Personalized nutrition: A review of genotype-based nutritional supplementation

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Nutritional disorders have become a major public health issue, requiring increased targeted approaches. Personalized nutrition adapted to individual needs has garnered dramatic attention as an effective way to improve nutritional balance and maintain health. With the rapidly evolving fields of genomics and nutrigenetics, accumulation of genetic variants has been indicated to alter the effects of nutritional supplementation, suggesting its indispensable role in the genotype-based personalized nutrition. Additionally, the metabolism of nutrients, such as lipids, especially omega-3 polyunsaturated fatty acids, glucose, vitamin A, folic acid, vitamin D, iron, and calcium could be effectively improved with related genetic variants. This review focuses on existing literatures linking critical genetic variants to the nutrient and the ways in which these variants influence the outcomes of certain nutritional supplementations. Although further studies are required in this direction, such evidence provides valuable insights for the guidance of appropriate interventions using genetic information, thus paving the way for the smooth transition of conventional generic approach to genotype-based personalized nutrition.

KEYWORDS

personalized nutrition, nutritional supplementation, nutrient, genotype, single nucleotide polymorphisms, nutrigenetics

Introduction

Nutrition disorders, such as obesity, cardiovascular disease, and diabetes, primarily driven by the unhealthy diet and/or lifestyle, are the leading cause of premature deaths worldwide (1). Adherence to dietary guidelines, with the recommended intake of specific nutrients, is necessary for health maintenance at the population level (2). However, this one-size-fits-all approach does not consider interindividual variations, which result

from varying responses to nutrients owing to different genetic predispositions, metabolic phenotypes, and microbial compositions. Therefore, personalized nutrition, which is adapted to individual needs, has been proposed to meet this challenge.

The concept of "personalized" or "precision" has been widely used since the Precision Medicine Initiative was launched in the United States in 2015 (3). Similar to precision medicine, personalized nutrition refers to the use of unique information about an individual to tailor nutritional interventions, including advice, products, and services, to assist them to gain improved health benefits than those derived using generic, population-based approaches. With the advances in "omics," such as genomic, transcriptomic, proteomic, metabolomics, microbiome and data technology, personalized nutrition has gradually become a reality (4, 5). Among them, genomics has evolved to the post-genomic era, and genomic information has been widely used to tailor personalized nutrition for certain nutritional supplementations, yielding the interdisciplinary science called nutrigenetics. According to the International Society of Nutrigenetics/Nutrigenomics (ISNN), the future of personalized nutrition should include three levels: "(1) conventional nutrition based on general guidelines for population groups by age, gender, and social determinants; (2) individualized nutrition that adds phenotypic information about the current nutritional status of individuals, and (3) genotype-directed nutrition based on rare or common gene variations" (6). This statement highlights future efforts from general dietary guidelines to stratified and genotype-based personalized approaches.

Genotype-based nutritional intervention has been evidently useful for individuals with genetic defects and has helped them effectively improve their health (7), especially for individuals with rare genetic disorders such as phenylketonuria, galactosemia, and vitamin D-resistant rickets (8). Till date, with the aid of candidate-gene approaches or genome-wide association studies (GWAS), several single nucleotide polymorphisms (SNPs) have been identified to have influence over the absorption, distribution, metabolism, excretion, and signal transduction of macronutrients and micronutrients (9–12). In this regard, a few genotypes have been further highlighted to discriminate individuals based on sensitivity to certain nutritional interventions, expanding the understanding of the implementation of personalized nutrition (13–20).

In this review, we summarize the critical genotypes that influence the levels of macronutrients and micronutrients and provide the evidence that genotypes may interact with nutritional supplementation or diet to alter nutritional response or disease risk (Figure 1; Table 1). The aim of this review is to provide insights into the use of nutritional genotypes to guide individuals to determine appropriate nutritional supplementation and ultimately achieve optimal health benefits.

