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Review

# The Advent of Nutrigenomics: A Narrative Review with an Emphasis on Psychological Disorders

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**ABSTRACT:** A new research field is emerging that combines nutrition and genetics at the molecular level, namely nutrigenomics. Several aspects of nutrigenomics are examined in this review, with a particular focus on psychological disorders. The origin of this field in the 20th century and its modern developments have been investigated. Various studies have reported the impact of genetic factors and diet on various chronic disorders, elucidating how the deficiency of several macronutrients results in significant ailments, including diabetes, cancer, cardiovascular disorders, and others. Furthermore, the application of nutrigenomics to diet and its impact on the global disease rate and quality of life have been discussed. The relationship between diet and gene expression can facilitate the classification of diet-gene interactions and the diagnosis of polymorphisms and anomalies. Numerous databases and research tools for the study of nutrigenomics are essential to the medical application of this field. The nutrition-gene interrelationships can be utilized to study brain development, impairment, and diseases, which could be a significant medical breakthrough. It has also been observed that psychological conditions are exacerbated by the interaction between gut microbes and the prevalence of malnutrition. This article focuses on the impact of nutrition on genes involved in various psychological disorders and the potential application of nutrigenomics as a revolutionary treatment method.

**Keywords:** bioinformatics, genetics, nutrigenomics, nutrition, psychological disorders

## INTRODUCTION

The convergence of nutrition and genomic sciences (nutrigenomics) is an emerging research field. It is a hybrid science in its nascent stages that aims to decipher the influence of nutrition on the expression of genes by integrating a wide range of disciplines, including molecular biology, biochemistry, nutrition, genomics, epidemiology, bioinformatics, and molecular medicine. It explains the prevalent correlations between genes and nutrients at the molecular level (Neeha and Kinth, 2013). According to Reddy et al. (2018), health and disease are defined by the hierarchical information flowing through DNA-RNA-protein-metabolite, collectively referred to as the "molecular fingerprint." The environment and food, both in terms of quality and quantity, are believed to have the greatest impact on an individual's health (Reddy et al., 2018). Furthermore, the mechanism by which gene expression could affect a person's health and the relationship between genotype and environment/nutrient as a result of the metabolic process, as well as how this could occur, should therefore be thoroughly discussed (Sales et al., 2014). In addition to an introduction and a description of this field, a hypothesis indicating a possible relationship between psychological disorders and nutrigenomics is presented in this review article. In addition, it is anticipated that it will promote the applications of nutrigenomics in the health sector and encourage readers to consider new scientific possibilities. The correlation between nutrigenomics and psychological conditions is a novel area of study that has not yet been mentioned directly in the scientific literature. If supported by additional research, this could become a potent treatment for mental health disorders. Nutrigenomics could reduce the need for medications that carry a high risk of side effects and withdrawal symptoms.

### Brief history of nutrigenomics

Garrod's groundbreaking research on inherited metabolic disorders at the turn of the 20th century led him to the conclusion that diet and genetics determine the phenotype (Mathers, 2017). Asbjörn Følling, a Norwegian sci-

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entist, identified phenylketonuria (PKU) as the cause of severe brain damage in two young children in 1934. PKU is an autosomal recessive phenylalanine (Phe) metabolism inborn error caused by the deficiency of phenylalanine hydroxylase (PAH). Most PKU and hyperphenylalaninemia variants are caused by mutations in the PAH gene on chromosome 12q23.2 (Williams et al., 2008). Patients are advised to avoid consuming foods containing the amino acid Phe.

Another example is lactose intolerance; approximately 65% of adults worldwide have impaired lactose digestion after infancy (MedlinePlus, 2017b). After weaning, the gene encoding lactase, the enzyme that digests lactose, is typically turned off. As a result, they are unable to digest milk products (Deng et al., 2015). In 2002, the gene that causes lactose intolerance was identified. Approximately 10,000 to 12,000 years ago, a polymorphism in a single DNA nucleotide occurred among Northern Europeans. With the revolution in molecular genetics and in regions with limited growing seasons, scientists set out to identify other genes that interfere with dietary components. From 1990 to 2003, scientists from around the world participated in the Human Genome Project, which determined the sequence of the human genome. This paved the way for the advancement of nutrigenomics. In 2007, multiple interrelationships between genes, diet, and diseases were observed (Neeha and Kinth, 2013). Currently, nutrigenomics is advancing in multiple regions of the world in order to uncover the truth behind these chronic diseases (Neeha and Kinth, 2013).

## Applications of nutrigenomics

Nutrigenomics attempts to classify the genes that increase the likelihood of diet-related diseases and to assist in overcoming the pathways underlying these genetic predispositions (Müller and Kersten, 2003). Determining certain etiological perspectives on chronic diseases [type II diabetes mellitus (T2DM), cancer, hypertension, obesity, and cardiovascular disorders (CVD) related to diet and chronic disease associations] is facilitated by the determination of a personalized diet, which suggests individual dietary needs based on an individual's genetic profile (Miggiano and De Sanctis, 2006; Mozaffarian, 2016). Therefore, there is an urgent need to accelerate nutrigenomics research in order to discover a cure for diseases caused by a deficiency in nutritious food (Mondal and Panda, 2020).

Nutrigenomics can also be used to classify relevant genes involved in diet-gene interactions and to diagnose polymorphisms that may have significant dietary effects and influence the genetic expression of environmental factors. Throughout life, genomes are exposed to a variety of environmental stimuli, including nutrition. Thus, genetic expression is highly dependent on and regulated by the nutrients and phytochemicals present in food (Garg et al., 2014). It may also be useful for expanding dietary neuroprotective mechanisms and identifying new natural compounds that may be more effective (i.e., activating genes that promote health and reducing the production of disease-promoting genes, which could be incorporated into potential neuroprotective strategies) (Virmani et al., 2013). Several studies have asserted that macronutrients (proteins and carbohydrates), micronutrients (vitamins), and naturally occurring chemicals (flavonoids, coumarins, and carotenoids) play a crucial role in gene regulation (Banerjee et al., 2015).

