Genotype-based personalised nutrition for obesity prevention and treatment: are we there yet?

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Abstract

Interactions between genotype and dietary intake include genetic moderation of the effect of dietary intake on disease development (nutrigenetics). Research on nutrigenetics has focused mainly on single-nucleotide polymorphisms (SNPs) and supports the notion that interactions between genes, diet, other lifestyle factors, disease, and time (life cycle span), contribute to the risk of most polygenic nutrition-related diseases. Typically, genotype-based personalised nutrition involves genotyping for a number of susceptibility SNPs associated with the prevention, or management, of a particular disease. Dietary advice is then personalised to the individual's genotype to ensure optimal prevention or treatment outcomes. To ensure evidence-based practice, research design and methodology, applied in the investigation of relevant associations, and confirmation of causality, should be appropriate and rigorous. The process of identifying SNPs associated with disease patterns is ongoing. Of note is that the combined effect on body mass index of the SNPs at the currently confirmed 32 loci is a modest 1.45%, bearing in mind that the estimated heritability of obesity is 40-70%. Conclusions formulated by various researchers on the translation of nutrigenetics research into personalised nutrition, including obesity prevention and management, indicate that scientists hold the opinion that more research is necessary before evidence-based practice in this area can be guaranteed.

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Introduction

According to De Caterina,[1] the interaction between diet and genotype is bidirectional. On the one hand, the environment (nutrients) can affect gene expression (nutrigenomics). On the other hand, genes can moderate the effect of environmental factors, such as dietary intake, on disease development (nutrigenetics). Recent research has also indicated that both under- and overnutrition can contribute to heritable changes in the genome, without changes in deoxyribonucleic acid (DNA) sequence (epigenetics). These changes are the result of molecular modifications of DNA through methylation, as well as histone (DNA packaging protein) modification.[2,3]

Epigenetic effects are specifically prominent during pregnancy, including the periconceptional period, but also during neonatal development, puberty, and in the aged.[3] Genes that may specifically hold epigenetic memories of early life experiences include those directly associated with energy intake, storage and use.[3] It is possible that epigenetics may influence obesity phenotype indicators. The findings by Lawlor et al,[4] that maternal overnutrition may contribute to the transfer of obesity from one generation to the next via epigenetic effects, supports this possibility.

To date, most research on nutrigenetics has focused on single-nucleotide polymorphisms (SNPs).[5] SNPs are point mutations in genes that account for most genetic variance involving differences in DNA sequence.[6] Results emanating from this work support the notion that interactions between genes, diet, other lifestyle factors, disease, and time (life cycle span), contribute to the risk of most polygenic nutrition-related diseases.[7-10]

When considering the association between genotype and disease risk, it is important to bear in mind that individual susceptibility SNPs, involved in the development of polygenic diseases, typically make a relatively small contribution to the overall homeostasis, function and health of an individual.[11] It follows that the presence of susceptibility SNPs does not necessarily result in the development of the disease in question. It must further be considered that a particular SNP could have both susceptibility and protective effects. A well-known example that illustrates this concept involves the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene. MTHFR plays a role in the remethylation of homocysteine to methionine.[12] The TT variant has been shown to result in increased homocysteine levels, increasing the risk for neural tube defects and

cardiovascular disease.[13] In contrast, Sharp and Little[14] concluded in their review that individuals with the TT variant may have a lower risk of colon cancer. Evidence shows that this decreased risk may be attenuated by the use of multivitamin supplements.[15]

The interpretation of nutritional genomics research and the application thereof in nutrition-related health care is clearly complex. To ensure evidence-based practice, the research design and methodology applied in the investigation of relevant associations, and confirmation of causality, should be appropriate and rigorous.[10]

Research design and methods for nutrigenetics research

The first line of evidence in nutrigenetics involves the establishment of associations between a particular genotype and one, or more, phenotype indicators of a particular disease (Table 1). In the case of obesity, phenotype indicators could include body mass index (BMI), waist circumference, percentage body fat, and related variables. For personalisation of nutrition interventions, the next step would be to establish the effect of the interaction between genotype and dietary indicators, e.g. total energy intake, on phenotype indicators. Once this association has been established, causality should be confirmed in an appropriately designed study (Table I). The outcome of causality testing can advise the formulation of genotype-based personalised dietary guidelines. Most publications on nutrigenetics report on associations between various genes and phenotype indicators. Publications on the effect of the interaction between genotypes and dietary indicators on phenotype indicators are less common, while appropriately designed interventions to confirm causality are extremely limited.