Genotype-based supplementation of macronutrients
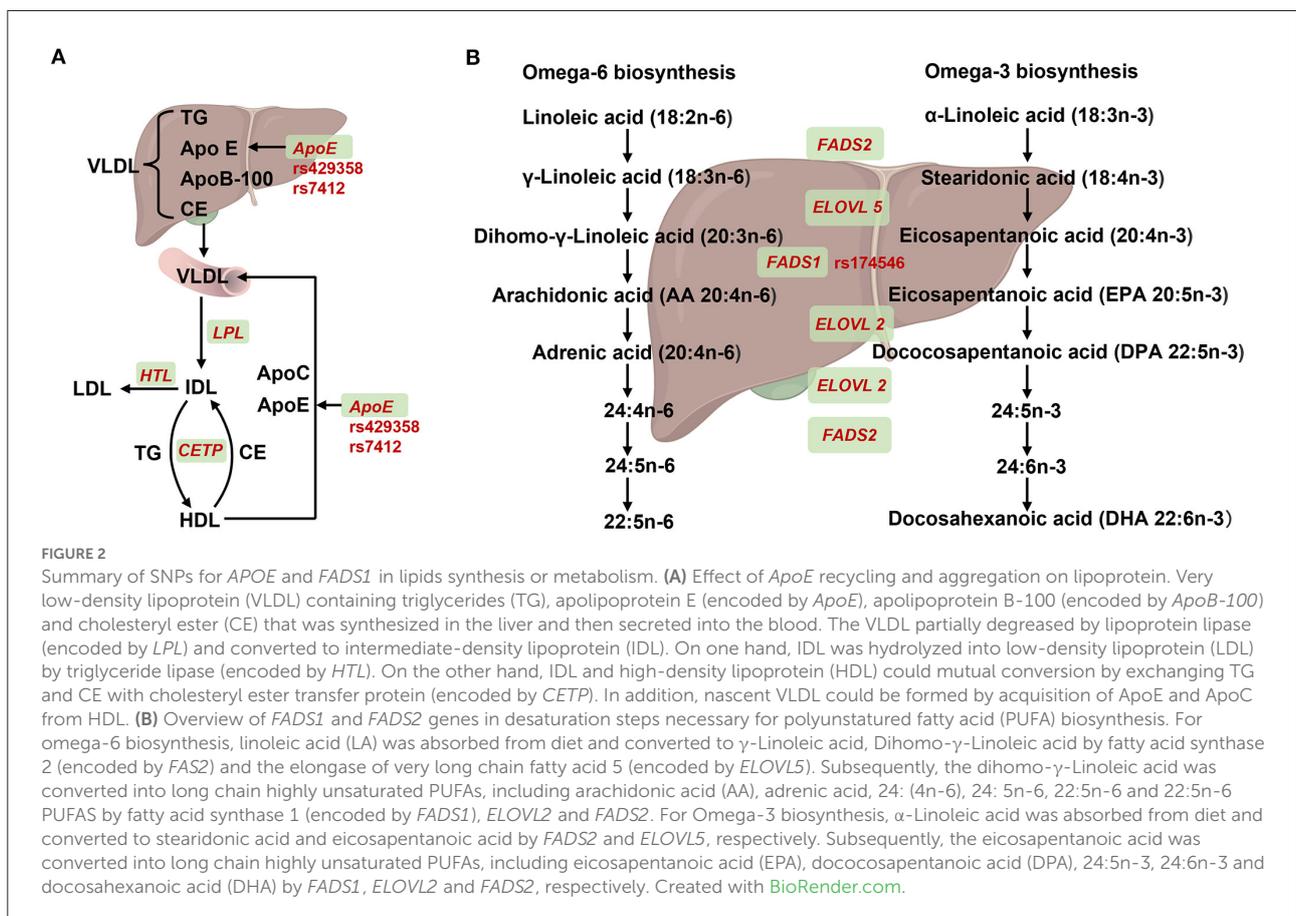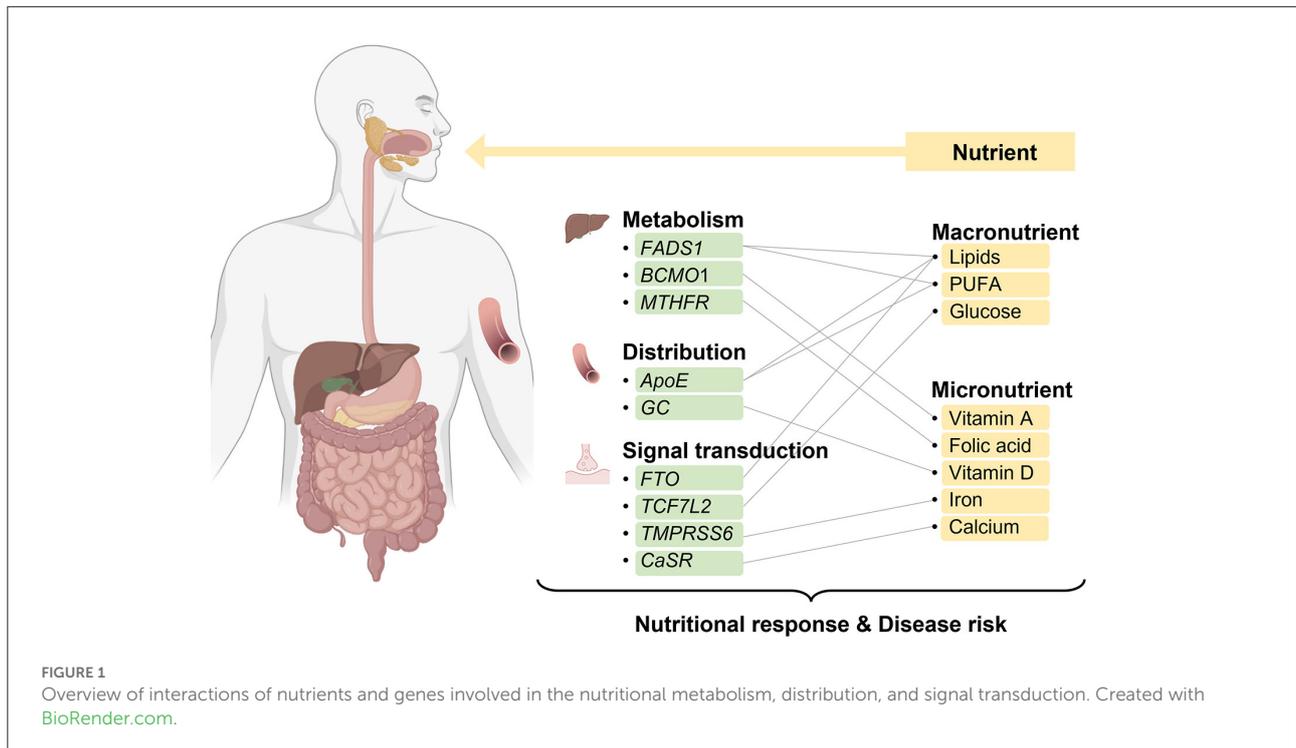
Lipids and *ApoE* polymorphism

Lipids are an essential class of hydrophobic biomolecules that include phospholipids, sterols, and triglycerides (TG). They are involved in maintaining energy balance, sustaining vital processes, controlling food intake, and regulating growth and reproduction. However, intake of excessive lipids, such as TG and low-density lipoprotein cholesterol (LDL), may lead to an increased risk of metabolic diseases.

