Nutrigenomics: An inimitable interaction amid genomics, nutrition and health

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Title: Nutrigenomics: ~~A *sui generis*~~ An inimitable interaction amid genomics, nutrition and health

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Abstract

Nutrigenomics is a study of how the genes and diet of a person interact. An individual's diet regime can drive gene regulation and its downstream ultimatum towards health illness through the food-receptor-gene network. Integrative science of genome-wide association along with nutrigenomics is investigating how genomic variation and receptor-mediated nutrient-sensing can optimize and maintain cellular homeostasis. Current scientific understandings have urged nutritional research to shift from traditional epidemiology and physiology to molecular biology, genetics and nutrigenomics which focus on deciphering the genomic, transcriptomic, proteomic and metabolomic effects of both nutrient deficiency and toxicity. From nutrigenomics point of view, nutrients are the potent signals/sensors that direct specific cells to undergo metabolic changes determining the result as a healthy or diseased individual. The varying cell sensing pattern towards a particular diet is known as 'dietary signature' that can be exploited for tailoring functional food and precision nutrition. 'Data mining' and various bioinformatics tools are helpful towards evidence-based intervention strategies by decoding nutrigenomics data as an ultimatum of which sound health is restored and diseases are prevented. This review is an attempt for the conglomeration of evolution of nutrigenomics, genome interaction and exploration of genomic tools to develop precision nutrition and food-based related disease.

Keywords: Omics, Dietary signature, Precision nutrition, Data mining

1. Introduction

Nutrition derived from plant and animal has a long term impact on human health and their interaction has been known for centuries (Vergères, 2013). In recent decades, the discovery of essential nutrients in our food, understanding biochemical pathways, and complex nutrient interaction with human metabolic processes have been reported (Nasir et al., 2020; Shi et al., 2015). The emphasis is given to understanding the mechanism of how nutrient interacts with other food-based chemicals, co-enzymes, hormones, enzymes, and genes to allow human growth, development and health maintenance throughout life (Bender, 2013). The change in the lifestyle and food habit patterns has happened over two centuries due to industrialization, rapid economic development, globalization and the increasing popularity of various food products in different countries (Drewnowski & Popkin, 1997). A sedentary lifestyle and change in food intake patterns (mainly carbohydrate and fat-rich food) have increased the risk of chronic diseases such as type 2 diabetes, cardiovascular disease, obesity, and different cancers (Kumar et al., 2018; Lal et al., 2021; Luo et al., 2021). Diet pattern is one of the key environmental factors which is involved in the pathogenesis and development of these lifestyle-related diseases (Carlberg et al., 2016b). Recent advances in clinical nutrition have demonstrated the importance of food and nutrient intake on health conditions and diseases. The specific nutrient and food concerning human health have been shown to have an association with gene expression and behavioural patterns of humans (Hernández-Coro et al., 2021).

Nutrigenomics is the science that describes the role of nutrients on gene expression and phenotype of humans (Müller & Kersten, 2003). Nutrition affects the metabolic pathway, homeostatic control and diet-related disease in humans. Moreover, nutrients act as a dietary signal which is detected by the cellular sensor and ultimately affects the gene and protein expression and, ultimately, the phenotype of an organism (Nathaniel Mead, 2007). A critical

barrier in understanding nutrition science is the variability and complexity of the human diet, which is consumed throughout the world. The human diet is composed of a complex mixture of biologically active molecules, consisting of both macro and micronutrients. Nutrition and the human body interact in a highly complicated way, involving multi-organ physiology and molecular mechanisms at all regulatory levels, including gene, gene expression, protein, and metabolites. Metabolomics approaches are used to explore the complex mechanism of phytochemical intake and human health (Manach et al., 2009). Nutrigenomics is the blend of high throughput omics technology, genetic profile analysis, dietary intervention, nutrition research and emphasis on the use of modern information technology (Corthésy-Theulaz et al., 2005; Ferguson et al., 2016). The gene expression and regulation due to nutrition influence metabolic processes and behaviour in humans. The degree of interaction of nutrition components with cell, enzymes and tissue leads to causing of pathological, physical and behavioural alterations in humans (Hernández-Coro et al., 2021). The molecules present in the human diet can directly affect the gene expression of humans by modulating the activity of transcription factors or stimulating the signalling cascade that ultimately induces transcription factors (Gopalakrishnan & Tony Kong, 2008).

There are many roles of nutrients derived from animal and plant origin in regulating human gene expression (Afman & Müller, 2006; Corthésy-Theulaz et al., 2005; Müller & Kersten, 2003; Nathaniel Mead, 2007; Sales et al., 2014). Some examples of the roles of phytonutrients include antioxidant and anti-inflammatory pathways, the effect on a hormone produced by fat cells, the interaction of fatty acid and cytokines in the cellular signalling pathway (González-Castejón & Rodriguez-Casado, 2011). Phytonutrients are also involved in the regulation, gene expression, and epigenetic changes in humans (Nasir et al., 2020). The importance of phytonutrients in the human microbiome, gutome and understanding of metabolic complexities has been now discovered (Costanzo et al., 2021).

Population-based studies have revealed links between genes and comparable nutrients. Different nutrients have unique target ligands, whereas pharmacology is characterised by the use of single drugs at low concentrations and the capacity to target a restricted number of biological targets (Efferth & Koch, 2011; Holen et al., 2016). Life forms have finely tuned genetics and decoded genomes thus providing nutrigenomics with an exploitable platform as model systems. Despite this, nutrigenomics analysis falls short of streamlining the research analysis. A viable strategy is to look for well-defined medical and pharmaceutical research procedures that are applicable to nutrition research. Nutrigenomics can help with nutrition-based drug development by profiling the nutritional genes of a person (Ferguson et al., 2016). Such data could help the researchers understand the working principles of dietary nutrients and their effects on health and illness.

2. Evolution of Nutrigenomics

Previous research has established how animals, particularly humans, evolved physiologically and phylogenetically as a function of the food they ingested (Rose et al., 2010). The latest advancement in sequencing technology, such as Next-generation sequencing (NGS), has made fast DNA sequencing to understand the expression of genetic code and possible biological function. This has made it possible to understand the role and impact of diet on genetic makeup (Ferguson et al., 2016). At the beginning of the twentieth century, the British Physician Archibald Garrod demonstrated the link between nutrition, genome and phenotypic traits (Scriver, 2008). The human genome mapping in 1990 by The Human Genome Project (HGP) directed the way for the modern age of nutrigenomics. Since then, several research has been undertaken on the interaction of genes and nutrition and their effect on an individual's body (Mathers, 2017). One of the significant discoveries from the HGP is the differences in gene sequence, which results in the differential responses due to environmental factors such as diet and nutrition. The genetic differences are characterised based on single nucleotide

polymorphisms (SNPs) that are key enablers in the scientific discipline of nutrigenomics or nutritional genomics (Gillies, 2003). The present scenario of maintaining health and wellness, of the important impact on the food industry, is providing a value chain from crops to the consumer on the understanding of human nutrition at the molecular level of gene expression. The genome of all species is subject to continuous selection pressure and genetic drift to adapt organisms for survival under changing environmental conditions. Due to the fact that individuals are constantly exposed to their diet and new dietary patterns, the gene–nutrient link is a long-standing evolutionary interaction that has happened throughout human history (Caradonna et al., 2020).

