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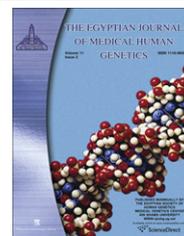
REVIEW

Nutritional genomics and personalized diet

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Abstract Nutritional genetics is considered as the combination of nutrigenomics and nutrigenetics. Nutrigenomics is establishing the effects of ingested nutrients and other food components on gene expression and gene regulation. It will also determine the individual nutritional requirements based on the genetic makeup of the person (personalized diet) as well as the association between diet and chronic diseases which will help to understand the etiologic aspects of chronic diseases such as cancer, type-2 diabetes, obesity and cardiovascular disease (CVS). Nutrigenetics on the other hand identifies how the genetic makeup of a particular individual co-ordinates his or her response to various dietary nutrients. It also reveals why and how people respond differently to the same nutrient. The present review will focus upon interaction of genetic background and diet with regard to development of such life threatening chronic conditions as obesity, cardiovascular disease (CVD), and cancer that are responsible for the majority of deaths in developed Western countries.

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1. Definitions

Nutritional genetics is not a single field, but is considered as the combination of two-nutrigenomics and nutrigenetics [1].

1.1. Nutrigenomics

Nutrigenomics is establishing the effects of ingested nutrients and other food components on gene expression and gene regulation, i.e., to study diet-gene interaction in order to identify the dietetic components having beneficial or detrimental health effects [1,2]. It will also determine the individual nutritional requirements based on the genetic makeup of the person (personalized diet) as well as the association between diet and chronic diseases which will help to understand the etiologic aspect of chronic diseases such as cancer, type-2 diabetes, obesity and cardiovascular disease (CVS) [2]. Nutrigenomics will also identify the genes involved in physiological responses to diet and the genes in which small changes, called polymorphisms, may have significant nutritional consequences and the influence of environmental factors on gene expression [3].

1.2. Nutrigenetics

Nutrigenetics on the other hand identifies how the genetic makeup of a particular individual co-ordinates his or her response to various dietary nutrients. It also reveals why and how people respond differently to the same nutrient [4].

Together these two approaches promise to deliver a critical part of the scientific knowledge needed to understand how diet affects the individual humans [1] and eventually nutrigenomics will lead to evidence-based dietary intervention strategies for restoring health and fitness and for preventing diet-related disease [5].

2. Gene diet disease interaction

2.1. Nutrigenetic diseases

Ninety seven percent of the genes have known to be associated with human diseases result in monogenic diseases. Modifying the dietary intake can prevent some monogenetic diseases [6], e.g., in phenylketonuria (PKU) food containing the amino acid phenylalanine, including high protein food such as fish, chick-

en, eggs, milk, cheese, dried beans, nuts, and tofu must be avoided. In case of defective aldehyde dehydrogenase enzyme, alcohol must be avoided. Patients having galactosemia (lack of a liver enzyme to digest galactose) should avoids diets which contain lactose or galactose, including all milk and milk products while in case of lactose intolerance (shortage of the enzyme lactase) patients should avoid milk and milk products [7].

2.2. Nutrigenomic diseases

Diseases and conditions that are known to have genetic and/or nutritional components are candidates for nutrigenomic studies to determine whether dietary intervention can affect the outcome. Differences in genetic makeup or genotype are factors in gastrointestinal cancers, other gastrointestinal conditions or digestive diseases, inflammatory diseases, and osteoporosis. Nutrient imbalances are factors in aging, alcoholism/substance abuse, behavioral disorders, cancer, cardiovascular disease (CVD), chronic fatigue, deafness, diabetes, immune disorders, macular degeneration, multiple sclerosis, neurological disorders, osteoporosis, Parkinson's disease and stroke [7]. Diseases that are known to involve in the interactions between multiple genetic and environmental factors such as diet include, many cancers, diabetes, heart disease, obesity and some psychiatric disorders [7].

