Review

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Nutrigenomics: SNPs Correlated to Lipid and Carbohydrate Metabolism

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Abstract

Background. Nutrigenomics - the study of the interactions between genetics and nutrition - has emerged as a pivotal field in personalized nutrition. Among various genetic variations, single-nucleotide polymorphisms (SNPs) have been extensively studied for their probable relationship with metabolic traits.

Methods. Throughout this review, we have employed a targeted research approach, carefully handpicking the most representative and relevant articles on the subject. Our methodology involved a systematic review of the scientific literature to ensure a comprehensive and accurate overview of the available sources.

Results. SNPs have demonstrated a significant influence on lipid metabolism, by impacting genes that encode for enzymes involved in lipid synthesis, transport, and storage. Furthermore, they have the ability to affect enzymes in glycolysis and insulin signaling pathways: in a way, they can influence the risk of type 2 diabetes. Thanks to recent advances in genotyping technologies, we now know numerous SNPs linked to lipid and carbohydrate metabolism. The large-scale studies on this topic have unveiled the potential of personalized dietary recommendations based on an individual's genetic makeup. Personalized nutritional interventions hold promise to mitigate the risk of various chronic diseases; however, translating these scientific insights into actionable dietary guidelines is still challenging.

Conclusions. As the field of nutrigenomics continues to evolve, collaborations between geneticists, nutritionists, and healthcare providers are essential to harness the power of genetic information for improving metabolic health. By unraveling the genetic basis of metabolic responses to diet, this field holds the potential to revolutionize how we approach dietary recommendations and preventive healthcare practices. ***Clin Ter 2023; 174 Suppl. 2 (6):200-208 doi: 10.7417/CT.2023.2488***

Key words: *Nutrigenomics, single-nucleotide polymorphisms, SNP, lipid metabolism, carbohydrate metabolism, personalized nutrition, metabolic disorders.*

Introduction

In recent years, the intersection of genetics and nutrition has garnered significant attention within the field of molecular biology and health sciences: in particular, the field of nutrigenomics, which focuses on elucidating the intricate relationship between an individual's genetic makeup and their dietary responses, has been in the limelight (1). To better understand what nutrigenomics encompasses, it is pivotal to comprehend some basic concepts. So far, it is well-established that every human being is unique; however, each person also has a unique nutritional blueprint inside their genes, the expression of which can be influenced by various bioactive food nutrients (2). Furthermore, genomic diversity varies among different ethnic groups, thus affecting nutrients bioavailability and their metabolism. Nutrigenomics usually involves multiple fields, including nutrition, molecular biology, epidemiology, bioinformatics, and genomics. It primarily uncovers how genetic variations influence the body's metabolism, nutrient absorption, and overall health outcomes (3).

The concept that individuals respond differently to the same diet is not new. However, recent breakthroughs in genetic sequencing have enabled researchers to explore the underlying genetic factors responsible for these variations (4). The holistic approach of nutrigenomics bridges the gap between genetics, nutrition, and health, aiming to develop tailored dietary recommendations for optimal well-being. This is particularly relevant in conditions that are influenced by both genetic and nutritional components. Genetic variations have been implicated in the development of various conditions—including gastrointestinal cancers, many gastrointestinal disorders, and inflammatory diseases (5, 6). Imbalances in nutrient levels contribute to issues like the aging process, alcoholism, various types of cancer, cardiovascular diseases (CVDs), hearing impairment, immune system dysfunctions, diabetes, and stroke (7).