In some way, it could be argued that we have been co-evolving concurrently with the food we consume and the world in which we live. An example of how anything changes over time is lactose intolerance (Pavlidis et al., 2015). Another metabolic error disease in phenylketonuria (PKU) results due to a deficiency of hepatic phenylalanine hydroxylase (the enzyme needed to convert phenylalanine to tyrosine) (Guzzetta, 1997). Both lactose intolerance and PKU are examples of a single gene defect with a single dietary factor exposure. For the most part, adults today are vulnerable to lactose indigestibility. This disorder induces lactose intolerance since the gene that encodes lactase is normally silenced shortly after birth. However, over 10,000 to 12,000 years ago, an unusual DNA mutation occurred in a few people in Northern Europe (Guimarães Alves et al., 2021). The SNP affecting the lactase gene in humans led to an increase in the substantial expression of that gene throughout adulthood. This long-term evolution conferred a survival advantage because people with the previously mentioned SNP could consume dairy products (Guimarães Alves et al., 2021).

Another fascinating example includes the genes that allow alcohol to be absorbed by the body in the liver and the stomach's lining. As European populations were exposed to a

greater amount of alcohol than Asian populations who were predominantly drinking tea, a greater degree of alcohol dehydrogenase (ADH) gene cluster expression was observed (Sikalidis, 2019). Among the Asian population, about half (approximately 50%) possess a form of ADH2 that contributes to unusually rapid alcohol conversion to acetaldehyde, which would be dramatically more detrimental than alcohol. Also, the normal aldehyde dehydrogenase 2 family member (ALDH2), manufactured by the liver, converts acetaldehyde into acetic acid. The mutant form of ALDH2 is only about 8 per cent as effective as the usual, wild-type enzyme in removing acetaldehyde. Therefore, the exposure of such a population to alcohol intake is much lower than for people of different European descent (Wall et al., 2003; Yan et al., 2021).

The nutrigenomics approach seeks correlations between gene activity and the environment by testing the genetic profile under various conditions (Neeha & Kinth, 2013). The first direct-to-consumer genetic test obtained regulatory approval in early 2017 and provided insight into certain diseases predispositions. It is debatable whether the services offered by commercial providers of health genetics are accurate or effective (Hogarth & Saukko, 2017). The theoretical pathologies of today require a systemic approach that explores the overall metabolic pathways. In nutrigenomics, the targets may be evaluated in a parallel manner. Gene expression in reaction to variations in the diet is an established occurrence in prokaryotes. Single-cell organisms can monitor the volume of such substances and the timing of exposure to it (Vergères, 2013).

3. Nutrigenetics and nutrigenomics: two sides of a coin

To assess the rise of nutrigenetics/nutrigenomics within the healthcare literature, PubMed was combed as a directory using the search terms "nutrigenetics" and "nutrigenomics" for each year from 2000 to 2019. The first papers on nutrigenetics or nutrigenomics appeared in

PubMed in the 2000s there were some publications on nutrigenetics before 2000. After its introduction in 1986, the number of reported publications grew substantially. Between 2005 and 2010, there was an increasing trend of 20 publications, a bit more than a 1,000 percent increase over the preceding year within five years. While terms such as nutrigenetics and nutrigenomics are frequently employed in contemporary scientific literature, the term originated in twentieth-century biological literature. Nutritional composition research in unicellular and multicellular life began early in the history of classical genetics (Roper, 1960). On the other hand, it must be stated that the first recorded use of the word did not occur until 1975. The term "nutrigenetics" was initially used in the context of treating hypoglycemia. Following its introduction, this term did not enjoy the same level of popularity in literature as it did in ordinary usage. On the other hand, the term nutrigenomics was first used in the literature in 2000, prior to the formation of the definition. In healthcare, nutrigenomics and nutrigenetics have a long history. The magazine was created in late 2007 in conjunction with the formation of the "International Society of Nutrigenetics/Nutrigenomics," which was founded in 2005. In the journal's inaugural edition, the society's president emphasised the critical need for current nutritional research and the relevance of genetics in healthcare (Simopoulos, 2008).

3.1. Nutrigenomics: simple or complex science?

Nutrigenomics has become a study that explores the interaction between genetics and dietary habits (Brennan & De Roos, 2021). Advanced nutritional researches may scrutinize how a person's genetic makeup is related to diet, or how a person's genetics make them respond differently to a given diet. The project is now underway to identify genes associated with various clinical outcomes and recognise and observe changes in the interaction between those genes as a result of dietary and lifestyle interventions (Peña-Romero et al., 2018). Nutrigenomics is growing because people have awareness about the potential gain of better

nutrition for their diet, especially in the form of less risk of eating habit disorders. With the recent development of this field, which bridges scientific areas such as nutrition, molecular biology, genomics, bioinformatics, epidemiology, and medical diagnostics, it is a young field that remains dynamic. Molecular genomics is used to explore how food affects genes. Every time we feed, our genes are expressed in a certain way. Knowledge of signals that influence the body's metabolism and regulate how many calories are burned or retained determines the amount of weight lost or gained. Knowing your genetic language and affecting your metabolism by adjusting how your body reacts to food will help you monitor your weight and your overall health (Drewnowski & Popkin, 1997; Hyman, 2006).

Over-nutrition has become the main medical and dietary priority due to current developments in diet-related illnesses. Nutrition research focuses on discovering how good nutrition can enhance overall body function. Numerous nutrients and the various ways they interact with several other biomolecules are needed to understand how nutrients function at the cellular level. This transition towards molecular science, genetics, and genomics, is because of findings from nutrition research conducted during the latter part of the 20th century. The scientific study of the impact of intra- (gene-gene interaction) and inter- (gene-body interaction) genetic material association is known as nutrigenomics (Rose et al., 2010; Sohel, 2020). Our regimen is more like a compilation of carbohydrates, lipids, and proteins; vitamins, minerals, and enzymes in food provide the body with energy and represent as the building blocks of life. It is the most significant indicator of our environment, from the time we are born to our latter days. Numerous fields of biology have benefited tremendously from our growing understanding of the genome and new sequencing technology. It prompted new interdisciplinary and sub-disciplinary studies in genomics and nutrigenomics. Nutrigenomics is the study of the relationship between our nutrition and our DNA. It is composed of genetic polymorphisms and epigenetic data (Prieto-Hontoria et al., 2011; Ronteltap et al., 2007).

3.2. Relationship between nutrigenetics and nutrigenomics

Additionally, both the general and professional literature also use the words "nutrigenetics" and "nutrigenomics" interchangeably. To put it another way, this is why the change from nutrigenetics to nutrigenomics happens. The description demonstrates how genetics and genomics are linked. Nutrigenetics was identified with the study of classical genetics. Nutrigenetics describes how genetic and nutrition factors can influence disease causation. Whether genetic variations influence an individualized approach to dietary intake, mainly in terms about just how genetics affects an individual's metabolic state or not is the next question (Ordovas & Mooser, 2004).

In a nutshell, nutrigenetics defines how an individual's genes influence the particular nutritional response. Nutrition genomics, nevertheless, has its foundations in the HGP, notably in the omics-era (Carlberg et al., 2016a). The focus is how food intake impacts gene expression, especially epigenomic, transcriptomic, proteomic, and metabolomic high-throughput assays (Sales et al., 2014). A metabolomic study conducted in premenopausal women reveals that diet soy isoflavone consumption can impact metabolic pathways involving osmolyte variation and energy metabolism (Solanky et al., 2005). The primary goal of nutrigenomics research is to develop and apply an individual's personalised nutritional omics profile, which includes their microbiome, or gutome. Nutrigenetics and nutrigenomics can be viewed as two facets of the same coin, which explains why the terms nutrigenetics/nutrigenomics have been condensed. Whereas in the past, nutrigenetics was interested in identifying SNPs and related haplotypes, through "genome-wide association studies (GWAS)", the more recent discipline of nutrigenomics emphasizes an explanation of the epigenome as a result of the diet with respect to high-throughput omics technology. Thus, nutrigenetics produces nutrigenomics, which may demonstrate how the possible genetic markers are determined by SNP discovery. If we have this knowledge, the application of

omics lab tests, such as genomics and metabolomics, may allow the construction of nutritional genomics studies using dietary and gene expression factors. In order to develop customized diet regimens to reduce illness and future health hazards, as well as to encourage health and longevity, repeated experiences between nutrigenetics and nutrigenomics create a detailed image of an individual's integrated metabolism (Ferguson et al., 2016).