Apolipoprotein (ApoE), its three isoforms, namely ApoE2, ApoE3, and ApoE4 encoded by ε2, ε3, and ε4 haplotype, respectively, plays key roles in the transport of cholesterol and functioning of cholesterol and other lipids in the brain (Figure 2A). This haplotype system comprises two non-synonymous SNPs rs429358 (T/C) and rs7412 (T/C) in the exon of *ApoE*, where ε2 haplotype is represented by TT, ε3 represented by TC, and ε4 represented by CC. Furthermore, rs769449 exhibits strong linkage disequilibrium with rs429358 (21). The ε4 allele, contributing to impaired LDL binding, has been positively associated with an increased risk of numerous diseases, such as cardiovascular diseases (CVDs) and Alzheimer's disease (AD). A study of 544 patients with hypertension or coronary heart disease indicated that *ApoE* ε4 carriers exhibited high total cholesterol, TG, and LDL levels (22). In addition, the *ApoE* ε4 allele has been reported as the strongest genetic risk factor for sporadic AD in genome-wide association meta-analyses (9).

Evidence suggests that the genotyping for *ApoE* may help develop a highly targeted approach to disease prevention. Adherence to Mediterranean diet, a well-known healthy dietary pattern, may lower AD related anatomical or clinical symptoms in individuals without ε4 genotype (23). In addition, long-chain n-3 polyunsaturated fatty acids (n-3 PUFA) may have a protective role in individuals without ε4 (24, 25). On the contrary, the association of unfavorable diet with increased disease risk in ε4 carriers has been reported. Diets high in saturated fatty acids may increase AD risks by seven folds in ε4 carriers than in non-carriers (26). Moreover, compared to ε4 non-carriers, afternoon snacks with a high glycemic load have been significantly associated with cognitive decline in ε4 carriers (13). These studies suggested that ε4 carriers might require a diet containing healthier lipids to prevent AD onset.

Lipids and *FTO* polymorphism

Fat mass and obesity-associated gene (*FTO*), involved in the expression of fat deposition and metabolism-related hormones and genes, is the first gene associated with obesity. Furthermore, SNP rs9939609, as well as the proxy SNP rs1121980 of *FTO*

FIGURE 1
Overview of interactions of nutrients and genes involved in the nutritional metabolism, distribution, and signal transduction. Created with BioRender.com.

FIGURE 2
Summary of SNPs for *APOE* and *FADS1* in lipids synthesis or metabolism. **(A)** Effect of *ApoE* recycling and aggregation on lipoprotein. Very low-density lipoprotein (VLDL) containing triglycerides (TG), apolipoprotein E (encoded by *ApoE*), apolipoprotein B-100 (encoded by *ApoB-100*) and cholesteryl ester (CE) that was synthesized in the liver and then secreted into the blood. The VLDL partially degreased by lipoprotein lipase (encoded by *LPL*) and converted to intermediate-density lipoprotein (IDL). On one hand, IDL was hydrolyzed into low-density lipoprotein (LDL) by triglyceride lipase (encoded by *HTL*). On the other hand, IDL and high-density lipoprotein (HDL) could mutual conversion by exchanging TG and CE with cholesteryl ester transfer protein (encoded by *CETP*). In addition, nascent VLDL could be formed by acquisition of ApoE and ApoC from HDL. **(B)** Overview of *FADS1* and *FADS2* genes in desaturation steps necessary for polyunstatured fatty acid (PUFA) biosynthesis. For omega-6 biosynthesis, linoleic acid (LA) was absorbed from diet and converted to γ-Linoleic acid, Dihomo-γ-Linoleic acid by fatty acid synthase 2 (encoded by *FAS2*) and the elongase of very long chain fatty acid 5 (encoded by *ELOVL5*). Subsequently, the dihomo-γ-Linoleic acid was converted into long chain highly unsaturated PUFAs, including arachidonic acid (AA), adrenic acid, 24: (4n-6), 24: 5n-6, 22:5n-6 and 22:5n-6 PUFAS by fatty acid synthase 1 (encoded by *FADS1*), *ELOVL2* and *FADS2*. For Omega-3 biosynthesis, α-Linoleic acid was absorbed from diet and converted to stearidonic acid and eicosapentanoic acid by *FADS2* and *ELOVL5*, respectively. Subsequently, the eicosapentanoic acid was converted into long chain highly unsaturated PUFAs, including eicosapentanoic acid (EPA), dococosapentanoic acid (DPA), 24:5n-3, 24:6n-3 and docosahexanoic acid (DHA) by *FADS1*, *ELOVL2* and *FADS2*, respectively. Created with BioRender.com.

has been correlated with obesity and diabetes (27). Maha et al. showed that *FTO* rs9939609 A/A genotype was significantly associated with impaired fasting glucose and insulin resistance (28). In addition, higher serum leptin and lower high-density lipoprotein levels were observed in the homozygotes of the *FTO* rs9939609 risk genotype (AA) compared to those with the TT genotype in overweight adults (29), suggesting the need of precise interventions for these high-risk population. In fact, individuals genetically predisposed to obesity particularly benefit by regulating dietary intake (30, 31) or following personalized diet (32), suggesting a crucial role of *FTO* in personalized nutrition.

n-3 PUFA and *FADS* polymorphism

n-3 PUFA, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential for maintaining health by contributing to organ development, membrane fluidity, and inflammation status. EPA and DHA can be synthesized by desaturases and elongases through the PUFA biosynthetic pathway, wherein fatty acid desaturase (FADS) enzymes including FADS1 and FADS2, are rate-limiting step enzymes (33) (Figure 2B).

