REVIEW

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Role of genetic polymorphism in nutritional supplementation therapy in personalized medicine

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Abstract

Genetic-guided nutritional supplementation therapy in personalized medicine is the type of treatment that prevents and acts against errors during the copying process of a cell's deoxyribonucleic acid (DNA), mistakes that lead to diversification in the DNA sequence at certain locations, called single nucleotide polymorphisms (SNPs). Positive results are quickly achieved using one of the four types of therapy. These types are: personalized, when individual human genetic variations drive individual treatment, preventive, with a tailored healthcare strategy and therapeutic preventive drugs and vaccines, participatory, when empowered patients make informed choices and take responsibility of their own health and predictive, using a proactive approach to health and medicine.

Keywords: DNA, single nucleotide polymorphisms, nutritional supplementation, healthcare strategy.

Introduction

Genome-oriented medicine analyzes genetic variations that influence disease susceptibility, disease progression, therapeutic response and unwanted drug reactions [1]. Genomics have applications in areas like ancestry, carrier status, identity (paternity, forensics), pharmaceutical response, health condition risk, athletic performance capability, over the counter (OTC) product response, toxin processing and predictive wellness profiling (aging, cancer, immune response) [2].

The central objective of personalized medicine is to adapt the diagnosis to the individual biological profile to the patients. Some studies showed that the reactions to drugs are extremely varied from one patient to another, from minor side effects to death. A study published in 1998 estimated that in 1994, in USA hospitals, about 2.216 million patients presented intense reactions to the drugs used, requiring admission medical supervision, while about 106 000 died because of the sides effects [3, 4]. Pharmacogenomics studies showed that there are over 2000 genes involved in the human body response to drugs [5]. Due to these reasons, there is considered that it is necessary a more intensely personalized medicine that should provide patients with the efficient drugs, with no side or harmful effects. Medicine has always been personalized, as doctors, when prescribing treatments, keep in mind the environment, behavior and genetic factors that may affect the disease response to drugs. Nevertheless, the genetic factors are extremely variable, and the pharmacogenomics studies in clinics are still limited [6]. Moreover, the drug action can be influenced by diet, alcohol intake or the metabolic profile of the individual. That is why the evaluation of the metabolic profiles for anticipating the efficiency of the administered drugs has important advantages. Genetic studies, and especially those on genetic polymorphisms, may provide the doctor with essential data for an accurate medical attitude for every patient. Genetic polymorphism refers to the reappearance, within a population of two or more discontinuous genetic variants, of a specific mark in such quantity, that they cannot be maintained simply by mutation. Examples include the sickle cell trait, the Rh factor, and the blood groups [7].

The genetic information indicates a potential, carried in the base sequence of an organism's deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) (in some viruses), according to the genetic code.

Single nucleotide polymorphisms (SNPs)

To make new cells, an existing cell divides in two. But first, it copies its DNA so that the new cells will each have a complete set of genetic instructions. Cells sometimes make mistakes during the copying process – kind of like typos. These typos lead to variations in the DNA sequence at particular locations, called single nucleotide polymorphisms, or SNPs [8]. SNPs can generate biological variation between people by causing differences in the recipes for proteins that are written in genes. The human gene variants are subject to evolution. They are named according to how frequently they occur: the type most widely distributed is the wild type (WT) (homozygous type), followed by the heterozygous type (HET), and, finally, the mutation (MUT), with less than 0.1% [9].

Medical scientific studies have revealed that it is not individual gene variants, which are responsible for the risk of a disease but that the interaction of various lifestyles with certain gene variants significantly influences health and disease [10, 11].

Considering genetic testing in the context of lifestyle

is a reasonable step at any age because small changes in lifestyle may have sizeable health effects. While knowing which polymorphisms an individual has does not enable us to predict whether they will develop a specific disease, it does enable us to identify risks in conjunction with an unadjusted lifestyle, and thus, we can take precautions [12].