4. Insight into diet-genome interaction by other Omics sciences

Omics tools (agri-genomics, nutrigenomics, nutri-proteomics, Ayurnutrigenomics, nutri-metabolomics and epigenomics) are potent tools to gain further insight into nutrient-gene interaction and their effect on the health of an individual (Banerjee et al., 2015; Nasir et al., 2020). Most nutrigenomics studies were based on DNA sequence or genotypes analyses of customised diets. Nevertheless, personally tailored nutrition needs to explore such aspects as proteome and metabolome. Food and drug metabolomics will lead to understanding how digestive microbial composition impacts the action of a drug (Elrakaiby et al., 2014). Regenerative medicine and metabolic proteomics would be based on the temporal and background variables. Different food components have been linked with particular effects and mechanisms of action, often involving changes in epigenetic and gene expression (Fig. 1). Transcriptomics, proteomics, metabolomics and epigenomics are four important platforms of extensive omics investigation in the science of nutrient and human genome interaction (Table 1). Keeping in mind the complexity of the human body and the feasible interaction between food and the body, it is understandable that the whole study of diet-body interactions (i.e. Nutri-omics) is essential to reaching a complete understanding of the effect of food components.

Table 1: Food component mediated expression of human gene and their activity

Component of food	Human gene expression	Activity of gene	Reference
Short chain fatty acid (butyrate)	Increases activity of (retinaldehyde dehydrogenases1) *RALDH1* and *RALDH2*	Immune protective responses against	(Costanzo et al., 2021)
Catechol-containing tea polyphenols	Reduced expression of human catechol-O-methyltransferase (COMT)	Involved in breast cancer	(Wu et al., 2003)
Genistein	Reduces the activity of Cytochrome P450 family 17 subfamily A member 1 (CYP17A1)	Associated with steroid hormone levels and premenopausal breast cancer risk	(Piller et al., 2006)
Folate	Folic acid increases methylation potential and DNA methyltransferase (DNMT) activity, modifies DNA methylation and ultimately decreases amyloid beta precursor protein (APP), presenilin 1 (PSEN1) and β-amyloid peptide binding protein (TM2D1) levels	Reduce the risk of breast cancer	(Alam et al., 2019)
	DNA methylation	Reduces risk of colorectal cancer	(Y.-I. Kim, 2004)
Quercetin	Inhibit the expression of cyclooxygenase 2 (*COX2)* and nitric oxide synthase 1 (*NOS1*; inducible gene) genes through the reducing the translocation of the Kappa-B nuclear factor from the cytoplasm to the nucleus	*iNOS* signaling interacts with COX-2 pathway in colonic fibroblasts	(Jeong et al., 2014)
Resveratrol	Modulate the expression of androgen receptors and cell cycle regulators	Putative anticancer activities in prostate cancer	(Sarafi et al., 2017)
	Post transcriptional regulation of KH-type splicing regulatory protein (KHSRP)	Beneficial effects against cancer, cardiovascular and chronic inflammatory	(Bollmann et al., 2014)

		diseases	
Choline	Increased the expression of peroxisomal acyl-CoA oxidase 1 (*ACOX1*)	Modulated Hyperglycemia	(Jiang et al., 2016)
S-adenosyl methionine (SAM)	Downregulated metastasis related genes stathmin 1 (*STMN1*) and TATA-box binding protein associated factor 15 (*TAF15*)	Restricts the growth, transformation and invasiveness of liver carcinoma cell lines	(Y. Wang et al., 2017)
	Reduced expressions ofDNMTs	SAM protects the anticancer effect of 5-FU (5-fluorouracil)	(HAM et al., 2013)
Betaine	Promoting the insulin-like growth factor 1 (*IGF1*)	Promotes lipolysis and inhibits lipogenesis	(Villa et al., 2017)
	Rise in *IGF1*mRNA	Promotes cell differentiation of human osteoblasts	(Villa et al., 2017)
	Protein kinase AMP-activated catalytic subunit alphas (PRKAA)	Activated AMPK can inhibit fatty acid synthesis and promote fatty acid oxidation	(Zhao et al., 2018)
	Restricted peroxisome proliferator activated receptor gamma (*PPARG*)	Regulates energy metabolism to relieve chronic inflammation	(Y. Kim et al., 2016)
	Reduced protein levels of X-box-binding protein1 (*XBP1*), an endoplasmic reticulum (ER) stress-related protein	Reduce hepatic gluconeogenesis and insulin resistance	(Ge et al., 2016)
Sulforaphane	Inhibited human telomerase reverse transcriptase (h *TERT*),	Inhibits the viability and proliferation of breast cancer cells	(Meeran et al., 2010)
	Epigenetic regulation of nuclear factor, erythroid 2 (*NFE2*) expression	Prevention of human colon cancer	(Zhou et al., 2019)
	High levels of *DNMT1* and *DNMT3a*	Breast and prostate cancer prevention	(Atwell et al., 2015)

Diallyl sulphide (DADS)	Increased cyclin dependent kinase inhibitor 1A (*CDKN1A*) expression High histone deacetylase (*HDAC*) activity	Protective effects on colon carcinogenesis	(Druesne et al., 2004)
	Reduced expression of cyclin B1 (*CCNB1*), cell division cycle 2 (*CDC2*), and cell divison cycle 25C (*CDC 25C*) upregulated levels of p^{21} mRNA expression	Prevention of esophageal squamous cell carcinoma	(Yin et al., 2014)
	Nuclear accumulation of *NFE2*	Dose-dependent attenuation of skin tumor	(Shan et al., 2016)
	Increased induced heme oxygenase 1 (*HMOX1*)and NAD(P)H quinone dehydrogenase 1 (*NQO1*) expression	Reduced inflammation and free radical mediated chronic diseases.	(Lin et al., 2019)
Kaempferol (Flavonol)	Reduced expressions of *DNMT*s	Prevention of colorectal cancer	(Berger et al., 2013)
	Decreased Histone deacetylase (*HDAC*)	Hepatoma and colon cancer prevention	(Xue et al., 2017)
	Decreased *HDAC*	Gastric cancer mitigation	(T. W. Kim et al., 2018)

4.1. Transcriptomics in nutrigenomics

Out of all omics platforms, transcriptomics is very widely exploited in food-nutrition research due to various advantages of the DNA microarray technology compared to other omics tools (Bünger et al., 2007). It involves the study of the level of RNA present in a sample, and results are also used to evaluate the expression level of a complete or a selected segment of genes. Various studies have reported the changes in global gene expression due to various dietary interferences like malnourishment, fasting, overnutrition, and intake of particular

dietary components (Kato et al., 2011). A transcriptomic study of the liver of rats treated with moderate caloric restriction was carried out. For one week or a month, rats were fed a diet containing 5 to 30% less food than an ad libitum-fed group. Among other genes, the cytochrome P450 (*CYP4A14*; family 4, subfamily a, polypeptide 14) gene's expression is influenced by variables such as food restriction (Saito et al., 2010). This gene can be used as a biomarker for food components that significantly affect energy utilisation. Even a very little amount of calorie restriction activated this gene. Another study revealed that caloric restriction regulates circadian clock gene expression in mice. The caloric restriction reprograms the circadian rhythm of mice by regulating (upregulation/downregulation) genes. The calorie restriction might have regulated the clock gene through basic helix-loop-helix ARNT like 1 (*BMAL1)* mediated mechanisms (Patel et al., 2016). The knowledge of transcriptomics will be helpful to know the genes related to the dietary pattern and cope with various dietary related issues.