Genotype-based personalised nutrition for improved health outcomes

Genotype-based personalised nutrition typically involves genotyping for a number of susceptibility SNPs, associated with the prevention, or management, of a particular disease. Dietary advice is then

Table I: Summary of pertinent points for research design and methods in nutrigenetics research

Research steps	Criteria for robust research	Challenges/limitations
Step 1 Establish associations for hypotheses formulation: Genotype X phenotype indicator Effect of genotype X lifestyle (diet) indicator on phenotype indicator	Study design: prospective observation of cohorts (vs. cross-sectional observational designs) to determine associations. Appropriate sample size to ensure representativeness. Use of appropriate genetic markers, robust (valid) lifestyle (diet) and phenotype indicators.	Poor study design. Small samples. Sampling bias. Almost total lack of assessment of lifestyle (diet) indicators.
Step 2 Confirmation of causality or hypothesis testing (interventions)	Prospective interventions to confirm causality. Appropriate sample size for sufficient statistical power. Use of appropriate genetic markers, robust (valid) lifestyle (diet) and phenotype indicators or outcomes. Prospective sampling of genotype groups. Equal number of subjects in the variant and wild type homozygote and heterozygote groups. Rotation of interventions across all genotype groups, and across race groups as relevant, which requires consecutive weigh loss periods and return to baseline weight, to "test" each "type of diet" in each of the three genotypes Confirmation of compliance.	Poor study design. Small samples Sampling bias, retrospective genotyping. Almost total lack of assessment and control for lifestyle (diet) indicators, as well as compliance thereto. Short duration of weight loss interventions (< 6 months). Lack of rotation across genotype groups, as it is extremely challenging, if not impossible.
Steps 1 and 2	Use of appropriate statistical analyses or tests or modelling. Validation of statistical models. Consideration of multiple-test burden that may result in false positives. Control for confounders or interactions, including gene-gene interactions, age, gender, race, disease, medication use, and geographical variation. Consolidation of outcomes in meta-analytic approaches. Consideration of systems genetics for integrative studies of gene-gene lifestyle (diet)-disease-time interactions.	Lack of control of confounders and validation of statistical modelling. Lack of meta-analyses on effect of genotype X lifestyle (diet) indicator on phenotype indicator, as well as confirmation of causality. Journal bias favours publication of positive results.

Compiled from Joost et al,[8] Kalupahana and Moustaid-Moussa,[9] Hall, Morley, and Lucke, [11] Wittwer et al,[12] Vimaleswaren and Loos,[16] Caulfield,[17] Ioannidis et al,[18] Rimbach and Minihane,[19] and Bouchard and Agurs-Collins[20]

personalised to the individual's genotype to ensure optimal prevention or treatment outcomes. With this in mind, the clinical application of such screening tests needs to be considered. Should screening only apply to individuals with a family history of a particular disease, or those with diagnosed risk indicators, or who present with the disease? Should healthy individuals with no diagnosable risks of a disease, or family history thereof, be screened? The latter may result in intervention in asymptomatic individuals, for a disease that may never develop,[7,21] as the predictive value of susceptibility SNPs is low.[8]

For application in evidence-based practice, susceptibility testing should meet the following criteria:

- The clinical validity of the test must have been clearly established,[22] following the steps outlined in Table I.
- Evidence-based, acceptable and accessible interventions must be available to those who test positive for a particular susceptibility genotype.[21]
- Health professionals, including dietitians, who are competent in interpreting the outcomes of such tests, and in counselling clients accordingly, must be in place.[11,22]

Whether or not these criteria are met by commercialised susceptibility gene screening, has been questioned in different forums.

Evans et al[24] contend that available interventions are often untested. They also mention that recommendations are very likely to be based on presumed benefit, rather than on outcomes of well-designed interventions. When considering genotype-based nutrition (lifestyle) counselling for obesity treatment, the counselling would most likely involve behaviour strategies aimed at changing dietary intake (decreased energy intake), and physical activity (increased energy expenditure), to a greater or lesser extent. These recommendations are in line with current non-genotype-based recommendations for the prevention and management of obesity. Whether or not gene screening would result in the fine tuning of such recommendations to measurably improve prevention or treatment outcomes significantly, is still ambiguous.