Scientists studying ruminants can generate large-scale mRNA, protein, and metabolite data using high-throughput 'omics' technologies. Ruminants occupy a unique niche in the animal kingdom and are the most important species that provide milk, beef, and wool to humans by consuming highly fibrous feed. Cattle, goats, and sheep have been used as models for ruminal fermentation and the processes by which tissues use nutrients for milk synthesis, development, accretion, and reproduction of fur for several years (Osorio et al., 2017). It is also used to

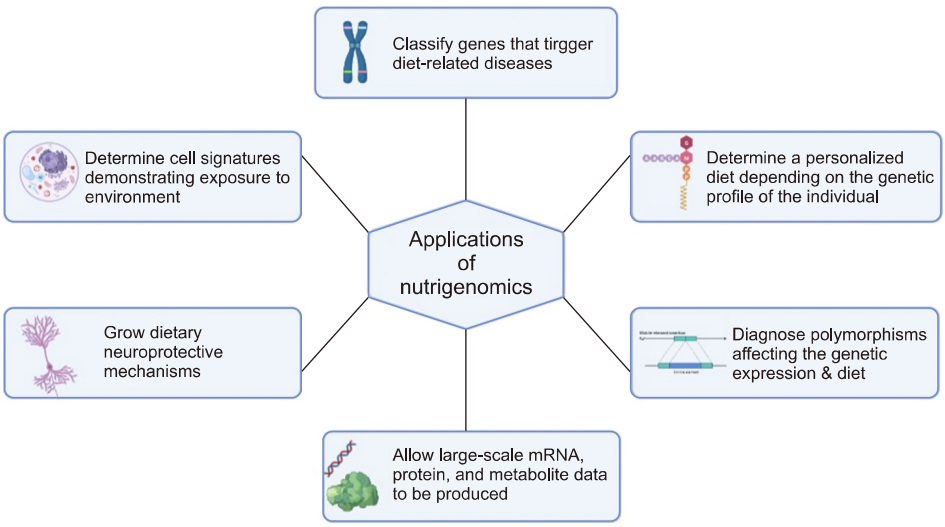


**Fig. 1.** Diagram illustrating the applications of nutrigenomics, including polymorphism diagnosis, a dietary determination based on the genetic profile, cell signatures, the development of neuroprotective dietary mechanisms, and gene classification influencing diet-related disorders. Created with Biorender (https://biorender.com/).

**Table 1.** Databases available for nutrigenomics research

| Database | Description | Website |
|---|---|---|
| A-YO-5 | Based on an open-source database structure, this database is freely available via the World Wide Web. | http://a-yo5.ch.a.u-tsokyo.ac.jp/index.phtml |
| vProtein | For discovery of amino acids from foods dependent on plants. Formulated to identify potential food complements to satisfy the protein needs of an individual (Woolf et al., 2011). | http://www.smarterbetter.design/vprotein/default/index |
| GxE | To study gene-environment interactions relevant to ailments including diabetes, cardiovascular disorders, and blood lipids (Lee et al., 2011). | http://biit.cs.ut.ee/gprofiler/gost |
| Nutritional Phenotype Database (dbNP) | This database was developed by Nutrigenomics Organisation (NuGO), it aims at storing biologically appropriate, pre-processed omics data and study phenotype and descriptive data. | https://bio.tools/dbnp |
| Barley Base | A plant microarray web database with built-in data visualization and mathematical analysis resources. Microarray data from the research on plants such as rice, wheat, maize, and soybean are also covered (Shen, 2005). | www.barleybase.org |

determine cell signatures that demonstrate environmental exposure and investigate the earliest alterations in disease progression (Sales et al., 2014). In lieu of nutrigenomics, human nutrition can be studied on multiple levels. By identifying key genes involved in dietary responses, nutrigenomics may also provide some indications of genes in which polymorphisms may be significant; these genes can then be investigated further in epidemiological studies. However, the degrees of complexity are uncertain (Rana and Shrivastava, 2011). The applications mentioned above of nutrigenomics are depicted in Fig. 1.

## TOOLS AVAILABLE TO STUDY NUTRIGENOMICS

Databases and tools are fundamental requirements for computational utilization in nutrigenomics. The database is referred to as the primary information source and is the most important requirement for additional data manipulation. Several steps, including data collection, verification, registration, storage, maintenance, and extraction, are performed in bioinformatics to emphasize the database. Some databases are designed specifically for nutrigenomics. The examples of the nutrigenomics database are depicted in Table 1 (Shen, 2005; Lee et al., 2011; Woolf et al., 2011; Wiwanitkit, 2012).

In the field of nutrigenomics, tools also play a significant role. They can be utilized for both forecasting future phenomena and elucidating existing scenarios. Table 2 describes several commonly employed nutrigenomics methods (Do et al., 2010; Fenech et al., 2011).

Numerous nutrigenomic studies employ modern techniques like microarrays, genomics, and bioinformatics to explain how nutrients influence gene expression. Such methods may provide new research that can improve nutritional regimens and identify new natural agents for the study of major diseases such as diabetes and cancer (Masotti et al., 2010).

## RELATIONSHIP BETWEEN NUTRIGENOMICS AND HEALTH

Many chronic diseases are caused by long-term consumption of an unhealthy diet and a negative lifestyle (Al-Mas-

**Table 2.** Tools available for nutrigenomics research

| Tools | Description | Website |
|---|---|---|
| GRS | Modern compression method to store and analyze data from Genome ReSequencing (Fenech et al., 2011). | http://gmdd.shgmo.org/Computational-Biology/GRS |
| BioConductor | Used for the analysis of sample size and relative power on gene expression profiling data. | Bioconductor - Help |
| Booly | A web tool and warehousing framework with a basic but scalable data model paired with the ability to conduct an efficient comparative analysis, including the use of Boolean logic to merge datasets and an advanced aliasing system to decode the same gene or protein's separate names (Do et al., 2010). | http://booly.ucsd.edu/ |
| SMM | Newly designed tool to research a foodborne pathogen, *Salmonella enterica*. | https://foodsafety.sjtu.edu.cn/SMM-system.html |

kari, 2010). Chronic diseases account for approximately 60% of deaths worldwide, which is twice as many as infectious diseases [World Health Organization (WHO), 2009]. Fifty three percent of deaths in India were attributable to non-communicable conditions (WHO, 2011). A dietary factor plays a crucial role in the development of chronic diseases such as obesity, cancer, diabetes mellitus, and CVD) (Rana et al., 2016). These diseases are strongly influenced by genetics, diet, and lifestyle. Both genetic and environmental factors are closely linked to the development of cardiovascular disease (Arshad et al., 2017). The utilization of novel bioactive foods and nutraceuticals for cardioprotection and management is on the rise. According to Thompkinson et al. (2014) foods rich in omega-3 fatty acids, antioxidant vitamins, and fiber may be advantageous for cardiovascular health (Voruganti, 2018).

