Review Article

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Nutrigenomics: Opportunities & challenges for public health nutrition

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The hierarchical information flow through DNA-RNA-protein-metabolite collectively referred to as 'molecular fingerprint' defines both health and disease. Environment and food (quality and quantity) are the key factors known to affect the health of an individual. The fundamental concepts are that the transition from a healthy condition to a disease phenotype must occur by concurrent alterations in the genome expression or by differences in protein synthesis, function and metabolites. In other words, the dietary components directly or indirectly modulate the molecular fingerprint and understanding of which is dealt with nutrigenomics. Although the fundamental principles of nutrigenomics remain similar to that of traditional research, a collection of comprehensive targeted/untargeted data sets in the context of nutrition offers the unique advantage of understanding complex metabolic networks to provide a mechanistic understanding of data from epidemiological and intervention studies. In this review the challenges and opportunities of nutrigenomic tools in addressing the nutritional problems of public health importance are discussed. The application of nutrigenomic tools provided numerous leads on biomarkers of nutrient intake, undernutrition, metabolic syndrome and its complications. Importantly, nutrigenomic studies also led to the discovery of the association of multiple genetic polymorphisms in relation to the variability of micronutrient absorption and metabolism, providing a potential opportunity for further research toward setting personalized dietary recommendations for individuals and population subgroups.

Key words Biomarkers - micronutrients - molecular fingerprint - nutrigenomics - recommended dietary allowances - stunting

Introduction

The notion that food affects the health is age-old. Now an emerging body of research evidence points that environment and diet (quality and quantity) are the main factors that influence the health and disease of an individual. Therefore, deciphering the critical determinants of diet that bring about positive or negative health outcomes has received overwhelming attention of the biomedical community, that led to the discovery of essential macro- (protein, fat and carbohydrate) and micronutrients (vitamins, minerals, *etc.*) and their physiological functions. Apart from providing the substrates for generating energy, a large number of food components are bioactive and affect the genome, transcriptome and proteome expression either directly or indirectly thereby, regulating the biological processes. Human diet is estimated to contain about 20,000 compounds, of which nearly 50 are essential for life. Systematic balance and turnover studies of these nutrients contributed to the approximation of their daily requirements which

forms the basis for setting the recommended dietary allowances (RDA)[1].

It is consistently demonstrated that regular intake of vegetables and fruits is linked with improved health quality and reduction in chronic lifestyle-related diseases[2,3]. Clinical and epidemiological studies also identified that many non-essential dietary components referred to as phytochemicals are capable of modulating health and wellness[3,4], and their possible mode of actions are being studied extensively. This reductionist approach in studying single nutrient/phytochemical effects on specific biochemical and molecular outcomes contributed enormously in understanding their physiological function and establishment of nutrient or disease-specific biomarkers. However, one would not anticipate such a scenario in the whole organism and more so in general population, and thus, its translation needs thoughtful consideration. For instance, cross-sectional studies showed a negative association of plasma β-carotene with degenerative diseases and certain forms of cancer[5-7], however, its supplementation was not found to result in beneficial outcomes[8]. It is later understood that plasma β-carotene levels are negatively influenced by underlying inflammation[9]. Therefore, biochemical and molecular level understanding of the nutrient absorption, utilization under contextual physiology is necessary to predict the cause and effect relationships. Anaemia has been a public health problem globally and is thought to be mainly due to concomitant iron deficiency. However, recent estimates suggest that only about 50 per cent anaemia is actually due to iron deficiency and a sizable proportion of the population is non-compliant to iron therapy[10]. Studies also demonstrated that the deficiencies of multiple micronutrients hamper the impact of iron supplementation on blood haemoglobin levels[11]. Underlying inflammation due to infectious or chronic disease may reduce the blood nutrient levels by reducing absorption and increased mobilization to tissues, leading to false positive results[12]. Since the majority of these essential nutrients are involved in energy metabolism, their requirements are also impacted by body composition, and basal metabolic rate which add further to this complexity. However, measurement of multiple nutrient status in the context of pathophysiology to formulate treatment regimen in clinical setup or a public health setting though essential and possible is not practical as yet with existing approaches.