Nutrition has both direct and indirect effects on gene expression, but the latter has a cascade of effects via cell signalling (Dauncey, 2014). In regards to a direct effect, many nutrients and metabolites interact with nuclear receptors/transcription factors such as retinoic acid (vitamin A), vitamin D, vitamin E, calcineurin, metal-responsive transcription factor 1 (*MTF1*), and fatty acids (peroxisome proliferator-activated receptors, PPARs; sterol regulatory element-binding proteins, SREBPs). Fatty acids give an illustration of the indirect nutritional effects on genes: their metabolism affects the intracellular energy balance, which ultimately alters the cellular nicotinamide adenine dinucleotide (NAD^+) homeostasis and the state of chromatin refurbishing, DNA function and gene regulation. Carbohydrates, amino acids, and energy status affect signalling molecules and receptors, with significant consequences for illness and health. Energy status profoundly influences hormone and growth factor concentrations. Polypeptide hormones (insulin-like growth factors; IGFs,

insulin, and brain-derived neurotrophic factor; BDNF) function through intracellular signalling pathways to activate gene transcription (Fig. 2). Endogenous ligands, including thyroid and glucocorticoid hormones, act on their nuclear receptors to regulate gene expression via transcription and regulation of chromatin structure (Dauncey, 2014; Šimečková et al., 2021).

4.2. Proteomics in nutrigenomics

Proteome study involves separation, quantification, and identification of proteins (Bahinipati et al., 2021). Prior to the emergence of three-dimensional (3D) gel electrophoresis, many proteins were detected using two-dimensional (2D) gel electrophoresis. After labelling with a fluorescent dye, segregated proteins are visible and quantified. Another technique, differential imaging gel electrophoresis, is based on the same premise, in that proteins from different samples are pre-labeled with distinct fluorescent dyes (Swatton et al., 2004). A study on mild caloric restriction in rats suggested differential expression of the protein in the liver. This metabolic condition in the rat leads to upregulation of prohibitin. Moreover, AMP-activated kinase (AMPK) protein was also reported to be enhanced when rats were exposed to a caloric restriction which was positively correlated with the expansion of lifespan (Takahashi et al., 2011).

4.3. Metabolomics and nutrigenomics

The goal of metabolomics research is to determine the total number of compounds (other than DNA and protein) present in a sample (obtained from daily nutrition); the metabolome is the collection of all metabolites metabolised by a biological system. Analysis of metabolites is full of difficulties and requires techniques with a high level of expertise because of the variation in the chemical and functional characteristics of metabolites, which is much higher than those of proteins and transcripts. Despite these challenges, metabolomics

is the most robust tool in food and nutrition research (Zivkovic et al., 2009). Numerous techniques are used for metabolome analysis, among which mass spectrometry (MS) and nuclear magnetic resonance (NMR) are prime options. It is easier to work with the NMR technique and suitable for a broad range of components, although it is less sensitive than techniques based on mass spectrometry (MS). Gas chromatography (GC)-MS or liquid chromatography (LC)-MS are utilised, depending on the properties of the target metabolites. Due to the pleiotropic effects of nutrients, their influence might result in metabolite alterations in a wide variety of metabolic pathways that appear to be unrelated. As a result, certain hidden relationships necessitate a comprehensive examination of all metabolites. Along with sample preparation and data collection, all drugs must be identified to improve retention, experimental strength, and reproductiveness (Manach et al., 2009).

There are many pieces of research on metabolomics in different staple crops, which has health benefits. Studies on large-scale metabolic profiling through GC-MS and ultra-high performance liquid chromatography (UHPLC)-MS/MS in rice revealed that *japonica* and *indica* cultivars have the divergent nutritional value in their grains. When *indica* and *japonica* grain were compared, it was found that *indica* grain contains a higher level of γ-tocopherol, γ-tocotrienol, and pyridoxate. These metabolites have significant health benefits (Hu et al., 2014). Metabolics analysis in about 70 rice genotypes indicates that the resistant starch and phytic acid content are negatively related to the glycemic index of rice. This strategy can be used to develop rice grains with slowly digestible starch to present lifestyle-related diseases such as type 2 diabetes and obesity (Kumar et al., 2020). When comparing transcriptome and metabolomic data from maize (GC-MS and UHPLC-MS-MS), it was discovered that coloured and white maize significantly up-regulate the phlobaphene and anthocyanin pathways, which play a vital role in human health (Hu et al., 2016). Metabolomics in a staple vegetable crop such as potato suggested that mealy texture (including ethylfuran, 2-

pentylfuran, isomenthone) as well as undesirable attributes such as bitter (3,4,5-trimethyl-2-cyclopenten-1-one), earthy (pentan-1-ol), and other off-flavours (5-methylhexan-2-one) were identified in potato cultivars (Bough et al., 2020).

The abundance of energy substrates encourages a greater array of genes to be regulated in order to preserve homeostasis (Rabinowitz & White, 2010). Fruits, vegetables, teas, spices, and traditional medicinal herbs may influence transcription factors in addition to or as an alternative to secondary metabolites (Fadaka et al., 2019). The metabolic processes are affected by these gene expression modifications, resulting in lipid and adipocyte differentiation changes. Additionally, the gene array findings have shown that many acetyl-CoA-responsive genes are linked to cell cycle progression, such as cell division. Cell division can, however, cause a decrease in acetyl-CoA levels. This study suggests that dropped considerably glycolysis and lower levels of acetyl-CoA correlate to diminished pluripotency (Moussaieff et al., 2015). Additionally, the acetyl-CoA level affects the cell signals that determine survival and death decisions. Low levels of acetyl-CoA stimulate the autophagy process, which is important for cellular quality control and survival during metabolic stress. Therefore, the acetyl-CoA and carbon dioxide ratio is a vital factor influencing major cellular decisions (Can et al., 2014).

4.4. Nutrigenomics and Epigenomics

The genome-wide study examines changes at the epigenetic level, a term that refers to variations in chromatin architecture such as DNA methylation and histone modification that occur in the absence of sequence variation (Nasir et al., 2020). Epigenetic alterations influence the expression of genes situated at the respective sites. Numerous nutritional components also have instantaneous and long-term consequences on the epigenetics, including how well an individual eats and the quality of supplements (vitamins, minerals) they take. The study of variations in gene expression that are not caused by changes in the

DNA sequence is known as epigenetics. A fascinating example of epigenetic alterations is the effect of nutrition during fetal evolution on the susceptibility to diseases due to change in lifestyle in later life. That is, during pregnancy when the mother underwent over or undernutrition became prone to increased risk of diseases like obesity, diabetes, hypertension and so on. In nutrigenomics, the nutrient interacts with the gene involved in the genesis of cancer and epigenetics has a role in targeting DNA methylation and histone modification (Elsamanoudy et al., 2016).