Micronutrient deficiencies can lead to DNA damage and a wide variety of chronic diseases (Fenech, 2010). According to studies, iron deficiency (ID) alters dopaminergic function. Other neurotransmitters, including serotonin and norepinephrine, are also affected. This was proved by the Madison monkey model by Coe et al. (2009). It demonstrates further that ID can cause neurological disorders (Lozoff, 2011). Zinc is also one of the most important minerals involved in synaptic function. During development, zinc regulates neuronal plasticity and synaptic activity. In zinc homeostasis, different transporters and importers are utilized. Zinc transporter 3 is the only transporter utilized in the brain's zinc homeostasis. It has been discovered that alterations in brain zinc status can result in a variety of neurological disorders. For example, impaired brain development and numerous neurodegenerative disorders, such as Alzheimer's disease, as well as mood disorders, such as depression, Parkinson's disease, and Huntington's disease (Prakash et al., 2015).

T2DM pathophysiology is significantly influenced by the interaction between genes and diet/nutrition. Resveratrol (*trans*-3,5,4'-trihydroxystilbene) is a natural nonflavonoid polyphenol compound found in grapes, blueberries, peanuts, and red wine that reduces diabetic complications in numerous organs and tissues, including the liver and pancreatic β-cells (Bagul and Banerjee, 2015). Vitamin D deficiency affects insulin secretion, insulin resistance, and β-cell function (Ortega et al., 2017).

During the expression of cancer genes, protein and metabolite functions begin to operate abnormally. Cancer is caused by tobacco, poor diet, lack of physical activity, excessive alcohol, certain infections, and mutations (Arshad et al., 2017).

Such associations are essential for comprehending the role that nutrients play in the development of various diseases.

**Implementation in the diet**

It is well known that food is a fundamental requirement for human growth and function. Food provides us with the nutrients and energy necessary to carry out various metabolic processes. A healthy diet and lifestyle are responsible for the prevention of a variety of common diseases and, in the end, promote overall health (Rana et al., 2016).

Diet is both necessary and directly modifiable, implying that improved knowledge of optimal nutrition has the potential to enhance the quality of life and reduce the incidence and prevalence of global diseases (Ferguson et al., 2016). Nutrigenomics may also contribute to fitness development strategies by enhancing our comprehension of disease mechanisms and enhancing novel practices for the diagnosis, suppression, and reversal of metabolic imbalances and abnormalities (Bidlack and Rodriguez, 2012). Dietary availability and amounts of energy, macro-, and micronutrients, and growth-promoting factors are determined by the type and composition of food. According to numerous studies, there are relationships between food, health, and illness. Diet plays a crucial role in the occurrence of major diseases such as diabetes, atherosclerosis, and cardiovascular disease (Virmani et al., 2006; Lillycrop and Burdge, 2012). Numerous plant-based foods have beneficial effects on the prevention of chronic diseases. Numerous food substances, such as green tea, soy, vitamin D, lycopene, and selenium, are extracted from natural resources and used to enhance human fitness (Cencic and Chingwaru, 2010).

The European Prospective Investigation of Cancer and The National Institutes of Health-American Association of Retired Persons Diet and Health Study concluded that the Mediterranean diet (MD) has beneficial effects on inflammation, cancer, and acute respiratory distress syndrome. Several interconnected processes involved in tumorigenesis and the inflammatory response (such as free radical production, NF-κB activation, and the expression of inflammatory mediators) are modulated by the MD and its bioactive nutrients (Ostan et al., 2015).

Individuals have distinct dietary preferences. People vary in relation to a vast array of essential natural factors. These factors are determined by chromosomal differences, such as male and female. Age and a person's particular life stage also contribute to differences (e.g., pregnancy, lactation, earliest stages, adolescence, pre- and post-menopause, and older). Natural impacts that are either exogenous and arbitrary or endogenous are the source of differences. Simple sugars, lipids, and high-quality protein are macronutrients that influence human health and genetic makeup. For instance, simple carbohydrate- and starch-rich foods are detrimental to individuals with insulin resistance but beneficial to athletes, who typically exhibit high insulin sensitivity. It is be-

lieved that high-protein diets can reverse the unfavorable metabolic programming of infants while also promoting muscle mass preservation in the elderly (Singhal et al., 2007; Symons et al., 2007; Zivkovic et al., 2007; Kussmann and Fay, 2008).

Diet alone is insufficient for disease management; a healthy lifestyle should be adopted alongside a healthy diet. Weight management, limiting alcohol and tobacco consumption, consuming a diet rich in fruits, vegetables, cereals, and plant-based oils, and engaging in regular physical activity are crucial for achieving the same. All of these factors contribute significantly to the prevention of lifestyle-related diseases. Alone, these factors will determine whether the majority of the population is at high or low risk for developing the disease (Astley and Elliot, 2005).

**Role in various disorders**

In order to comprehend how specific nutrients can alter an individual's genotype (DNA, mRNA, and proteins), the interaction between specific nutrients and a gene must be understood. This has paved the way for the creation of natural bioactive compound-fused foods for individuals with relatively similar genetic makeup. The expression of genes can be regulated, modified, and altered by nutrition without affecting the DNA sequence. Dietary gene expression in transcriptional, translational, and post-translational alterations, as well as epigenetic processes, play crucial roles in certain instances (Dauncey, 2014; Rana et al., 2016).

The roles of n-3 polyunsaturated fatty acids (PUFA) in the central nervous system were investigated using global screening techniques at the transcriptome and proteome levels. Cholesterol and fish oil, which are rich in PUFA, were observed to modify the expression of various genes involved in raft formation and membrane protrusions. Using protein microarrays, they discovered a decreased concentration of signaling pathway proteins such as phospholipase C $\gamma$ and kinase C $\beta$ (Puskas and Kitajka, 2006).

Nutrition is crucial for the control and prevention of cardiovascular disease. A nutritious diet can influence the expression of genes involved in lipid biosynthesis and metabolism, including arachidonate 5-lipoxygenase, apolipoprotein E (APOE), lipoprotein lipase, fatty acid synthase, and peroxisome proliferator-activated receptors (Dimitriou and Dedoussis, 2012). By modulating gene expression or interfering with the signaling cascade, the nutritional composition of diet systems is known to affect the inflammatory process (Shivappa et al., 2015). Vitamin E and its isoforms possess powerful anti-inflammatory and antioxidant properties. Tocopherol ($\alpha$-T) supplementation decreases the levels of C-reactive protein, interleukin-8, and plasminogen activator inhibitor-1 in both human and animal subjects. Isoform $\gamma$-T was found to be effective at reducing reactive nitrogen species and also exhibited anti-inflammatory properties (Rana et al., 2016).