The molecular fingerprint is a dynamic process as environmental (including nutrition), social factors and infections affect this molecular fingerprint. The impact of nutrition could, therefore, vary among individuals and specific population subgroups grounded on their molecular fingerprint. Hence, studying the context-specific diet/nutrient-induced changes in molecular fingerprint should be the way forward, and such comprehensive understanding of metabolic networks (referred to as Systems Nutrition) in the context of health and disease should reduce the false positives. The technological developments in high-throughput genomics analyses: single-nucleotide polymorphisms (SNPs), quantitative transcriptional, proteomic, metabolite changes coupled with bioinformatics should serve as a ladder to reach the goal of defining nutrition and diet-induced (contextual) changes in molecular fingerprints which is a formidable but exciting challenge. These molecular fingerprints are also expected to provide information on potential biomarkers of nutritional status, disease progression and response to intervention.

Genomics technologies

The Human Genome Project provided ample information about structure and function of the genome, helped in annotating plethora of genes and their end products, the proteins. It is now known that eukaryotic transcription is variable due to genetic polymorphisms and is controlled by a number of factors including nutrients, infection, *etc*[13]. Therefore, understanding the complement of mRNA types and abundance helps in predicting contextual regulatory mechanisms. However, this may not always follow an expected trend, as the expressed mRNA invariably exerts its function by its translational product, the protein. Alternate splicing of transcribed RNA and translational regulation gives rise to multiple proteins (often with very different function) with variable abundance, and finally, the protein function and its half-life are highly regulated, manifesting in metabolite changes, an outcome of specific genomic information[14]. Therefore, it is imperative to understand the complement of proteins and metabolites in a given context to better explain the physiological or pathological condition.

Several disciplines of high-throughput technologies aimed at collective characterization of biomolecules have been developed. For example, microarrays[15] (base pairing mechanisms of DNA and RNA) and next-generation sequencing technologies (based on sequencing of RNA)[16] assess the relative changes in global gene expression, which when cast into pathways help in understanding the changes in possible biochemical mechanisms modulated by test

condition compared to normal/control. The discovery of soft ionization mass spectrometry techniques such as matrix-assisted laser desorption ionization and electrospray ionization facilitated the biomolecule analysis[17]. The great advantage of these methods is the possibility of both identification and analysis of a few hundred to thousands of proteins or metabolites in a single run and in a few hours. Moreover, the high sensitivity of these methodologies overcomes the often-limiting biological sample availability. Metabolic pathways are highly interconnected forming complex web of networks. The end products of any metabolism are the real manifestation of gene expression of any physiological and regulatory process. Metabolomics is the qualitative and quantitative analysis of all metabolites in a biological system including cell, plasma and tissue[18]. The two key methods employed in metabolomics are mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy. MS-based approaches use gas and liquid chromatography, and capillary electrophoresis. Therefore, a collection of these tools is applied in nutritional research, under the umbrella term nutrigenomics or systems nutrition. Nutrigenomics includes nutrigenetics (the study of DNA including SNPs), transcriptomics (mRNA), proteomics (complement of proteins) and metabolomics (complement of metabolites) technologies applied in the context of nutrition[19].

Nutrigenomics

Basic studies have shown several nutrients and bioactive phytochemicals act as signalling molecules: they bind to cellular sensors such as transcription factors or directly to the promoters that influence the expression of gene and protein and subsequently metabolite production. For example, ingestion of carbohydrate-rich food results in upregulation of glycolytic and lipogenesis enzymes. However, it downregulates the expression of gluconeogenesis enzymes. In addition, genomic approach encouraged to elucidate the variations in genetic makeup of an individual which subsequently shows differential response to nutrition and risk to nutrition-related disorders. For instance, persons suffering from phenylketonuria caused by a mutation in phenylalanine hydroxylase coding gene[20], must avoid diet containing phenylalanine. In addition, genetic variations or polymorphisms in genes that code for proteins/enzymes [5,10-methylene tetrahydrofolatereductase (*MTHFR*)] have been shown to affect the catalytic activity[21], which in turn influences the individual nutrient requirements and metabolism.

Nutrigenomics addresses the diet or nutrient-induced changes in transcriptome, proteome and metabolome, while nutrigenetics deals with the effect of the genetic disposition: mutations, SNPs, copy-number variation and epigenetic changes on the nutrition biology[19]. Epigenetics describes the heritable changes caused by mechanisms other than alterations in the DNA sequence. Emerging technologies in the field of epigenetics are unravelling the molecular mechanisms as to how genetic information other than DNA sequence can affect the gene function, particularly the impact of diet and environment on genomic, transcriptional and developmental regulation including DNA methylation, acetylation, histone modification paramutations and gene silencing. Although nutrigenomics is expected to be an integrated platform, due to the complexity of technologies and expertise required, it is currently being applied only to collect targeted/untargeted information at different strata of biological information flow (genomics, transcriptomics, proteomics and metabolomics) by different investigators. It is anticipated that integration of these datasets coupled with modern bioinformatic tools should rapidly revolutionize our understanding of the interaction of nutrition with health and disease.

