Using personal genetic information for improved weight loss: A sequential intervention study

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ABSTRACT

Background. The genetic contribution to obesity is widely accepted and estimated to be in the range of 60-80 %. The 12th update of the Human Obesity Gene Map lists 253 quantity trait loci involved in body weight regulation, including rare, high penetrance monogenic causes for severe obesity. Most of these loci have diagnostic value only and have no influence on treatment or prevention of obesity. Only a fraction of these loci are known to have an influence on the body's response to certain weight loss strategies, but these bear the potential for clinical application of genetic information to the affected individuals benefit in preventing or treating obesity. We hypothesize, that evaluating the genetic status of individuals to determine responses to weight loss strategies may enable the creation of a more effective weight loss strategy for individuals.

Methods. Initially, scientific literature was scanned for evidence of common genetic variations that influence the body's response to the weight management factors: fat content of diet, carbohydrate content of diet, exercise as weight loss strategy and calorie reduction as weight loss strategy. 303 individuals ranging from normal body weight (BMI between 19 and 24.99) to severe obesity (BMI above 40) were genotyped for 7 single nucleotide polymorphisms. Participants adhered to a 3-week standard diet, followed by a 3-week "genetic diet" (a genetically personalized weight management strategy). The weight loss effectiveness of both strategies was recorded and compared.

Results. Participants reduced their body weight following the standard diet by an average of 1.5 kg (-1.486 ± 1.384 s.d.) over a period of 3 weeks. The same participants reduced their body weight following the genetic diet by an average of 3.6 kg (−3.647 ± 1.926 s.d.) over the same time period, which corresponds to a 2.5-fold greater weight loss and was statistically highly significant (SE=0.136, P<0.001). People of different initial body weights responded differently well to the genetic diet, whereby individuals with a normal BMI (19 to 24.99) appeared to respond to the genetic diet with a greater efficiency.

Discussion. Using genetic information for personalized weight loss strategies appears to award significant benefit in obesity prevention or treatment.

Subjects Genetics, Obesity

Keywords: Genetics, Polymorphism, Obesity, Intervention

INTRODUCTION

Obesity has a strong genetic component. Early estimates suggested that 40–70% of the variability in obesity-related traits is heritable (Comuzzie and Allison, 1998). Indeed, the Human Obesity Gene Map identified hundreds of loci implicated in obesity; the 2005 update tallied 253 loci (Rankinen et al., 2006) and more recent genome-wide analyses have expanded this to over 500 loci (Yengo et al., 2018). However, testing for all these loci would mostly serve diagnostic purposes – for example, identifying rare monogenic forms of obesity – without necessarily guiding effective treatment or prevention for the individual. In practical terms, common obesity arises from complex interactions among multiple genes and lifestyle factors (Comuzzie and Allison, 1998). While excessive caloric intake and insufficient exercise are well-known risk factors, not everyone with a “high-risk” lifestyle develops obesity (Shook et al., 2014). This observation suggests that genetic differences modulate individual responses to lifestyle. In other words, two people may follow the same diet or exercise regimen yet experience dramatically different weight outcomes, in part due to their genetic makeup (Adamo et al., 2005; De Luis et al., 2007; Fujisawa et al., 1998; Kurokawa et al., 2001; Lee et al., 2010; Lindi et al., 2002; Martí et al., 2002; Østergård et al., 2005; Phares et al., 2004; Rankinen et al., 2006; Sakane et al., 1997; Shiwaku et al., 2003; Sonestedt et al., 2009; Sonestedt et al., 2011).

This has spurred interest in nutrigenetics and exercise genomics: understanding how specific genetic polymorphisms influence the outcome of weight loss strategies, with the ultimate goal of personalizing obesity interventions. Here we review evidence for several well-studied gene variants – FABP2 (rs1799883), PPARG (Pro12Ala, rs1801282), ADRB2 (Gln27Glu, rs1042714), ADRB3 (Trp64Arg, rs4994), APOA2 (−265T>C, rs5082), APOA5 (−1131T>C, rs662799), and FTO (rs9939609) – and their impact on weight loss or gain under

different dietary and exercise conditions. We focus exclusively on human, peer-reviewed studies, retaining a scientific, evidence-based perspective throughout.

Fat Content in Diet and Genetic Variants

Conventional wisdom holds that body weight is strictly a matter of caloric balance – i.e., "a calorie is a calorie" regardless of macronutrient source, and excess fat intake inevitably leads to fat storage (Shook et al., 2014). However, a number of studies contradict this simplistic view by demonstrating gene–diet interactions: calories from fat do not affect all individuals equally. One notable example involves a common variant in the PPARG gene. Memisoglu et al. (2003) reported that among people consuming a high-fat diet, those with the PPARG C/C genotype (Pro12Pro) were significantly more obese, whereas carriers of the alternative G (Ala12) allele appeared resistant to high dietary fat – they did not gain as much weight from a fatty diet. This finding was independently replicated by Robitaille et al. (2003) in 720 participants, reinforcing that the Pro12Ala (rs1801282) polymorphism in PPARG modulates fat intake effects on adiposity. Interestingly, a later intervention study by Garaulet et al. (2011) provided further insight. In a 12-month Mediterranean-style weight loss program with ~1,465 obese subjects, Garaulet's team observed a significant gene–diet interaction: when total fat intake was high, individuals carrying the Ala12 variant of PPARG lost less weight than those with the Pro12Pro genotype. In contrast, when dietary fat was low, weight loss was more comparable between genotypes. In other words, Ala12 carriers were at a disadvantage for weight loss if their diet remained high in fat, suggesting they benefit more from fat restriction (Garaulet et al., 2011).