Therefore, both disciplines aim to unravel diet/genome interactions; however, their approaches and immediate goals are distinct. Nutrigenomics will unravel the optimal diet from within a series of nutritional alternatives, whereas nutrigenetics will yield critically important information that will assist clinicians in identifying the optimal diet for a given individual, i.e., personalized nutrition [8].

The following five tenets of nutritional genomics serve as a conceptual basis for understanding the focus and promise of this emerging field [3]:

1. Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases.
2. Common dietary chemicals can act on the human genome, either directly or indirectly, to alter gene expression or structure.
3. The degree to which diet influences the balance between healthy and disease states may depend on a person's genetic makeup.

4. Some diet-modulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.

5. Dietary intervention based on the knowledge of nutritional requirements, nutritional status, and genotype (i.e., personalized nutrition) can be used to prevent, mitigate, or cure chronic disease.

3. Single nucleotide polymorphism (SNP)

Most of the genes have small sequence differences – polymorphisms – that vary among individuals. Single nucleotide polymorphisms (SNPs) are the most common type of variation [4].

The single nucleotide polymorphisms consortium is mapping polymorphic regions of the genome that control individual phenotypic differences among the human population. The importance of this genetic variation to the varying needs for and physiological responses to the particular nutrients was stated by Ames [9]. Missense single nucleotide polymorphisms occur about 1 in every 1000 bases in expressed genes, so one expects that there will be many more polymorphisms to be found in micronutrient and dietary studies. Specific genetic polymorphisms in human populations change their metabolic response to diet and influence the risk patterns of disease as SNPs are similar to variations in a recipe. Each gene is a recipe for a specific protein or group of proteins that either regulate biological functions or serve as structural building blocks for tissues (e.g., collagen). Some SNPs change the recipe for the gene so that either a different quantity of the protein is produced or the structure of the protein molecule is altered [3].

These genetic polymorphisms lead to alteration of the response to the dietary components by influencing absorption and metabolism. Epigenetic events can induce changes in DNA methylation pattern and thus influencing over all gene expression that can be modified in response to the food components. Many dietary constituents affect post translation events and many account for at least part of the variation in response to the dietary components [10].

One of the best-described examples of the effect of SNPs is the relationship between folate and the gene for MTHFR – 5,10-methylenetetrahydrofolate reductase. MTHFR has a role in supplying 5-methylenetetrahydrofolate, which is necessary for the re-methylation of homocysteine to form methionine. Methionine is essential to many metabolic pathways including production of neurotransmitters and regulation of gene expression. Folate is essential to the efficient functioning of this MTHFR. There is a common polymorphism in the gene for MTHFR that leads to two forms of protein: the wild type (C), which functions normally, and the thermal-labile version (T), which has a significantly reduced activity. People with two copies of the wild-type gene (CC) or one copy of each (CT) appear to have normal folate metabolism. Those with two copies of the unstable version (TT) and low folate accumulate homocysteine and have less methionine, which increases their risk of vascular disease and premature cognitive decline [11].

4. Nutrigenomics and chronic disease

The present review will focus upon interaction of genetic background and diet with regard to development of such life threatening chronic conditions as obesity, CVD, and cancer that are responsible for the majority of deaths in developed western countries [3]. The nature of these interactions is indeed very complex.

4.1. Nutrigenomics and obesity

Obesity is the commonest nutrition-related disorder and is the core element of a group of metabolic abnormalities (metabolic syndrome) which also commonly includes insulin resistance and hyperinsulinemia, hypertension, impaired glucose tolerance, and noninsulin-dependent diabetes mellitus [12]. Also obesity and associated metabolic anomalies dramatically increase the risk of developing a variety of chronic diseases including CVD and cancer [13,14]. However, individual susceptibility to obesity strongly depends on the genetically determined patterns of energy balance regulation [15].