GWAS on serum n-3 and n-6 PUFA showed that *FADS1/FASD2* strongly affected serum PUFA levels (8). Additionally, Szilvia et al. demonstrated that all haplotypes carrying the *FADS1* rs174546 minor allele were associated with lower Δ-5 desaturases (D5D) activity, which has been associated with plasma long-chain PUFA and lipid levels in 1,144 European adolescents (34). Previous studies also indicated that the *FADS1* rs174546 C/T allele was an important determinant of plasma TG concentrations (35). In addition, several other *FADS1* SNPs have been significantly associated with PUFA levels, such as rs174537 (including three variants G/G, G/T, and T/T) and rs174547 (C/T) (36–38).

Cumulative evidence suggested that the link between PUFA intake and the risk of CVD could be altered using genetic differences in *FADS* (39). In a large cohort study, α-linoleic acid (ALA) intake was inversely associated with ischemic stroke in rs174546 TT genotype carriers with low D5D activity (14). Moreover, the findings that infants who received fish oil supplements exhibited significantly higher erythrocyte DHA levels were only noticed in homozygous for the minor rs174546 as well as other linkage disequilibrium SNPs (40). Nevertheless, more studies are required to employ *FADS1* genotyping to personalized nutrition.

Glucose and *TCF7L2* polymorphism

Glucose metabolic disorders may play an important role in the pathogenesis of diabetes, CVD, cerebrovascular diseases, and hypertension. SNPs in genes such as *TCF7L2*, *GCKR*, *G6PC2*, and *ALOX5* play an important role altering in glucose metabolism (41–45). Among them, *Transcription Factor-7-Like-2* (*TCF7L2*), which belongs to the T-cell factor/lymphoid enhancer factor (TCF/LEF) family, is the most common susceptibility gene for type 2 diabetes mellitus (T2DM) (46). Studies have further identified that *TCF7L2* rs7903146 polymorphism was associated with glucose homeostasis and obesity-related parameters. A meta-analysis of 115,809 subjects indicated that *TCF7L2* rs7903146 polymorphism was significantly associated with susceptibility to T2DM (47). It was also reported that *TCF7L2* rs7903146 T allele was associated with elevated glycated-hemoglobin levels in healthy individuals (11). Moreover, Li et al. indicated significant associations between rs7903146 and body mass index or waist circumference and elevated blood glucose levels (48).
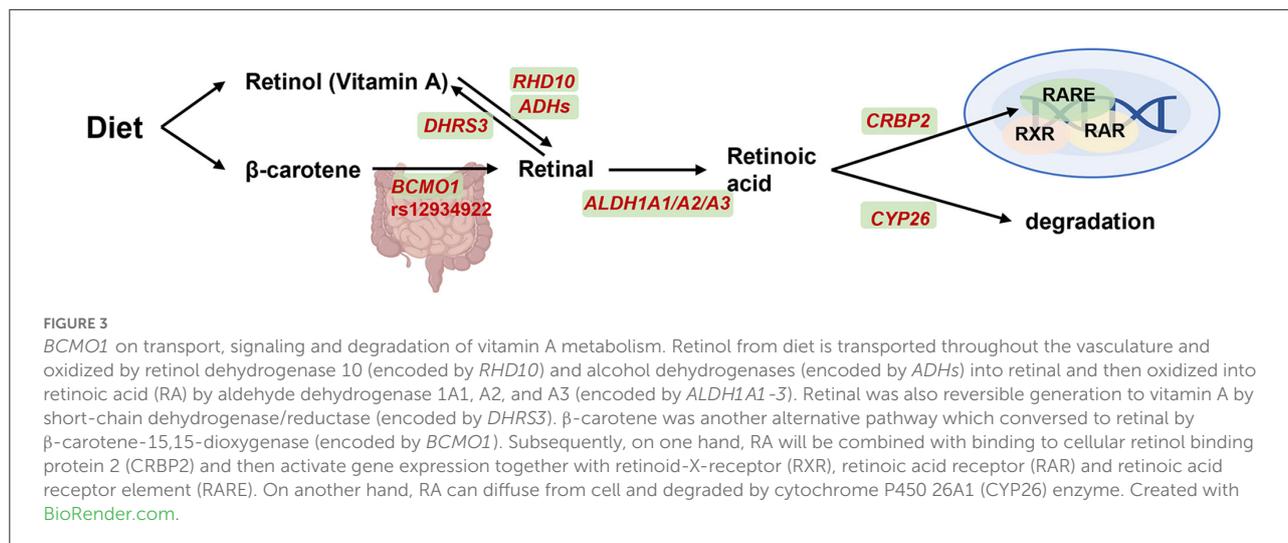
The interaction of *TCF7L2* and diet on glucose homeostasis has been actively investigated. Lu et al. indicated that *TCF7L2* rs7903146 polymorphism affected glucose tolerance and free fatty acid metabolism in adults. They also found that monounsaturated fatty acid concentrations and percentages were greater in females with the TT genotype than in those with the CC genotype in oral glucose tolerance test, and that TT carriers with high HOMA-IR exhibited significantly higher fasting free fatty acid concentrations, lower disposition index, and elevated glucose area under the curve than CC carriers (15). These results indicated that *TCF7L2* SNP-based intervention can be helpful for regulating glucose levels using dietary intervention.

Genotype-based supplementation of micronutrients

Vitamin A and *BCMO1* polymorphism

Vitamin A, a fat-soluble vitamin, is derived from two different sources: the preformed vitamin A from animal-based food, and carotenoids with provitamin A activity from plant-based products (49). The conversion of β-carotene from dietary carotenoids to retinal is the first step in the utilization of vitamin A (Figure 3) (50). Vitamin A plays an important role in maintaining visual function, promoting cell proliferation and differentiation, enhancing immune function, promoting body growth and bone metabolism, and improving hemoglobin levels. Vitamin A deficiency may cause dry eye, infectious diseases such as measles, malaria, diarrhea and respiratory infections, resulting in severe complications such as growth retardation, anemia and even death.