These human studies collectively illustrate that PPARG genotype can determine whether a high-fat diet leads to weight gain or hampers weight loss, highlighting the value of genetically tailored diet advice. A similar pattern has been documented for other genes. Variants in FABP2, APOA2, APOA5, and FTO have all been linked to differential responses to high-fat diets. The FABP2 gene encodes an intestinal fatty acid–binding protein, and its common Ala54Thr variant (rs1799883) influences fat absorption and metabolism. Carriers of the Thr54 allele (risk variant) tend to have higher lipid oxidation and, in some studies, higher BMI – especially when consuming a high-fat diet (Lefèvre et al., 2005; Levy et al., 2001). In fact, at least 16 publications have shown that individuals with the FABP2 Thr54 allele, or with analogous "risk" alleles in APOA2, APOA5, and FTO, experience greater weight gain or adiposity with increasing fat intake, whereas those with the alternative alleles are partly protected against diet-induced obesity (Agren et al., 1998; Albala et al., 2004; Corella et al., 2007; Corella et al., 2009; Corella et al., 2011a; Corella et al., 2011b; Hubáček et al., 2007; Lefèvre et al., 2005; Levy et al., 2001; Mattei et al., 2009; Pratley et al., 2000; Sánchez-Moreno et al., 2011; Sonestedt et al., 2009; Sonestedt et al., 2011; Tanofsky-Kraff et al., 2009).

For example, the APOA2 −265T>C variant (rs5082) has been consistently associated with body-weight differences depending on saturated fat intake. Corella et al. (2007) first showed that individuals with the APOA2 C/C genotype had higher BMI only if they ate a diet high in saturated fat, whereas on a low-sat-fat diet this genotype had no obesity risk. This gene–diet interaction was later replicated in multiple cohorts (Corella et al., 2011). In a very recent analysis of the DIETFITS randomized trial, Lai et al. (2025) specifically examined APOA2 and diet type: overweight subjects were assigned to healthy low-fat vs. low-carb diets for 12 months. The results revealed that APOA2 genotype indeed influenced diet response: participants with the TT genotype (no C allele) lost significantly more weight on the low-carbohydrate (higher-fat) diet than on the low-fat diet at 3, 6, and 12 months. In contrast, carriers of the C allele (CT or CC) saw no sustained advantage on the low-carb diet – by 12 months their weight loss was similar on both diets (Lai et al., 2025). An interaction between APOA2 genotype and saturated fat intake on 1-year weight change was observed, reinforcing that the optimal diet may differ by genotype. Notably, if subjects did not adhere to the intended fat intake (i.e. genotypes aside, they didn't truly follow low-fat or low-carb guidelines), then no genotype effect was seen (Lai et al., 2025). This underscores that genotype can shape how one's body reacts to diet composition, but the effect emerges only when the dietary contrast (e.g. high vs. low fat) is actually present.

The APOA5 gene (apolipoprotein A-V), which plays a role in triglyceride metabolism, provides another illustration. The APOA5 −1131T>C polymorphism (rs662799) is a known risk factor for hypertriglyceridemia and has been linked to obesity. Aberle et al. (2005) investigated how carriers of this variant respond to a short-term low-fat diet. In a study of 606 overweight men put on a fat-restricted diet, they found that BMI reduction was significantly greater in carriers of the APOA5 C allele than in those with the T/T genotype. In other words, individuals with the risk allele (C) actually lost more weight when dietary fat was cut – consistent with the idea that their genotype made them more sensitive to fat calories. Aberle et al. concluded that a calorie- and fat-reduced diet is especially beneficial for APOA5 C allele carriers and should be recommended for those individuals (Aberle et al., 2005). This targeted advice is supported by recent long-term trials. For instance, de Luis et al. (2022) conducted a 9-month hypocaloric diet intervention (Mediterranean style) in 269 obese patients and observed that although all genotypes lost weight, metabolic improvements differed by APOA5 genotype. Non-C carriers (TT genotype) showed significant decreases in triglycerides, insulin, and HOMA-IR (insulin resistance index) after weight loss, whereas C allele carriers did not see such improvements despite similar weight loss.

Thus, the APOA5 variant may also influence the quality of weight loss – with C allele carriers potentially needing a more aggressive fat restriction or additional interventions to achieve the same cardiometabolic benefits. Compelling evidence also implicates the famous FTO gene (rs9939609). FTO was the first common obesity-susceptibility gene identified by GWAS, and its A allele is associated with higher weight. Subsequent research discovered that lifestyle factors can modulate FTO's effect. Sonestedt et al. (2009) reported

that the FTO risk allele's impact on BMI was accentuated in those consuming a high-fat diet but blunted in those eating fewer fats. In agreement, Corella et al. (2011b) found a significant interaction between saturated fat intake and FTO genotype on BMI in two U.S. populations. Specifically, individuals homozygous for the FTO risk allele (A/A) had a higher BMI than others only if they had high saturated fat intake; at lower fat intake, the BMI difference by genotype disappeared. For example, in one cohort, the obese-risk genotype had an average BMI ~1.5 kg/m² higher than non-carriers when saturated fats were above the mean, but showed no excess BMI when saturated fat intake was below average (Corella et al., 2011b). At least a dozen studies (including Tanofsky-Kraff et al., 2009; Qi et al., 2012) have replicated the finding that FTO's influence on adiposity is mitigated by a healthy diet.

In summary, ample research demonstrates that calories from fat do not have the same effect in everyone – genetic polymorphisms can make certain individuals gain more weight from high-fat diets, whereas others are relatively insensitive to dietary fat. This challenges the one-size-fits-all approach to obesity management and opens the door to genotype-tailored dietary recommendations.

Carbohydrate Content in Diet

Just as with dietary fat, genetic differences can alter how individuals handle high-carbohydrate diets. One prominent example involves the β2-adrenergic receptor gene (ADRB2), which influences lipolysis and energy expenditure. The ADRB2 Gln27Glu variant (rs1042714) has been associated with obesity risk, and its effect appears to depend on carbohydrate intake. In a study of Spanish adults, Martínez et al. (2003) showed that those with the ADRB2 27Glu allele (G allele) had a nearly three-fold higher odds of being overweight (odds ratio ≈2.6) if they consumed more than 49% of their calories from carbohydrates, compared to people with the same genotype eating a lower-carb diet. In contrast, among individuals eating a moderate-carb diet, the genotype had much less impact on weight (Martínez et al., 2003). Thus, it was not just the number of calories, but the form of calories (carbs vs. fat) that determined obesity risk in ADRB2 Gln27Glu carriers.

