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Nutrigenetics of Blood Cholesterol Concentrations: Towards Personalized Nutrition

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Abstract

Purpose of the Review To summarize achievements made in the field of nutrigenetics to personalized nutrition. Moreover, the limitations and challenges observed to enable clinical utilization are discussed.

Recent Findings Currently, with the availability of low-cost genetic testing and new bioinformatics tools, significant developments have occurred to allow issues inherent to the highly complex nature of genetic data to be tackled. Moreover, new statistical methods have uncovered combinatory patterns of SNPs that collectively explain the high interindividual variability in response to dietary interventions. Yet, the application of these results to personalized dietary recommendations is not straightforward.

Summary Data from gene-nutrient interaction studies have provided evidence to understand the inter-individual variation differences in blood cholesterol responses. A need exists for guidelines and regulations in order to apply nutrigenetics to personalized nutrition. Moreover, a multisystem approach including genetics, microbiome and environment is needed to achieve possible practical applications.

Keywords Gene-nutrient interactions · Lipid · Cardiovascular disease · Single nucleotide polymorphisms · Genetic variant

Introduction

Cardiovascular disease (CVD) is still the most common cause of death globally, and 80% of premature heart disease and stroke are estimated to be preventable [1•], with lifestyle modifications, including diet, considered as the first line of treatment [2]. The completion of the Human Genome Project has led to a better understanding of human genetic variability and with the advent of affordable genotyping and sequencing technologies, our understanding of the genetic basis of CVD has greatly increased. Genome-wide association studies (GWAS) enable the scanning of the entire genome in order to identify genes and/or loci significantly associated with a given phenotype [3, 4]. To date, 161 loci have been associated with coronary artery disease and CVD risk factors such as dyslipidemia, type 2 diabetes, elevated blood pressure, and body mass index [5••, 6, 7]. Despite these advances, it has to be stressed that only a small part of the total variance of factors associated with CVD can be explained by genetics [8]. Indeed, certain environmental factors, including dietary habits, may interact with an individual's genetic characteristics and lead to the disruption of metabolic pathways which may contribute to the development of CVD. Thus, the possibility of offering personalized nutrition advice to individuals with a genetic susceptibility for dyslipidemias or CVD risk is a promising strategy. In this narrative review, we discuss the

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progression of the research on gene-nutrient interaction studies for CVD risk and dyslipidemias, in particular, elevated blood cholesterol. Moreover, we will describe the future challenges in the field of nutrigenetics as it relates to personalized nutrition.

Contribution of Single SNP Studies to Nutrigenetics of Dyslipidemia

Nutrigenetics explores the interactions between genes and nutrients and their effects on human health [9]. Early studies in nutrigenetics provide strong evidence of the relationship between single-nucleotide polymorphisms (SNPs) and single dietary components. For example, it has been previously shown that carriers of the A-allele for a SNP located in the promoter region of *APOA1* exhibited higher HDL-C concentrations when they consumed a diet high in PUFA [10]. This was one of the first studies showing that changes in diet might compensate for the genetic effects influencing blood cholesterol concentrations. Thus, the idea of personalized nutrition recommendations based on genetics has become a new approach to improve health.

Another example is the evidence related to *APOE*. It is well-known that certain *APOE* polymorphisms have been associated with higher risk of CVD occurrence [11]. In particular, carriers of the APOε4 isoform have a 46% increased risk of CVD compared to carriers of the APOε3 [11]. In the early 1990s, it was found that carriers of APOε4 had higher serum total cholesterol concentrations after consuming a high-cholesterol diet (800 mg/d) compared to APOε2 carriers [12, 13]. Moreover, early studies from Ordovas and colleagues also showed that APOε4 carriers benefited more from a low-fat, low-cholesterol diet in lowering their plasma cholesterol concentrations [14]. These studies show that knowledge of an individual's genetic background might improve the outcomes of a dietary intervention.