Previous studies revealed that DNA methylation is directly linked with chromatin remodelling, which might be induced by the nutrient enzyme DNMT. This enzyme catalyses the transfer of a methyl group from S-adenosylmethionine to specific sites on the DNA (Sales et al., 2014). S-adenosylmethionine metabolizes compounds from food *viz*., folic acid, vitamins B6, B12, B2, choline, and methionine. DNA hypermethylation also inhibits transcription, whereas DNA hypomethylation is related to some kinds of cancer, including prostate cancer and hepatocellular carcinoma (Stefanska et al., 2011). Non-protein-coding RNAs, RNA editing, and telomere regulation are other epigenetic pathways. It is still a significant portion of the genome of non-coding RNAs that play critical roles in development, overall health, and illness (Qureshi & Mehler, 2012). Previous tentative results indicate that small non-coding RNAs have a major role in the mechanism of transcription, epigenetic processes, and gene silencing. The expression of ncRNAs can be affected by environmental factors, including nutrition (Tiffon, 2018). A well-known example of a metabolite sensor is the enzyme AMPK which is activated by the ratio of the concentrations of AMP and ATP. When cells consume adequate amounts of ATP and little else, AMP concentration rises like a signal of nutritional stress. AMP attaches to both the γ-subunit of the AMPK hetero-trimer and triggers the kinase enzyme. If AMPK activity is low, it will be marked in a cell by histone phosphorylation (Wan et al., 2018). A high food intake results in an increased AMP

level, no AMPK activity, and a different histone phosphorylation pattern, leading to a different gene expression pattern. Since ATP is the major energy source for cells, the metabolic state of even a cell can be expressed by the ATP/AMPs ratio, the SAM/SAH ratio, the NAD/NAD^+ ratio and the acetyl-CoA/CoA ratio. When high levels of methyl group donors, such as methionine and glucose, become available, SAM initiates KMTs and acetyl-CoA stimulates histone acetyltransferase (HATs), giving rise to chromatin methylation and acetylation, respectively. In addition, high levels of nutrients suppress AMPK and NAD^+ signalling, leading to histone hyperacetylation and histone deacetylation. Moreover, it inhibits DNMTs and CoA, thereby blocking HATs (Hatori et al., 2012).

4.5. Human gutome and microbiomics

The human gutome describes the interaction between the microbiome and the human digestive system. The idea of the human gutome was introduced in 2011 (Dimitrov, 2011). Microbiomics and metagenomics represent recent developments, both serving to advance the understanding of human-microbe interactions that may be employed in the treatments of infectious diseases (Cho & Blaser, 2012). Measuring metabolically diverse gut bacteria activity may be the key to unlocking the relationship between metabolic phenotype and diet and biology, and/the molecular association. Modulating microbial activity in the host internal *milieu* and dietary preferences can aid in diet classification in communities and nutritional management (Hattori & Taylor, 2009). The only kind of bacteria used in yoghurt and dairy products are lactobacilli and bifidobacteria, and these strains are classed as "functional" because their biological properties are thought to support human health and reduce disease (Masoumi et al., 2021). At this time, the ways in which probiotic microorganisms influence the human immune system are not fully understood even if it is already known that the gut immune system is immunomodulatory. The microbiota supports food uptake, and provides a unique environment for bacterial development. It is possible to quantify their interactions

using animal, cell culture, bacterial proteomics, and human in vitro methods. Additionally, animal research indicates that perhaps the microbiota alters the supply of indigestible polysaccharides to absorbable simple sugars (Cristofori et al., 2021). "Bacterial proteomics" (metaproteomics) has shown the gut microbiota in carbohydrate metabolism is strongly expressed in people with Crohn's disease 2. Omics tools have been exploited for studying the effects of food on human microbiota (Verberkmoes et al., 2009).

5. Precision Nutrition

Precision nutrition holds the enormous capability to boost human health. Many factors like nutrigenomics to phenotyping need to be understood in planning personalized and unbiased nutritional protocols for individuals or population sub-sections. One of the important aim of field of precision nutrition is to plan or design tailored nutritional charts for both the prevention and management of chronic metabolic diseases (i.e., type 2 diabetes and cardiovascular diseases) (D. D. Wang & Hu, 2018). In addition to genetics, precision nutrition draft include, other aspects such as food choices, dietary habits, physical activity, microbiota and metabolome. Metabolic disorders are things that need to be managed and avoided, and the creation of dietary recommendations and personalized health support are some of the main precision nutrition goals. Initiatives aimed at providing more comprehensive and dynamic nutrition information for individuals throughout their lifetime serve the purpose of ensuring individuals have ample nutrition advice during their lifetime (Demetrowitsch et al., 2020). Other aspects such as food, lifestyle, exercise, the microbiome, and the metabolome also significantly affect health. Once the human genome was mapped, a lot of research has been done to explore genetic factors that explain inter-individual variations in response to different diets. Studies supporting these statistical correlations currently have not been established to the point that these can be applied as generalized dietary guidelines in most cases (de Toro-Martín et al., 2017). Because of this, although many

of the findings are still not fully understood, others have been planned and evaluated in both the public and private sectors. Individualized dietary recommendations, avoiding lactose, gluten, and phenylalanine-containing foods, have been in effect for several years due to the hypolactasia diagnosis, the celiac disease ruling out, and the phenylketonuria screening. The private sector also uses genetic testing and diet customization to help with health and nutritional decisions. Dietary recommendations that solely rely on genetics embody a person's ability to customize their food choices based on their genetic predisposition. The second definition is similar to the precision nutrition definition. Still, it refers to a research design that incorporates a diverse range of variables that allow for a more precise and complex nutritional approach (Betts & Gonzalez, 2016). Because of this, while a customized diet that bases your diet on your genetic information has already been shown to be successful in numerous studies, including the ones above, it is still possible that precision nutrition lacks adequate proof of success due to its complexity.

Studies conducted in the last year using gene-environment interactions to study biological traits (gene markers) and metabolic health have discovered essential knowledge about the effect of macronutrient intake on fat mass accumulation, obesity, and body composition (San-Cristobal et al., 2020). These results can be generally extended to precision nutrition because findings from these studies, all about macronutrient intake, open the door to making successful individualized diets. Goni et al., (2015) have studied a "genetic risk score" (GRS) in regard to overweight prediction, and furthermore, their work has shown the impact of different nutrients on the predictive value of this GRS. The GRS is a single genetic profile that reflects 16 other genetic markers. A great deal of the scientific community thinks that recognising environmental factors would be a prominent aspect of the precision nutrition sector. Besides genetics, other elements must be addressed when devising food strategies. The effectiveness of personalized dietary guidelines in predicting reactions to nutritional

intakes is significant, so the findings of this study should be taken seriously. Metabolomics and gut microbiomics are becoming important factors in the field of precision nutrition as dietary and genetic factors (Tebani & Bekri, 2019). According to researchers, the future of precision nutrition will not be established on nutrigenetics. Many approaches beyond genetics also need to be acknowledged when constructing personalized or tailored diets (Mills et al., 2019).

6. Tools for exploration of bulk genomic data

Over the last few years, there has been rapid evolution in the area of genomics and proteomics, which has generated a huge amount of biological data. For extracting and utilising information from these data, advanced computational analyses are crucial. Computational biology and bioinformatics are used to deal with these data to interpret enormous biological data (Merelli et al., 2014). The important field of research in bioinformatics is applying and developing data mining tools for developing databases and solving the biological issue. Data mining in bioinformatics comprises structural analysis of proteins, finding new genes, disease detection and dissection, designing drugs for a specific disease, remedy for the disorder, the interaction between proteins and genes, and subcellular location of protein and metabolites. The database is an important primary source of information for further manipulation in bioinformatics (Shastry & Sanjay, 2020)

Bioinformatics is the technique that enables the processing, grouping, integration, and storage of complex data generated by biomics research. The difficult issue is to integrate all fragmented data information in a meaningful manner (Table 2). The translation of genes into proteins and metabolites is predicted using newly developed software and technology that is linked to biochemical pathways (Corthésy-Theulaz et al., 2005).