This finding has since been supported by additional research. For instance, a meta-analysis by Zhang et al. (2014) confirmed that the ADRB2 Gln27Glu polymorphism is associated with increased obesity susceptibility overall (pooled OR ~1.20 for carriers of Glu27). Moreover, epidemiologic studies in Asia have found that gene–environment interactions contribute to this risk – e.g., one study reported that the ADRB2 variant in combination with high caloric intake and smoking was linked to higher obesity prevalence (Lee et al., 2011).

Although fewer gene–carbohydrate interaction studies exist compared to fat, current evidence suggests that genetic factors like ADRB2 can make some people particularly carb-sensitive in terms of weight gain. In practical terms, an individual with the ADRB2

27Glu allele might be more likely to gain weight on a high-carb diet than someone with the Gln27Gln genotype, even if total calories are similar. It's worth noting that not all polymorphisms show interactions with carbs; for example, in the FTO study mentioned earlier, carbohydrate intake did not significantly modify the FTO–BMI association (Corella et al., 2011b).

Nevertheless, for certain genotypes such as ADRB2 Gln27Glu, a lower-carbohydrate (or lower glycemic) diet may be a more effective strategy to prevent overweight. In summary, the form of calories (fat vs. carbohydrate) can differentially impact body weight depending on one's genes, reinforcing the need for personalized nutrition.

Different Response to Weight Loss Strategies

Beyond predisposition to gain weight, genetics can also influence how successfully one loses weight when following a structured program. Lindi et al. (2002) provided an illustrative early example. They followed participants in a 3-year lifestyle intervention (combining calorie restriction and regular exercise) and found that subjects carrying the PPARG Pro12Ala G allele (Ala12 variant) lost 2.5 times more weight on average than those without this allele (8.3 kg vs. 3.4 kg weight loss over three years) (Lindi et al., 2002). Clearly, the same regimen of diet and exercise produced markedly different outcomes based on genotype. Interestingly, the PPARG Ala12 (G) allele also showed a drawback: one year after the program, the G-allele carriers had greater weight regain (a stronger "yo-yo" effect) than the others. This suggests a genetic influence not only on initial weight loss success but also on the long-term maintenance of weight loss.

Such findings have spurred larger trials to examine gene–intervention interactions. Notably, the U.S. Diabetes Prevention Program (DPP) – a randomized trial of >3,000 individuals at high risk for diabetes – analyzed PPARG Pro12Ala effects on changes in adiposity. Franks et al. (2007) reported a significant interaction between PPARG genotype and treatment type on weight change. In the DPP, participants were assigned to intensive lifestyle modification (diet + exercise), metformin (medication), or placebo. After 1 year, the Ala12 carriers tended to lose more weight with lifestyle intervention than Pro/Pro individuals, whereas on metformin the genotype effect differed. Figure 1 of that study showed clear divergence: Ala12 carriers in the lifestyle group had greater weight loss than those with Pro12Pro (while little difference was seen in the placebo group). The genotype-by-treatment interaction was statistically significant ($p=0.01$). Additionally, DPP found that the Ala12 allele was associated with a greater reduction in central (visceral) fat in some conditions, and this effect varied by dietary fat quality – for example, Ala carriers on metformin lost more visceral fat if their polyunsaturated fat intake was higher (Franks et al., 2007).

Specific gene effects are very much real – they may just be subtle or context-dependent. For instance, another gene implicated in differential weight loss is ADRB2. While one 2016

trial (FLAIR study) did not find an overall effect of ADRB2 Gln27Glu on weight loss for the whole group, there was a suggestive finding that among men in a supervised exercise program, those with the Glu27/Glu27 genotype had slightly greater weight and BMI reductions than those with Gln27 (Szendrei et al., 2016). This hints that ADRB2 might modulate response in certain subgroups (such as by sex or exercise intensity).

Taken together, these data reinforce that two people on the same weight loss program can have different outcomes partly due to genetic differences. Knowing a patient's genotype for key polymorphisms like PPARG could one day help predict if they will be a "high responder" or "low responder" to a given strategy, and thus guide the choice of intervention.

Weight Loss Through Exercise

Increasing physical activity is a cornerstone of obesity treatment (Shook et al., 2014). However, genetics can determine how effective exercise is for weight loss in a given person. The ADRB3 gene, which encodes the β3-adrenergic receptor mainly found in adipose tissue, provides a well-documented example. The common Trp64Arg missense variant (rs4994) in ADRB3 has been linked to obesity predisposition, especially in certain ethnic groups. Martí et al. (2002) reported that individuals homozygous for the ADRB3 Trp64Arg variant (T/T genotype in their notation, corresponding to Trp64Trp) were more likely to be overweight, but crucially this genetic risk manifested only in those with a sedentary lifestyle. When carriers of the risk genotype engaged in regular exercise, their obesity rates were no higher than non-carriers – in essence, physical activity neutralized the genetic predisposition (Martí et al., 2002). This finding is empowering: it suggests that even if one has "bad genes," an active lifestyle can overcome that disadvantage.

The interaction between ADRB3 and exercise was confirmed in multiple studies. For instance, Sakane et al. (1997) put obese young women on a supervised exercise program and found that those carrying the ADRB3 Arg64 variant (often denoted as the C allele) lost significantly less weight compared to those with the wild-type Trp/Trp genotype. Despite identical training regimens, the Arg64 carriers on average saw smaller reductions in body weight and fat. In Sakane's study, Trp/Trp individuals lost more weight through exercise, whereas Arg64 carriers were somewhat "resistant" to the weight-loss effects of exercise (Sakane et al., 1997). At least 11 other studies have observed similar genotype differences in exercise-induced weight loss (Adamo et al., 2005; De Luis et al., 2007; Fujisawa et al., 1998; Kurokawa et al., 2001; Lee et al., 2010; Lindi et al., 2002; Østergård et al., 2005; Phares et al., 2004; Rankinen et al., 2006; Shiwaku et al., 2003; Sonestedt et al., 2009).

A 2016 controlled trial in Spain (the PRONAF study) examined both ADRB2 Gln27Glu and ADRB3 Trp64Arg in the context of a 22-week exercise + diet program. They found no large effect of ADRB2 on overall weight loss, but ADRB3 Arg64 carriers showed a blunted fat-

loss response: after the intervention, those with the Arg allele had a higher fat mass and body-fat percentage than participants without the allele, despite everyone undergoing the same training and caloric deficit (Szendrei et al., 2016). This aligns with the idea that the Arg64 variant confers exercise resistance for fat loss.

