity, aerobic exercise weekly along with 10,000 steps per day as measured with a pedometer. Dietary compliance was measured with two-day food records collected at baseline and three months. Additionally, BW, tricep and subscapular skinfold thickness, WC, BF% as determined by the Brozek equation and a blood sample was measured/taken at baseline and three months. Genotyping was determined from peripheral leukocytes. Overall, while all participants experienced a significant reduction in BW, BMI, BF%, WC, and total cholesterol from baseline to three months ($p<0.01$), participants with the wild-type allele pattern also demonstrated significant reductions in HDL ($p<0.05$), LDL ($p<0.05$), and TG ($p<0.01$). Moreover, participants with the wild-

type allele pattern demonstrated greater reductions in BW and BMI ($p<0.01$) [48].

Similarly, a more recent three-month investigation was conducted in 260 apparently healthy, obese (average BMI 37 kg/m^2) men and women (55 men, 166 women), with an average age of approximately 45 years old [49]. Participants were randomized into groups consisting of similar total kcal and macronutrient prescription (1400 kcal/d, 45% kcal CHO, 35% kcal fat, 20% kcal protein) with differences in MUFA and PUFA content between groups. The MUFA group included a dietary prescription of 67.5% fat calories as MUFA and 10.8% fat calories as PUFA, while the PUFA group included 55.5% fat calories from MUFA and 22.7% fat calories from PUFA. The exercise intervention consisted of 60 minutes per day of aerobic activity, three days per week. At baseline and three months, the following measures were collected: three-day food records, BW, blood pressure, body composition via bioelectrical impedance, and a blood sample. As demonstrated in previous investigations, all participants experienced significant reductions in BMI, BW, FM, and WC from baseline to completion ($p<0.05$), regardless of genotype or diet group. Individuals with the wild-type allele pattern following the PUFA diet also demonstrated a significant reduction in BG, insulin, HOMA, TC, LDL, and TG from baseline ($p<0.05$). When comparing genotypes within the diet groups, reductions in WC were significantly greater in mutant-type following the MUFA diet ($p<0.05$), whereas reductions in BMI were greater in wild-type allele pattern ($p<0.05$). In the PUFA diet, participants with the mutant-type allele pattern exhibited greater reductions in BW, WC, and fasting insulin ($p<0.05$), whereas participants with the wild-type allele pattern exhibited greater reductions in BMI, FM, WHR, and calculated HOMA ($p<0.05$) [49].

Conclusively, evidence is mixed regarding baseline ADRB3 rs4994 genotype and response to weight loss interventions. The investigations that did not demonstrate significant differences between genotype either did not include a specific dietary intervention with minimal exercise intervention (i.e. only counseling to reduce total energy intake, and increase daily walking) [43,44], included a specific dietary intervention but with no exercise intervention [12], or did not include a dietary prescription but included a specific exercise intervention [45]. These findings suggest that both a specific dietary prescription and exercise intervention is needed to elicit changes between genotype. Coordinately, the investigations that demonstrated a significant difference between genotype included specific exercise interventions along with detailed dietary interventions [47,49].

Use in Genetic Profiling for Weight Loss: Mutation at ADRB3 rs4994 has demonstrated a significant role in lipid metabolism and association with obesity [37-42]. Among weight loss interventions, current evidence suggests a specific dietary and exercise component is necessary within the investigation to promote weight loss. Regarding the dietary component, evidence suggests a hypocaloric, moderate CHO, higher fat, adequate protein diet to promote improvements in body composition in individuals with the mutant-type allele pattern. Further, increase PUFA content within the diet may improve body composition and biochemical markers related to glucose and lipid metabolism in individuals with the wild-type allele pattern. Regarding the exercise component, it appears as though participation in 60 minutes of moderate to high intensity aerobic activity three days per week for at least three months is necessary.

ADRB2 (rs1042713 and rs1042714)

Association with Obesity: Beta-2-adrenergic receptor (ADRB2) is a G-protein coupled receptor that is widely distributed across the body in adipocytes [50]. The influence of catecholamines on the adrenergic receptors, specifically ADRB2, modulates lipolysis and lipogenesis [51]. Two of the most common genetic mutations associated with ADRB2 occur at codon 16 and 27 [51]. At codon 16 (rs1042713), arginine (Arg) replaces glycine (Gly). The allele pattern homozygous for glycine (Gly/Gly) is considered the wild-type allele pattern, whereas the allele patterns including arginine (Arg/Gly, Arg/Arg) are considered the mutant-type. The frequency of the mutation varies depending on the population. For example, allelic frequency of arginine in Europeans is about 51-64% whereas the frequency in East Asians is 71-85%. Additionally the frequency of mutation is most common in women [51]. At codon 27 (rs1042714), glutamic acid (Glu) replaces glutamine (Gln) [51]. Thus homozygous carriers of glutamine (Gln/Gln) contain the wild-type pattern, and carriers of glutamic acid (Glu/Gln, Glu/Glu) are considered mutant-type. At the global level, the frequency of a mutation at codon 27 is about 30% [51].