The application of nutrigenomics to neurodegenerative diseases is extremely significant. Neurodegenerative diseases are a diverse group of disorders characterized by the progressive degeneration of the central nervous system or peripheral nervous system's structure and function (Agnihotri and Aruoma, 2020).

Brain function is largely determined by interactions between genetics and environmental factors, such as diet, age, stress, and daily activities. Changes in gene expression are dependent on dietary intake, which primarily affects the brain. Epigenetic events suggest key mechanisms by which nutrition is associated with the pathogenesis of age-related cognitive decline. Different dietary supplements, food sources, and diets have both immediate and long-term effects on the epigenome (Mahmood et al., 2020).

Nutrition plays an important role in epigenomics; however, its precise function is uncertain due to the complex interplay between nutrient constituents, epigenetic regulators, and specific genotypes. According to previous research, multiple neuropsychiatric and neurological disorders, such as dementia, Parkinson's disease, schizophrenia, bipolar disorders, Alzheimer's disease, and primary brain tumors, are associated with epigenetic pathways. Brain function has a significant effect on the effect of nutrition on gene expression, which can be mitigated by individual variations in different gene variants such as mutations, single nucleotide polymorphisms (SNPs), and copy number variants (CNVs). A polymorphism in the angiotensin gene, for instance, can determine how a person's blood pressure responds to dietary fiber. SNP arrays can also be the most effective method for detecting cancer-causing somatic and germline genetic variants (Dauncey, 2013).

APOE polymorphism is a prominent example of a genetic polymorphism that is specifically influenced by a nutrient. The APOE e4 gene increases the likelihood of developing Alzheimer's disease (Neeha and Kinth, 2013). Lifelong consumption of methyl donors, including choline, folate, vitamins B6 and B12, and methionine, is necessary for optimal growth and physiological function in the body. The overproduction of reactive oxygen species or inhibition of antioxidant systems in mitochondria can result in severe oxidative stress, which plays a key role in the pathogenesis of neurodegeneration. According to previous studies, some vegetables and fruits, particularly green leafy vegetables and nuts, are strongly associated with a reduction in the rate of age-related cognitive decline (Agnihotri and Aruoma, 2020). Another study by Caramia (2008) discovered that consumption of fish and

fish oil promotes brain development and gene expression to brain maintenance during aging via a nutrigenomic mechanism (Caramia, 2008).

Significant studies indicate that various genetic and environmental factors, such as diet and nutrition, are associated with neuropsychiatric, neurodevelopmental, and neurodegenerative disorders. Several aspects of neurology, including neurodevelopment, neurogenesis, neuron roles, synapses, and neural networks, are influenced by nutritional factors in specific brain regions. The associations between nutrition and genes play an essential role in brain development, impairment, and disorders.

## ROLE IN MAJOR PSYCHOLOGICAL CONDITIONS

The impact of nutrigenomics on psychological disorders could be a pivotal point in understanding the dynamics of this emerging field of science. The role of nutrigenomics as a panacea for psychological disorders is poorly understood due to insufficient research and, consequently, experimental evidence. The authors have dissected the effect of specific nutrients on the genes involved in major psychological disorders, which affect an alarmingly high percentage of the global population. Analyzing major genes encompassing a variety of psychological conditions and obliquely relating them to the nutrients by which they are affected, a hypothesis was formulated in this regard. This could prove to be a viable and cost-effective treatment method.

### Nutrition and psychological distress

Several studies demonstrate that nutritional abnormalities increase the intensity of psychological distress. For example, a study revealed that anxiety, obsessive-compulsive disorder (OCD), and depression could be the result of malnutrition (Mattar et al., 2011).

PUFA status has also been associated with neuropsychiatric disorders, including depression and suicidal risk. The relative functions of PUFA levels and DNA methylation for diagnostic and suicide attempt status were also calculated using logistic regression studies with the least absolute shrinkage and selection operator. PUFA associations with suicide attempt status were observed to be explained within regulatory regions by Elovl5 DNA methylation results (Haghighi et al., 2015). Studies have also demonstrated the role of abnormal brain serotonin 5-hydroxytryptamine (5-HT) biochemistry as a sensitive biological mechanism in the onset of mood disorders. Since brain serotonin development is limited by the availability of its plasma dietary amino acid precursor tryptophan (TRP), it is believed that a variety of foods and dietary amino acids influence the availability of TRP by altering brain 5-HT synthesis (Markus, 2008).

The relationship between mood and food is another area of research need. According to a number of studies, the size and composition of a meal should more closely reflect the consumer's natural eating habits. A person's disposition may be adversely affected by deviations from normal eating habits. By increasing opioidergic and dopaminergic neurotransmission throughout the brain, sweetness and high energy intensity sensory feedback, such as a fatty texture, may improve mood and alleviate stress symptoms (Gibson, 2006; Wahl et al., 2017).

In addition to playing a role in anxiety and trauma-related disorders, the gut microbiome also plays a role in anxiety and trauma-related disorders. It was discovered that the microbiome plays a crucial role in the development of the hypothalamic-pituitary-adrenal axis and stress reactivity in adulthood. 16S rRNA sequencing was employed to investigate and compare the microbial composition of different individuals (Malan-Muller et al., 2018).

### Major genes involved in various psychological conditions

***Depression*:** Depression is one of the most common mental disorders, with nearly 264 million cases worldwide (WHO, 2020). The serotonin transporter gene (*SLC6A4*/5HTT), the serotonin-transporter-linked promoter region (*5-HTTLPR*), and the serotonin receptor gene 5-hydroxytryptamine receptor 2A (*HTR2A*), and brain-derived neurotrophic factor (BDNF) are among the most important genes involved in depression and anxiety disorders. SLC 6A4 encodes 5HTT, which controls serotonergic neurotransmission and serotonin concentration at extrasynaptic sites and synaptic clefts (Su et al., 2009; Lam et al., 2018). The HTR2A gene encodes the 5-HT2A receptor, which is responsible for postsynaptic serotonin signaling and serves as a target for several antidepressants (Genesight, 2017; https://genesight.com/articles/get-to-know-a-gene-htr2a/). TRP, an essential amino acid required for serotonin synthesis, is not biosynthesized in the body and must be obtained from dietary sources.