On the other hand, research on the FTO gene offers a more optimistic message. A landmark meta-analysis of 218,000 adults by Kilpeläinen et al. (2011) demonstrated that physical activity can attenuate the effect of FTO risk alleles on obesity risk. In physically inactive people, carrying the FTO A allele was associated with a higher odds of obesity; but in active individuals, that increased risk was about 27% lower. In practical terms, being active cut the "penalty" of the obesity-risk gene by about one-third (Kilpeläinen et al., 2011). This finding – since replicated in other cohorts – indicates that exercise can compensate for genetic susceptibility, reinforcing public health messages that "your genes are not your destiny."

In summary, while certain polymorphisms like ADRB3 Trp64Arg can make weight loss through exercise more challenging, an overall body of evidence (including FTO studies) suggests that sufficient physical activity can overcome many genetic predispositions. From a clinical standpoint, individuals known to have an "exercise-resistant" genotype might be counseled to combine exercise with other strategies (or pursue higher intensity training) to achieve results, whereas those with favorable genotypes might see quicker benefits from exercise-alone programs.

Weight loss through calorie reduction

Calorie restriction (dietary energy reduction) is another primary approach for weight management (Shook et al., 2014). Once again, genetics appears to influence how effective simple calorie-cutting will be for a given person. Matsuo et al. (2009) reported that a polymorphism in PPARG (Pro12Ala rs1801282, discussed earlier) explained about 7% of the variance in weight loss on a calorie-restricted diet in a study of Japanese adults. In their trial, carriers of the Ala12 (G) allele lost significantly more weight under caloric restriction than those with the Pro/Pro (C/C) genotype (Matsuo et al., 2009). This suggests that people with the Ala12 variant may have a metabolic profile that responds better to dieting – perhaps due to differences in insulin sensitivity or adipocyte function (since PPARG is a key adipose gene).

The PPARG Pro12Ala effect has been echoed by other research. For example, in the Finnish Diabetes Prevention Study, Ala12 carriers on a low-calorie diet plus lifestyle regime showed greater improvements in central obesity measures than non-carriers, as mentioned above (Lindi et al., 2002; Franks et al., 2007).

On the other hand, not all genes identified in observational studies show strong effects in diet interventions. A question was raised whether the FTO risk allele makes it harder to

lose weight through diet. Interestingly, multiple intervention studies – including large trials like Look AHEAD and meta-analyses – have found that FTO genotype does not substantially affect the amount of weight lost when calories are restricted (e.g., Gao et al., 2011; Garaulet et al., 2013). In other words, A allele carriers can lose just as much weight on a diet as T carriers if they adhere to the diet. This is a reassuring point: an obesogenic genotype doesn't necessarily doom an individual's diet efforts, even if it raised their risk of gaining weight in the first place.

Meanwhile, the APOA5 rs662799 variant (−1131T>C) again emerges as significant in pure dietary interventions. Aberle et al. (2005), as noted, found C allele carriers had greater BMI reduction on a short-term low-fat diet. They also observed that plasma triglyceride improvements with dieting were genotype-dependent, consistent with APOA5's role in lipid metabolism. A more recent randomized trial by de Luis et al. (2021) investigated 2-year changes in lipid profile with different fat intakes among obese patients, and found a significant interaction between APOA5 genotype and dietary fat intake on weight loss and triglyceride changes (de Luis et al., 2021). Generally, C allele carriers benefited more from lower-fat, higher–omega-6 diets, showing larger drops in weight and triglycerides, whereas T/T homozygotes had more flexibility. These findings led the authors to recommend that APOA5 C-allele carriers adopt a low-fat, calorie-reduced diet for optimal weight loss outcomes (de Luis et al., 2021).

In summary, evidence is accumulating that genetic makeup can account for some of the person-to-person variation in weight loss from calorie restriction. Polymorphisms in genes like PPARG and APOA5 may make the difference between a person losing, say, 5% of their body weight versus 0% when they cut calories. It is important to acknowledge that behavioral factors (adherence, appetite, etc.) ultimately dominate; however, genetics might explain why one diligent dieter sheds pounds easily while another equally diligent dieter struggles. As our understanding grows, genetic testing could potentially identify individuals for whom standard calorie-cutting is less effective, prompting consideration of alternative or adjunct strategies (such as higher protein ratio, medical therapy, or personalized macronutrient distribution).

Summary of genotypes and correlating phenotypes

The following table summarizes the phenotypes associated with the various genotypes in these 7 SNPs (table 1).

Table 1: Genotype-phenotype association of the selected SNPs

Gene	SNP	WT Allele	Mut Allele	Carb sensitive genotypes	Fat sensitive genotypes	Exercise Responder genotypes	Calorie reduction responder genotypes
FABP2	rs1799883	G - Ala	A - Thr		A/G and A/A		
PPARG	rs1801282	C - Pro	G - Ala		C/C	C/G and G/G	C/G and G/G
ADRB2	rs1042714	C - Gln	G - Glu	C/G and G/G			C/G and G/G
ADRB3	rs4994	T - Trp	C - Arg			T/T	
APOA2	rs5082	T	C		C/C		
APOA5	rs662799	A	G		A/A		A/G and G/G
FTO	rs9939609	T	A		T/A and A/A	T/A and A/A	

Conclusion

Modern obesity research clearly shows that “what works for one person may not work the same for another” due to genetic differences. Variants in genes like FABP2, PPARG, ADRB2, ADRB3, APOA2, APOA5, and FTO do not cause obesity in isolation, but they modify the body’s response to diet and exercise. Risk alleles in some of these genes predispose individuals to gain more weight on high-fat or high-carbohydrate diets, whereas protective alleles can confer resistance to those environmental risk factors. Similarly, in weight loss interventions, these polymorphisms can influence how much weight (or fat) is lost through exercise or caloric restriction.

The studies reviewed here – from observational cohorts to randomized trials – provide a proof-of-concept for personalized weight management. In practice, a clinician might design a diet plan based on a patient’s genotype: for example, recommending a low-fat diet to an APOA5 C carrier, or emphasizing exercise for an ADRB2 Gln27 carrier, or perhaps focusing on portion control in an ADRB3 Arg64 carrier who might not respond as well to exercise alone. We are moving toward an era of “precision nutrition” and “precision lifestyle” in which genetic testing, alongside clinical judgement, could help tailor obesity treatment to maximize efficacy for each individual.