Multiple polymorphic genes encoding central and peripheral determinants of energy intake and expenditure have been revealed over the past decade. Food intake control may be affected by polymorphisms in the genes encoding taste receptors and a number of peripheral signaling peptides such as insulin, leptin, ghrelin, cholecystokinin, and corresponding receptors [15]. Polymorphic central regulators of energy intake include hypothalamic neuropeptide Y, agouti-related protein, melanocortin pathway factors, CART (cocaine- and amphetamine-regulated transcript), some other neuropeptides, and receptors for these molecules. Potentially important polymorphisms in the genes encoding energy expenditure modulators (alpha- and beta-adrenoceptors, uncoupling proteins, and regulators of adipocyte growth and differentiation) are also known [15].

4.2. Nutrigenomics and CVD

CVD is the primary diet-related chronic disease of the modern time and the inflammation is emerging as underlying many chronic disorders including CVD. CVD can be characterized as a group of multifactorial conditions associated with obesity, atherosclerosis, hypertension, and thrombosis. All of these pathologic entities are known to be closely related to both genetic factors and environmental influences. Diet is considered as one of the environmental influences and a strong relationship between diet composition and CVD risk is well established [16–19].

Obesity per se is a major cardiovascular risk factor, thus polymorphic genes involved in energy balance control certainly provide "favorable" or "unfavorable" background for the development of CVD [15].

Atherosclerosis constitutes the key element in the pathogenesis of CVD and it can be regarded as a complex combination of lipid transport and metabolism disorder with chronic inflammation [16,20]. Permanently elevated plasma levels of total cholesterol, LDL cholesterol, and triglycerides predispose to the development of atherosclerotic plagues, whereas increased high density lipoprotein (HDL) cholesterol levels appear to be protective [15]. Genetic variation in genes encoding for apolipoproteins, some enzymes and hormones can alter individual sensitivity to develop the cardiovascular diseases. Some of these variants are susceptible for dietary intervention, for example: Individuals with the E4 allele in the apolipoprotein E gene show higher low-density lipopro-

tein-cholesterol(bad cholesterol) levels with increased dietary fat intake compared with those with the other (E1, E2 and E3) alleles receiving equivalent amounts of dietary fat [21].

ApoA1 is primarily found in the HDL particles. AG to A transition in the promoter of APOA1 gene is associated with increased HDL-cholesterol concentration but the results across studies are not consistent [22]. Ordovas et al. [23] found that the allele A was associated with the decreased serum HDL levels. The genetic effect was reversed, however, in women who ate more polyunsaturated fatty acids (PUFA). In men, this type of fat effect was significant when alcohol consumption and tobacco smoking was considered in the analysis. Also specific polymorphism in genes encoding lipid transport proteins, their receptors, and lipid-processing enzymes and inflammation related proteins were shown to be associated with the characteristic changes in blood lipid concentrations [24–28].

One polymorphism(-5′4 cc) in the hepatic lipase gene is associated with an increase in protective HDL levels compared with the TT genotype (common in certain ethnic groups such as African–Americans) in response to high fat diet [21].

4.2.1. Hypertension
Arterial hypertension constitutes an important pathogenetic element in CVD. It is now well understood that numerous genetic factors are involved in blood pressure regulation and some genetic patterns can be responsible for raising blood pressure, which characterizes essential (primary) hypertension [29]. Hypertension is one of the components of the obesity-associated metabolic syndrome [12], and influence of dietary factors altering energy homeostasis appears to predispose to blood pressure elevation. It is well known that the loss of weight in hypertensive obese individuals usually leads to simultaneous blood pressure decrease [30].

Sodium chloride is the only dietary risk factor well defined to predispose to hypertension. However, blood pressure responses to increases and decreases in dietary salt intake may be heterogenous, as only about 15% have sodium-sensitive hypertension. For the other 85%, eliminating salt from the diet has no effect on their blood pressure [31].

Polymorphic genes implicated in blood pressure regulation include renin-angiotensin system genes including those encoding angiotensinogen (AGT), angiotensin converting enzyme (ACE), and aldosterone synthetase (CYP11B2) [29]. However, no evidence of the interactions between polymorphic variants of these genes and dietary factors is available. On the other hand sodium transport/metabolism-related genes such as those encoding epithelial sodium channel (ENaC) subunits, adducin, and 11B-hydroxysteroid dehydrogenase are certainly of interest, given well-proven association between dietary salt intake and hypertension [31]. There are also some reports associating human hypertension with polymorphisms in some G-proteins (G protein_subunit, GNAS1) and adrenergic receptors but evidence is not sufficient [15]. So nutrigenomics is addressing why some people can control their hypertension with diet, whereas others require drugs.

