

MOLECULAR AND GENETIC ASPECTS OF HEALTH RISKS AND THEIR ASSOCIATION WITH ADVERSE ENVIRONMENTAL CONDITIONS AND DIETS (SYSTEMIC REVIEW)

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At present, it is vital to examine adverse effects produced on gene expression by negative environmental factors and nutrients. In this study, our aim was to generalize data available in literature on an association between health risks and polymorphisms of genes that participated in xenobiotic detoxification and allergic status, food intolerance included, in adults and children. We also considered influence exerted by various components in diets on gene expression.

Available research data indicate that GSTP1 and SOD gene polymorphisms have their effects on a decline in detoxification and antioxidant functions and early development of allergic, occupational and oncological diseases under exposure to harmful chemicals. Micronutrients in diets that can protect from adverse effects produced by chemicals can act not only as substrates but also as detoxification enzyme inducers. Great quantities of biologically active compounds in the Mediterranean diet are assumed to be able to modulate functional activity of certain genes. Such nutrients as polyphenols, flavonoids, catechins, glucosinolates, anthocyanins, stilbenes, carotenoids, polyamines spermidine and spermine produce anti-genotoxic and anti-carcinogenic effects.

Use of combined nutrigenetic and phenotypic data seems a promising trend in effective modeling of a healthy diet.

The research data outlined in this review indicate there is solid evidence that health risks can depend on a genotype, phenotype and quality of the environment. These risks also differ depending on a diet. Modeling a healthy diet based on available knowledge on nutritional genetic and nutritional genomics is a promising trend within non-carcinogenic health risk management, including risks of oncological diseases caused by exposure to adverse environmental factors.

Keywords: *gene polymorphism, detoxification, environment, phenotype, genotype, nutritional genetics, nutritional genomics, nutrients, biologically active compounds.*

Contemporary molecular genetic research is developing rapidly attracting experts of various specialties since it provides them with an opportunity to conduct profound studies with their focus on health effects of environmental and lifestyle factors on the human body in terms of genetic predisposition to a

disease. There are multiple genetic features determining individual responses to environmental exposures. Molecular genetic studies are particularly relevant in the regions with highly developed industries posing risks of adverse health outcomes, especially in children. High prevalence of pediatric allergies,

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including food intolerance, in such regions is of special concern and requires serious efforts aimed at identifying causes of metabolic disorders [1–4]. There are also studies that concentrate on developing new approaches to prevention of diseases and preservation of proper homeostasis allowing for genetic peculiarities¹. However, very few studies investigate issues concerning combined effect of ordinary nutrients and adverse environmental factors on gene, proteome, and metabolome expression. In this review, we examine publications on human responses to food quality and certain environmental factors.

In this review, **our aim** is to summarize literary data on the relationship between health risks and polymorphisms of genes that participate in xenobiotic detoxification and allergic status, food intolerance included, and on effects produced by diets on gene expression in adults and children.

Materials and methods. We performed a search for original research articles on the topic in SNPedia, PubMed, Web of Science, eLIBRARY, and Google Scholar search engines using the following keywords: gene polymorphism; gene expression; ST, SOD, NAT genes; transposable element; allergies; xenobiotics; heavy metals; food; food intolerance; epigenomics; epigenetics; nutritional genomics, and nutritional genetics. Of 396 search results, 73 papers were selected for this review.

Results and discussion. It is relevant to examine body responses to environmental exposures, especially in industrially developed areas where industrial pollutants pose serious health risks, bearing in mind that these responses depend, inter alia, on personal heredity. A high prevalence of environmental diseases in such areas, especially among children, raises concern and requires special efforts

aimed at identifying causes of metabolic disorders [1, 5].