Ultimately, tackling obesity will likely require integrating genetic data with behavioral, medical, and environmental strategies. The hope is that by understanding a patient’s genetic profile, we can choose the weight loss strategy (diet type, intensity of exercise, etc.) that aligns best with their biology, thereby enhancing results and helping more people achieve sustainable, healthy weight reduction.

The aim of this study

This study aims to evaluate the potential for genetically personalized weight loss strategies compared to standard weight loss advice. Participants were initially counselled with standard weight loss advice generally known to the general population: “Eat less, exercise more”. This evaluated the efficiency of weigh loss with the rules widely known over a 3 week period. After a 2 week break, each individual received their genetically personalized weight loss program. For this, we have created an algorithm to identify the genetic traits relevant for weight loss and personalized the weight loss recommendations for each individual. The results of a 3 week weight loss phase following the genetic weight loss program were then compared to the results of the standard program.

MATERIALS & METHODS

Subjects

Three hundred three subjects were recruited through advertisements on the internet and magazines to participate in an 8-week weight loss program. We selected participants if they were at least 18 years of age and had a body mass index (BMI) above 18. In total 303 subjects, of which 51 were male and 252 were female aged 19 to 86 were selected. Table 2 displays the characteristics of the participants. Eighteen subjects were previously diagnosed with hypothyroidism. The aim and design of the study was explained to subjects before obtaining the written and informed consent.

Table 2: Participants descriptive characteristics

n=303	
Age (years)	41.51±12.96 s.d.
Body weight (kg)	84.00±18.00 s.d.
BMI (kg/m^2)	29.41±5.38 s.d.

Study Structure

Participants received a booklet containing nutritional and lifestyle counselling advice as given by the official German institution, “Deutsche Gesellschaft für Ernährung”, which is the basis for most nutritional counselling currently conducted in Germany. Participants read the instructions and received instructions to make weekly records of their body weight and perceived adherence to the nutritional guidelines. After 3 weeks of following this diet, participants were given 2 weeks to return to their original lifestyle and nutrition. After these 2 weeks, participants received their genetic results and personalized recommendations in written form. After having read the genetic information, participants were asked a number of questions to ensure that they fully understood the information. After having answered the questions correctly, participants were instructed to follow the genetic diet for a period of 3 weeks and to make daily records of their perceived adherence to the nutritional advice, exercise advice and daily body weight.

Sample and DNA Extraction

Participants were instructed to neither eat nor drink for a period of at least 30 minutes before the buccal swab samples were collected using Sarstedt forensic swabs. The extraction procedure was carried out using the BioRobot Universal system from Qiagen and following the manufacturer’s instructions and using the extraction kit QIAamp 96 DNA Swab BioRobot Kit from Qiagen. DNA was eluted in 150 µl TE and stored at 4°C until use.

Genotyping

Genotyping was done using the TaqMan® system owned by Life technologies/ThermoFisher Scientific. Reactions were performed in 384 well reaction plates using the original TaqMan™ Genotyping Master Mix according to the manufacturer’s instructions. 0.5 µl TaqMan assay was mixed with 2.5 µl nuclease free water, 5 µl TaqMan™ Genotyping Master Mix and 2 µl purified DNA suspended in TE buffer. 384 well plates were sealed using Opti-Seal optical disposable adhesive foil. Plates were vortexed briefly (1000 rpm, 200 seconds) and centrifuged at 2000 rpm for 5 minutes to collect the reaction mix in the bottom of each well. Thermal cycling was performed in a ViiA ® 7 Real-Time PCR System. Reactions were performed using 39 cycles of 95°C for 15 seconds and 60°C for 60 seconds. Data collection was performed using the ViiA7-Software.

The assays in use were:

- SNP rs1799883 (TaqMan Assay Number C_761961_10)
- SNP rs1801282 (TaqMan Assay Number C_1129864_10)

- SNP rs1042714 (TaqMan Assay Number C_2084765_20)
- SNP rs4994 (TaqMan Assay Number C_2215549_20)
- SNP rs9939609 (TaqMan Assay Number C_30090620_10)
- SNP rs5082 (TaqMan Assay Number C_11453334_10)
- SNP rs662799 (TaqMan Assay Number C_2310403_10)

Determining diet type

As 5 different polymorphisms independently influence the fat sensitivity of a person, subjects were classified in one of 6 categories. The lowest “fat-score of 0 %” was given to individuals with the non-fat sensitive allele in all 5 polymorphisms. The highest fat-score of 100 % was given to individuals with fat sensitivity genotypes in all 5 polymorphisms. Any intermediate genotype received a score proportional to the number of fat sensitive genotypes at these 5 loci.

As there is only one polymorphism influencing carbohydrate sensitivity, rs1042714 C/G and G/G genotypes received a carb-score of 100 % and carriers of the homozygous C/C genotype received a carb-score of 0 %.

Taking different macronutrient balances from common low carb and low fat diets, appropriate macronutrient balances were assigned to each genetic nutritional type as follows:

Table 3: Macronutrient balance assigned by diet type

Legend: Carbohydrate, fat and protein balances are given in percentage of calories from macronutrient source.

Fat-Score	0 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	45 %
Fat	35 %
Protein	20 %

Fat-Score	16 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	47 %
Fat	33 %
Protein	20 %

Fat-Score	33 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	48 %
Fat	32 %
Protein	20 %

Fat-Score	50 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	49 %
Fat	31 %
Protein	20 %

Fat-Score	66 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	51 %
Fat	29 %
Protein	20 %

Fat-Score	83 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	53 %
Fat	27 %
Protein	20 %

Fat-Score	100 %
Carb-Score	100 %
Were assigned to:	
Carbohydrates	55 %
Fat	25 %
Protein	20 %

Fat-Score	>16 %
Carb-Score	0 %
Were assigned to:	
Carbohydrates	65 %
Fat	20 %
Protein	15 %

The genetic diet ensured, that the macronutrient balance of each subject followed his/her assigned targets as defined in table 3.