Genotype-based personalised nutrition for the prevention and treatment of obesity

Obesity develops when energy intake exceeds energy expenditure. According to Stipanuk,[23] the interaction between genotype and environmental factors possibly explains the majority of variance in body weight: "Obesity is most likely to occur when a genetically susceptible individual encounters an environment that is conducive to obesity".

Identification of susceptibility genes for obesity initially followed the candidate gene approach (Table II). The latest (2005) and last update of the obesity gene map, reported 127 genes associated with obesity phenotype indicators.[24] In 2010, Vimaleswaran and Loos[16] reported that findings for only 12 of these genes were replicated in 10, or more, studies. When considering these results, it must be borne in mind that many other studies report no, or opposite, associations for these 12 genes. The conclusions regarding true associations thus remain contradictory. In recent years, a number of larger-scale studies and meta-analyses have shown robust associations between four of these genes and obesity indicators. These four genes include melanocortin 4 receptor gene (*MC4R*; involved in the regulation of food intake and energy homeostasis), adrenergic B3 receptor (*ADRB3*; involved in regulation of lipolysis and thermogenesis), prohormone convertase 1/3 gene(*PCSK1*; involved in activating prohormones to hormones involved in energy metabolism regulation), and brain-derived neurotropic factor gene (*BDNF*; involved in eating behaviour, body weight regulation and hyperactivity) (as summarised by Vimaleswaran and Loos).[16] Research on the effect of the interaction between genotype for these genes and diet (and other lifestyle) indicators on obesity indicators is scarce, while well-designed interventions to confirm causality could not be traced.

Table II: Identification of susceptibility genes for obesity: candidate gene and genome-wide association approaches

Candidate gene approach
First edition of the obesity gene map, based on the candidate gene approach. Published in 1996. Yearly updates, with the last edition published in 2005. Hypothesis-driven identification of candidate genes, based on current understanding of biology and pathophysiology. Genes selected based on functional role in relevant metabolic pathways, evidence from animal studies, monogenic forms of obesity, and association studies. SNPs within, or near, candidate genes, for a condition or disease of interest, e.g. obesity, are considered. Limited success, mainly due to small, inadequate samples. Large samples or meta-analyses are needed to detect small effects (odds ratios 1.2-1.3).
Genome-wide association approach
Initiated in 2005. Investigates entire genome, with no prior assumptions regarding potential associations and functionality. Aims to identify previously unsuspected loci associated with a condition or disease, e.g. obesity, in large samples. Genome-wide association typically comprises two or more stages: *Stage 1: Discovery phase* Genotyping for > 100 000 gene variants across the genome. Testing for associations with disease or disease indicators with significance threshold: p-value $< 5.0 \times 10^{-8}$. This may result in false positive outcomes. *Stage 2: Replication phase* Significant associations identified in the discovery phase are taken forward for replication (validation). Only replicated findings are deemed to be "true hits". The next stages would involve fine mapping of relevant genetic regions (loci) to identify the functional single nucleotide polymorphisms, and subsequent identification of biological pathways that explain associations.

Adapted from Vimaleswaren and Loos[16]

The complexity of translation of nutrigenetics-related information into evidence-based dietary guidelines can be illustrated using the *ADRB3* Trp64Arg polymorphism that has been included in some commercial gene screens for personalisation of weight-loss recommendations, as an example. Meta-analysis of association studies has shown that Arg64-allele carriers have a 0.24 kg/m^2 higher BMI, compared to the Trp64Trp homozygotes in Asians.[25] This association was not found in Caucasians.[25,26] One of the very few studies on the effect of the interaction between the presence of the ADRB3 Trp64Arg polymorphism, and diet indicators on BMI (obesity phenotype indicator), was conducted by Miyaki et al[27] in Japanese subjects. These researchers concluded that only Arg 64 allele carriers with the highest energy intakes exhibited an increased obesity risk. A number of researchers have also investigated the effect of the *ADRB3* Trp64Arg polymorphism on the response to a standard conservative diet (thus not personalised according to genotype, and is not a confirmation of causality) in Caucasians (sample sizes 25-85)[27-30] and Asians (sample sizes 24-88).[29-31] Asian, but not Caucasian, Arg64 allele carriers, were found to lose less weight and fat, especially visceral fat, when exposed to a conservative weight loss programme. Translation of these findings into genotype-based personalised weight-loss guidelines could involve recommendations for very low energy intakes and high levels of physical activity for Asian Arg64 allele carriers. Whether such genotype-based guidelines are truly effective should be tested in well-designed intervention studies, once causality has been established. No such research could be traced for the *ADRB3* Trp64Arg polymorphism, indicating that screening for this SNP for personalisation of weight-loss diets would be premature at this point in time.