4.2.2. Arterial thrombosis
Thrombosis of arteries affected by atherosclerosis constitutes the main mechanism leading to acute coronary and cerebrovascular syndromes. Impaired balance of multiple factors constituting blood coagulation system can lead to hypercoagulative state increasing thrombosis probability. Both the environmental and genetic factors are involved. Diet, especially excessive fat ingestion can trigger postprandial hypercoagulative state [32]. Gene polymorphisms affecting hemostasis (as genes encoding platelet surface glycoproteins, and coagulation factors) have been implicated [33,34]. Blood coagulation is counterbalanced by the anticoagulant and fibrinolytic systems that also include polymorphic factors [34].

4.2.3. Homocysteine metabolism
Hyperhomocysteinemia is now regarded as an independent risk factor in the development of cerebrovascular and coronary heart disease as well as venous thrombosis [35].

5. Nutrigenomics and cancer

Cancer is a process composed of multiple stages in which gene expression, and protein and metabolite function begin to operate aberrantly [36]. In the post-genomic era, the cellular events mediating the onset of carcinogenesis, in addition to their modulation by dietary factors, has yielded important information in understanding of this disease [37]. Inherited mutations in genes can increase one's susceptibility for cancer. The risk of developing cancer can be markedly increased if there is a gene-diet interaction. Studies of twins show that the likelihood of identical twins developing the same cancer is less than 10%, indicating that the environment plays an important role in cancer susceptibility [7].

Evidence of genome and epigenome damage biomarkers, in the absence of overt exposure of genotoxins, are themselves sensitive indicators of deficiency in micronutrients required as cofactors or as components of DNA repair enzymes, for maintenance methylation of CpG sequences and prevention of DNA oxidation and/or uracil incorporation into DNA [38].

Diet considered as a source of either carcinogens (intrinsic or cooking-generated) present in certain foods or constituents acting in a protective manner (vitamins, antioxidants, detoxifying enzyme-activating substances, etc.) [39]. It is clear that carcinogen metabolism-affecting polymorphisms may modify probability of contact between carcinogens and target cells, thus acting at the stage of cancer initiation [15].

Influences of polymorphisms of gene encoding factors involved in hormonal regulation are most strongly manifested in hormone dependent tumors such as breast, prostate, ovarian and endometrial cancers. Polymorphisms in sex hormone receptor genes comprising those encoding estrogen receptor, progesterone receptor, and androgen receptor have been shown to be associated with cancer risk modulation [15]. Dietary factors can certainly interact with hormonal regulation. Obesity strongly affects hormonal status. At the same time some food components, such as phytoestrogens are known to be processed by the same metabolic pathways as sex hormones [40], thus their cancer-preventive effect can be modulated by the polymorphisms mentioned here.

5.1. Diet and increased risk of cancer

There are various examples of the effects of diet on cancer risk.

There is an increase risk of colorectal cancer with high consumption of red meat [21]. N-Acetyl transferase (NAT) is a

phase II metabolism enzyme that exists in two forms: NAT1 and NAT2. Several polymorphisms exist in NAT1 and NAT2, some of which have been associated NAT capabilities of slow, intermediate, or fast acetylations. NAT is involved in acetylation of the heterocyclic aromatic amines found in heated products especially well cooked red meet. During cooking of muscle meat at high temperature some aminoacids may react with creatinine to give heterocyclic aromatic amines (HAA). HAA can be activated through acetylation to reactive metabolites which bind DNA and cause cancers. Only NAT2 fast acetylators can perform this acetylation. NAT fast acetylator genotype had a higher risk of developing colon cancer in people who consumed relatively large quantities of red meat [21].