Determining strategy type

To determine the relative effectiveness of exercise and weight loss based on the genetic profile, 5 different polymorphisms were used.

The lowest exercise-score of 0 % was given to subjects carrying none of the exercise responder genotypes and the highest score of 100 % was given to subjects carrying all 3 of the exercise responder genotypes.

Similarly, the lowest calorie-score of 0 % was given to subjects carrying none of the calorie reduction responder genotypes and the highest score of 100 % was given to subjects carrying all 3 of the calorie reduction responder genotypes.

In order to determine where the main focus of the weight loss strategy should be (exercise or calorie reduction or both), both scores were combined to a final percentage using the formula:

Final exercise score (%) = (100 * exercise-score) / (calorie-score + exercise-score)

Final calorie score (%) = (100 * calorie-score) / (calorie-score + exercise-score)

Determining daily nutritional calories and exercise requirements

To estimate the basic metabolic rate at rest (BMR), the formula by Mifflin-St.Jeor was used (Mifflin et al. 1990). The total target daily calorie deficit for every subject was the smaller number of either 45 % of the basic metabolic rate at rest or 850 kcal. Calorie deficit was however split up between calorie reduction in diet and increased expenditure through exercise. The minimum calorie reduction (below the basic metabolic rate at rest) for every subject was 25 % of his/her basic metabolic rate at rest. The minimum expenditure of calories through additional exercise was 50 kcal. The remaining calories where then shared out among the two strategies according to the final exercise and final calorie scores.

The final daily calories to be ingested were then determined by the formula:

Daily kcal = BMR – (25 % of BMR) – (surplus calorie deficit * final calorie score)

Daily exercise kcal = 50 kcal + (surplus calorie deficit * final exercise-score)

Lifestyle change instructions to subjects

Subjects were given a number of different options to change their diet according to the genetic requirements. For one, they were given 8 complete daily menus that contained exactly the correct amount of daily calories and the correct macronutrient balance for their genetic type. In addition, they were given lists of food types together with a bar chart displaying if this type of food contains the correct macronutrient balance for their genotype. Participants were free to choose which diet intervention they preferred to use.

To reach their required level of calorie expenditure, participants were given a table of potential exercises together with the time they needed to perform these exercises to expend the required calories. Participants were free to choose which exercises to perform and on how many days per week to perform them, but they were required to reach the required calorie expenditure per day on average.

Statistical Analysis

Values are expressed as the mean ± standard deviation. Using the online calculator at www.evanmiller.org/ab-testing/t-test.html, the 2-sample T-Test was used for statistical analysis. Significance was determined as being a p-value smaller or equal to 0.05.

RESULTS

Weight loss through standard diet

Subjects generally lost weight during phase 1 of the study, which was the standard diet. The mean weight loss over 3 weeks was 1.486 kg (mean -1.486±1.384 s.d., $p<0.001$) ranging from an actual weight gain of 2 kg to a weight loss of 7 kg in 3 weeks. The mean of compliance to the requirements was 72 % (mean 72.205±15.095 s.d.).

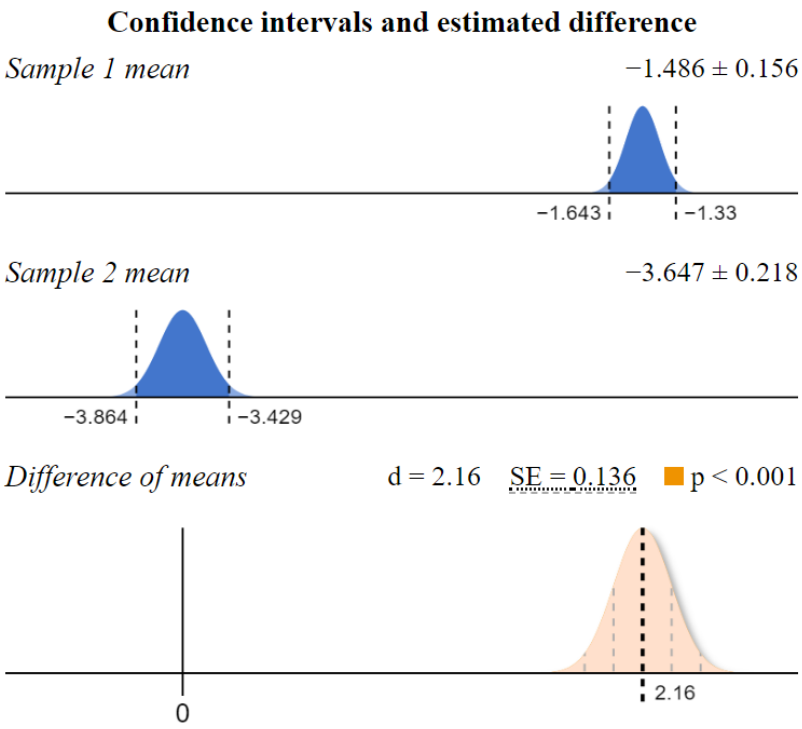
Weight loss through genetic diet

During phase 2, the genetic diet, subjects generally lost weight. The mean weight loss over 3 weeks was 3.65 kg (mean -3.647±1.926 s.d., $p<0.001$) ranging from an actual weight gain of 1.1 kg to a weight loss of 13 kg in 3 weeks. The mean of compliance was 84 % (mean 84.053±14.753 s.d.).

Comparative weight loss

Taking all participants into consideration, participants lost on average 2.5-fold as much body weight on the genetic diet, as they did on the standard diet, which was highly statistically significant ($p<0.001$). Diagram 1 shows the weight loss differences between standard diet and genetic diet.

Diagram 1: Weight loss differences between the two diet types



Legend: Sample 1 mean was the standard diet, Sample 2 mean was the genetic diet.

Comparative weight loss at different BMI-levels

Subjects with different entry BMI responded differently to the genetic diet (diagram 2).

BMI 19 – 24.99

Subjects with a BMI between 19 and 24.99 (n=58) lost on average 0.87 kg in 3 weeks on the standard diet (mean -0.871±0.777 s.d.) and 2.86 kg in 3 weeks on the genetic diet (mean -2.864±1.442 s.d.) which corresponds to a 3.3-fold greater weight loss efficiency and was highly statistically significant (p<0.001).