Somebody who carries the polymorphism for a higher risk of inflammation such as "couch potatoes" who carry the APOE4 (apolipoprotein E4 gene) polymorphism and eat a high-fat diet, have a 3- to 4-fold increased risk of developing Alzheimer's disease [13–15]. In people with genetic lactose intolerance, permanent consumption of dairy products (even of lactose-free milk) either negatively affects hormone production and compromises neurotransmitter balance (promoting the spread of a disease of old age, Alzheimer's disease); or it stimulates the production of antibodies against milk proteins (in the long run, the casein will cause constipation, fatigue, etc.). The late effects go subjectively unnoticed over years, are seen as related to other causes, or accepted as inevitable [16].

A heterozygous genotype is generally associated with a weak to moderate genetic predisposition for a modified activity of the respective isoenzyme [17]. The accumulation of several variant genotypes coding for isoenzymes of the same family of enzymes can have a major impact on the corresponding metabolic pathway [18].

A homozygous genotype is, depending on the affected isoenzymes, linked to a significant increase or decrease of the enzyme activity [19]. Some ("zero") genotypes are associated with a total absence of enzyme activity either through an absence of biosynthesis of the protein or through the expression of a truncated, non-functional protein.

Although a genetic predisposition can be present, a personalized diet and supplementation as well as a change in lifestyle will allow the patient to act against the potentially negative effects in a targeted and personal way.

Disorders in the lipid metabolism are implicated in the etiopathogenesis of atherosclerosis. Genotypes that have an influence on risk factors associated with the development of atherosclerosis for the following genes [20, 21]:

▪ Carriers of the defective ApoB-100 have an elevated risk for premature atherosclerosis if not treated [elevated low-density lipoprotein (LDL)-cholesterol] [22].

▪ ApoE is a glycoprotein of 299 amino acids (34 kDa), which participates in uptake of cholesterol and triglyceride-rich lipoproteins as well as in the regulation of their catabolism. Carriers of E4 genotype have high atherogenic potential, high cholesterol and high LDL-cholesterol [23].

▪ The LDL receptor (LDLR) plays an essential role in the lipid metabolism. Mutations, which decrease affinity or break the bonds of LDLR with its ligands, are associated with familial hypercholesterolemia (FH). Familial hypercholesterolemia is a common genetic cause of premature coronary heart disease [24].

▪ If the PCSK9 protein is functional, it is involved in the degradation of LDLRs in lysosomes. The PCSK9 gene can be affected by "gain of function" and "loss of function" variations. The "loss of function" – variation of PCSK9 (R46L) is associated with hypocholesterolemia and a decreased PCSK9 activity.

▪ The HMGCR gene codes for the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) enzyme. This enzyme plays an important role in cholesterol biosynthesis by exerting a limiting activity on cholesterol production. The HMGCR (C-911A) variation is associated with elevated cholesterol levels.

▪ Cholesteryl ester transfer protein (CETP) is a pro-atherogenic plasma glycoprotein. It facilitates the transfer of the cholesterol esters from high-density lipoprotein (HDL) to very-low-density lipoprotein (VLDL) and LDL, thus diminishing the protective HDL-cholesterol effect. Carriers of the B2 allele show a reduced CETP enzyme activity and elevated HDL and ApoA1 levels.

▪ The LPL (S291N) polymorphism is associated with an increase of triglyceride levels. The D9N polymorphism is associated with a decreased LDL particle size.

▪ Genotype 514CC – carriers of the homozygous variant genotype for the LIPC (lipase C, hepatic type) gene show a reduced efficiency for statins at the level of cholesterol.

▪ Fatty acid-binding protein 2 (FABP2) is only expressed in enterocytes. This protein has a high affinity for saturated and unsaturated fatty acids. Its function consists in the uptake and the intracellular transport of long-chain fatty acids. The phenotype associated with the homozygous variant 54TT genotype is characterized by an increased affinity for long-chain fatty acids, which induces an increased uptake of fatty acids in the duodenum and an increase of the pre- and postprandial triglyceride levels in the plasma. This may lead to a low metabolism rate, a tendency to gain weight/increase the body fat and to problems related to bodyweight or body fat reduction.