β-carotene 15,15'-monooxygenase 1 (BCMO1) is the most critical enzyme involved in retinoid metabolism (51). Leung et al. identified two common nonsynonymous SNPs (R267S: rs12934922; A379V: rs7501331) in the open reading frame of

FIGURE 3
BCMO1 on transport, signaling and degradation of vitamin A metabolism. Retinol from diet is transported throughout the vasculature and oxidized by retinol dehydrogenase 10 (encoded by *RHD10*) and alcohol dehydrogenases (encoded by *ADHs*) into retinal and then oxidized into retinoic acid (RA) by aldehyde dehydrogenase 1A1, A2, and A3 (encoded by *ALDH1A1 -3*). Retinal was also reversible generation to vitamin A by short-chain dehydrogenase/reductase (encoded by *DHRS3*). β-carotene was another alternative pathway which conversed to retinal by β-carotene-15,15-dioxygenase (encoded by *BCMO1*). Subsequently, on one hand, RA will be combined with binding to cellular retinol binding protein 2 (CRBP2) and then activate gene expression together with retinoid-X-receptor (RXR), retinoic acid receptor (RAR) and retinoic acid receptor element (RARE). On another hand, RA can diffuse from cell and degraded by cytochrome P450 26A1 (CYP26) enzyme. Created with BioRender.com.

BCMO1 with 42 and 24% variant allele frequencies, respectively (52). *In vitro* R267S + A379V double mutant exhibited reduced BCMO1 activity by 57%, whereas female carriers with A379V alone or both R267S and A379V variant alleles exhibited a reduction of 32 and 69%, respectively, in the conversion of beta-carotene to retinol (52). Recently, in a study with 693 Filipino children and adolescents showed that A379V TT variant was inversely related to vitamin A status (53). These results suggested that the polymorphisms in *BCMO1* should be considered for future vitamin A-supplementation recommendations.

Several studies have investigated plasma or tissue response in carriers of vitamin A variants with carotenoid-rich diet. For example, in a 3-week cross-over intervention, 23 healthy subjects were daily provided with juices containing lycopene and β-carotene, and then classified as strong or weak responders based on their plasma carotenoids response profile. *BCMO1* was found to modify these responses, as A/T vs. C genotype in *BCMO1* rs12934922 appeared to be associated with plasma β-carotene changes, while *BCMO2* did not show similar effect partially due to its low frequency (54). Another study examined 11 polymorphisms in putative genes associated with carotenoid metabolism, and *BCMO1* rs12934922 was found to exhibit the strongest effect on carotenoid responses, with the T-allele resulting in elevated lycopene accumulation in plasma and prostate tissue (16). These studies suggested that genetic variations, particularly in *BCMO1* rs12934922, could influence the degree of plasma response to dietary carotenoids, thereby highlighting the need to examine this genotype when considering personalized vitamin A supplementation.
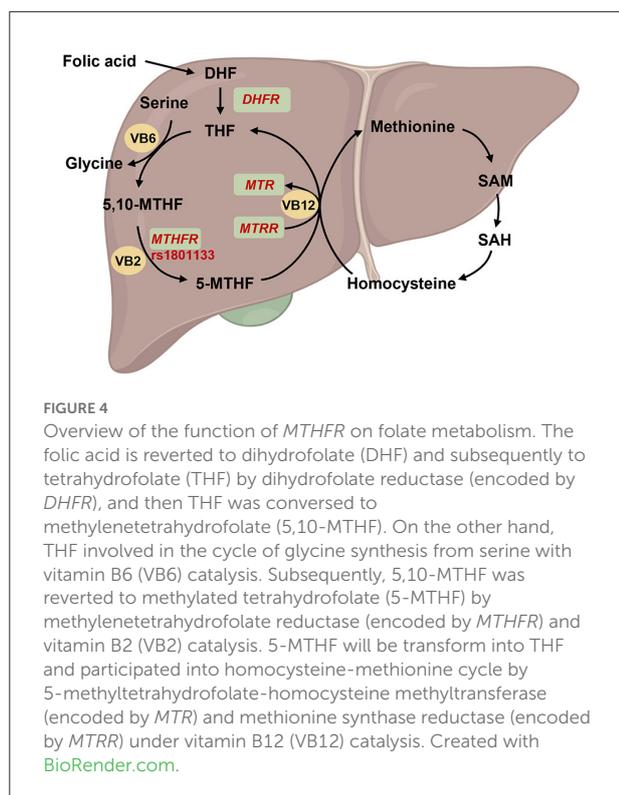
Folic acid and *MTHFR* polymorphism

Vitamin 9, naturally occurring as folic acid, is synthesized by plants and microorganisms. It cannot be synthesized by humans due to the lack of a complete folate biosynthetic pathway. Furthermore, as folic acid is involved in the biosynthesis of nucleotides, amino acids, and certain vitamins, humans must ingest and absorb folic acid derived from diet (55). Folate deficiency can cause many diseases in both young and old age (56), such as fetal pathologies, neural tube disease (57), anemia (58), and depression (59).

As 5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folic acid metabolism, its polymorphism can decrease enzyme activity by 60%, resulting in disorders associated with folate metabolism as well as a variety of other diseases (Figure 4). Till date, 14 rare mutations with severe enzymatic deficiencies and one mutation rs1801133 (C677T) with a milder enzymatic deficiency in *MTHFR* have been reported (60, 61). In addition, serum folic acid concentrations were lower in individuals with the *MTHFR* rs1801133 TT genotype than in individuals with the CC or CT genotypes (62). Moreover, the risk genotype of rs1801133 has been found to be associated with various diseases, including diabetes, CVDs, cancer, and vascular disorders (62, 63). Several studies have also revealed that *MTHFR* polymorphisms might be associated with the elevation levels of homocysteine, thus exacerbating CVD risk (64).