Challenges & opportunities

India is encountering rapid socio-economic, epidemiological, health and nutritional transition for the last 2-3 decades[22,23]. Malnutrition, particularly undernutrition-related complications continue to influence major sections of the population. On the other hand, the parallel burden of overnutrition is resulting in obesity and associated chronic lifestyle disorders such as type 2 diabetes, cardiovascular diseases and cancers[23,24]. Inspite of the fact that the global burden of undernourishment is progressively moving to overnourishment, undernutrition prevails widely in South Asia, especially in India, causing both conditions to coexist with micronutrient deficiencies[25]. Notwithstanding significant progress in child-nutrition outcomes in the recent years, about 40 per cent of Indian children aged under five are as yet stunted and underweight[26]. Usually, rural people in India survive on insufficient diets as the mean intakes of all the food groups and nutrients were observed to be below the RDA[27]. Especially, micronutrient inadequacies are prevalent in India, even in school children of high-income families, high incidence of anaemia (14-88%) and low dietary iron intakes have been detected, and 44-66 per cent of the affluent

schoolchildren had vitamins A, B2, B6, B12 and C deficiencies[27,28]. Sixty per cent of global deaths in 2005 were caused by chronic diseases, particularly cardiovascular diseases, cancers, respiratory diseases, diabetes and obesity[28]. By 2020, it is anticipated that non-communicable diseases (NCDs) will represent 80 per cent of the global disease burden, triggering seven out of every 10 deaths in developing countries[29]. Therefore, the promises of nutrigenomics must be utilized in addressing growing epidemic problems of both under- and overnutrition.

Stunting

Stunting, short height for age is the impaired growth and development of children mainly due to malnutrition and repeated infections. The prevalence of stunting in Indian children decreased by 10 per cent between NFHS-3 and NFHS-4 surveys[30], which could be attributed to multiple government supported nutrition programmes. Recently, Indian government launched National Nutrition Mission to reduce undernutrition, stunting and anaemia in young children, adolescent girls, women, pregnant women, lactating mothers[31].

Linear growth is regulated by a network of genetic, metabolic, endo-, exo- and autocrine hormonal-mediated cell signalling mechanisms many of which are nutrition-sensitive. The nutritional sensitive growth hormone, *i.e.* insulin-like growth factor-1 (IGF-I) axis is viewed as the major regulatory system of childhood growth[32,33]. Physiologically nutrients are divided into type 1 and 2. While the type1 nutrition deficiency (iron, B-vitamins, *etc.*) will manifest in biochemical changes without affecting the linear growth, the type 2 nutrient inadequacy/deficiency such as protein, zinc, magnesium, phosphorus and potassium manifests in growth faltering with no changes in their blood levels[34]. Consumption of nutritionally poor and predominantly plant-based diets has been shown to be associated with stunting. Increasing the intake of energy, protein, Zn and other nutrients has shown only modest improvements[35]. A metabolomic study[36] has demonstrated that the essential amino acid levels in serum of stunted children are low. In addition, the circulatory levels of conditionally essential amino acids (arginine, glutamine and glycine), other biogenic amines, amino acid metabolites, proteinogenic amino acids, glycerophospholipids and sphingomyelins are lower in stunted children. Chondral growth plate is the basis for the linear growth of children[37]. It is now known that bone growth by the chondral plate is controlled by mTORC1 (mammalian target of rapamycin complex 1), which in turn is controlled by the availability of leucine[38].

Interestingly, leucine showed the strongest association with stunting in the above-mentioned metabolomics study. Similarly, Zn which is associated with stunting, also shown to regulate the activity of the mTORC1 through the activation of its upstream effector PI3 Kinase/Akt pathway[39]. Further, reduced levels of sphingomyelins and glycerophospholipids in stunted children have been observed. Sphingomyelins (synthesized from phospholipids) are required for myelination of the neurons during child development[36]. The balanced activity of mTORC1 is also demonstrated to be essential for myelination of central nervous system[40]. In the context of already available information on the critical roles of mTORC1 on anabolic activities *i.e.*, nucleotide, protein synthesis, ribosomal biogenesis, lipid synthesis and inhibition of autophagy, understanding the mTORC1 regulation and its modulation by nutrition should aid in understanding of this complex area of public health importance as well as to design evidence-based intervention programmes.