Table 2: Databases in the major omics fields that contribute to nutrigenomics investigations

Database Name	Database Site/Homepage	Usage
Genomics and epigenomics		
GenBank	www.ncbi.nlm.nih.gov/GenBank	Comprehensive publicly available annotated DNA sequence information
European Nucleotide Archive (ENA)	www.ebi.ac.uk/embl/	Sequence assembly information and functional annotation
DDBJ (DNA Data Bank of Japan)	www.ddbj.nig.ac.jp/	Omics data analysis and sharing
SRA (Sequence Read Archive)	http://www.ncbi.nlm.nih.gov/sra	Repository of high throughput sequencing data
RefSeq	http://www.ncbi.nlm.nih.gov/RefSeq	Annotated reference sequences of DNA, RNA and amino acids
Entrez Molecular Sequence Database System	https://www.ncbi.nlm.nih.gov/Web/Search/entrezfs.html	Integrated access to nucleotide and protein sequence data with 3D structure

		information
Ensembl	www.ensembl.org/	Comparative genomics, evolution, sequence variation and transcriptional regulation of vertebrate species
Ensembl-Genomes	www.ensemblgenomes.org/	Comparative genomics, evolution, sequence variation and transcriptional regulation of non-vertebrate species
miRBase	www.mirbase.org/	miRNA sequences and annotation
tRNAdb	trnadb.bioinf.uni-leipzig.de/	Compiled tRNA sequences and tRNA genes
EPD (Eukaryotic Promoter Database)	epd.vital-it.ch/	Validated promoters for selected model organisms
TRED (Transcriptional Regulatory Element Database)	rulai.cshl.edu/TRED/	Promoter annotation, data regarding transcription factor binding and regulation
Roadmap	http://www.roadmapepigenomics.org/data	Epigenomic

Epigenomics project		maps in association with human disease
Human Epigenome Browser	http://epigenomegateway.wustl.edu/	Atlas for epigenomics
Track Data Hubs	https://genome.ucsc.edu/cgi-bin/hgHubConnect?redirect=manual&source=genome.ucsc.edu	Web-accessible directories of genomic data that can be viewed on the UCSC Genome Browser
dbSNP	https://www.ncbi.nlm.nih.gov/snp/	Information about single nucleotide variations, microsatellites, and insertions, deletions, genomic and RefSeq mapping for both common variations and clinical mutations.
OMIM (Online Mendelian Inheritance in Man)	www.ncbi.nlm.nih.gov/omim	Compendium of human genes and genetic phenotypes
CGAP	https://www.hsls.pitt.edu/obrc/index.php?page=URL10487	Tools needed

(Cancer Genome Anatomy Project)	07577	to decipher the molecular anatomy of the cancer cell from a annotated index of the genes related to cancer.
dbGaP	view.ncbi.nlm.nih.gov/dbgap	Interactive data interpretation between genotype and phenotype in Humans
GWAS central	www.gwascentral.org/	Genetic association studies
IGSR (International Genome Sample Resource) & 1000 Genomes Project	www.1000genomes.org/	Catalogue of human variation and genotype data
Trasncriptomics		
GEO (Gene Expression Omnibus)	www.ncbi.nlm.nih.gov/geo	Functional genomics data repository
ArrayExpress	www.ebi.ac.uk/arrayexpress/	Storage of data from high-throughput functional genomics experiments

mESAdb (microRNA Expression and Sequence Analysis DataBase)	https://www.hsls.pitt.edu/obrc/index.php?page=URL20110217162456	Sequence analysis and expression profile of microRNAs.
Proteomics		
UniProt	www.uniprot.org/	Protein sequence and functional domain information
PRIDe	www.ebi.ac.uk/pride/	Proteomics identification database
PeptideAtlas	www.peptideatlas.org/	Compendium of peptides identified in a large set of tandem mass spectrometry
gpmdb	gpmdb.thegpm.org/	Proteomics data analysis, reuse & validation
RCSB-PDB	www.rcsb.org	Archived information about the 3D shapes of proteins, nucleic acids, and complex assemblies
STRING	http://string-db.org	Protein-protein interaction and

		functional enrichment analysis
Metabolomics		
PubChem	pubchem.ncbi.nlm.nih.gov/	Information regarding chemicals
ChEMBL	https://www.ebi.ac.uk/chembl/	Aid the translation of genomic information into effective new drugs
ChEBI (Chemical Entities of Biological Interest)	www.ebi.ac.uk/chebi/	Collection of molecular entities focused on 'small' chemical compounds
KEGG Compound Database	www.genome.jp/kegg/compound	Metabolome informatics resource integrating genomics and chemistry
ChemSpider	www.chemspider.com/	Chemical structure database
HMDB	www.hmdb.ca	Information about small molecule

		metabolites found in the human body and their usage for metabolomic, clinical chemistry, biomarker discovery
METLIN	metlin.scripps.edu/	Experimental MS/MS data lipids, steroids, plant and bacteria metabolites, small peptides, carbohydrates, exogenous drugs/metaboli tes
MassBank	www.massbank.jp/?lang = en	Public repository for sharing mass spectral data
NIST (National Institute of Standards and Technology) Chemistry WebBook	webbook.nist.gov/chemistry/	Access to a variety of physical and chemical property data on well defined chemical species and reactions
BMRB (Biological Magnetic Resonance	www.bmrb.wisc.edu/metabolomics/	Repository NMR spectroscopy on proteins,

Data Bank)		peptides, nucleic acids, and other biomolecules
NMRShiftDB	https://pubchem.ncbi.nlm.nih.gov/source/NMRShiftDB	Allows for spectrum prediction (13C, 1H and other nuclei) as well as for searching spectra, structures and other properties
PRIMe	prime.psc.riken.jp/	High-throughput metabolite analyses

Reactome	www.reactome.org	Built-in bioinformatics tools for the visualization, interpretation and analysis of pathway involving proteins and multiple reactions
BioCyc	www.biocyc.org	Collection of several pathways and databases coupled with software tools
SMPDB (Small Molecule Pathway Database)	www.smpdb.ca/	Pathway elucidation and discovery associated with small molecule found in

		humans

6.1. Bioinformatics and Gene Ontology database

Over the past few years, public databases containing biological knowledge allows us to systematically analyse a large pool of gene lists to get information related to the significant biological aspects (Waagmeester et al., 2019). The principle behind the enrichment study is that if a predicted biological procedure is occurring in a given analysis, the related co-functioning genes should have a higher chance to be selected as a relevant functional group by high throughput screening technologies. This kind of approach increases the probability to identify the correct biological processes linked to the mechanism under study (Huang et al., 2009b). Thus, a set of high throughput enrichment tools (e.g., Onto-Express, DAVID, FatiGO, EASE, GOminer, ProfCom, EASE, ProfCom etc.) have been developed since 2002 to support the user to understand the regulation of genes working behind biological mechanisms (Huang et al., 2009a).

6.2. Web interface of NutriGenomeDB

NutriGenomeDB was built using the Ruby on Rails framework. Differential expression data of genes for each experiment is hosted in a platform of MySQL database (Martín-Hernández et al., 2019). The database can be searched with either one or multiple gene symbols to get expression profiling of obtained nutrigenomics gene sets. Interactive tables containing the results were implemented using DataTables (JavaScript) and can be downloaded in either PDF or Excel format. Two different kinds of open source libraries were used to implement interactive visualisations on the gene-centred exploratory module. After interrogating the stored genes for a particular gene sets, the multiline plot visualization, allowing gene expression levels exploration across the nutrigenomics related experiments and was implemented through Plotly's Python graphing library (Cansdale, 2021). The expression heatmap profiling, able to cluster the nutrigenomics experiments based on the query genes

differential expression profiling, was built using Clustergrammer web based tool and JavaScript and Python libraries (Fernandez et al., 2017). For the gene signature functionality comparison analysis, the Gene Set Enrichment Analysis algorithm was implemented (Subramanian et al., 2005), using a reference database (obtained nutrigenomics gene sets). Submitted queries to the phenotype oriented analysis module are allotted with a unique job ID and remain stored for one month on the webserver for later accession. The identified genes correlating with experiments can be used for statistical over-representation test of molecular functions through the web service-oriented PANTHER database (Mi et al., 2021).