▪ The wild type PP for the peroxisome proliferator-activated receptor gamma (PPARγ) (P12A) polymorphism is associated with increased pre-prandial insulin levels and an increased glycemia (glucose level in the blood). Carriers of the "P" allele present a reduced sensitivity to insulin compared to non-carriers of this allele. A PPARα deficiency decreases insulin sensitivity. The homozygous variant genotype CC is considered as the risk genotype for type 2 diabetes. The presence of the "P" allele is associated with higher pre-prandial insulin levels and hyperglycemia in comparison with carriers of the homozygous variant genotype AA [25].

▪ The presence of the heterozygous genotypes for the leptin (LEP) (A-2548G) and leptin receptor (LEPR) (Q223R) polymorphisms is associated with significantly increased leptin levels in the blood, which represents a risk factor for obesity and type 2 diabetes.

▪ The homozygous variant TT genotype detected for the guanine nucleotide-binding protein (GNB3) (C825T) polymorphism is associated with arterial hypertension and components of the metabolic syndrome (*e.g.*, dyslipidemia, hypercholesterolemia, insulin resistance and obesity) (Table 1).

Weight control

In order to increase the energy expenditure and stimulate adiponectin-dependent metabolic processes, patients are advised to eat sufficient amounts of protein, include ginger and capsaicin-rich food in meals, drink

green tea or supplement with green tea extract, reduce the amount of calories in their diet, consume omega-3 fatty acids, palmitoleic and oleic acids, increase the intake of polyphenolic compounds such as *p*-coumarin, quercetin and resveratrol and reduce their linoleic acid consumption. For a better appetite control, try to exercise regularly, have a regulate sleep pattern, avoid sugars and food with high glycemic index, increase your intake of tryptophan, reduce the amount of calories in your diet and prefer food rich in protein and fiber. Optimize your lipid metabolism by including olive oil and seed oil in your meals, increasing your isoflavone intake, avoiding high carbohydrate and high fat intake before physical activity, considering lotus leaf extract combined with L-carnitine supplementation, enriching your breakfast with calcium and vitamin D and bringing your chromium intake to an adequate level (100–150 μg/day) and also, by avoiding low energy diets. Consuming food high in dietary fibers (soluble fibers) and omega-3 fatty acids, avoiding saturated fat intake (bacon, butter, etc.) and increasing your intake of choline will improve your cholesterol levels.

Table 1 – ***Nutri- and pharmacogenetic recommendation***

Genes encoding for:	Recommendation (nutrition)	Effects	Recommendations (drugs)
Apolipoprotein B (ApoB)	Low-fat and low-cholesterol diet; polyphenols such as flavonoids	↓ LDL and triglycerides; ↑ HDL	
Apolipoprotein E (ApoE)	Omega-3 fatty acids, soluble fibers	LDL-cholesterol ↓	
3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR)	Oleic acid (to be found in dietary oils, *e.g.*, olive oil, peanut oil)	Cholesterol synthesis ↓ *via* inhibition of HMGCR	Hypo-cholesterolemic treatment ↓ → statins
Low-density lipoprotein receptor (LDLR)	Red yeast rice, conjugated linoleic acid (in soy products, dairy products)	LDL-cholesterol ↓	Hypo-cholesterolemic treatment ↓ → statins
Protein convertase subtilisin/ kexin type 9 (PCSK9)	Nutrition rich in carbohydrates	Gene expression ↑	
ATP-binding cassette transporter subfamily A member 1 (ABCA1)	Anthocyanins (red berries, *e.g.*, cranberries, raspberries), sesamin	ABCA1 stimulation *via* PPAR*α* (peroxisome proliferator-activated receptor alpha)	Hypo-cholesterolemic treatment ↓ → statins
Cholesteryl ester transfer protein (CETP)	Allicin (to be found in garlic), poly-unsaturated fatty acids, anthocyanins	CETP activity ↓, HDL-cholesterol ↑	
Hepatic triglyceride lipase C (LIPC)	Products rich in soluble fibers (cereals, fruits and vegetables, legumes)	HDL levels ↑	
Lipoprotein lipase (LPL)	Saponins (red Korean ginseng), mulberry leaf extracts	LPL activity ↑, HDL ↑	

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ATP: Adenosine triphosphate.