In spite of ADRB2's role in lipid metabolism and the high frequency of mutation that occurs at codon 16 and 27, there is mixed evidence regarding a relationship with overweight/obese status. Two meta-analyses assessing men and women of varying populations, ages, and weight classifications did not demonstrate any significant associations between mutations of ADRB2 at codon 16 or 27 and increased risk of obesity or adverse health markers associated with obesity [51,52].

In contrast, regarding the mutation at codon 16 (rs1042713), two investigations, conducted in men and women demonstrated a significant association between the wild-type allele pattern and prevalence of obesity [53,54]. Additionally, a significantly higher BMI, WC, HC, WHR, total cholesterol, LDL, TG, leptin and insulin levels were demonstrated in individuals with the wild-type allele pattern [54]. Along with these findings, two longitudinal studies, one over a six year time period and one over a 23 year time period, conducted in men and women, demonstrated a significant association between obesity in men carrying the wild-type allele pattern, and obesity in women carrying the mutant-type allele pattern [55,56]. In a five year longitudinal study conducted in individuals who were normal weight at baseline, significant increases in BMI, WHR, FM, and BP were exhibited after five years in men and women carrying the glycine allele, which is part of the wild-type and heterozygous mutant-type allele patterns [57].

Furthermore, some investigations have also demonstrated an association with obesity and the mutation at codon 27 (rs1042714). In two recent meta-analyses, the presence of the mutant-type allele pattern demonstrated a significant association with obesity risk, with increased risk in Asians, Pacific Islanders, and American Indians [51,52]. In investigations comparing normal weight to overweight/obese individuals, regardless of weight, individuals homozygous for the mutant-type allele pattern demonstrated significantly ($p<0.05$) higher BMI [50,53,58], WC and HC [50], TG [50,53,58], fasting leptin and insulin [50], and incidence of type 2 diabetes [53]. Moreover, a higher risk of obesity was demonstrated in individuals homozygous for the mutant-type allele pattern [53,58]. In the previously mentioned five year longitudinal study, significant increases in BMI, WHR, FM, and BP were exhibited after five years in men and women carrying the mutant-type allele patterns [57].

Overall, this evidence suggests a possible relationship between mutations at codon 16 and 27 of ADRB2 and the prevalence of obesity. Considering the known role of ADRB2 in regards to thermogenesis and lipid metabolism, further research regarding ADRB2 genotype at codon 16 and 27 in relation to success in a weight loss intervention is

warranted.

Weight loss interventions: Few investigations have assessed the relationship between genotypes of the common mutations in ADRB2 and health outcomes from a weight loss intervention. Regarding the mutation at codon 27, Bea et al. [45] demonstrated significant increases in lean soft tissue in individuals within the exercise group carrying the mutant-type allele patterns in comparison to mutant-type carriers in the control group ($p<0.05$). The wild-type carriers in the exercise group did not demonstrate significant changes in lean soft tissue. As previously mentioned, this investigation did not include a dietary component within the weight loss intervention.

The remaining weight loss trials regarding ADRB2 genotype at codon 16 and 27 consist primarily of dietary interventions, with some investigations only providing guidance/encouragement for participation in regular physical activity. In a 12-month intervention exclusively assessing health outcomes in relation to mutations at codon 27, 62 apparently healthy, obese (BMI >30 kg/m^2), postmenopausal (average age ~39 years old) women were prescribed a very low calorie diet, with no specific instruction regarding macronutrient intake, for three months followed by a nine month weight maintenance period [59]. During the first three months, the very low calorie diet consisted of ~700 kcal/d [60] and participants attended weekly group sessions with an RD [59]. As for the exercise component, participants were instructed to keep a daily physical activity log including activity type, duration, and perceived intensity. At baseline, three months, and 12 months, BW, WC, and body composition via DXA were measured. As a whole, all participants lost weight and experienced favorable changes in body composition. A significant reduction in gynoid body fat percentage favoring the wild-type allele pattern was demonstrated ($p<0.03$) [59].

Additionally, Saliba et al. [61] conducted a seven week dietary intervention assessing outcomes related to baseline genotype of mutations at codon 27 and codon 16. In this trial, 109 apparently healthy, obese (average BMI 30-34.9 kg/m^2), premenopausal (average age 30-39 years old) women were prescribed individualized diets consisting of a 600 kcal deficit based on individualized estimated energy requirements, with no specific prescription regarding macronutrient intake. The dietary intervention consisted of three individual counseling sessions and two group sessions. As for the exercise component, participants attended one group session that provided information regarding increasing physical activity from baseline. BW was measured at baseline and seven weeks. Overall, no significant differences were exhibited between health outcomes and polymorphisms of ADRB2 at codon 16 or 27 [61].