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Nutrigenomics and Obesity

Obesity is deemed a core element of metabolic disorders, which usually includes impaired glucose tolerance, hyperinsulinemia, and noninsulin-dependent diabetes mellitus. The susceptibility to developing obesity is dependent upon genetically determined patterns of energy balance regulation (8). In the last ten years, significant advancements have unveiled numerous polymorphic genes responsible for regulating both central and peripheral factors, influencing energy intake and expenditure. Polymorphisms within these genes can impact the regulation of food consumption. These genes encompass taste receptor coding genes as well as various signaling peptides (like insulin, leptin, ghrelin, and cholecystokinin) along with their respective receptors, which collectively play a pivotal role in controlling food intake (9). Hypothalamic neuropeptide Y, agouti-related protein, and various factors within the melanocortin pathway are among the central regulators responsible for polymorphic energy intake (10, 11). Furthermore, significant genetic variations have been identified in the genes governing energy expenditure modulation. These genes include alpha and beta-adrenoceptors, uncoupling proteins, as well as regulators involved in the growth and differentiation of adipocytes (12).

Another aspect of obesity is inflammation. In obese individuals, macrophages infiltrate adipose tissues and stimulate the release of inflammatory molecules, including interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α), along with inflammatory modulators, like adiponectin and leptin (13, 14). Nutritional components are key factors that can modulate metabolic inflammation in obese individuals (15). Diets rich in sugars and refined grains can increase the expression of pro-inflammatory cytokines. On the other hand, the Mediterranean diet (MedDiet), being rich in monounsaturated fatty acids, can decrease the expression of inflammatory cytokines (16-19); similarly, fruits and vegetables can provide adequate quantities of health-promoting bioactive compounds (20, 21). In a randomized control trial by Camargo et al., the effect of MedDiet on reducing pro-inflammatory gene expression was validated. Their findings showed that MedDiet, enriched with virgin olive oil, lowered the expression of NF-kB p65 gene and elevated IkB α gene expression (22). NF-kB has been linked with elevated levels of proinflammatory cytokines, such as IL-6 and TNF-α (23).

Nutrigenomics and CVDs

Similar to obesity, CVDs are also influenced by a combination of genetic factors and environmental factors (diet). Research has established a strong link between diet composition and the risk of CVD (24, 25). Furthermore, obesity is also a risk factor for CVDs. Atherosclerosis, a complex process involving disruptions in lipid metabolism and chronic inflammation is considered central to the pathogenesis of CVD (26). Persistent elevation of total cholesterol, LDL cholesterol, and triglyceride levels in the blood contributes to the formation of atherosclerotic plaques, while higher levels of high-density lipoprotein (HDL) cholesterol appear to offer protection. Genetic diversity in genes responsible for apolipoproteins, enzymes, and hormones can influence an individual's susceptibility to CVD. Some of these genetic variants are responsive to dietary modifications. For instance, individuals carrying the E4 allele in the apolipoprotein E gene tend to have higher levels of LDL cholesterol compared to those with other alleles (E1, E2, and E3) (27). Apolipoprotein A1 (ApoA1), mainly present in HDL particles, is associated with HDL-cholesterol concentration (28).

Notably, research by Ordovas et al. (29) demonstrated that the A allele was correlated with reduced serum HDL levels. Interestingly, this genetic effect was reversed in women who consumed more polyunsaturated fatty acids (PUFA). In men, this relationship was more pronounced when accounting for alcohol consumption and smoking. For instance, a specific polymorphism in the hepatic lipase gene is linked to increased protective HDL levels when compared to the TT genotype (more common in certain ethnic groups, like African–Americans), particularly in response to a high-fat diet (30). A study by Estruch et al. reported that a PUFA-enriched diet (such as extra virgin olive oil) can decrease the low-density lipoprotein receptor-related protein (LRP1) gene expression (31). Similarly, another study by Llorente-Cortés et al. showed that dietary components can modulate the expression of pro-atherothrombotic genes in susceptible individuals (32). Apart from obesity and CVDs, the role of various nutritional factors is well-established in other conditions including polycystic ovary syndrome, retinal diseases, lymphedema and COVID-19 (33-39).