This hypothesis was recently examined in a large randomized trial, the Food4Me project [15]. Data from 5562 European participants were collected during 1 year [15]. Of these, the first 1607 participants were recruited into a randomized clinical trial, with the purpose of investigating the effectiveness of three types of nutritional interventions differing in their degree of personalization: (1) receiving healthy eating guidelines, (2) advice based on each individual's dietary intake and anthropometric profile (weight, body mass index, and waist circumference), or (3) advice based on an individual's dietary intake, anthropometrics, and genetic data related to five genetic variants in *FTO*, *FADS1*, *TCF7L2*, *APOE*, and *MTHFR* [15]. For the purpose of our review, we will focus only on the outcomes related to *APOE*. The results showed that knowledge of genotypic data in *APOE* resulted in significantly greater reductions in dietary intake of total and saturated fat compared to receiving healthy eating guidelines alone [16•]. However, individuals carrying the APOε4 isoform did not show a greater reduction in dietary fat intake compared to non-carriers of the risk allele. Although this intervention only followed participants for 6 months, its results suggest that personalized nutrition advice facilitates changes in behavior which may result in improvement of health in the longer term. In addition to this, data from the Food4Me study showed that factors such as age, alcohol intake, baseline concentration of total cholesterol, glucose, stearic acid, docosapentaenoic acid, eicosapentaenoic acid, eicosenoic acid, and trans-fatty acids in blood were significantly associated with the response after the intervention [17••]. Thus, more work is needed for a deeper understanding of the interactions between genetics and other factors, such as environment and lifestyle, influencing an individual's response to a dietary intervention. It might require the use of larger databanks from robust studies together with artificial intelligence technologies in order to fully understand these interactions.

Contribution of Combinatory Patterns of SNPs to Nutrigenetics of Dyslipidemia

Although the study of the effect of a specific SNP on the variability in the response to a dietary intervention provides valuable information, it can only constitute a first step in the building of mathematical models aiming at predicting this response in new subjects. Indeed, such models would likely include many SNPs, in genes involved in lipid metabolism and transport, that combined would increase the sensitivity and specificity of these predictive models. For example, a study in 101 normolipidemic adults found that after consumption of three servings/day of dairy (low-fat milk, low-fat yogurt, and cheese) for 4 weeks, carriers of the GG genotype of rs6720173 in *ABCG5* who also carried the G-allele of rs3808607 in *CYP7A1* had higher total cholesterol and LDL-C concentrations compared to C-allele carriers of rs6720173 who also carried the TT genotype of rs760241 in *DHCR7* [18]. Moreover, a re-analysis of this study also showed that carriers of the C-allele of rs6720173 in *ABCG5*, TT genotype of rs3808607 in *CYP7A1*, and GG genotype of rs760241 in *DHCR7* had reductions in LDL-C concentrations (− 0. 37 mmol/L) compared to those with the combination of GG genotype of *ABCG5*, G-allele of rs3808607 in *CYP7A1* and A-allele of rs760241 in *DHCR7* who showed an increase in LDL-C concentrations (+ 0.38 mmol/L) after the intervention [19•]. Thus, these results showed that carrying a particular set of alleles in several genes influenced the response to a dietary intervention.

Another study examined the effect of the consumption of 2 g/day of plant sterols over 28 days on blood cholesterol in relation to *APOE* and *CYP7A1* genotypes in 63 mildly

hypercholesterolemic individuals [20]. This study found that carriers of GT and GG genotypes of rs3808607 in *CYP7A1* and with the APOε4 isoform had a greater decrease in LDL-C concentrations after plant sterol consumption compared to carriers of the TT genotype of rs388607 and with the APOε3 isoform [20]. Furthermore, this study replicated previous findings from De Castro Orós et al., where carriers of the AA genotype of rs3808607 in *CYP7A1* showed only 2 to 6% reduction in total cholesterol concentration compared to carriers of the AC+CC genotypes who showed up to 6.7% reduction in total cholesterol concentration [21].

Additionally, following DNA array genotyping and focusing only on SNPs in 126 candidate genes, it was shown using partial least squares regression that a combination of 42 SNPs could explain a significant part of the variance in the postprandial chylomicron triacylglycerol response to dietary fat in 33 healthy male adults [22••]. All these studies highlight the additive effects of several SNPs which, taken individually, may have a small significant effect, but when combined together could explain a significant part of the variability in response to a diet/nutrient.

Besides the fact that interesting findings have emerged from gene-nutrient interaction studies, we are still quite far from personalized nutrition based on genetics only. Currently, machine-learning technologies are innovative tools with a great potential to integrate multiple features to identify better predictors to design an individualized dietary intervention. In this regard, a further aspect to consider is the important role of the microbiome.