Studies on *MTHFR* have been successfully used to develop disease prevention strategies. In the China Stroke Primary Prevention Trial, the antihypertensive drug enalapril, in addition to folic acid supplementation, significantly reduced the risk of stroke in adults with hypertension, while *MTHFR* rs1801133 TT genotype did not benefit those with low baseline folic acid levels even upon folic acid supplementation, implying that higher dosage of folic acid is needed for individuals at risk of CVD with disadvantageous *MTHFR* genotype (17). Interestingly, riboflavin (vitamin B2), the co-factor for MTHFR in folate metabolism, has also been used to regulate blood pressure (65, 66) or homocysteine levels (67), but such

FIGURE 4
Overview of the function of *MTHFR* on folate metabolism. The folic acid is reverted to dihydrofolate (DHF) and subsequently to tetrahydrofolate (THF) by dihydrofolate reductase (encoded by *DHFR*), and then THF was conversed to methylenetetrahydrofolate (5,10-MTHF). On the other hand, THF involved in the cycle of glycine synthesis from serine with vitamin B6 (VB6) catalysis. Subsequently, 5,10-MTHF was reverted to methylated tetrahydrofolate (5-MTHF) by methylenetetrahydrofolate reductase (encoded by *MTHFR*) and vitamin B2 (VB2) catalysis. 5-MTHF will be transform into THF and participated into homocysteine-methionine cycle by 5-methyltetrahydrofolate-homocysteine methyltransferase (encoded by *MTR*) and methionine synthase reductase (encoded by *MTRR*) under vitamin B12 (VB12) catalysis. Created with BioRender.com.

beneficial effects were only reported in the rs1801133 TT group, suggesting that vitamin B2 might compensate for the loss of MTHFR activity. In summary, these studies help improve the implementation of more precise and effective folic acid recommendations while considering *MTHFR* polymorphisms.

Vitamin D and *GC* polymorphism

Vitamin D is an important fat-soluble vitamin, which is primarily synthesized in the skin upon exposure to ultraviolet B radiation (UVB) in sun exposure. In the circulation, vitamin D and its products are transferred into the liver and kidneys by vitamin D binding proteins (VDBP, encoded by *GC*) (Figure 5). Vitamin D regulates the absorption of calcium and phosphorus, maintains the levels of blood calcium and phosphorus levels, and promotes normal bones and teeth development. However, the widespread distribution of VDBPs in the body indicates its unconventional role beyond calcium and phosphorus regulation, including regulation of cell proliferation and differentiation, synthesis, and secretion of cytokines and other hormones. Moreover, vitamin D is critical in preventing cancer, immune diseases, and diseases of the endocrine system.

Several VDBP polymorphisms have been identified to affect vitamin D levels that contribute to health outcomes (68), with the most common polymorphisms being rs4588 and rs7041 in

GC, which may correlate with serum vitamin D levels (70, 71). Spyridon et al. demonstrated that mothers with the CC genotype for rs2298850 and rs4588 polymorphisms showed elevated 25(OH)D concentrations (72). Dong et al., also showed that *GC* SNPs including rs17467825, rs4588, rs2282679, rs2298850, and rs1155563, were significantly associated with maternal 25(OH)D concentrations (73). Furthermore, a recent study confirmed the rs4588 and rs7041 polymorphisms were more frequent in the T2DM patients, compared to the control group (74). These results showed that rs4588, rs7041, and other *GC* SNPs may be correlated with not only serum vitamin D status but also the risk of T2DM.

Ongoing studies have shown that genetic predisposition related to the vitamin D metabolic pathway could modify the response of 25(OH)D after vitamin D supplementation or UVB exposure. Nimitphong et al. (69) reported that *GC* rs4588 CC carriers exhibited an increase in 25(OH)D levels compared to those with risk genotypes CA or AA, upon daily vitamin D_3 supplementation for 3 months; however, this interaction was not observed for vitamin D_2 supplementation. Nonetheless, when more genes were included, the effects of genetic variants persisted. In addition, Nissen et al. indicated that carriers of all four risk alleles of *GC* rs4588 (A) and *CYP2R1* rs2060793 (G) were the least benefitted from the consumption of vitamin D_3-fortified food or UVB exposure (73). Moreover, in a larger randomized controlled trial, Yao et al. verified that the subjects with the risk genotype of *GC* exhibited a significantly lower increase in 25(OH)D response after 20-week vitamin D_3 supplementation, and that the genetic factors, evaluated as genetic risk score encompassing four variants of *GC*, *VDR* and *CYP2R1* genes exerted greater impact on 25(OH)D response than did non-genetic factors (75). Therefore, these studies suggested that genetic factors, perhaps more important than non-genetic factors, could provide valuable insights for appropriate vitamin D recommendations, as those with the risk genotype of *GC* and other vitamin D metabolism-related genes may require increased vitamin D consumption or UVB exposure.
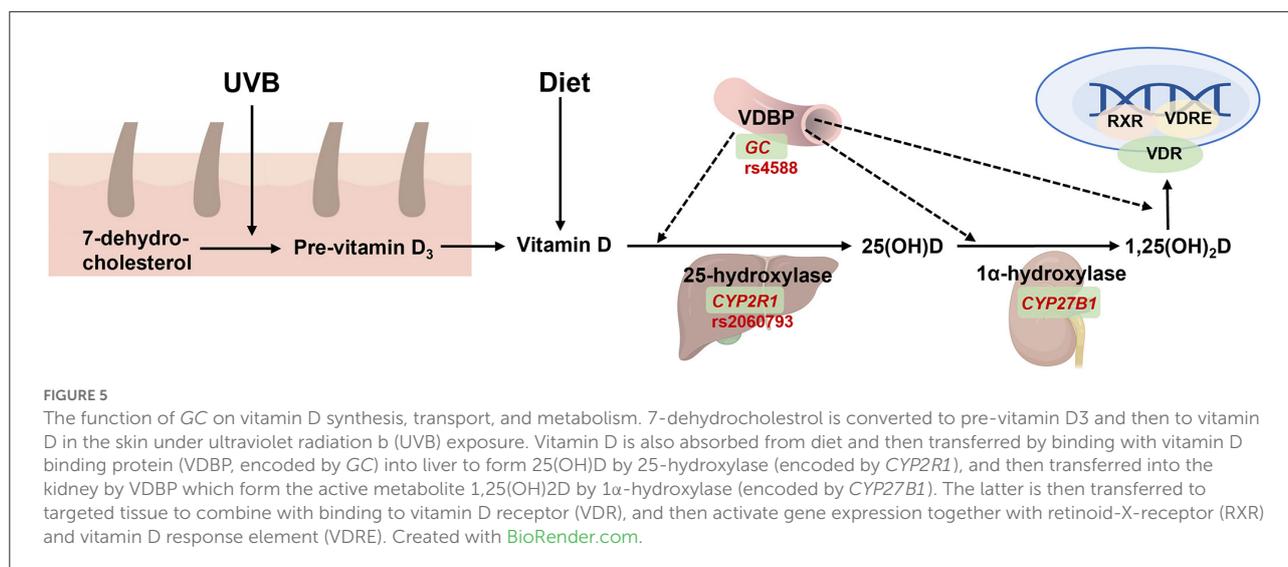
Iron and *TMPRSS6* polymorphism