Consequently, the analysis of published data on associations between gene polymorphisms and environmental factors and a risk of health disorders posed by exposure to environmental toxicants is of current interest in hygiene. It facilitates effective management of detected risks with nutrients being among helpful instruments. It is also important to understand the effect produced by polymorphism of the genes responsible for detoxification and development of environmental diseases on changes in the immune response. Some studies have demonstrated that interactions between genes and the environment can influence early formation of the immune system pattern and subsequent development of such allergic diseases as bronchial asthma and atopic dermatitis [6–8]. Besides, there exists convincing evidence that infants' exposure to adverse environmental factors plays a key role in gene activation or suppression by changing DNA methylation. Gene expression changes thus determining a phenotype and risks of a disease [9].

Various environmental toxicants are known to be able to stimulate production of reactive oxygen species inducing inflammation and sensitization and causing damage to cells of the respiratory epithelium [10, 11]. Susceptibility to inflammation is deemed to be characterized by inherited deficiency of detoxification efficiency. Glutathione-S-transferases (GST) coded by the GSTP1, GSTT1, and GSTM1 genes are among the enzymes able to conjugate many hydrophobic and electrophilic compounds with reduced glutathione and to detoxify a wide range of toxins and carcinogens [12–14].

Gene polymorphism can lead to partial or complete loss of glutathione-S-transferase

¹ Volobuev V.V., Polunovskii V.V., Tsvetkovich A.V., Seledtsova L.A. Pat. RF RU 2691145. Sposob formirovaniya individual'nykh dieticheskikh rekomendatsii na osnove DNK anali-za: patent na izobretenie [Patent Number RU 2691145 C2. A method of developing individual dietary recommendations based on DNA test results], 2019.

activity. The SNP database contains descriptions of 13 single nucleotide polymorphisms (reference sequences) of the most frequently investigated GSTP1 gene, four of the GSTM1 gene, and three of the GSTT1 gene². Since GSTP1 is the dominating GST that participates in xenobiotic detoxification and is expressed intensively in the respiratory epithelium of the lung [15, 16], it is postulated that the altered GSTP1 activity in the bronchial tissue can affect xenobiotic detoxification causing inflammation and oxidative stress [17]. Some studies showed that the GSTP1 Val105/Val105 genotype was less frequent in patients with a history of atopy while GSTP1 Ile105/Ile105 was more frequently found in those with severe bronchial obstruction/hyperresponsiveness than in healthy people [18]. However, it was later reported that carrying the GSTP1 Val105/Val105 slow activity genotype was associated with airway inflammation in asthma [19]. The studies examining South African schoolchildren revealed a significant protective effect against atopy in children with one or two copies of the allele G of glutathione-S-transferase GSTP1 rs 1695 [20].

Another study confirmed the role played by genes controlling the anti-oxidant system in the development of childhood allergic disease following the exposure to traffic-related pollution in infants (0–1 years). High levels of inhalation exposure to nitrogen oxide made children with the Ile105Val/Val105Val GSTP1 genotypes more susceptible to allergens [21].

Bad habits, such as smoking, can increase the toxic burden. Some researchers gave convincing evidence of the relationship between specific detoxification-gene variants, ability to detoxify components in cigarette smoke in smoking mothers, and the orofacial cleft risk [22]. However, in population studies, small samples represent a serious

challenge for estimating the association between gene polymorphisms, environment and sensitization to common allergens.

Poor detoxification of environmental carcinogens can affect susceptibility to these chemicals and induce neoplasms; the latter can, in its turn, depend on the activity of certain genes. For example, experts observed an obvious interaction between the GSTT1-null and the N-acetyl-transferase 2 (NAT2) slow activity genotype that influenced susceptibility to colorectal cancer was observed [23]. The CYP1A1 gene polymorphism (G allele of rs1048943 and C allele of rs4646903) can increase risks of colorectal cancer by raising the levels of activated metabolites with high carcinogenic potential [24]. N-acetyltransferases (NAT) catalyze the enzymatic acetylation of aromatic amines, mainly xenobiotics. The most abundant data in literature are available in studies that investigate the role played by histone acetylation providing gene transcription activity in the development of lung and colorectal cancer [25, 26]. Smokers with the GSTM1-null genotype are at a higher risk of bladder cancer [27].