A recent study that reported plasma proteomic profiles among children with different anthropometric indices[41] identified the positive association of proteins implicated in bone mineralization, activation of innate immunity, and nutrient transport with height for age (HAZ). Interestingly, IGF-1, a marker of growth was also found to be positively associated with HAZ in this study. However, two IGF-binding proteins (IGF-BP) showed a strong correlation with HAZ than IGF alone. Since IGF activity is regulated by IGF-BP, these are more likely to be sensitive markers of growth compared to IGF-1. This study also demonstrated a unique plasma protein association with various anthropometric indices including height, weight, BMI, upper arm muscle and fat, as these are driven by different metabolic and regulatory pathways. Another notable observation in this study was the positive association of carnosinase 1 with height, weight and musculature. Carnosinase hydrolyzes the antioxidant dipeptide carnosine predominantly found in skeletal muscle, into β-alanine and histidine[42]. Little is known about the function of carnosinase 1 in bone growth, and studies have reported its decreased activity in muscle-related disorders such as myopathy, protein-energy malnutrition and cachexia[43,44]. Therefore, it is predicted that carnosinase levels might serve as a potential marker of muscle mass, which needs to be validated further.

The results of the metabolomic/proteomic studies in the context of stunting not only confirmed what was known but also identified multiple biomarkers associated with different anthropometric indices during growth. Furthermore, this information will provide opportunities to take on some pertinent challenges: what are the normal/ideal levels of indispensable amino acids in blood regarding growth in children, can their levels be used as early predictors of stunting, can these be used to follow the response to treatment/supplementation, does mTORC1 activity help to predict stunting early (at least protein deficiency induced) and brain development, to what extent typical diets across populations contribute to these essential amino acids, does supplementing these essential amino acids along with energy help to achieve growth standards in children. However, inflammation, a major confounder in all biological studies, also negatively influences the growth, leads to stunting independent of nutrition[45] and thus this aspect needs to be considered in designing studies and interpreting results.

Micronutrient deficiencies

Micronutrients (vitamins and minerals) play a fundamental role in various physiological and biological processes as cofactors for enzymes or the essential structural components of proteins and implicated in the regulation of several metabolic functions in the body. Micronutrient deficiencies referred to as hidden hunger, propagated mostly through dietary inadequacies, are not apparent but ubiquitous affecting more than two billion people globally, and one-third of them are residing in India[46,47]. Micronutrient deficiency can also occur due to poor bioavailability and absorption irrespective of the dietary intake.

Human body has developed efficient mechanisms to cope up with nutrient deficiency and excess by regulating nutrient flux through stores, intestinal absorption and obligatory excretory pathways. It is known that mutations in specific genes are associated with altered nutrient homeostasis and adverse health outcomes including mortality. For instance, a mutation in divalent metal ion transporter-1 that mediates intestinal iron absorption is found to be associated with anaemia in both rodents and humans[48]. On the other hand, mutations in genes that alter iron, homeostasis have been shown to cause hemochromatosis, a condition of excessive iron accumulation[48]. Similarly, a mutation in ZIP-4 which mediates intestinal Zn absorption, leads to its severe deficiency manifesting in acrodermatitis enteropathica, a rare human genetic disorder[49]. Using exome sequencing approach, it has been reported that mutations in retinol binding protein-4 (vitamin A transport protein in the human blood) gene in a consanguineous pedigree leads to reduced serum vitamin A levels and is associated with developmental abnormalities and retinal degeneration[50].

In the human genome, SNPs are expected to occur about once every 1000 base pairs taking the tally to expected three million SNPs, making their analysis a herculean task, but for a new approach called SNP arrays[51]. Further, SNP arrays can be tailored for targeted genes for a specific area of research based on existing knowledge and databases of SNPs (The International HapMap Project)[52] and thus are one of the most versatile methodologies available.

It is clear that either micronutrient inadequacy or micronutrient abundance can alter genome stability and these impacts may likewise rely on nutrient-nutrient and nutrient-gene interactions, which is influenced by genotype. Micronutrient status or chronic diseases related to micronutrient metabolism are known to be influenced by SNP. Nutrients have the potential to interact with SNPs to augment or reduce the chances of getting disease. A classic example is C677T and A1298C polymorphism in *MTHFR* gene which results in its reduced activity, leading to the less efficient conversion of homocysteine to methionine[21]. Hyperaccumulation of homocysteine, in turn, is associated with neural tube defects, vascular disorders and certain forms of malignancies. There is substantial proof that supplementation of folate can encounter the negative effect of these polymorphisms with a decrease in plasma homocysteine levels. In this regard, folate-mediated one-carbon metabolism genes and gene-nutrient interactions appear to be modifiers of genetic influence on colorectal cancer risk[53].