A recent study used an algorithm incorporating genetic and microbial factors to study 92 CVD-related proteins [23]. This study found that genetics and microbial factors collectively explained up to 77% of inter-individual variation [23]. Other studies have also highlighted the influence of the gut microbiome on the high inter-individual variability in response to a dietary intervention. For example, a study used an algorithm to predict the postprandial glucose response (PPGR) of 800 participants to design individualized nutrition plans [24••]. The analysis included blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measurements. The analysis demonstrated that the prevalence of *Eubacterium rectale* was associated with lower PPGR, whereas *Parabacteroides distasonis* was associated with higher PPGR. Furthermore, this algorithm was validated in 100 participants, where this replication achieved similar results compared to the original cohort of 800 participants. Indeed, these results show that the gut microbiome could also be key to identifying responders and non-responder to a dietary intervention [24••]. Therefore, complex algorithms need to integrate multiple features to design individualized dietary interventions. In this regard, the acceptance of genetic testing among the public is high and continuously growing [25]. Therefore, transparency in methodologies among studies, validation, and replication in larger randomized controlled clinical trials are needed.

Nutrigenetics and Personalized Nutrition: Challenges Ahead

To date, nutrigenetics studies have shown that the effects of genes might be mitigated by lifestyle modifications, which stresses that personalized dietary recommendations, adapted to an individual's genetic characteristics, may reduce the prevalence of dyslipidemia, and therefore prevent or delay the development of CVD and other chronic diseases. However, many gaps and limitations need to be overcome. First, the translation of the information evolving in the field of nutrigenetics to health professionals is still in the early stages [26]. A survey conducted among 373 registered dietitians revealed that these professionals do not feel qualified to integrate information from nutrigenetics studies into their practice [27]. Therefore, in the near future, educators, nurses, and health professionals will require appropriate education and training to implement results from nutrigenetic analysis into personalized dietary recommendations [28••]. In this regard, the Global Nutrigenetics Knowledge Network has issued several guidelines to evaluate the scientific evidence in order to assist in integrating this information for clinical practice [29]. These guidelines are the beginning of better standardization of research protocols to report and replicate gene-nutrient interactions. Furthermore, the National Human Genome Research Institute has developed more reliable sources such as GeneCard® (human gene database) and PhenX tool (a web-based catalog of standard protocols for collecting data for phenotypes and environment factors to identify gene-environment interactions) to standardize procedures for data collection related to nutrigenetics studies [30, 31]. Thus, better guidelines and transparency of the methods used for the validity of the gene-diet associations might allow the field of nutrigenetics to become an important part in personalized nutrition [29].

Second, validation and replication of findings from gene-nutrient interaction studies are still needed prior to being used for personalized dietary advice. Ordovas et al. [32] describe that the major weakness in the field of nutrigenetics is the low reproducibility among studies, lack of evidence from well-designed randomized controlled trials, and a follow-up of individuals over time. Yet, the potential usefulness of this research field calls for increased efforts to decipher the numerous gene-diet interactions that can influence the way an individual responds to a specific diet. Indeed, although many factors are involved in the interindividual variability of response to diets, genetics has the advantage of being stable over the lifetime and thus allows for prevention of diseases with late or progressive onset, such as CVD.

Third, it would be necessary to evaluate the use of the information from gene-nutrient interaction studies in health nutrition policies. In this context, dietary reference intake recommendations must be individualized according to genotype [33]. There is currently no substantial information in support of this application. Finally, the use of the information from nutrigenetic studies raises ethical, legal, and social issues that researchers and health

professionals must address before reaching clinical applications [33, 34].

Conclusion

The field of nutrigenetics is rapidly, and, given appropriate replication of current results, this information possesses the potential to be directly applied towards personalized dietary recommendations to manage, treat, or prevent CVD. As discussed here, there is an increased understanding of how genes influence the variability of individuals' responses to dietary interventions. However, standardized protocols and regulations are needed before the information from nutrigenetics studies can be used for personalized nutrition recommendations. Moreover, a need exists to incorporate multi-omic measures to understand the molecular dynamics during the development of CVD, which might provide essential information for tailoring dietary advice.

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Compliance with Ethical Standards

Conflict of Interest Itzel Vazquez-Vidal and Charles Desmarchelier declare that they have no conflict of interest. Peter J. H Jones has received research grants from Nutritional Fundamentals for Health Inc., Mitacs, and the International Life Sciences Institute. He also owns stock in Nutritional Fundamentals for Health Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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