Iron, as an essential trace element, regulates vital physiological processes in the body, including DNA synthesis, electron transport and oxygen transport. As iron homeostasis and metabolism are tightly regulated, iron surplus or deficiency can lead to various diseases (76).

Transmembrane protease serine 6 (TMPRSS6), which is responsible for iron absorption and recycling, is critical for iron homeostasis. GWAS have shown that *TMPRSS6* variants were most associated with serum iron, soluble transferrin receptor, and hemoglobin levels (12). Specifically, the *TMPRSS6* rs855791 T genotype with a non-synonymous amino

TABLE 1 Summary of nutrigenetic evidence for the role of nutritional supplementation in personalized nutrition.

Nutrition	Gene	SNP	Common Allele	Risk Allele	Risk Genotype	Health issue	Studies for genotype-based personalized nutrition*	Ref
Lipid	*ApoE*	rs429358 rs7412	T T	C C	ε4: C/C	Cardiovascular and Alzheimer's Disease	(1) *ApoE* non-ε4 → (Mediterranean diet → ↓AD risk)	(18)
							(2) *ApoE* non-ε4 → (PUFA → ↓cognitive decline)	(19, 20)
							(3) *ApoE* ε4 → (Saturated fat → ↑AD risk)	(21)
							(4) *ApoE* ε4 → (High glycemic load snack → ↑cognitive decline)	(11)
	FTO	rs1121980	C	T	CT, TT	Obesity and appetite	(1) *FTO* rs1121980 (T) ↑(Personalized intervention → weight loss)	(25–27)
n-3 PUFA	*FADS1*	rs174546	C	T	CT, TT	Cardiovascular disease	(1) *FADS1* rs174546 (TT) → (ALA → ↓ischemic stroke)	(12)
							(2) *FADS1* rs174546 (TT) → (DHA supplementation → ↑erythrocyte DHA)	(35)
Glucose	*TCF7L2*	rs7903146	C	T	CT, TT	Diabetes and obesity	(1) *TCF7L2* rs7903146 (TT) → (OGTT → ↑plasma free fatty acid, glucose response)	(13)
Vitamin A	*BCOM1*	rs12934922	A	T	AT, TT	Dry eyes, delayed growth, and infectious diseases	(1) *BCOM1* rs12934922 (A/T)↑(dietary carotenoid → plasma β-carotene response)	(47)
							(2) *BCOM1* rs12934922 (T)↑(dietary carotenoid → plasma and prostate carotenoid response)	(14)
Folic acid	*MTHFR*	rs1801133	C	T	CT, TT	Fetal pathologies, neural tube disease, anemia, hypertension	(1) *MTHFR* rs1801133 (TT) ↓ (folic acid supplementation → ↓stroke risk)	(15)
							(2) *MTHFR* rs1801133 (TT) → (Vitamin B2 supplementation → ↓blood pressure)	(58, 59)
							(3) *MTHFR* rs1801133 (TT) → (Vitamin B2 supplementation → ↓ homocysteine)	(60)
Vitamin D	*GC* *CYP2R1*	rs4588 rs10741657	C A	A G	CA, AC, AG, GG	Rickets, osteoporosis, diabetes mellitus, tuberculosis and chronic obstructive pulmonary disease	(1) *GC* rs4588 (A) + *CYP2R1* rs10741657 (G) ↓(UVB treatment or vitamin D_3 fortified food → plasma 25(OH)D response)	(65)
							(2) *GC* rs4588 (CC) ↑(VD$_3$ supplementation→ plasma 25(OH)D response)	(67, 68)
Fe	*TMPRSS6*	rs855791	C	T	CT, TT	Iron-deficiency anemia, diabetes mellitus	(1) *TMPRSS6* rs855791 (T)↓(iron supplementation → serum hemoglobin, iron and ferritin response)	(69)
Ca	*CaSR*	rs17251221	A	G	AG, GG	Nephrolithiasis, and Alzheimer's disease	Unknown	

* For simplicity, studies were expressed as "genotype(s) modify (diet→ outcome)." For example, "BCO1-rs12934922 (A/T)↑(dietary carotenoid→ plasma carotenoid response)" means that BCO1-rs12934922 (A/T) genotype showed stronger response to dietary carotenoid for plasma β-carotene, compared to its counterpart genotype. AD: Alzheimer's disease; PUFA: polyunsaturated fatty acid; ALA: α-linoleic acid; OGTT: oral glucose tolerancetest.