The GSTP1 Ala114/Val114 gene polymorphism can promote earlier development of occupational diseases related to airborne chemical hazards, allergen-induced asthma, and respiratory hypersensitivity, whereas the GSTP1 Ile105/Val105 genotype protects from them [28]. Literature sources provide data on the association between GSTP1 Ile105Val and Ala114Val polymorphism and ophthalmic pathology in workers employed in metallurgy and exposed to chemical factors and high temperatures [29]. The GSTP1 Ile105Val genotype was shown to be a potential risk factor causing both inflammatory and dystrophic changes in the eye [30].

Superoxide dismutases (SOD) also play a significant role in detoxification. They are a widely spread group of antioxidant metallo-

² SNPs3D. Available at: <http://www.snps3d.org> (October 02, 2022).

proteinases, which consists altogether of three genetically different isoforms coded by the SOD1, SOD2, and SOD3 genes, the activity of which is apparent in the cytoplasm, mitochondria, and extracellular space, respectively. The best-studied SOD1 gene affects lipid metabolism by inhibiting activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase [31, 32]. Single nucleotide polymorphisms (SNPs) in workers exposed to occupational hazards can change gene activity, moderate the protein function, and have some other effects at the molecular level. This may lead to less effective detoxification and antioxidant protection and earlier development of occupational diseases and neoplasms. Thus, the results of studying the relationship between occupational lead exposure and brain tumors give certain evidence of the fact that lead can induce multiform glioblastoma and meningioma through the mechanisms of oxidative damage [33, 34].

Genetic characteristics of the SOD2 haplotypes (TAA, TCA, TCG, and CCG) influence the risk of lung tumors in the conjunction with the smoking status and a number of cigarettes per day; at the same time, people with the TCG haplotype have a lower risk of lung adenocarcinoma, which confirms the hypothesis about the effect produced by a genetic profile on detoxification [35].

Susceptibility to noise-induced hearing loss also can depend on the genetic background. A Chinese case – control study established a noise protection factor in rs2070424 of the SOD1 gene in A allele carriers compared with those with the G allele [36].

At least 45 % of the human genome is comprised of transposable elements (TEs), which have been recently shown to participate in cellular functions and gene remodeling. TEs induce irreversible genetic lesions making the host's genome develop multiple protective mechanisms that involve a wide range of inhibition ways to minimize their effects. Regulation of epigenetic modifications and DNA-associated histone proteins

using small RNA is aimed to suppress TEs expression. Suppression of TEs proliferation and related harmful mutations is considered to be the main function of cytosine methylation. Genome demethylation activates TEs expression while DNA hypomethylation is most closely connected with carcinogenesis as a potential TEs deregulation [37, 38]. Environmental pollution, including that with heavy metals, influences interactions between TEs and genome by enhancing adverse effects of the contaminants [39].

Metabolic processes in the body reflect a complex process of interaction with the environment. The overwhelming majority of nutrients enters the body through the gastrointestinal tract; it is, therefore, of interest to investigate changes in gene expression in response to the intake of various food components and in relation with adverse health effects of environmental factors. Such studies typically aim to search for ways to prevent many diseases. Xenobiotic metabolism is associated with detoxification enzymes. Chemoprotective micronutrients can act not only as substrates but also as inducers of these enzymes. For example, it is assumed that abundant biologically active compounds in the Mediterranean diet can modulate functional activity of GSTM1, GSTT1, GSTP1, and NAT2 genes [40]. Nutriogenetic studies often investigate GSTP1, GSTM1, GSTT1, and NAT2 isozymes. Deletion GSTM1 and GSTT1 polymorphisms were shown to result in a complete loss of enzymatic activity whereas other SNPs such as the GSTP1 p.Ile105Val (c.313A>G) (rs1695) reduced enzymatic activity of the NAT2 (590G>A-rs1799930) [40–42].