Existing indirect evidence suggests that TRP supplementation alters affective states via effects on the central nervous system. Since the 1960s, it has also been used as a treatment for sleep-related issues and depression (Gibson, 2018). Experiments on TRP depletion provide one of the strongest indications that serotonin plays a role in the pathophysiology of depressive disorders. Acute changes in diet are used to induce a temporary decrease in serotonin activity in the brain by decreasing the availability of TRP, which serves as its precursor. A study revealed that the depletion of TRP does not cause significant mood changes in individuals with no risk factors for depression; however, patients who have recovered from depression can exhibit symptoms of the disorder. Recovered depressed individuals who undergo catecholamine

depletion with alpha-methyl-*para*-tyrosine exhibit a similar pattern (Cowen and Browning, 2015). Consequently, administering foods containing high concentrations of TRP and those with serotonin-boosting properties may aid in alleviating depression and enhancing mood cognition. However, this would necessitate experimental evidence and additional study.

Depression and anxiety are also associated with lower BDNF levels. BDNF induction increases synaptic spine density via a Ras/extracellular signal-regulated kinase pathway-dependent mechanism. Low or dysfunctional levels of BDNF may result in dysfunctional synaptic plasticity, a decline in excitatory neurons and glutamate, and eventually depression (Yang et al., 2020).

***Eating disorders*:** The serotonin transporter gene SLC6A4 plays a significant role in eating disorders as well. It was observed that individuals with bulimia nervosa (BN) and binge eating disorder have low concentrations. According to a meta-analysis, the S-allele of the 5-HTTLPR gene is responsible for both eating disorders, particularly anorexia nervosa (AN) (Gorwood, 2004; Calati et al., 2011). In cases of eating disorders, excessive doses of selective serotonin reuptake inhibitors are typically prescribed. TRP supplementation was beneficial for individuals with the 5-HTTLPR S/S' allele. There is a need for additional research in this area in order to provide a clearer picture (Gibson, 2018).

The influence of diet and exercise on BDNF was investigated using a crossover study. It was discovered that a low-carbohydrate diet and exercise have concomitant benefits on metabotropic factor expression, metabolic activities, and cognition, which are augmented by the combination of two dissimilar lifestyle factors in individuals at risk for developing metabolic, cognitive, or CVDs (Gyorkos et al., 2019). In addition, numerous studies have reported that the BDNF Met66 allele is strongly associated with eating disorders. Their results indicate that the BDNFA allele rs6265 (Met66) is associated with AN (Ribasés et al., 2005; Dmitrzak-Weglarz et al., 2007). Another study assessed the effects of dietary leucine (1.5～3%) on mice subjected to a 28-day voluntary exercise protocol. Results demonstrated that 1.5% leucine supplementation significantly increased BDNF in the brain (Zeeni et al., 2017).

Gene FTO (associated with fat mass and obesity) is involved in eating disorders. It contains both oxidative DNA demethylase and dioxygenase activity. The FTO gene is also associated with human body mass index and obesity (Jia et al., 2011). Previous research states that the FTO allele may play a significant role in both BN and AN. Müller et al. (2012) hypothesized that the rs9939609 A-allele of the FTO gene is associated with BN and AN. The presence of carbohydrates in the diet is associated with FTO mRNA expression. Sucrose, glucose, and lactose were negatively correlated with FTO mRNA expression in subcutaneous adipose tissue of obese patients, whereas fructose was positively correlated with FTO mRNA expression (Yuzbashian et al., 2019). The FTO gene is linked to the presence of macronutrients in the body. Doaei et al. (2017) concluded that the FTO gene expression in the hypothalamus is proportional to macronutrient levels. Future research is necessary to evaluate the long-term effects of dietary interventions in this instance.

***Anxiety and mood disorders*:** It is known that foods with high antioxidant properties increase BDNF levels. Other nutrients that could increase this gene's expression may be useful in reducing anxiety-related disorders. According to studies, resveratrol increases the concentration of BDNF in the brain parenchyma and BDNF levels in serum (Wiciński et al., 2017).

The monoamine oxidase A (MAOA) gene is another significant gene involved in anxiety and mood disorders. MAOA gene encodes the MAOA enzyme and participates in the disintegration of the neurotransmitters serotonin, norepinephrine, epinephrine, and dopamine. These neurotransmitters are associated with the regulation of mood, sleep, emotions, stress response, and the signal transmission in the brain that controls physical movement. MAOA degrades monoamines found in the diet. It appears to be especially important in the breakdown of excessive tyramine, which is present in cheese and other foods. MAOA appears to play a role in normal fetal brain development (MedlinePlus, 2017c).

***Bipolar disorder*:** A study discovered a connection between bipolar disorder (previously known as manic-depressive illness/manic depression) and alleles at three MAOA markers. It was observed that bipolar patients have lower MAOA concentrations than healthy subjects (Lim et al., 1995). Another study demonstrated that the MAOA-CA and MAOA-VNTR polymorphisms have significant correlations with bipolar disorder in female patients (Eslami Amirabadi et al., 2015).

A study on rhesus monkeys examined the relationship between fetal ID and MAOA genotype. ID and MAOA polymorphisms in humans suggest that this association may be a significant predictor of cognitive abilities (Golub and Hogrefe, 2014). The discovery that fruits and vegetables contain metabolites that inhibit MAO-A and -B activity provides a natural treatment option for neurological disorders (Marzo et al., 2022).

Piperine, an alkaloid found in *Piper longum* (long pepper), has been shown to inhibit the MAOA gene. It has antidepressant-like properties and is thus employed as an antidepressant (Lee et al., 2005). In order to determine the role of specific nutrients in modulating MAOA gene expression, additional research is required (National Institute of Mental Health, 2020).

*Ankyrin-3* (*ANK3*) is one of the few associated genes for bipolar disorder. However, its molecular basis remains unknown. A recent study found that a rare loss-of-function splice site SNP (rs41283526*G) in an isoform of ANK3 protects against schizophrenia and bipolar disorder. This suggests that this isoform plays a role in the etiology of diseases. The analysis of human RNA indicates that the available data set strongly supports this hypothesis (Hughes et al., 2018). According to a number of studies, lithium is an effective treatment for Ank3-related disorders. An experiment was conducted to determine which biological processes in the region of the hippocampus are affected by lithium treatment and haploinsufficiency of ANK3. It was hypothesized that the psychiatric response of $Ank3^{+/-}$ mice is linked to the disruption of the kinesin cargo system, which disrupts neuronal ion channels and glutamate receptor transport. Lithium is known to reverse this molecular signature, demonstrating the development of anterograde kinesin transport as its action mechanism for enhancing psychiatric-related Ank3-related behavior (Gottschalk et al., 2017). Caffeine consumption, water consumption, and the consumption of particular vegetables appear to affect lithium levels in the body. Additionally, it appears to have a negative relationship with salt (Gitlin, 2016).