Genome-wide association study (GWAS)

A genome-wide association study is an approach that involves rapidly scanning markers across the genome (≈0.5 M or 1 M) of many people (≈2 K) to find genetic variations associated with a particular disease. A large number of subjects are needed because associations between SNPs and causal variants are expected to show low odds ratios, typically less than 1.5, and, in order to obtain a reliable signal, given the very large number of tests that are required, associations must show a high level of significance to survive the multiple testing correction. Such studies are particularly useful in finding genetic variations that contribute to common, complex diseases.

Other risk factors

The heterozygous genotype TA for the FTO rs9939609 (fat mass and obesity-associated gene) is associated with a genetic predisposition for a loss of satiety, which may lead to the development of overweight. Support the anti-inflammatory capacities by: a reduction of the LDL-cholesterol level, a reduction of the triglycerides (TG) level and an increase in the HDL-cholesterol level, using omega-3 fatty acids, soluble fibers – *Psyllium*, conjugated linoleic acid (CLA) – monacolin [26].

Increase of the HDL-cholesterol level by: an inhibition of the cholesteryl ester transfer protein (CETP) activity, using aged garlic extracts (allicin, alliin, ajoene), anthocyanins (polyphenols), omega-3 and omega-6 fatty acids.

Detoxification and oxidative stress

The detoxification system consists of two phases, which involve different enzymes. An imbalance of these two phases and especially an impaired phase II detoxification are responsible for the accumulation of toxins and carcinogenic compounds. The patient's personal results on gene variations may affect the detoxification capacity.

Genetic polymorphisms in genes encoding enzymes involved in the detoxification of xenobiotics can lead to exaggerated side effects towards environmental pollutants and toxins such as those generated by cigarette smoke, frying of food at high temperatures, dental amalgam, solvents and paints, drugs, etc. Prolonged or chronic exposure to even small amounts of xenobiotics may aggravate in these cases the side effects of incomplete detoxification. In this case, it is necessary to avoid these products. Furthermore, adequate and customized nutrition may enhance the activity of an individual's detoxification and reduce the side effects.

The production of free radicals such as O_3 or H_2O_2 has both endogenous and exogenous causes. Our body has a perfect system for defense against these free radicals. The body's own protective enzymes are a part of this system. They include the superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione S-transferase (GST). These enzymes can literally catch the so-called reactive oxygen species (ROS), which is why they are also called free radical scavengers.

Oxidative stress is the imbalance which arises when too many free radicals are formed that cannot be removed by the endogenous enzymatic defense system. An accumulation of free radicals is the result.

Some genotypes are associated with a reduction of

the predictive enzyme activity and thus contribute to a decrease of the phase II detoxification capacity and to an accumulation of potentially toxic metabolites regarding some substrates. It is recommended to reduce the exposure to substrates and inducers of genes with specific genotypes. In this case, as for genotypes associated with a reduction of the organism's antioxidant defense, performing an oxidant stress markers panel is recommended. The interpretation of the results must therefore take into account the medication history and the exposure of the patient to xenobiotics. Additional supplementations with vitamin E, selenium, lycopene and omega-3 fatty acids are especially recommended for carriers of the variant genotypes for GSTM1, GSTT1 and GSTP1. An increase in the production of glutathione by the body, regardless of the genotypes, may reduce the oxidative stress and provides a better protection against many toxic substances.

Role of genetic polymorphism in cancer

Cancer is a major public health problem all over the world. In 2012, there were recorded about 14.1 million cases of cancer and about 8.2 million deaths by cancer, according to the GLOBOCAN estimations [27].

The development and progression of cancer is a process that develops in various stages, where the alteration of oncogenes, tumor suppressor genes and stability genes are responsible for tumor genesis [28].