Single Nucleotide Polymorphisms (SNPs) and Metabolic Significance

At the heart of nutrigenomics lie single nucleotide polymorphisms (SNPs), the most common form of genetic variation among individuals (40). SNPs involve the substitution of a single nucleotide base at a specific position in the DNA sequence. While most SNPs have no discernible impact on health, some can significantly affect the function of proteins, enzymes, and other molecules involved in metabolism. These functional SNPs can contribute to variations in nutrient metabolism and response to dietary components. Previously, Ames highlighted the critical role of this genetic diversity in influencing the individualized requirements for nutrients and subsequent physiological responses (41). Within expressed genes, missense single nucleotide polymorphisms are encountered at an approximate frequency of 1 in every 1000 bases (42). Therefore, it is reasonable to anticipate an abundance of additional polymorphisms that will emerge from studies focused on micronutrients and dietary behaviors. Each gene can be likened to a recipe dictating the synthesis of particular proteins or protein groups. These proteins either orchestrate pivotal biological processes or serve as the foundational constituents of bodily structures like collagen. Some SNPs introduce modifications to the gene's recipe, leading to either the production of a distinct protein quantity or the transformation of the structural arrangement of protein molecules (43).

Aim of the review

Currently, there is a lack of literature that provides comprehensive evidence on SNPs related to lipid and carbohydrate metabolism. This review aims to provide the current body of evidence regarding the latest developments regarding SNPs in lipid and carbohydrate metabolism.

Methodology

For this review, a comprehensive search was carried out in PubMed and Google Scholar to find relevant studies on the topic. We used Boolean operators AND and OR to combine appropriate keywords. The search terms used included "Nutrigenomics" OR "Nutrient-gene interactions" OR "Nutrigenetic variations" AND "Lipid metabolism" OR "Fatty acid metabolism" OR "Cholesterol metabolism" AND "Carbohydrate metabolism" OR "Glucose metabolism" AND "Single Nucleotide Polymorphisms" OR "Genetic variations" OR "Polymorphic genes". The study selection was limited to meta-analyses, multicenter studies, reviews, systematic reviews, observational studies, case-control studies, longitudinal/prospective studies, retrospective studies, and randomized controlled trials. We further refined our search by limiting the publication to English studies only. Furthermore, texts available only in abstract form were excluded.

Results and Discussion

Polymorphisms and Their Possible Effects on Nutrition

Polymorphisms play a key role in establishing how our bodies absorb, metabolize, and respond to nutrients. These variations can ultimately lead to the development of health-related conditions. Genetic polymorphisms linked to diverse metabolic pathways have been investigated through genome-wide association studies (44). Furthermore, the connections between genetic variations and dietary consumption have been explored through epidemiological and interventional research (45). For example, some instances of such associations include 1) the relationship between the APOA2 (c.2265T>C) variant and saturated fatty acid intake, as well as body mass index; 2) the correlation between MTHFR variants and homocysteine levels; 3) the link between CYP1A2 variants and the hypertensive response triggered by caffeine (46, 47). The genomic revolution of the past few decades has propelled our understanding of genetics to unprecedented heights. The mapping of the human genome, launched in 1990 and finished in 2003 opened doors to a treasure trove of information about our genetic blueprint. Within this genetic diversity lies the key to comprehending why some people thrive on certain diets while others struggle, and why certain nutritional interventions yield remarkable results for some but not for others (48, 49).

The influence of polymorphisms on nutrition is multifaceted: for instance, the well-known MTHFR gene variant affects the enzyme responsible for converting folate into its active form, which is crucial for various biological processes, including DNA synthesis and repair (50). Individuals with this polymorphism may have an impaired ability to metabolize folate, which makes them more susceptible to certain health issues, like neural tube defects and cardiovascular diseases. MTHFR has been associated with increased breast cancer risk in individuals with reduced intake of vitamin B6, vitamin B12, and folate. However, a review by Chen et al. has reported that MTHFR C677T gene polymorphism is associated with breast cancer risk among Asians, but not Caucasians (51). Understanding these genetic nuances is crucial for tailoring personalized nutrition recommendations.

Carbohydrates, Their Metabolism, and Their Role

Among the essential macronutrients, carbohydrates emerge as a focal point of this intersection between nutrition and genetics. Their metabolism within the human body plays a pivotal role in energy production, cellular function, and disease susceptibility. Carbohydrates have long held the limelight in the realm of nutrition. From ancient civilizations subsisting on grains to modern diets shaped by cultural and industrial shifts, they have been a dietary staple. Comprising sugars, starches, and fibers, carbohydrates serve as a primary source of energy for the human body (52).