It is essential to realise the public health application in the area of genomics and omics science, which is a constantly evolving concept that might help in the prevention of disease and health promotion. In this novel context, personal data can be correlated from different sources (administrative and public health databases, clinical and research records, registries, genealogy, economics, sociodemographics etc.) for health research or health planning. To identify gene-environment interaction and get statistical significance, the association of large amounts of such datasets is necessary. The flow and sharing of data across the international and regional borders is a potential approach to achieving such statistical analysis. A number of initiatives were started in order to get a better understanding of stakeholder views toward these issues. For example, the Human Genome Epidemiology Network (HuGENet) was established by the Office of Public Health Genomics in the USA to help in the translation of genetic research findings for preventive medicine and public health (http://www.hugenavigator.net). The HuGE Navigator serves as an integrated, searchable knowledge database of human genome epidemiology and genetic associations. The DataSHaPER (DataSchema and Harmonization Platform for Epidemiological Research; http://www.datashaper.org), is another platform created by a multidisciplinary consortium coordinated by three international organizations: Promoting Harmonization of

Epidemiological Biobanks in Europe (PHOEBE), Public Population Project in Genomics (P-3G) and CPT Canadian Partnership for Tomorrow Project (CPT) (Borugian et al., 2010; Knoppers et al., 2008). As the size and complexity of omics related datasets and related information grow, reporting standards are playing a key role. Interoperability among the standards, however, becomes more crucial for the development of software applications. For instance, Genomics Standards Consortium (GSC) (http://www.ebi.ac.uk/bioinvindex) developed a new prototype infrastructure (BioInvestigation Index) which is the first set of publicly available multi-omics datasets (Table 1). The integration of genome or molecular science with advanced engineering science is beginning to transform era of life science in which the physiological and pathological information of the human body can be quantitatively described in silico through diverse organisational hierarchies ranging from organs to individuals, molecules to cells, and across multiple time and size scales.

7. Conclusion

In the present scenario of change in food habits and lifestyle, people all around the globe ar risk of the development of diet related diseases. Moreover, different studies signify that dietary modification might lower the risk of developing chronic and lifestyle-related diseases. Nutrigenomics is an emerging discipline that possesses a high potential that can be used for the prevention and management of diet-related diseases *viz*., diabetes, cancer, obesity, and other diseases. The individual's health condition is affected by the combination of the metabolic response of diet and gene expression. Specific bioactive components in the food might be helpful to prevent disease which is diet/ non-diet based. Likewise, epigenetic modification is shown to have a substantial role in the occurrence of disease and pathogenesis. Moreover, plant metabolomics has also contributed significantly to understanding low molecular weight metabolites that are directly/indirectly associated with

human nutrition. The combination of nutritional research and different omics technologies will be helpful to explore and understand more about this field for the benefit of humankind. Circadian rhythm is an essential mechanism of every living being, highly regulated by nutritional components. The gut microbiome plays a crucial role in the human digestive system and provides immunity influenced by multiple environmental factors. The crosstalk/interplay of gut microbiome in the pathogenesis of food allergy could be explored in future studies to prevent food allergies. The information in the present review will help health professionals and scientists design a tailor-made diet to prevent lifestyle-related diseases like diabetes, cancer, and potential diet-based diseases.

8. Declaration

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval: As the manuscript is a review article, ethical approval is not applicable.

Consent to participate: Not applicable.

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Figure captions

Fig. 1: Insight overview into diet-genome interaction by other Omics sciences. The diet of humans and animals might regulate the growth and development by various changes in the level of metabolomics, proteomics, transcriptomics, microbiomics and epigenomics.

Fig. 2: Basic Signaling Mechanism of nutrients mediated control of different omics mechanism in human which is mediated by various nutrients which acts as the signalling molecules. This eventually leads to the formation of functional proteins and metabolites.

Conflicts of interest

The authors confirm that the works presented in this manuscript has no conflicts of interest.

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Sincere regards
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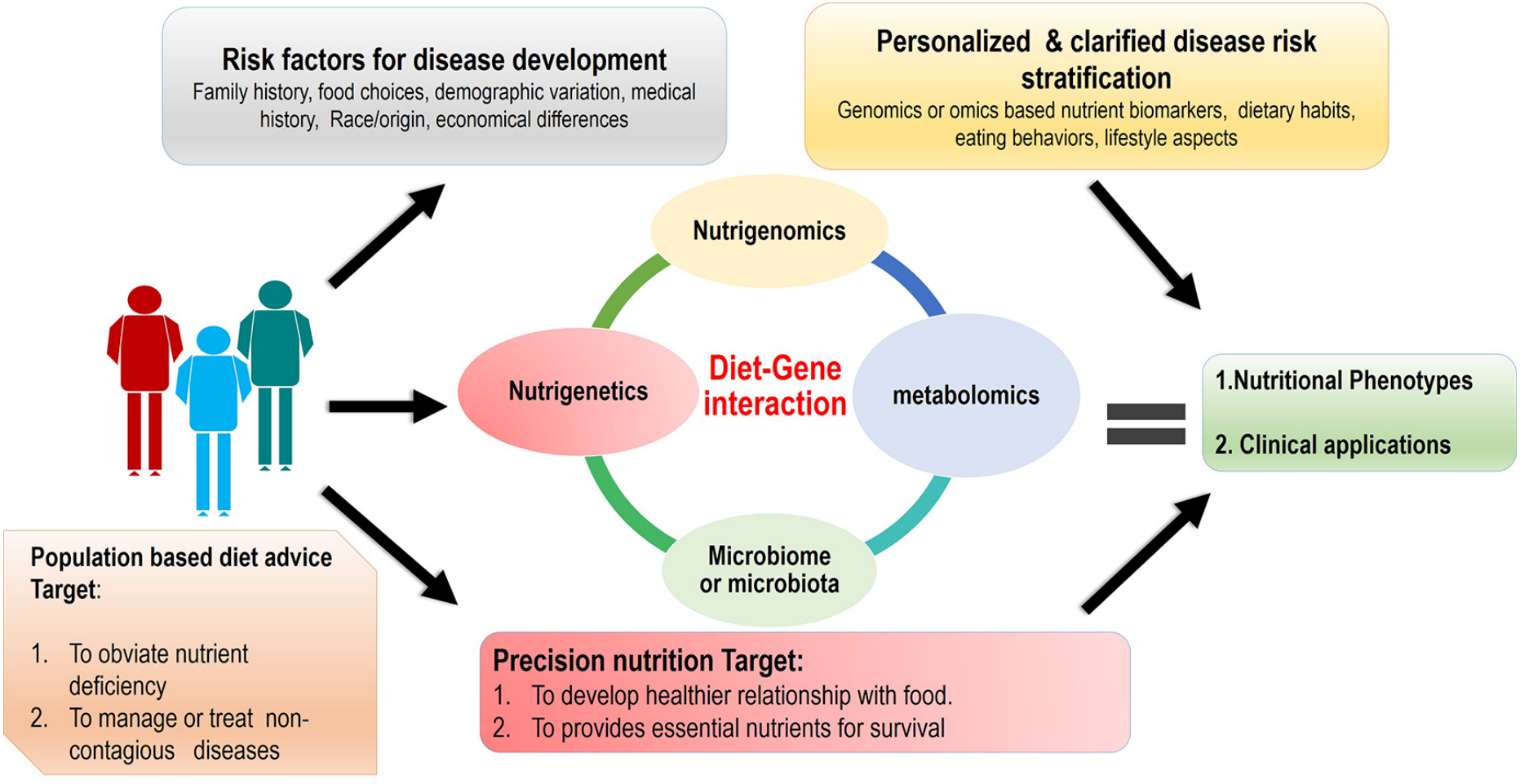
Graphical Abstract