Some genotypes predispose to an increase of phase I inducibility, with an increased risk for the production of toxins and carcinogens from the following substrates: imipramine, trimipramine, clomipramine, clozapine, propranolol, theophylline, caffeine, estrogens and tamoxifen, chlorinated polycyclic aromatic hydrocarbons (dioxin), petroliferous extracts, phenothiazines, indolocarbazoles (combustion products and tobacco smoke), nicotine and insulin. Some variations of cytochrome P1A1/cytochrome CYP2B6 (CYP1A1/CYP2B6) lead to an overexpression of the enzyme, which may result in an increased production of activated metabolites [27]. The polymorphisms linked to a change of the enzyme activity are the following: CYP2E1*5A, CYP2E1*5B and CYP2E1*6. If the variant alleles are present, the enzyme activity is slowed down. Carriers of the alleles CYP2E1*5A and CYP2E1*5B have an increased risk for an intoxication if they are regularly exposed to plastics. Furthermore, carriers of the variant alleles have an increased risk to develop a hepatocarcinoma in the case of alcoholism. The occurrence of the CYP3A5*3C allele leads to a reduction of the enzyme activity of CYP3A5.

CYP2C9*2 (C3608T) and CYP2C9*3 (A42614C) are the most frequently occurring variant alleles in Caucasians, which reduce the activity of the enzyme. The wild-type allele is named CYP2C9*1. Carriers of the homozygous variant or the compound heterozygous genotype generally display a "poor metabolizer" (PM) phenotype, *i.e.*, have a reduced capacity to metabolize CYP2C9 substrates. Genotyping of CYP2C9 allows identifying individuals who have a predisposition for an increased relative risk of blood clotting complications as well as of adverse drug reactions in the case of a treatment of epilepsy or diabetes [28].

CYP2C19*2 (G681A) and CYP2C19*3 (G636A) are the most frequently occurring variant alleles in Caucasians, which lead to a strongly reduced enzyme activity. Genotyping of CYP2C19 allows to identify individuals who have a predisposition for an increased relative risk of thrombosis and associated cardiovascular events (stroke, heart attack) with fatal outcome in some cases, as well as of adverse side effects of treatments with anticonvulsants and antidepressants [29].

The glutathione conjugation (GST) polymorphism results in a significant reduction of the enzyme activity and reduction of the organism's antioxidant defense [30]. The most important substrates of GSTs are polycyclic aromatic hydrocarbons (PAHs), epoxides, quinones, alkyl and benzyl halides as well as stilbene. The GST activity is essential for the elimination of "cellular debris", which are the result of an attack by free radicals (peroxidized lipids, altered DNA and oxidized proteins). The homozygous variant genotype for GSTT1*0 is associated with a reduction of the organism's antioxidant defense. Persons who carry the GST-T1*0 variation have an increased sensitivity to GSTT1 substrates (methyl bromide, chlorodinitrobenzene, *trans*-stilbene oxide) and have an impaired detoxification of heavy metals (mercury, lead, cadmium).

The relative risk for an increased sensitivity towards heavy metals is increased due to the presence of GSTM1, null genotype. Among the three variations of GSTM1, there is a homozygous 0/0 (zero) variation, which results in a total deficiency of the enzyme [31]. To protect the cells from oxidative stress that is increased due to the lack of GSTM1 enzyme, it is very important that the patient has a high uptake of antioxidants like vitamin C, lycopene or carotene. The patient can support glutathione conjugation by consuming precursors and co-factors of glutathione. L-cysteine, L-glycine, glutamic acid, methionine as well as alpha-lipoic acid, magnesium or selenium are examples.

A genetic variation present in the catechol-O-methyltransferase (COMT) gene can reduce the activity of COMT enzyme. To support the methylation process, the following treatment is initiated. Magnesium, vitamins B6, B9 and B12 support the synthesis of S-adenosylmethionine (SAM), a substance indispensable for the methylation processes carried out by COMT enzyme. SAM cannot be found in food, it is produced by the human body. If the COMT enzyme expressed in the patient's body presents a reduced activity, the risk that catechol estrogens get oxidized into DNA-damaging quinones is increased. However, many antioxidants present in fruits and vegetables, *e.g.*, vitamin C, vitamin E and alpha-lipoic acid can help to reduce oxidation processes and the patient profits from the high consumption of fruits and vegetables. Curcumin is also capable to reduce the oxidation of catechol estrogens and the patient should integrate turmeric into nutrition. The patient should consider to drink green tea rich in polyphenols that may reduce catechol estrogen oxidation and may help to prevent DNA damage [32].