The dopamine D4 receptor (DRD 4) is yet another gene linked to bipolar disorder. It influences the postsynaptic action of dopamine and is also implicated in various neurological processes; it exhibits polymorphism and is one of the most extensively studied genes in relation to psychiatric disorders. It has also been observed that the affinity of dopamine toward the receptor is diminished in individuals with the long-form (i.e., when the number of repeats exceeds six). This gene's genotype 4/6 is strongly associated with anxiety and depressive disorders (Gafarov et al., 2020).

***Schizophrenia*:** The *AKT1* (serine/threonine protein kinase) gene has also been implicated in schizophrenia through association studies and decreased protein expression in the brains of schizophrenia patients (Thiselton et al., 2008). This gene aids in the production of AKT1 kinase, a protein that plays a crucial role in signaling pathways (MedlinePlus, 2017a). There are numerous causes of schizophrenia, such as vitamin B-3 and B-6 deficiency, mineral deficiency, most notably zinc deficiency, and cerebral reactions. In addition to standard treatment, the therapy based on these recommendations includes a balanced diet rich in vitamins and minerals, with an emphasis on foods known to cause psychosis. These programs may facilitate a more rapid recovery than standard therapy alone (Hoffer, 1975). Folic acid, vitamin D, and vitamin B12 are beneficial in the treatment of schizophrenia (Brown and Roffman, 2014).

***Dementia*:** A major gene involved in dementia is the APOE gene. It is associated with catabolic processes of cholesterol and the activation of nitric oxide synthase activity and is known to have lipid-binding activity. APOE is expressed in the brain and yolk syncytial layer and has been linked to Alzheimer's disease, cerebrovascular disease, and numerous other conditions [Zebrafish Information Network (ZFIN), 2010a at https://zfin.org/ZDB-GENE-010724-18]. The function of APOE is to transport cholesterol between neurons and non-neuronal cells. Cholesterol plays a significant role in the brain's synaptic activities and neuronal plasticity. Consequently, APOE is crucial for cholesterol homeostasis and also plays a role in neurodegenerative disorders (de Chaves and Narayanaswami, 2008). Docosahexaenoic acid (DHA) and sesamol, which are known to lower cholesterol, may serve to upregulate this gene, whereas cholesterol-raising foods may serve to downregulate this gene.

***Post-traumatic stress disorder (PTSD)*:** FK506 binding protein 5 (FKBP5) is a gene that appears to be associated with PTSD (ZFIN, 2010c at https://zfin.org/ZDB-GENE-030616-630). It is hypothesized to play a role in chaperone-mediated protein folding and isomerization. FKBP5 is expressed in the brain and gastrointestinal tract, and its orthologs are associated with major depressive disorders. The experimental findings of a study demonstrated that treatment with quercetin significantly increased the expression of FKBP5 (Donoso et al., 2019).

Lactoperoxidase (LPO) is a milk component. In order to examine the effect of LPO on the digestive tract, an intestinal microarray analysis was performed on mice exposed to LPO. The uptake of LPO results in the upregulation of 78 genes associated with immunity, cell death, the cell cycle, and metabolism and the downregulation of 9 immunity-related genes. The most upregulated gene was FKBP5, which also regulates immunophilin (Wakabayashi et al., 2007).

The catechol-o-methyltransferase (COMT) gene has also been linked to PTSD. COMT is involved in methylation and a number of diseases, including attention deficit hyperactivity disorder, eating disorders (such as BN), and cognitive disorders, among others (ZFIN, 2010b at https://zfin.org/ZDB-GENE-050913-117). *COMT* $Val^{158}Met$ polymorphism (rs4680) also appears to influence PTSD. A study was conducted using the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) to investigate the role of such polymorphisms in PTSD. It was found that the rates of PTSD were low in the subjects with *COMT* $Met^{158}$ allele and also had better functionality in comparison to $Val^{158}/Val^{158}$ at 26 weeks after traumatic injury. However, the relationship between PTSD and the outcomes remains unclear and will be the subject of future study (Winkler et al., 2017).

***OCD*:** Other studies have found a connection between

COMT and OCD. Met158 allele of COMT was found to be associated with OCD (Pooley et al., 2007). Vitamin D is believed to reduce the mRNA and protein expression of COMT in human uterine leiomyoma HuLM cells and inhibit COMT enzyme activity (Sharan et al., 2011). However, it is unknown if it affects COMT expression in neuronal cells. Thus, additional research is required to identify additional nutrients that influence the gene.

***Substance use disorder*:** ADH1B [alcohol dehydrogenase 1B (Class I)] is one of the most significant genes involved in substance use disorder. ADH1B encodes the β subunit of alcohol dehydrogenase, which is essential for ethanol metabolism (oxidizing ethanol into acetaldehyde). Aldehyde dehydrogenase genes further convert acetaldehyde to acetate (Dodge et al., 2016). Macgregor et al. (2009) hypothesized a link between genetic variation and alcohol-related behavior. The *ADH1B Arg48His* polymorphism influences both alcohol-induced flushing and alcohol consumption in the European population. In conclusion, *ADH1B* is associated with substance use disorder (Macgregor et al., 2009).

Substance use disorder is also associated with the dopamine receptor $D_2$-encoding DRD2 gene. This receptor inhibits adenylate cyclase activity, thereby inhibiting the production of cyclic adenosine monophosphate (cAMP) and protein kinase A, a class of cAMP-dependent enzymes. D2 receptors primarily inhibit the synthesis of dopamine, an essential neurotransmitter for brain function. Mitogen-activated protein kinase and Akt signaling pathways are also activated by D2 receptors. According to previous research, the DRD2 gene may be effective against alcoholism. Increased expression of the DRD2 gene would reduce alcohol consumption (Thanos et al., 2001; Mishra et al., 2018).