While the fundamental role of carbohydrates as an energy source is widely acknowledged, the interplay between carbohydrate consumption, genetic makeup, and health outcomes has only recently been illuminated through the lens of nutrigenomics. The journey begins with the digestion of complex carbohydrates into simpler sugars, such as glucose. The roles of carbohydrates extend beyond their energy-providing function: a prime example are dietary fibers, a subset of carbohydrates that is indigestible by human enzymes but act as substrates for gut microbiota. This symbiotic relationship between the gut microbiome and dietary fibers underscores the emerging concept of "second genome," where microbial genes actively interact with our human genes to influence metabolism, immunity, and disease susceptibility (53). Nutrigenomics research has demonstrated how certain genetic variants impact the body's response to dietary fibers, potentially affecting the microbial composition of the gut and subsequently influencing an individual's risk of obesity, inflammatory disorders, and even mental health conditions (54).

Lipids, Their Metabolism, and Their Role

One area of particular interest within nutrigenomics is the study of lipids—a diverse group of organic molecules that play fundamental roles in cellular structure, energy storage, and signaling. Understanding lipid metabolism and its role in human physiology is essential for uncovering the intricate connections between our dietary habits, genetic predispositions, and the development of various health conditions. Lipids, encompassing diverse molecules such as fatty acids, triglycerides, phospholipids, and cholesterol, serve as the structural foundation of cellular membranes, contributing to their integrity and fluidity. Central to the

Table 1. Carbohydrate-Related Genes, Their Polymorphisms, and Their Association with Metabolic Traits and Obesity-Related Risks

RsID	Gene	Polymorphism function	Alleles	wt/mt	References
rs266729	ADIPOQ	Diminished hormone levels	G/G	mt/mt	(55)
		Diminished hormone levels	C/G	wt/mt	
		Typical	C/C	wt/wt	
rs2167270	LEP	Risk of high BMI and insulin resistance	A/A	mt/mt	(55)
		Risk of high BMI and insulin resistance	G/A	wt/mt	
		Typical	G/G	wt/wt	
rs7799039	LEPR	Increased risk of high BMI	A/A	mt/mt	(56, 57)
		Increased risk of high BMI	A/G	wt/mt	
		Typical	G/G	wt/wt	
rs5219	KCNJ11	Impaired glucose-induced insulin secretion with high BMI Greater impairment of insulin release	T/T	mt/mt	(58, 59)
		Impaired glucose-induced insulin secretion with high BMI	C/T	wt/mt	
		Typical	C/C	wt/wt	
rs11185098	AMY1	Lower amylase activity Bad at breaking down carbs	A/A	mt/mt	(60)
		Intermediate amylase activity Still good at breaking down carbs	A/G	wt/mt	
		Typical	G/G	wt/wt	
rs659366	UCP2	Increased risk of higher BMI	T/T	mt/mt	(61-65)
		Increased risk of higher BMI	C/T	wt/mt	
		Typical	C/C	wt/wt	
rs1800849	UCP3	Lower glucose levels Better weight loss on high protein/low carb diet	A/A	mt/mt	(66)
		Less weight loss No decrease in glucose or insulin levels on high protein/low carb diet	A/G	wt/mt	
		Typical	G/G	wt/wt	
rs1801282	PPARγ2	Increased risk of insulin resistance	G/G	mt/mt	(67, 68)
		Increased risk of insulin resistance	C/G	wt/mt	
		Typical	C/C	wt/wt	
rs116987552	PYGM	Absence of the enzyme	A/A	mt/mt	(69)
		Deficiency of the enzyme	G/A	wt/mt	
		Typical	G/G	wt/wt	

study of nutrigenomics is the realization that our genetic makeup influences how our bodies interact with and respond to dietary components, including lipids. Genetic variations can impact enzymatic activities involved in lipid metabolism, affecting the way we process and utilize dietary lipids. For example, certain individuals may possess genetic variants that lead to decreased activity of enzymes responsible for breaking down specific types of dietary fats (70). As a result, these individuals might have a higher risk of accumulating excess fat and facing associated health challenges.