Furthermore, a three month dietary intervention in 78 apparently healthy, obese (34 ± 2.8 kg/m^2), premenopausal (average age 36.7 ± 7 years old) women, provided individualized dietary prescriptions based on a 600 kcal deficit derived from the individual's estimated energy requirements, including an activity factor of 1.3 (low physical activity) [62]. Participants also attended weekly dietary counseling sessions with an RD. Unfortunately no exercise component was included in this study. The following measures were collected at baseline and completion of the study: three-day food records, BW, body composition via DXA, WC, and resting metabolic rate. By the end of the intervention there were no significant changes in outcomes demonstrated among allele patterns at codon 16. At codon 27, individuals with the mutant-type allele patterns demonstrated significantly greater reductions in BW ($p=0.002$) and lean mass ($p=0.001$) in comparison to wild-type allele pattern [62].

In a five month intervention exclusively assessing the mutation at codon 16, 150 apparently healthy, overweight and obese (BMI 27-38 kg/m^2) men and women (39 males, 111 females), aged 20-50 years old were provided a very low calorie diet for two months, followed by instruction to maintain the newly achieved body weight for the last three months [63]. The diet consisted of a formula containing 50 g CHO/d, 7 g fat/d, 52 g protein/d (~500 kcal/d). No exercise component was included in this study. At baseline, two months, and five months, BW and body composition via the BOD POD were measured. While all participants experienced significant reductions in BW, BMI, FM, percent FM, WC, and hip circumference ($p<0.001$) from baseline to five months, no significant differences were found between genotypes [63].

Overall, of the three investigations that assessed polymorphisms at codon 16, none of the investigations demonstrated significant differences in health outcomes from baseline to completion of the dietary intervention [61-63]. However, considering the association with obesity demonstrated in individuals with the wild genotype at codon 16 [53-57], and the role of ADRB2 in lipid metabolism and influence on energy expenditure, more weight loss interventions in relation to genotype at codon 16 are warranted. Regarding the five trials that assessed ADRB2 polymorphisms at codon 27, only one investigation demonstrated a greater reduction in BW with the mutant-type allele pattern [62]. Further, inconsistent findings regarding changes in lean mass with regards to the mutant-type allele pattern exist, with one trial demonstrating a reduction in lean mass [62] and another exhibiting an increase [45]. These findings may be attributed to variances in methodologies, such that the latter trial consisted only of an exercise intervention, while the former solely implemented dietary intervention. Interestingly, in an investigation including diet and exercise, gynoid body fat percentage was reduced in individuals with the wild-type allele pattern [59]. Summarily, evidence from the aforementioned investigations suggests implementation of a hypocaloric diet, along with exercise prescription, to promote improved measures of body composition.

Use in genetic profiling for weight loss: As mentioned previously, on account of the high frequency of mutation at codons 16 and 27, role in lipid metabolism, and subsequent influence on energy expenditure, baseline allelic patterns in these sequences of ADRB2 may serve importance in relation to weight status [55]. The wild-type allele pattern at codon 16 has been associated with overweight/obesity status and related adverse health effects [53-57]. Equitably, there is evidence to suggest implementation of a hypocaloric diet to promote improved measures of body composition in individuals with the wild-type allele pattern at codon 16 [62]. In contrast, the mutant-type allele patterns at codon 27 have more frequently been associated with overweight/obese weight status [50-53,57,58]. Current evidence suggests implementation of a hypocaloric diet, along with exercise prescription, to promote improved measures of body composition in individuals with the mutant-type allele pattern [45,59,62].

Summary: Genetic Profiling to Optimize Weight Loss Interventions

Determining baseline variation in candidate genes provides insight regarding clinical intervention, diet, and exercise [8]. Among the few investigations that have used genetic profiling in correspondence with weight loss interventions, the candidate genes assessed have been relatively inconsistent [7-9]. However, the genetic profile used by Dopler-Nelson et al. (FABP2, rs1799883; PPARG2, rs1801282; ADRB3, rs4994C3; ADRB2, rs1042713 and rs1042714) was the most practical

and demonstrated clear, significant effects [9]. Furthermore, research supports a strong association between each candidate gene in this profile and obesity/obesity-related adverse health outcomes [13-15,25-28,38-42,50-53,55-58]. Collectively, evidence suggests implementation of a hypocaloric diet with variations in fat and CHO content pending allelic pattern of the gene, and inclusion of an exercise component [16,17,19,20,29,31,34,35,45,47-49,59,62]. Thus, more weight loss interventions genotyping for FABP2 (rs1799883), PPARG2 (rs1801282), ADRB3 (rs4994C3), and ADRB2 (rs1042713 and rs1042714) together to dictate dietary intervention, while including an exercise component, may be useful in improving health outcomes from participation in a weight loss intervention.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

RBK conceived the idea of the review. AC wrote the review. RK helped draft the manuscript.

Author's Information

This review is part of the literature review for AC's doctoral dissertation project. RK is AC's mentor.

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