***Autism spectrum disorders*:** SHANK3 or ProSAP2 (SH3 and multiple ankyrin repeat domains 3) is a major gene involved in autism spectrum disorders. SHANK3 is a scaffolding protein that plays a crucial role in nerve cell such as cell-to-cell communication. They are also required for the formation and maturation of dendritic spines, which are involved in the transmission of nerve impulses (MedlinePlus, 2017d). As abnormal *SHANK3* was associated with cognitive deficits, including autism spectrum disorders, Durand et al. (2007) concluded that mutations in the SHANK3 gene cause autism spectrum disorders. SHANK3 also binds to neuroligins, which are essential for the formation of synapses. Autism spectrum disorder and cognitive disorders are also caused by mutations in the X-linked neuroligin 3 (NLGN3) and NLGN4 genes. Numerous studies have demonstrated that mutations in synaptic genes such as NLGN3 and NLGN4 also cause autism spectrum disorders (Jamain et al., 2003).

Supplemental zinc is advantageous against autism spectrum disorders. In addition to reversing the altered synaptic function, an increase in zinc intake reverses the effect of autism spectrum disorder-related behaviors. Consequently, foods containing zinc are effective in the treatment of autism spectrum disorders (Fourie et al., 2018). Administration of proline rich foods such as broccoli, bell pepper, and soy protein also reduces autism spectrum disorder symptoms (Alexandrov et al., 2017).

***Personality disorders*:** The calcium voltage-gated channel subunit alpha1 C (CACNA1C) gene plays a significant role in personality disorders. Calcium channel activity and voltage-gated ion channel activity are encoded by the CACNA1C gene. This gene has been linked to a number of psychiatric disorders. A study suggested a possible association between the CACNA1C gene and bipolar disorder. It was reported that the rs1006737 allele of the CACNA1C gene is associated with an altered mean cortical thickness in patients with bipolar disorder (Smedler et al., 2019).

It has been observed that several nutrients influence the genes that are primarily involved in psychological conditions. If such nutrients are supplemented or depleted according to the specific disorder in addition to standard therapy, it could revolutionize the current situation and become a phenomenal treatment for mental disorders, according to our hypothesis. All of these indirect gene-diet associations are summarized in Table 3. Nonetheless, as indicated in the "Existing research" column of Table 3, there is a dearth of published research to support the claim. The aforementioned associations between genes and nutrients can pave the way for a variety of strategies to reduce the incidence of psychiatric disorders and promote overall mental health.

## CHALLENGES AND RISKS INVOLVED

The greatest challenge for nutrigenomics is to compile such a catalogue of associations between nutrients and genes, then use these data to develop an integrated structure for how the complex mechanism operates, and then evaluate these theories. The current catalogue of genetic variations that result in metabolic inefficiency (SNPs and CNVs) is extremely limited. There must be thousands of SNPs that alter metabolism, but there are only about 200 SNPs for which metabolic effects are confirmed in the published literature. Only a subset of these affects nutritional needs in a substantial proportion of the population (Zeisel, 2010). Table 1 (Povel et al., 2012); Tables 2 and 3 (Wang et al., 2014); Table 2 (Zhu et al., 2017) provide additional information regarding SNPs reported to have metabolic effects provide (Wu et al., 2021).

Calculating the effect of diet on genes is extraordinarily complex; techniques for measuring food intake are frequently less precise than genetic or biochemical measure-

**Table 3.** Possible interaction between genes and diet in major psychological disorders

| Serial No. | Psychological condition | Major genes involved | Foods/nutrients affecting the gene[1)] | Existing research (if any)[2)] |
|---|---|---|---|---|
| 1 | Depression | (SLC6A4/5HTT), (5-HTTLPR), (HTR2A) (Su et al., 2009; Lam et al., 2018) https://genesight.com/articles/get-to-know-a-gene-htr2a/ | TRP and serotonin<br>TRP (L-tryptophan) supplements are believed to decrease depressive symptoms.<br>Food rich in serotonin and tryptophan: salmon, nuts and seeds, nuts and seeds, turkey and poultry, and pineapple<br>Green tea, dark chocolate, soy, blueberries, and fatty fish | Yes (Gibson, 2018) |
| | | BDNF (Yang et al., 2020) | | Yes (however, foods relating to BDNF haven't been efficiently researched yet) |
| 2 | Bipolar disorder | Ankyrin 3 (Hughes et al., 2018) | Lithium | No |
| | | Dopamine D4 receptor (Gafarov et al., 2020) | – | |
| | | Monoamine oxidase A (Lim et al., 1995; Golub and Hogrefe, 2014) | Iron | |
| 3 | Schizophrenia and other psychotic disorders | AKT1 (Thiselton et al., 2008; MedlinePlus, 2017a) | High fat and high sucrose, polyunsaturated fatty acids, and high phosphate | No |
| 4 | Dementia | Apolipoprotein E, amyloid beta precursor protein (ZFIN at https://zfin.org/ZDB-GENE-010724-18) (de Chaves and Narayanaswami, 2008) | Vegetable oil, estrogen, sesamol, and docosahexaenoic acid | No |
| 5 | PTSD | FK506 binding protein 5 (ZFIN at https://zfin.org/ZDB-GENE-030616-630) | Quercetin, (milk) lactoperoxidase, fish oil, high fat and high sugar diet, fructose, maize, vitamin D, *Medicago sativa* fiber, and seed oil of *Brassica napus* | No |
| | | COMT (ZFIN at https://zfin.org/ZDB-GENE-050913-117) (Winkler et al., 2017) | | No |
| 6 | Eating disorders | FTO (Müller et al., 2012) | Carbohydrates and macronutrients | No |
| | | 5-HTTLPR (Gorwood, 2004; Calati et al., 2011)<br>Met allele of the functional BDNF rs6265 (Val66Met) | Low protein diet, acute tryptophan protein, fat diet, and blueberries | No |
| | | Lower level of BDNF increases anxious and worrisome behaviors (Ribasés et al., 2005; Dmitrzak-Weglarz et al., 2007) | High fat and high carbohydrates decrease hippocampal BDNF level | No |
| 7 | Autism spectrum disorder | SHANK3 (Durand et al., 2007) | Proline rich foods: broccoli, bell peppers, gelatins, soy protein concentrate, and zinc supplements | No |
| | | Neuroligin 3 and 4 (Jamain et al., 2003) | Requires further research | No |
| 8 | OCD | COMT (Pooley et al., 2007) | As mentioned above | No |
| 9 | Phobias | Requires further research | – | – |
| 10 | Substance use | Alcohol dehydrogenase 1B (Class I) (Arg48) (Macgregor et al., 2009) | Requires further research | No |
| | | Dopamine receptor D2 (Thanos et al., 2001; Mishra et al., 2018) | TAGs and protein rich food | No |
| 11 | Personality disorders | CACNA1C (Smedler et al., 2019) | Requires further research | No |