A significant association of 28 SNPs among 11 candidate genes has been shown with the variability of vitamin E absorption or bioavailability[54,55]. Most of these genes were also found to be previously associated with postprandial triglyceride response, which is expected as vitamin E absorption and transport is akin to fatty acids. The SNPs in four genes that are directly involved in vitamin E intestinal absorption and metabolism are identified to be associated with inter-individual variability. These are pancreatic lipase, Niemann-Pick disease type C1 (NPC1) like intracellular cholesterol transporter-1, ATP binding

cassette subfamily G member1, and apical sodium bile acid transporter, which are directly implicated in vitamin E digestion and intestinal absorption[54].

Two studies on humans demonstrated that SNPs in β-carotene monooxygenase gene altered the β-carotene to vitamin A conversion efficacy[54,55]. A recent study[56] demonstrated a significant association of β-carotene absorption with 25 SNPs among genes directly involved in its absorption and metabolism. This study showed a significant association of ELOVL2 (fatty acid elongase-2), which is implicated in the conversion of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA), with β-carotene absorption. We have also demonstrated the EPA but not DHA treatment abrogates the intestinal carotenoid absorption through downregulation of lipid transporter expression[57]. Therefore, apart from SNPs in nutrient-specific genes other transacting SNPs could also account for variations in micronutrient bioavailability and metabolism.

Genomics approaches to recommended dietary allowance

In principle, RDA depends on different sorts of evidence: depletion-repletion studies; nutrient intakes of evidently healthy people from their diet; epidemiological findings of nutrient status in populations in relation to intake and in some cases deduction of information from animal studies. Ideally, the estimated average requirements (EARs) needs to be measured in controlled settings along with its associated variation to set the RDA[58]. In practice, due to the paucity of data, RDAs are being set using the factorial approach considering nutrient losses and requirements adjusted for absorption/bioavailability. RDAs by definition exceed the requirement of 98 per cent of the population and are not suitable to assess the dietary inadequacy[58]. Since individual nutrient requirements vary among the general population, EARs may be ideal to measure the dietary inadequacy. The EAR can be derived from actual dietary intakes of the population (if distributed normally) or by measuring the individual variations in nutrient absorption or response to treatment. However, there is no such data available among the Indian population. Furthermore, understanding the inter-individual variability among micronutrient absorption and its association with genetic polymorphisms through genome-wide SNP mapping should guide the future research in setting RDAs for specific individuals or population subgroups.

Metabolic syndrome (MetS)

Metabolic syndrome (MetS) is characterized by a set of traits such as central obesity, insulin resistance, dyslipidaemia, fatty liver, and hyperglycaemia, leading to type 2 diabetes and cardiovascular disease. Genetic susceptibility has significant importance in the development of MetS[59]. In the course of time, the human genome has not changed significantly; however, the occurrence of the MetS augmented indicating the drastic effects of environmental factors on the genome. Till now, only a few genetic loci/genes associated with MetS are reported. For instance, Genome-Wide Association Study (GWAS) identified more than 50 loci associated with diabetes and obesity, many of which are novel[60]. Genes related to lipid metabolism, apolipoprotein B, apolipoprotein E, fatty acid binding proteins, transcription factor 7-like 2 and perilipin are associated with disturbed postprandial lipid metabolism a feature of MetS[61,62]. In addition, genetic variants related to inflammation including interleukin (IL)-1, IL-6, tumour necrosis factor-alpha (TNFα) and lymphotoxin showed a growing risk for central obesity, diabetes and MetS[63-65]. Many other genetic variants in genes including *FTO* (fat mass and obesity associated protein) and acetyl-CoA carboxylase β are also reported to show an increased risk for MetS[66,67]. By using genome editing approach such as CRISPER-CAS9 Claussnitzer *et al*[68], were able to restore the brown adiposity from white adiposity by converting *FTO* risky alleles into non-risky alleles using patient-derived primary adipocytes. These results unequivocally suggested the causative role of genetic polymorphisms in the development of MetS. Similarly, a dietary supplement with apple polyphenols (AP) reduced body weight gain and improved glucose tolerance, insulin resistance, and hyperleptinaemia, in diet-induced obese rat model for a duration of eight weeks[69]. Further, supplementation with AP it was shown the reduction in methylation of two CpG sites in the leptin promoter of rat epididymal adipocytes[69]. In the FUNGENUT study, Kallio *et al*[70] tried two distinctive carbohydrate foods: a rye pasta and an oat-wheat-potato with low and high postprandial insulin response, respectively, in individuals with MetS to study the global gene expression in subcutaneous and adipose tissue. Around 71 genes expression were decreased in the rye-pasta fed individuals that were related to insulin signalling and programmed cell death whereas three months oat-wheat-potato diet increased the expression of 62 genes associated with stress, IL, and cytokine-chemokine-mediated immunity