Induction of glutathione-S-transferase is intensified by isothiocyanates (sulforaphane) contained in cruciferous vegetables; these substances become involved into biotransformation of phase II detoxification, thus promoting clearance of carcinogens and preventing DNA alterations [43]. Some studies found a relationship between the excessive

intake of cruciferous vegetables and colorectal adenomas. The established link between low activity of GSTP1 GG (A313G) and/or GSTA1 TT (C69T), accumulation of glucosinolates, secondary metabolites found in Brassicaceae and related families, and cancer is obviously associated with expression of the 1-CYP1A2 phase gene induced by indole-3-carbinole (glucosinolate derivative) and accumulation of genotoxic products. Long-term stimulation with excessive quantities of cruciferous vegetables does not help neutralize slow activity by glutathione-S transferases [44]. Flavonoids conjugate with glucuronide and sulfate and are excreted with urine and bile. As a result, polymorphisms of the UDP-glucuronosyltransferase and sulfotransferase can facilitate changes in the phytochemical clearance and flavonoid effectiveness. Genetic polymorphisms in the enzymes that metabolize phytochemical substances can partially explain different levels of risk of certain diseases; they should also be considered within the context of other aspects of human genetics [44, 45]. Rocket (*Eruca vesicaria* subsp. *sativa*) that contains carotenoids, vitamin C, dietary fiber, polyphenols and glucosinolates, is distinguished among cruciferous vegetables as the plant having a pronounced antigenotoxic effect [46].

The potential of dietary interference in inflammation becomes obvious through changes in methylation of the GSTP1 gene and LINE-1 (a transposable element in the gene sequence that changes their transcription activity; it belongs to retrotransposon family in the human genome) [47] as well as telomere length ratio. The DNA methylation mechanism underlies antioxidant and anti-inflammatory effects of the functional components of foods (catechins, flavonoids, anthocyanins, stilbenes, and carotenoids) [48]. Dietary polyamines spermidine and spermine produce many physiological effects similar to those produced by antioxidant and anti-inflammatory agents [49]. Fermented rice bran inclusion in the diet can also help reduce

DNA damage by reactive oxygen species (ROS) and associated inflammation at earlier stages of a disease [50]. Data have been accumulated on the impact of flavonoids, such as genistein, quercetin, and epigallocatechin gallate, on biological systems in the human body. They induce Nrf2/ARE nuclear receptors that regulate expression of antioxidant enzymes and phase II detoxification enzymes coded by such genes as GST (P, T, M) SULT, NAT, NQO1, UGT, and GPX [51]. Various studies have proven that dietary polyphenols (epigallocatechin in green tea, turmeric acid in cinnamon, resveratrol in grapes, and curcumin in curcuma) can induce dramatic changes in epigenome of tumor cells and be used for cancer prevention [52]. Many nutrients, being ligands of various transcription factors, can affect the immune response and inflammatory reactions, e.g. phytoestrogens in fruits and vegetables that exert their influence on relevant receptors thereby producing anti-inflammatory, antioxidant and anti-tumor effects [53]. It is assumed that the protective effect produced by soya against prostate cancer is associated with epigenetic modifications (demethylation) of DNA in tumor suppressor genes by the CpG island promoter [54]. Dietary intake of a wide range of antioxidants can be inversely associated with the risk of stomach cancer altered by genetic variants rs 1871042 in the GSTP1 gene [55]. Without normal functioning of GSTT1, increased consumption of dried meat during pregnancy accounted for a higher risk of brain tumors in children [56].

Diallyl disulfide (DADS) in garlic was shown to activate genes regulating normal cell division, similar to sulforaphane in cruciferous vegetables [57]. Basic mechanisms of effects produced by DADS in prevention and/or treatment of diseases include inhibition of inflammation, oxidative stress, and cellular apoptosis. In addition, DADS can produce neuroprotective effects and protect endothelium of the heart and other organs from cell or tissue damage caused by toxic

cants [58]. Garlic oil was established to have a protective effect against hepatocarcinogenesis induced by nitrosodiethylamine (NDEA). The activity of nuclear transcription factors of the peroxisome proliferator-activated receptor and anti-inflammatory effects can be, at least partially, associated with modulation of enzymes involved in liver phase I detoxification, including cytochrome P450 (CYP2E1, CYP1A2 and CYP1A1), and phase II enzymes, including glutathione-S-transferases (GST) [59, 60].