A combination of excess body weight and physical inactivity are estimated to account for one fifth to one third of several of the most common cancers, specifically cancers of the breast (postmenopausal), colon, endometrium, kidney and esophagus (adenocarcinoma) [41].

Specific dietary irritants, such as salts and preservatives have been suggested as being carcinogens for gastric cancer [42].

C667T polymorphism in MTHFR gene which reduces enzymatic activity is inversely associated with occurrence of colorectal cancer. Low intake of folate, vitamin B12, vitamin B6 or methonine are associated with increased risk for cancer in CC or TT phenotype of MTHFR gene [43].

It was reported that a stronger relationship existed between the risk of developing hepatocellular carcinoma in Sudanese population and consumption of peanut butter with aflatoxins with the glutathione S-transferase M1 null genotype compared to those lacking the genotype [44].

5.2. Diet and cancer prevention

Cancer prevention studies have shown that all of the major signaling pathways deregulated in different types of cancer, are affected by nutrients. Pathways studied include: carcinogen metabolism, DNA repair, cell proliferation/apoptosis, differentiation, inflammation, oxidant/antioxidant balance and angiogenesis [45]. So far, more than 1000 different phytochemicals have been identified with cancer-preventive activities [46].

Dietary fibers have a protective effect against bowel cancer [7].

Long chain polyunsaturated fatty acids (LC-PUFA) beneficially affect physiological processes including growth, neurological development, lean and fat mass accretion, reproduction, innate and acquired immunity, infectious pathologies of viruses, bacteria and parasites; and the incidence and severity of virtually all chronic and degenerative diseases including cancer, atherosclerosis, stroke, arthritis, diabetes, osteoporosis, neurodegenerative, inflammatory, and skin diseases [47–51].

Fish oil, rich in omega-3 fatty acids, inhibits the growth of colonic tumors in both invitro and invivo systems [52–54].

Bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification. Plant foods can modulate detoxification enzymes as flavonoids, phenols, isothiocyanates, allyl sulfur compounds, indoles, and selenium [55,56]. As a result carcinogen activation, covalent adducts with the individual nucleic acids of DNA or RNA are formed. It has also been found that reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, and hydroxyl radicals attack DNA bases, resulting in potential mistranscription of DNA sequence [57]. Such disruptions can interfere with DNA replication and thus produce mutations in oncogenes and tumor suppressor genes. ROS can also result in breakage of DNA strand, resulting in mutations or deletions of genetic material [58].

6. Ethical, legal and social issues in nutrigenomics

Nutrigenomics raises ethical, legal and social issues particularly with respect to how the public may access nutrigenetic tests and associated nutritional and lifestyle advice [59].

Five areas have been identified by international experts [60] in the context of both basic nutrigenomics research and its clinical and commercial uses: (i) health claims benefits arising from nutrigenomics, (ii) managing nutrigenomic information, (iii) delivery methods of nutrigenomics services, (iv) nutrigenomics products, and (v) equitable accessibility to nutrigenomics. Hence it is important to elevate the depth of depate to understand and manage all these area.

7. Conclusion

Nutrigenomics offers the potential of important health benefits for some individuals. Primary care physicians have minimal training in nutrition and genetics, and medical geneticists are in high demand and short supply [59]. Dietetic practitioners are experts in nutrition science and interest in nutrigenomics is growing among members of this professional group. However, as with physicians, dietetics practitioners would require considerable training to bring nutrigenomics into their practice capacity [59].

In recent years, a high-resolution recombination map of the human genome has provided and increased the information on the genetic order of polymorphic markers and the SNP map of the human genome [61]. It is hoped that the map of SNPs in the human genome will provide powerful molecular tools to decipher the role of nutrition in human health and disease and help defining optimal diets [10]. Advanced genetic analysis in combination with twin studies may provide opportunities to understand the basis of complex traits and the role of individual genotypes on the development of polygenic diet-related diseases such as cancer and CVS [62].

Thus nutrigenomics treats food as a major environmental factor in the gene–environment interaction, with the final aim to personalize food and nutrition and ultimately individualize strategies to preserve health, by tailoring the food to individual genotype [22].

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