The influence of dietary lipids on gene expression adds another layer of complexity to the nutrigenomic landscape. Emerging research suggests that dietary lipids can act as signaling molecules, modulating gene expression and influencing metabolic pathways. Omega-3 and omega-6 fatty acids, for instance, have been shown to regulate the expression of genes involved in inflammation, lipid oxidation, and insulin sensitivity (71, 72). Variations in lipid metabolism genes can impact the production of these lipid mediators, influencing an individual's susceptibility to chronic inflammatory conditions and cardiovascular diseases.

SNPs Correlated to Macronutrients

The food we consume not only provides our body with the energy to function, but also act as a foundation for our overall well-being. However, the impact of nutrition goes beyond the generic understanding of food as mere sustenance. Macronutrients, including lipids and carbohydrates, play a crucial role in energy production, growth, and overall health. The efficiency of our body's metabolism is influenced by genetic factors, which can vary significantly among individuals due to SNPs. Individuals with different genetic profiles respond differently to macronutrient intake. Studying SNPs allows us to understand how an individual's genetics might impact their ability to metabolize and utilize lipids and carbohydrates. This knowledge can lead to personalized dietary recommendations that optimize health outcomes. Certain genetic variations can increase the susceptibility to metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular diseases. Identifying and understanding SNPs associated with these conditions can aid in early disease detection and prevention. Knowledge of genetic variations

Table 2. Lipid-Related Genes and Their Polymorphisms

RsID	Gene	Function	Alleles	wt/mt	References
rs174547	FADS1	Decreased fatty acid desaturase enzyme activity	C/C	mt/mt	(55)
		Decreased fatty acid desaturase enzyme activity	T/C	wt/mt	
		Typical	T/T	wt/wt	
rs1558902	FTO	Risk for high BMI, but not associated with problems related to obesity Better response to high-protein diets	A/A	mt/mt	(73-76)
		Somewhat increased risk for high BMI	A/T	wt/mt	
		Typical	T/T	wt/wt	
rs5082	APOA2	Increased risk of high BMI, particularly with diets rich in saturated fats	G/G	mt/mt	(40, 77-79)
		Typical	A/G	wt/mt	
		Typical	A/A	wt/wt	
rs662799	APOA5	32% increase in triglyceride levels	G/G	mt/mt	(40, 77, 80-82)
		16% increase in triglyceride levels	A/G	wt/mt	
		Typical	A/A	wt/wt	
rs5128	APOC3	Higher fasting plasma levels of APOC3, TG, TC and LDL-C	G/G	mt/mt	(40, 77, 83)
		Higher fasting plasma levels of APOC3, TG, TC and LDL-C	C/G	wt/mt	
		Typical	C/C	wt/wt	
rs2070895	LIPC	Significantly higher HDL-C level	G/G	mt/mt	(77, 84, 85)
		Significantly higher levels of FPG, TC, TG	G/A	wt/mt	
		Significantly higher levels of FPG, TC, TG	A/A	wt/wt	
rs987237	TFAP2B	Better response to high-protein diets for weight management	A/A	mt/mt	(84, 86)
		Typical	A/G	wt/mt	
		Typical	G/G	wt/wt	
rs11591147	PCSK9	Decreased LDL-cholesterol	T/T	mt/mt	(87-90)
		Decreased LDL-cholesterol	G/T	wt/mt	
		Typical	G/G	wt/wt	
rs72646508	PCSK9	Decreased LDL	T/T	mt/mt	(87, 88, 91)
		Decreased LDL	C/T	wt/mt	
		Typical	C/C	wt/wt	
rs505151 E670G	PCSK9	Increased LDL	G/G	mt/mt	(87, 88, 92-94)
		Increased LDL	A/G	wt/mt	
		Typical	A/A	wt/wt	
rs328	LPL	Lower triglycerides	G/G	mt/mt	(95-97)
		Lower triglycerides	C/G	wt/mt	
		Typical	C/C	wt/wt	
rs268	LPL	Higher triglyceride	G/G	mt/mt	(96, 98)
		Higher triglycerides	A/G	wt/mt	
		Typical	A/A	wt/wt	
rs1800592	UCP1	Weak protein activity Probable increase of abdominal fat and high BMI	C/C	mt/mt	(61, 99)
		Probably typical risk for high BMI	C/T	wt/mt	
		Typical	T/T	wt/wt	
rs3734398	ELOVL2	Decreased conversion of EPA to DHA	C/C	mt/mt	(100, 101)
		Decreased conversion of EPA to DHA	C/T	wt/mt	
		Typical	T/T	wt/wt	