There are two types of N-acetyltransferase (NAT): NAT1, which is principally synthesized in the bladder and NAT2, which is of hepatic origin. The substrates of these two enzymes are largely identical and include

aromatic and heterocyclic amines, nitrosamines and hydrazines (contained in grilled meat, tobacco, cured products, dyes and synthetic stains). In presence of a polymorphism, it is recommended to avoid long-term exposure to the substrates of interest [33].

Sulfotransferase (SULT) is an enzyme involved in the phase II detoxification that belongs to the family of sulfotransferases (SULTs). SULT-1A1 detoxifies many endogenous and exogenous substances such as steroids, catecholamines, iodothyronine and tamoxifen. The variant allele SULT1A1*2 is associated with a significantly decreased enzymatic activity compared to the wild-type allele SULT1A1*1.

A genetic background impacting on oxidative stress predisposes the patient to a reduced antioxidant defense against highly reactive superoxide radicals. This may result in significant damage to cell structures and increased inflammatory responses, processes that may ultimately lead to various diseases. The heterozygous genotype 16AV for the superoxide dismutase-2 (SOD-2) (A16V) polymorphism is associated with a slightly reduced enzymatic activity of the Mn-dependent SOD-2 enzyme, slightly increased oxidative stress and thus a slightly higher relative risk for cardiovascular and environmental diseases. The two polymorphisms A5V and G94A of the SOD-1 gene are associated with a reduced enzyme activity and thus with increased oxidative stress in the cells. They are associated with an increased relative risk for the development of various pathologies, in particular neurodegenerative diseases [34].

The analyzed P198L polymorphism in glutathione peroxidase (GPX) gene leads to a reduced enzyme activity and is associated with a genetic predisposition for oxidative stress. Some studies have shown that this polymorphism is associated with the accumulation of heavy metals, particularly lead, and the development of meningiomas and multiform astrocytomas.

In order to support the antioxidation processes, smoking and alcohol consumption should be stopped. Oxidative stress induced by alcohol is usually the result of a deficiency of the antioxidant defenses combined with the production of ROS by the chain of mitochondrial electron transport, cytochrome P450 CYP2E1 (inducible by alcohol) and activated phagocytes. Optimization of the defense against free superoxide radicals can be further implemented using vitamins C and E, *N*-acetylcysteine, alpha-lipoic acid, resveratrol and high uptake of aliments rich in antioxidants, polyphenols and flavonoids. Furthermore, free radicals of hydroxyethyl are generated by CYP2E1 during the metabolism of alcohol. Diet containing optimal levels of manganese, zinc, copper and magnesium can protect against these free radicals. Manganese is a cofactor of SOD2 enzyme and should be taken up in sufficient amounts *via* nutrition to support the impaired SOD2 enzyme activity [35, 36].

Conclusions

Considering the genetic polymorphism, a drug therapy can be started, guided according to the pharmacogenetic, nutrigenetic and nutrigenomic principles. Also, an analysis can be elaborated over the evolution of a pathology or how the patient responds to a particular therapy when experiencing some pathology. Genetic-guided nutritional supplementation therapy in age management is not only a personalized, preventive medicine, but also a possibility of customization, based on genetic evidence. In this context, genetic polymorphism evaluation brings into clinical practice the possibility of identifying certain degenerative health conditions in early stages even when there is merely a propensity to involution. In the same time, it could offer a means to characterize intimate mechanisms underlying the pathogenesis of these diseases. Consequently, genetic polymorphism testing provides scientific basis for a personalized therapeutic plan using the novel nutrigenomic and nutrigenetic mechanisms to compensate for deficits, to lessen the effects of identified genetic predispositions and also to generate epigenetic transformations, all in an attempt to influence a specific pathology.

Conflict of interests

The authors declare that they have no conflict of interests.

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