BMI 25 - 30

Subjects with a BMI between 25 and 30 (n=129) lost on average 1.49 kg in 3 weeks on the standard diet (mean -1.493±1.367 s.d.) and 3.45 kg in 3 weeks on the genetic diet (mean -3.45±1.639 s.d.) which corresponds to a 2.3-fold greater weight loss efficiency and was highly statistically significant (p<0.001).

BMI >30

Subjects with a BMI greater than 30 (n=116) lost on average 1.78 kg in 3 weeks on the standard diet (mean -1.787±1.539 s.d.) and 4.25 kg in 3 weeks on the genetic diet (mean -4.257±2.234 s.d.) which corresponds to a 2.4-fold greater weight loss efficiency and was highly statistically significant ($p<0.001$).

Weight loss in Hypothyroidism patients

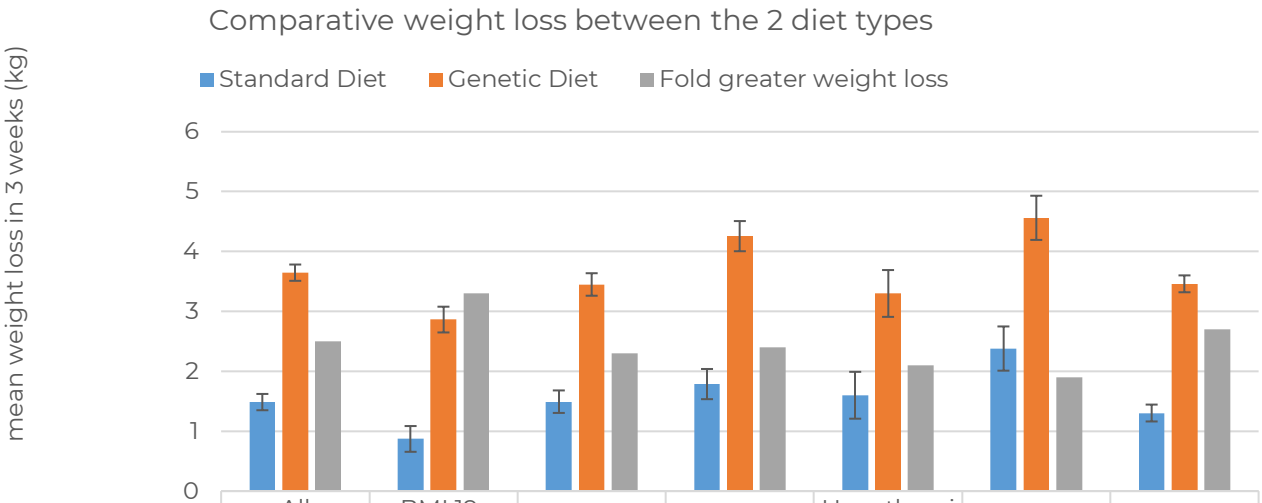
Subjects suffering from hypothyroidism appeared to also benefit from the genetic diet with a 2.1-fold greater weight loss (mean of mean -1.6±0.878 s.d. vs mean of mean -3.3±1.407 s.d.) which was highly statistically significant ($p<0.001$).

Weight loss efficiency by sex

Male subjects (n=51) had a mean weight loss of 2.38 kg in 3 weeks on the standard diet (mean -2.38±1.502 s.d.) and the mean weight loss on the genetic diet was 4.56 kg in 3 weeks (mean -4.563±2.167 s.d.), which corresponds to a 1.9-fold greater weight loss on the genetic diet, which was highly significant ($p<0.001$).

Female subjects had a mean weight loss of 1.30 kg in 3 weeks on the standard diet (mean -1.306±1.289 s.d.) and a mean weight loss of 3.46 kg in 3 weeks on the genetic diet (mean -3.461±1.823 s.d.). This corresponded to a 2.7-fold greater weight loss on the genetic diet and was highly significant ($p<0.001$).

Diagram 2: Weight loss comparison between the 2 diet types

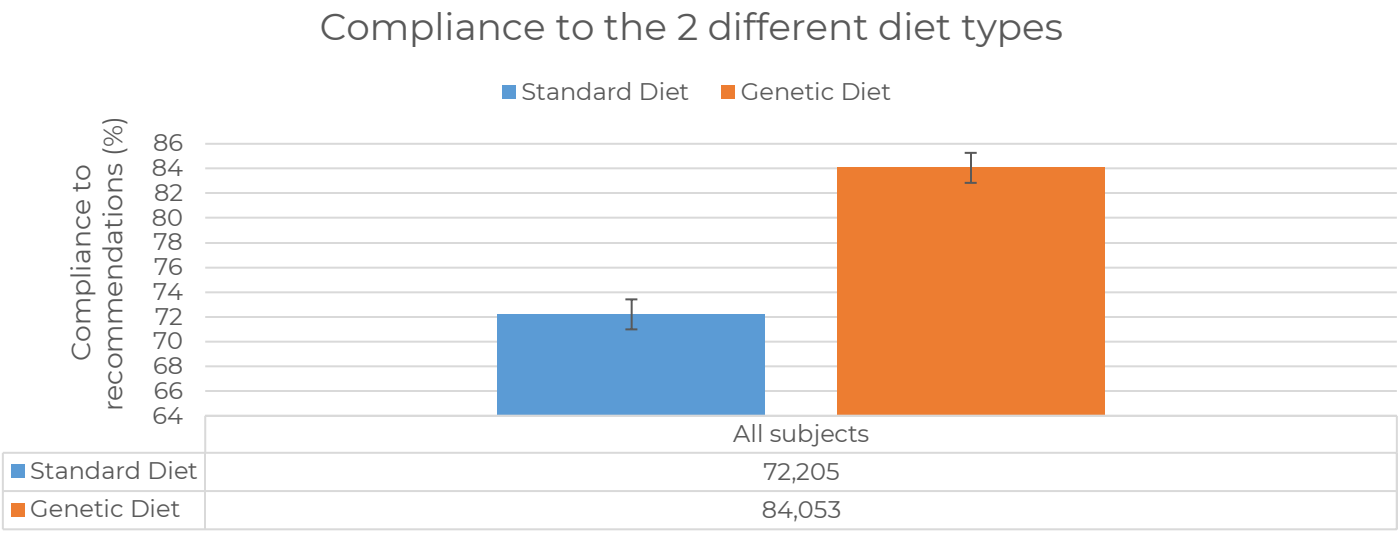


	All subjects	BMI 19-24.99	BMI 25-30	BMI >30	Hypothyroidism	Male	Female
Standard Diet	1,486	0,871	1,493	1,787	1,6	2,38	1,3036
Genetic Diet	3,647	2,864	3,45	4,257	3,3	4,563	3,461
Fold greater weight loss	2,5	3,3	2,3	2,4	2,1	1,9	2,7