can guide the development of targeted interventions and therapies for individuals with specific genetic predispositions, which could involve customized dietary plans or the use of specific medications to counteract the effects of certain SNPs.

Key Genes and SNPs in Lipid and Carbohydrate Metabolism

Several genes are known to harbor SNPs that influence lipid and carbohydrate metabolism. Some of the most important genes and SNPs in this context include:

ApoE Gene: The ApoE gene is associated with cholesterol metabolism and plays a role in lipid transport. Specific SNPs in this gene have been linked to variations in cholesterol levels and the risk of cardiovascular diseases. Furthermore, it has been shown that ApoE is linked with age-related risk for Alzheimer's disease and plays critical roles in Aβ homeostasis (102).

Pparg Gene: The Pparg gene is involved in regulating lipid and glucose metabolism. Certain SNPs in this gene can impact insulin sensitivity, lipid storage, and the risk of type 2 diabetes (103). A study by Hevener et al. reported that muscle-specific Pparg deletion resulted in insulin resistance in mice (104).

FTO Gene: The FTO gene is associated with obesity and appetite regulation. Variants of this gene have been shown to affect energy expenditure and the preference for high-calorie foods. A study by Hunt et al. reported that BMI increases associated with FTO genotypes begin in youth and are maintained throughout adulthood (105).

SLC2A2 Gene: This gene encodes a glucose transporter and is vital for glucose uptake into cells. SNPs in SLC2A2 can impact glucose homeostasis and the risk of diabetes.

LIPC Gene: The LIPC gene encodes an enzyme that plays a role in lipid metabolism. Certain SNPs in this gene are associated with variations in HDL cholesterol levels.

The field of nutrigenomics is still evolving, and there are several promising directions for future research. As we gather more data on the interaction between SNPs and macronutrient metabolism, we can develop more precise nutrition guidelines, tailored to an individual's genetic makeup. This could revolutionize dietary recommendations and improve health outcomes. While SNPs are important, epigenetic modifications – changes in gene expression without altering the DNA sequence – also play a role in macronutrient metabolism. Future research could focus on understanding how diet and lifestyle choices interact with genetic and epigenetic factors. Exploring how genetic variations and their effects on macronutrient metabolism differ among different ethnicities and geographical populations could provide a more comprehensive understanding of the complex interactions.

Conclusions

Each individual harbors a unique nutritional pattern, encoded within their genes. Bioactive compounds in food and essential nutrients wield an influence over how these genes are manifested. Significant evidence has demonstrated that food like the Mediterranean diet can influence the functioning of various genes. These diets can reduce inflammation and thus the progression of various chronic diseases. Studying the connection between SNPs and how our bodies process fats and carbohydrates has a lot of potential in the field of nutrigenomics. This could greatly improve how we understand individualized nutrition and taking care of our health. Figuring out how genes and our diet interact is important because it could lead to personalized advice on what to eat, spotting health issues early, and creating treatments that are tailored to each person. As scientists keep learning more, nutrigenomics could really change how we think about staying healthy in the future.

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Conflicts of interest statement

Authors declare no conflict of interest.

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