pathway[70]. Along these lines, nutrigenomics encourages a more noteworthy comprehension of the impact of nourishment on metabolic pathways and how this procedure goes incorrect in nutrition-linked disorders. Based on genotypic information, genome editing tools are now being used for treating life-style disorders including cardiovascular diseases, hypertension by correcting the risky alleles of the gene (variant SNPs) responsible for diseases[71].

Complications of diabetes & obesity

Long-term uncontrolled diabetes results in cardiovascular, renal, ocular (cataract, glaucoma, retinopathy), and neurological (peripheral and central neuropathy) complications. These short- and long-term complications are responsible for increased morbidity and mortality and pose a great burden to the economies of many countries. Hyperglycaemia is the major factor of microvascular complications, while insulin resistance and hyperglycaemia appear to play a key role in the aetiology of macrovascular complications. Several reports have shown that obesity, prediabetes and MetS also increase the risk of diabetic complications[72,73]. In general, every diabetic patient could develop these complications if hyperglycaemia alone were the reason for pathology. Multiple elements are probably engaged with the predisposition of diabetic person to complications. Therefore, it is important to understand these multiple factors and more importantly the interactions/interplay between micronutrients and molecular events in causation and progression of diabetic complications. Diabetes is known to alter the nutritional status, particularly micronutrient status. These alterations may be responsible for the development of some of the diabetic complications. An association between diabetic retinopathy (DR) and higher prevalence of vitamin B12 deficiency has been shown[74]. Lowered plasma levels of Zn, Mn and Co have been found in patients with DR compared to duration-matched diabetes patients without retinopathy[75]. Studies have also reported that severe DR patients have lesser plasma Mg levels than diabetic persons with minimal retinal changes, suggesting hypomagnesaemia as a risk factor for DR[76]. The evidence is also being accumulated that some of the signalling processes involved in diabetes complications are susceptible to nutritional modulation. For example, lower levels of folic-acid and other B-group vitamins are related with greater risk of vascular injury by elevating the homocysteine levels[77]. Homocysteine has been widely studied as a biomarker and a risk factor for vascular disorders including diabetic complications[74]. In addition, levels of other metabolites (*e.g.*, homocysteine, glutathione, some amino acids, lipids and cytokines) are a manifestation of altered nutrition and genetic variation (nutrigenomics)[78,79]. Using SNP arrays, it has been found that 96 SNPs are associated with DR patients (unpublished data) but yet to understand their effect on micronutrient-mediated metabolic networks. Metabolites can also influence the organization and functioning genome (nutrigenetics/epigenetics)[78,79]. Some of these metabolites, genetic/ epigenetic variations may serve as biomarkers of complications of diabetes and obesity.

Conclusion

Currently it is almost affordable to have one's genome determined, providing data on a wide range of variations in critical genes of metabolic pathways requiring micronutrients as cofactors. The key challenge is to decide if it is conceivable to use these data earnestly to give reliable and predictable early markers of undernutrition, micronutrient deficiencies, MetS and its related complications and dietary recommendations for better health outcomes. Nutrigenomics can also help in assessing the interindividual variability of nutrient absorption and utilization, thus facilitating personalized dietary recommendations for specific health outcomes. Therefore, nutrigenomics will be an important area of nutrition research in future. Some of the potential implications of nutrigenomics on public health are as follows: (*i*) RDA or safe upper limits for population subgroups/individuals; (*ii*) match the nutrient intake combination (nutriome) with the genome profile so that DNA stability, genomic and proteomic profile, metabolism and cellular functions occur in a homeostatically sustainable manner; (*iii*) will give better understanding of data from epidemiological and clinical intervention studies with respect to health impacts of dietary factors; (*iv*) designing optimized intervention strategies; (*v*) appropriate diagnostic tools to assess and monitor micronutrient status and response to intervention.

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