According to Vimaleswaran and Loos,[21] genome-wide association (GWA) scans are rapidly contributing to more insight in the field of obesity genetics. Through GWA scans, the *FTO* gene (fat-mass and obesity-associated gene) has been confirmed as the first gene that is unquestionably associated with common obesity. Ongoing research to identify the functional role of the *FTO* gene in relevant metabolic pathways, indicates that it is most probably implicated in controlling energy homeostasis and eating behaviour.[34-39] Certain SNPs in this gene have also been associated with increases in BMI, as well as decreased lipolytic activity, independent of BMI.[35,40] However, investigation of the effect of the interaction between FTO genotypes and diet indicators on obesity indicators, as well as confirmation of causality, is only beginning to emerge.

The process of identifying further loci (specific locations of genes on chromosomes) associated with obesity is ongoing. Speliotes et al[41] reported 18 new loci that are associated with BMI at genome-wide significance level (p-value $< 5.0 \times 10^{-8}$), bringing the total number of such loci to 32. These findings were based on a GWA meta-analysis, including approximately 249 796 individuals of European ancestry. Speliotes et al[41] predict that 284 further common loci with effects on BMI, similar to the confirmed loci, may be identified in future. It is important to note that the combined effect of the SNPs at the 32 confirmed loci on the variance in BMI is a modest 1.45%, bearing in mind that the estimated heritability of obesity is estimated to be 40-70%.[40] Furthermore, resequencing and fine mapping of most of the identified loci still need to be carried out to identify causal SNPs. Clear connections to the biology of weight regulation are also not known for most of the loci. Speliotes et al[41] emphasise that

Table III: Ethics-related points for consideration in the implementation of genotype-based personalised nutrition

Key aspect	Points to consider
Robust causality and intervention effectiveness (utility) evidence	Limited availability of robust evidence, both for causality and effectiveness of genotype-based nutrition. This may result in non-evidence-based recommendations and practice.
Analytical validity of genotyping	Occurrence of laboratory errors in gene analyses. This may be especially true for uncontrolled online and home test kits.
Informed consent	Informed consent should cover the small risk contribution of single-nucleotide polymorphisms to polygenic diseases, available interventions, deoxyribonucleic acid banking or storage, and disclosure of information (intended and unintended) to relatives. The testing of children for adult onset polygenic diseases (with parents' consent) is a concern.
Test recommendation, interpretation and subsequent counselling	The availability of health professionals, including dieticians, who are competent in recommending, interpreting the outcomes of evidence-based tests for susceptibility single nucleotide polymorphisms, and appropriate counselling of clients.
Privacy of information and discrimination	Protection of privacy rights, i.e. right not to disclose test results to employers, medical and other insurance providers. This is complicated by a lack of understanding of the nature of polygenic conditions, as well as the associated low-risk contribution of single-nucleotide polymorphisms by employers, insurance companies and society, which may result in various forms of discrimination.
Advertising and media coverage of tests and public expectation	Advertisements and media coverage of commercial tests contribute to popular understanding of genotype-based personalised nutrition. They may not necessarily reflect evidence-based information, and may result in consumers being misled or even harmed. Public expectation is not necessarily motivated by the discovery of hidden abnormalities, but rather by the need for reassurance (that members of the public have no unusual problems).
Psychological impact	A positive test may result in anxiety about increased disease risk, while the risk for development of the disease may be low. This might result in a fatalistic approach to personal health management, and might divert attention away from modifiable lifestyle risks. A negative test may cause relief, resulting in a perception of "no genetic risk", and a maverick approach ("No need to heed the guidelines for a healthy lifestyle") .
Equity	Availability to all sectors of the population.

Compiled from Bergman et al,[8] Hall et al[11] Levesque et al,[42] Caulfield,[17] DeBusk et al[44] Harvey-Berino et al,[45] Austin,[46] McGovern et al,[47] Kotze and Badenhorst,[48] Juth,[49] Huijgen et al.[50]

genomic and experimental studies should be designed to elucidate functionality of the identified SNPs to provide much-needed insight into the biology of obesity.