[1)]The major genes associated with numerous psychological disorders are listed in column 2. In column 4, the nutrients that have an effect on these genes are listed, creating an indirect relationship between the nutrients and the psychological condition. This facilitates the development of nutrigenomics with regard to psychological disorders.
[2)]The existing research column signifies that there is negligible research linking nutrigenomics to mental illnesses. If the nutrients affecting the genes involved in psychological disorders are targeted in the patients, it might transpire as a prodigious treatment strategy.
SLC6A4, a member of the solute carrier family 6; 5-HTT, serotonin transporter protein; 5-HTTLPR, serotonin-transporter-linked promoter region; HTR2A, 5-hydroxytryptamine receptor 2A; TRP, tryptophan; BDNF, brain-derived neurotrophic factor; AKT1, a serine/threonine protein kinase; ZFIN, Zebrafish Information Network; COMT, catechol-*O*-methyltransferase; FTO, fat mass and obesity-associated/alpha-ketoglutarate-dependent dioxygenase; SHANK3, SH3 and multiple ankyrin repeat domains 3; CACNA1C, calcium voltage-gated channel subunit alpha1 C.

ments. There is a dearth of innovative methods for dietary exposure assessment, and there is a dire need for a more comprehensive toolkit for researchers examining how diet interacts with genotype to assess phenotype (Penn et al., 2010).

According to a study conducted online by Hurlimann et al. (2014), it cannot be concluded that nutrigenomics and nutrigenetics can reconfigure foods as medicines. The development of nutrigenomic services is gradual, but there is no evidence of increased technical capacity to facilitate their delivery. Diet and genetics education for primary care physicians is insufficient, and medical geneticists are in high demand. Dietetic practitioners and nutrition science specialists in this specialized community in nutrigenomics continue to increase (Castle and Ries, 2007).

## FUTURE ASPECTS

In order to investigate the interaction between diet and genes, a sophisticated analytic strategy and bioinformatics are required. In the past few years, there have been enormous technological advancements. It will be the bioinformatics aspect (data processing, clustering, dynamics, and integration of the diverse "omics" ranges, etc.) that will require advancements for nutrigenomics to expand further (García-Cañas et al., 2010).

Transcriptomics, proteomics, and metabolomics are unified by the integrated analytical approach. It is also useful for determining the effects of novel functional foods and nutraceuticals on the global expression of genetic statistics and cellular functions. It offers a novel method for identifying biomarkers for testing the efficacy of bioactive functional food substances (Elliott and Ong, 2002). Therefore, molecular biomarkers that permit early detection of the onset of disorder or the pre-disease state are necessary (Afman and Müller, 2006). Omics research is currently employed to identify active ingredients and enhance agricultural yields by enhancing functional components in a variety of plant species (Nayak et al., 2021).

Functional foods are those food substances that have specific health-promoting properties beyond their nutritional value (Chadwick et al., 2013). Therefore, they are closer to drugs than they are to traditional foods. Some of the products currently available on the market include foods that reduce cholesterol and probiotic yogurts (Chadwick, 2004).

The creation of beverages and foods can be used to treat and prevent a variety of diseases. For instance, patients with celiac disease, PKU, and a few other disorders are prescribed a special diet. The use of ketogenic diets is advised for the treatment of intractable epilepsy (Simopoulos, 2002).

However, there is a great deal of vulnerability regarding the marketing and risks of functional foods, such as concerns about overuse without direction. As much as eating utilitarian foods may be part of a healthy lifestyle, it is difficult to strike a balance because it promotes a particular perspective on nutrition (Bhardwaj, 2007).

In addition, the added costs of production, marketing, and distribution of personalized products by food companies make them prohibitively expensive for the general public (van Trijp et al., 2007). If nutrigenomic foods emerge as a new food category, there may be novel demand in the regions of marketing and distribution, necessitating additional business planning. Before production can begin, high-quality products and extensive market research are required (Chadwick, 2004). Due to increased scientific and technical research, consumer perceptions of food have shifted from conventional to functional, healthier, and more nutritious foods (Sharma et al., 2021).

Currently, pharmaceuticals are relatively dependent on nutrigenomics. As data mining in nutrigenomics has enormous potential in the field of medicine, the concept of nutrigenomics may one day play an important role in preventing nutrition-related diseases (Wiwanitkit, 2012).

Furthermore, it is necessary to identify the mechanisms underlying the relationship between diet and phenotype to utilize genetic blueprints or genotypes in dietary disease prevention (Afman and Müller, 2006).

Within the next 5 to 10 years, significant advances are anticipated in nutritional genomics research involving the integration of systems biology and genomics in order to understand common diseases. There is a possibility that functional food companies will collaborate with biotechnology companies and that large multinational corporations will invest in an integrative biological approach. Future public policies should incorporate nutrigenomics from a broader clinical relevance and health management perspective (Bhardwaj, 2007). Moreover, as the focus of our paper, the nutrigenomics of psychological disorders, if thoroughly researched, has the potential to become a major milestone in the near future and help millions of people who are suffering with such conditions.

## CONCLUSION

Nutrigenomics has the potential to become an effective tool for disease management, thereby enhancing the global health care system. Understanding the pathophysiology of chronic illnesses relies heavily on genetics and nutrition. The most well-known application of nutrigenomics is the identification of critical genes in gene-diet interactions, which requires further study. Thus, the influence of macronutrient deficiencies can be demonstrated

in various neurologic and other conditions. Epigenetic regulation of gene expression is also crucial for age-related cognitive decline. It can also be demonstrated that an individual's psychological stress is exacerbated by nutritional disorders. In order to obtain better results, it is necessary to address the difficulties and dangers associated with this field of study. The impact of nutrigenomics on mental disorders has not been adequately studied; therefore, additional research is required to unfold the current dynamics and reveal a transformative science for these conditions that could represent a quantum leap in medical science.

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## AUTHOR CONTRIBUTIONS

MB conceptualized and finalized the article along with B and PV. MB also wrote the manuscript with inputs from CC, GS, and SG. All authors gave final approval for publication.

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