There are also data on the impact exerted by polyunsaturated fatty acids on lipid metabolism and thermal genesis [61–64].

Gut microbiota plays a significant role in metabolic processes in the body and correction of allergies as immune system disorders. Microorganisms help metabolize bioactive compounds contained in foods (ellagic acid and ellagitannins are metabolized into urolithins), thus modulating their bioavailability. In addition, gut bacteria produce numerous bioactive low molecular weight compounds able to play a role in epigenetic processes (e.g., folic acid, butyrate, biotin, and acetate) and are responsible for absorption and excretion of such elements as zinc, selenium, iodine, and cobalt [65, 66]. Experiments on rats and human cell line THP-1 demonstrated the effect of inducing expression of IL-8, TNF α and IL-10 cytokine genes by exposure to three probiotic strains *Lactobacillus rhamnosus* K32, *Bifidobacterium longum* GT15, and *Enterococcus faecium* L-3 and their supernatants. In particular, in human cell culture, enterococci and products of lactobacillus metabolism stimulated only TNF α expression. It, in its turn, activated Nf-kB, a major transcription factor able to control expression of genes responsible for the immune response, apoptosis and cellular cycle. Live *Bifidobacterium longum* GT15 caused simultaneous expression of genes responsible for formation of IL-8, TNF α , and IL-10 cytokines while live *Enterococcus faecium* L-3 increased mRNA that coded

TNF α [67]. Gut microbiota can influence the activity of histone deacetylase (HDAC) through microbe metabolites. This enzyme is involved in various pathologies and diseases, from cancer and colitis to cardiovascular diseases and neural degeneration. HDAC is inhibited by butyric acid produced by human gut bacteria following the consumption of dietary fibers contained in berries, fruits, vegetables, and legumes [68].

Jagoë with colleagues [69–71] reported individual variations of gene expression associated with obesity and blood pressure after food deprivation and consumption in the same person. A complex adaptive program is usually activated during fasting; it induces transcriptional changes that facilitate protein degradation and suppress glucose oxidation in muscles [70], giving the opportunity to determine a molecular phenotype in the context with a disease. Moreover, a transcriptional response to food intake is stable [69].

The data presented in this review provide convincing evidence that human health risks can depend on the genotype, phenotype, and environmental factors. Besides, an individual diet may also modify risks [71]. If we understand how environmental factors and nutrients influence the genome, DNA hypomethylation, histone acetylation, and other little-studied metabolic processes in the body, we can manage these complex processes more effectively.

It is worth noting, however, that human studies are usually limited by the search for marker genes and the analysis of gene associations in population groups with this or that disorder, chronic diseases or in people who stick to a specific diet with exactly known contents of certain nutrients. Such studies are considered to be unable to provide unambiguous results since statistical correlations become less significant when pooling data obtained on different populations and ethnic groups. Responses to dietary interferences may vary considerably between people even within the same genetic sub-group [42, 72].

Achievements in precision nutrition have given the opportunity to identify genetic mutations that can increase the risk of certain diseases, including cancer, in case of specific nutrient deficiencies. These mutations can potentially serve as new or unconventional biomarkers for predicting diseases and pre-clinical signs [73]; they can be also used in individual diet modeling to reduce adverse environmental effects, increase body detoxification capabilities and resistance. A promising trend in this sphere is an attempt to combine nutriogenetic and phenotypic data, biomarkers included, to create a new nutrition model.

Conclusions. The data presented in this review provide convincing evidence that human health risks can depend on the genotype, phenotype, and environmental factors. Be-

sides, an individual diet may also modify risks. Nutrition modelling based on expertise in genomics, epigenomics, nutritional genetics, and nutritional genomics is a promising trend in managing risks of environmental, occupational, and other non-communicable diseases, including cancer.

A complex approach to assessing personalized clinical and phenotypic characteristics, such as individual food preferences, food intolerance and allergies, cultural and social factors, lifestyle and environmental factors is required for creating individual and group nutrition models aimed at disease prevention.

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