Highlights

- Nutrigenomics related to study a nutritional aspects using molecular techniques
- Genomic variation and receptor-mediated nutrition sensing studied in nutrigenomics
- A dietary signature might be used to design functional food and precision nutrition
- In future study, gut microbiome crosstalk could be explored against food allergy



Graphics Abstract

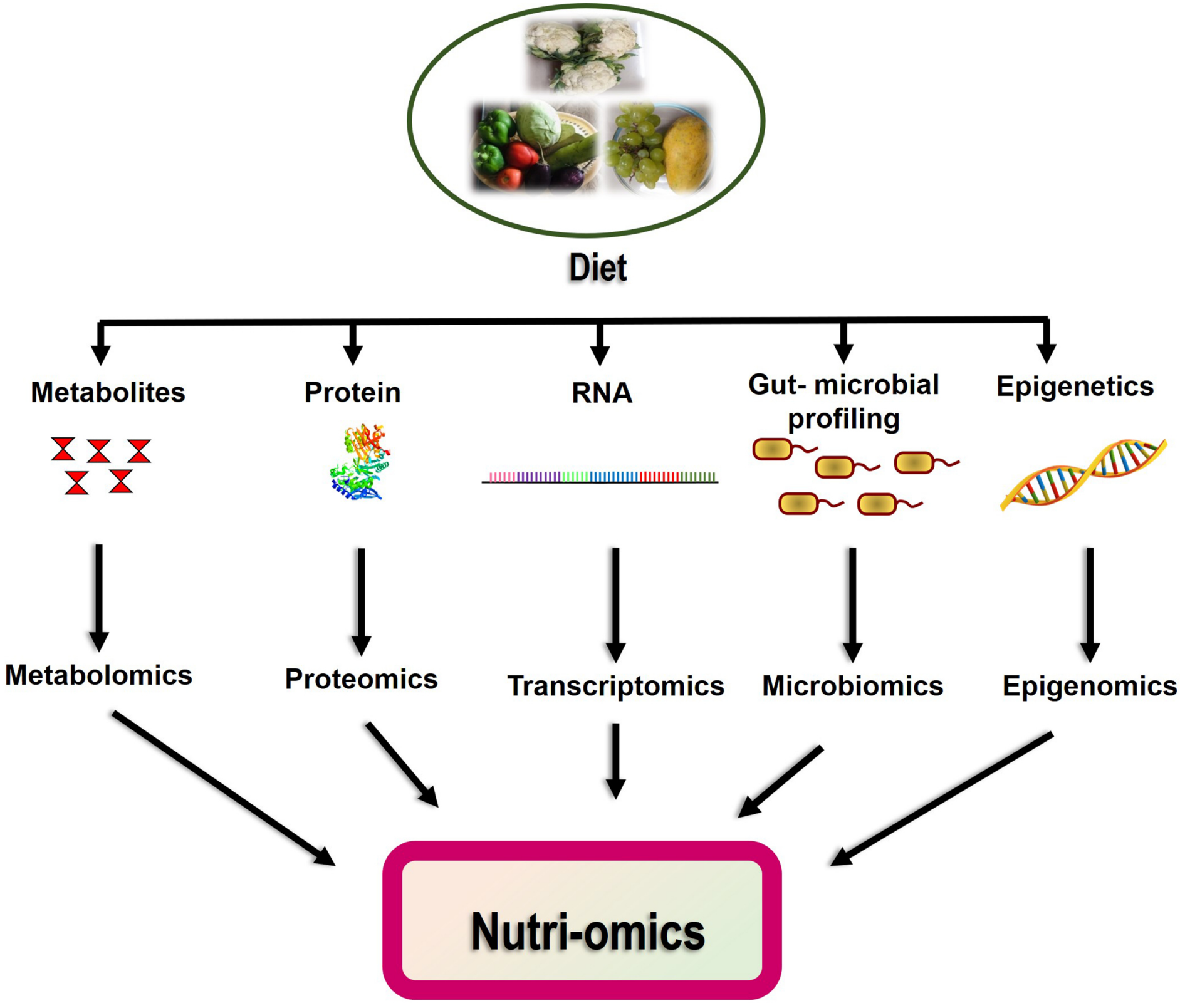

Diet
Metabolites
Protein
RNA
Gut- microbial profiling
Epigenetics
Metabolomics
Proteomics
Transcriptomics
Microbiomics
Epigenomics
Nutri-omics

Figure 1

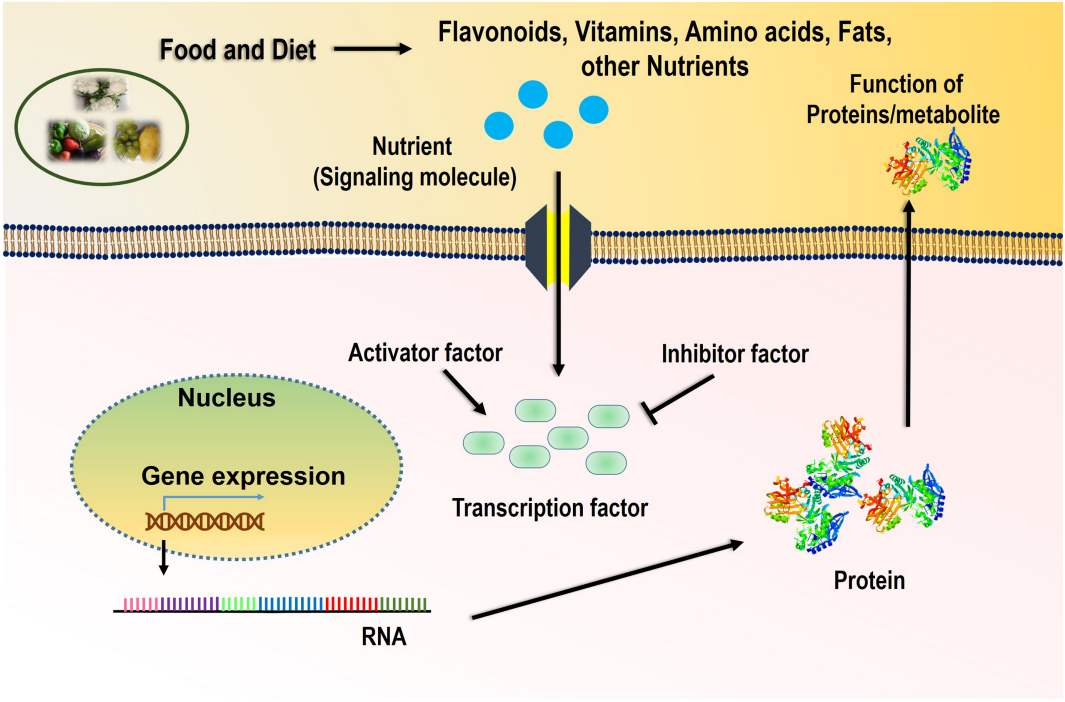

Food and Diet
Flavonoids, Vitamins, Amino acids, Fats, other Nutrients
Function of Proteins/metabolite
Nutrient (Signaling molecule)
Activator factor
Inhibitor factor
Nucleus
Gene expression
Transcription factor
Protein
RNA

Figure 2