Ethical issues related to genotype-based personalised nutrition

The increasing application of nutrigenetics research outcomes in genotype-based personalised nutrition has resulted in a discourse on potential ethical issues (Table III) on various platforms. According to Levesque et al,[42] ethical developments in this field have been outpaced by nutrigenetics bioscience. Marketing of genotype-based personalised nutrition, especially online, and often without the input of appropriately qualified health professionals, now seems to be common practice. The potential nonadherence to relevant ethical principles, as mentioned in Table III, and lack of regulation in this regard, are serious concerns. It may be argued, as Ioannidis[17] points out in an editorial on "personalised genetic prediction", that "we adopted nearly all pregenomic-era tests without waiting for large, well designed, pragmatic randomised trials". However, Ioannidis goes on to say that "we should not use past mistakes as an excuse for present inaction". This view supports that of Caulfield,[43] who, after their investigation of marketing dilemmas associated with current nutrigenetic services, concluded that it is important for more research to focus on the ethical, legal, and social aspects of such services, to ensure evidence-based, cost-effective practice in the prevention, or treatment of, common nutrition-related diseases.

Conclusion

The escalation of identification of new loci associated with obesity indicators seems daunting. It is clear that translation of these insights into evidence-based guidelines for the prevention and treatment of obesity depends on the identification of causal SNPs in loci associated with BMI, establishment of the functional roles of identified SNPs in obesity-related metabolic pathways, investigation of the effect of the interaction between genotypes for specific SNPs and lifestyle (dietary intake and physical activity) indicators on obesity indicators, and confirmation of causality. All these outcomes should be integrated, using, for example, systems genetics to account for interactions between genes, diet, other lifestyle factors, disease, and time (life cycle span).

Conclusions formulated by various researchers on the translation of nutrigenetics research into personalised nutrition, including obesity prevention and management, indicate that generally, scientists hold the opinion that more research is necessary before evidence-based practice in this area can be guaranteed (Table IV).

Ultimately, when behaviour change for the improvement of health outcomes is considered, whether genotype-based or not, some practice-related issues will remain. The most pertinent of these are that people will continue to develop diseases, while non-compliance to prevention or disease management guidelines, disparities in access to health services, and the potential for unproven and fraudulent medical practices and malpractice, will remain as challenges.[2] In an editorial in *Nature outlook*, Grayson[51] summarises the situation as follows: "Some people predict an age of diets customised to individual energy needs and disease susceptibility. But no matter how good the science is, or how well we are able to exploit food as an agent of healthfulness, we will still be eating for pleasure for some time yet".

Meanwhile, while evidence seems to be accumulating for possible personalisation of nutrition based on genotype, Simopoulos[52] recommends the dissemination of dietary guidelines that are in line with the *South African food based dietary guidelines* at population level, to prevent disease and improve nutrition-related health outcomes in general.

Table IV: Selected conclusions on the status of genotype-based personalised nutrition in peer-reviewed publications, 2007-2010

Author	Quote
Joost et al[8]	"Current attempts to derive dietary recommendations, based on a few single SNPs presently known to be associated with particular complex diseases, appear largely experimental."
Bergman et al[7]	"At present, the evidence base for genotype-specific dietary advice is limited. This may change, but it seems too early to estimate how autonomy and benefits should be balanced against each other in such a possible future."
Rimbach and Minihane[19]	"Although the evidence base in nutrigenetics is growing, with sufficient data to provide a 'proof of principle' of its potential utility in public health, this area currently suffers from a lack of consistent findings."
Bouchard and Agurs-Collins[20]	"Finally, a major challenge will remain as to how to translate advances in our understanding of gene-behaviour interaction effects for public health consumption, when promoting weight gain prevention, and for clinical practice, in the context of treatment of obesity, and its associated morbidities."
Kussmann et al[3]	"Genome-wide associations have identified a number of (candidate) risk loci for the development or (early) onset of certain diseases, including common and complex ones. However, the power of these risk loci to predict health trajectories, has, so far, been small, even if several loci have meanwhile been replicated, and taken together in a combined score."
De Caterina[1]	"The background science is there, but how close are we to the goal of implementing personalised nutrition based on genetic knowledge? We are not there yet."

Authors are presented in ascending order, based on publication date.

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