Compliance

Taking all subjects into account, there were significant differences in self-reported compliance. The mean compliance for the standard diet was 72 % (mean 72.205±15.095 s.d.) while the mean compliance for the genetic diet was 84 % (mean 84.053±14.753 s.d.). Diagram 3 shows the difference of 11.848 % which was highly significant (p<0.001).

Diagram 3: Compliance rates of the different diet types



Success rates of the different diet types

Overall, 86 % of subjects lost weight on the standard diet (261 of 303 in total), while 98 % of subjects lost weight on the genetic diet (298 of 303 in total). Restricting the analysis to subjects, who complied 80 % or more (n=194), the success rate on the genetic diet increases to 99 % (192 of 194 in total). These individuals also lost 2.7 times as much weight on the genetic diet as on the standard diet (mean -1.455 ±1.378 s.d. vs. mean -3.888±1.734 s.d., p<0.001).

DISCUSSION

The results of this study concluded that the use of the genetic diet awards a 2.5-fold efficiency in reducing body weight. Different entry BMI groups appeared to benefit differently from the genetic diet, whereby individuals of normal body weight (19 to 24,99) appeared to benefit most with a 3.3-fold weight reduction efficiency. While male subjects lost most weight on the genetic diet (mean of 4.6 kg in 3 weeks), they experienced the least benefit from the genetic diet (only a 1.9-fold greater weight loss), which is due to the higher weight loss efficiency of the standard diet in men. Patients suffering from hypothyroidism appear to also benefit from the genetic diet with a 2.1-fold greater weight loss, which was highly statistically significant ($p<0.001$).

The study results appear conclusive, but the study design also bears some limitations, that need to be considered. The aim of this study was to compare the efficiency of weight loss with generally known principles (eat less, exercise more) available to anyone without a genetic test and compare this efficiency with the genetic program with all of its aspects, including genetics, guided intervention and different approach to permissible calories per day. Besides the influence of personal genetic factors, other aspects of the “genetic diet” may also contribute to greater weight loss when compared to standard nutritional counselling. For one, the greater motivation to follow personalized recommendations is likely to play a significant role. In fact, people adhered 11.8 % more stringently to the genetic recommendations than they did to the standard diet, which is a significant factor in itself (considering that compliance is one of the main issues with weight loss programs). The aspect of the requirement to take daily measurements and records is likely to also increase compliance (compared to a purely informational counselling approach), but since this was a requirement in both diets, it is likely to affect compliance in both diets equally.

Another non-genetic aspect that might improve weight loss on the genetic diet might be the more stringent instructions. The standard diet aimed at informing subjects about the important aspects of weight loss in form of general information given in writing from a nutritional institute in Germany. While the genetic diet also informed participants, it focused more on instructions of how to put these recommendations into practice, which is likely to increase effectiveness in itself.

The order of the diets for each participant might also have unforeseen influence on the comparison. General (though scientifically unconfirmed) wisdom states, that weight loss tends to be fast at first, but slow down after 2-3 weeks. Should this be true, this might put the genetic diet at a disadvantage as it was performed second. Whether the 2 week break between the two diets influenced this possible effect is unknown.

One important aspect of this study was that participants were able to complete this at home without professional guidance or observation other than e-mail support and written reports explaining the results and instructions. While this bears the risk of false

information being submitted by participants (who do however have no incentive to do so), it demonstrates that this approach might be viable for use at home and without expensive and professional observation, making it more suitable for wide adoption.

To summarize the potential beneficial aspects of the genetic diet over standard nutritional counselling that might improve its efficiency:

1) Genetically adapted macronutrient balance
2) Genetically adapted intensity of calorie reduction
3) Genetically adapted intensity of exercise program
4) Greater motivation due to (genetic) personalization
5) Greater compliance due to (genetic) personalization
6) Greater effectiveness of stringent instructions

In light of these limitations it is important to not see this study as the effect of genetic information alone, but the combination of genetic information together with the greater motivation associated with genetic information plus the potential added benefit of a stringent program to follow the instructions.

How big a role the actual genetic tendencies play in the effectiveness of the program cannot be determined with accuracy within this limited study. A scientifically interesting approach would be to repeat the experiment, but give participants the reverse of their actual genetic recommendations. This would allow to measure the difference between the program using the correct genetic data and incorrect genetic data and would give more insight into the role of the genetic basis in this program.

Conflict of interest

The authors of this study are employees of Novogenia GmbH, a private commercial genetic laboratory that also funded this research. The scientific review focuses on the scientific evidence and basis of products being sold by the company.

CONCLUSION

We conclude that the genetic diet employed within this study may lead to an up to 3.3-fold greater weight loss when compared to standard nutritional counselling.

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RAW DATA

	Weight loss Standard diet			Weight loss genetic diet				
	mean	SE	SD	mean	SE	SD	x-fold	p
All subjects	1.486	0.136	1.384	3.647	0.136	1.926	2.5-fold	<0.001
BMI 19-24.99	0.871	0.215	0.777	2.864	0.215	1.442	3.3-fold	<0.001
BMI 25-30	1.493	0.188	1.367	3.45	0.188	1.639	2.3-fold	<0.001
BMI >30	1.787	0.252	1.539	4.257	0.252	2.234	2.4-fold	<0.001
Hypothyroidism	1.6	0.391	0.878	3.3	0.391	1.407	2.1-fold	<0.001
Male	2.38	0.369	1.502	4.563	0.369	2.167	1.9-fold	<0.001
Female	1.3036	0.141	1.289	3.461	0.141	1.823	2.7-fold	<0.001