FIGURE 5
The function of *GC* on vitamin D synthesis, transport, and metabolism. 7-dehydrocholestrol is converted to pre-vitamin D3 and then to vitamin D in the skin under ultraviolet radiation b (UVB) exposure. Vitamin D is also absorbed from diet and then transferred by binding with vitamin D binding protein (VDBP, encoded by *GC*) into liver to form 25(OH)D by 25-hydroxylase (encoded by *CYP2R1*), and then transferred into the kidney by VDBP which form the active metabolite 1,25(OH)2D by 1α-hydroxylase (encoded by *CYP27B1*). The latter is then transferred to targeted tissue to combine with binding to vitamin D receptor (VDR), and then activate gene expression together with retinoid-X-receptor (RXR) and vitamin D response element (VDRE). Created with BioRender.com.

acid substitution (A736V) reduced the enzymatic activity of TMPRSS6. Furthermore, each copy of the minor alleles A and G of the rs855791 polymorphism decreased serum ferritin by 4.50 g/L and by 5.00 μg/L, respectively, in under-2-year-old children in Indonesia (77). Pei et al. also demonstrated that homozygotes with the *TMPRSS6* rs855791 C genotype mitigated iron deficiency anemia in women at reproductive age, especially in those with menorrhagia (78). A recent study showed that the rs855791polymorphism was significantly associated with decreased iron levels in the participants from Saudi Arabia (79). Moreover, Gan et al. revealed that the rs855791 and rs4820268 polymorphisms were both significantly associated with plasma ferritin, hemoglobin levels, iron overload risk, and T2DM risk in a Chinese population (80), suggesting the role of *TMPRSS6* in iron homeostasis as well as disease risk.

Since not only iron deficiency, but also iron overload can exert adverse effects, it is critical to tailor personalized iron supplementation to ensure iron homeostasis. De Falco et.al. (81) indicated that for patients with persistent iron-deficiency anemia, carriers of the *TMPRSS6* rs855791 risk allele (T) exhibited reduced serum iron changes upon oral iron supplementation. Nevertheless, further studies are warranted to investigate the effects of *TMPRSS6* in the management of iron nutritional status.

Calcium and *CaSR* polymorphism

Calcium is one of the primary constituents of human body, and its active form is vital to maintain the integrity of cell membranes, regulate excitation of muscles, and monitor various functions of cells. Calcium deficiency is associated with diseases of a variety of tissues and systems, such as bone, endocrine, cardiovascular and cerebrovascular, nervous, digestive, urinary,

reproductive, and nervous systems (82), all of which could be prevented with the use of calcium supplementation (83, 84).

Calcium-sensing receptors (CaSRs), members of the family of G protein-coupled receptors, are mainly located in the parathyroid gland and maintain the homeostasis of calcium by regulating the secretion of parathyroid hormone (85). A GWAS of 20,611 individuals of European ancestry showed that the rs17251221 polymorphism was associated with elevated serum calcium levels and accounted for 0.54% of the variance, and that the G allele of the same polymorphism was also associated with higher serum magnesium levels, lower serum phosphate levels, and lower bone mineral density in the lumbar spine (86). Another genome-wide meta-analysis on serum calcium revealed that a missense variant rs1801725 accounted for 1.26% of the variance in serum calcium levels, with the strongest association exhibited in individuals of European descent, whereas similar association was observed for rs17251221 in individuals of Indian Asian descent (87). However, to the best our knowledge, no studies have determined the effects of the interaction between the *CaSR* genotype and dietary intervention on calcium levels or health outcomes, thereby necessitating further investigation for the precise management of calcium levels.

Conclusion and prospect

With the rapidly progressing fields of nutrigenetics, accumulation of genetic variants has been identified to influence both macronutrient and micronutrient levels, as well as individual responses to dietary intake. Such variants are valuable to develop appropriate personalized dietary interventions, thus ensuring the transition of generic dietary guidelines to genotype-directed nutrition.

However, several challenges may hinder the widespread adoption of personalized nutrition. Firstly, nutrition-related diseases, such as CVDs and T2DM, are considered as polygenic in nature, and are thus influenced by multiple genes with small or medium effects. Therefore, polygenic risk scores of more than a few variants may provide more information to predict the outcome of personalized nutritional intervention (88). Secondly, diseases result from the interaction of genes and environmental factors. For example, individuals with genetic predisposition to obesity may have increased odds of weight gain compared to general population when they consume the same amount of sugar-sweetened beverages (89). In this regard, deep phenotyping using advanced "omics" technologies including epigenomics, transcriptomics, proteomics, metabolomics, and microbiome may help to discover the underlying gene-environment interactions and explain the missing hereditary (90, 91). Thirdly, "omics" technologies generate a large amount of data, requiring the use of advanced analytical methods such as machine learning (92, 93), which has been applied in multiple stages of personalized nutrition, including blood glucose monitoring (94), body weight management (95), disease risk assessment (96) and nutritional management (97). For example, by integrating blood biomarkers, diet, anthropometrics, and gut microbiota, a machine-learning algorithm could accurately predict the postprandial glycemic response, and therefore assisting in blood glucose homeostasis (4). Fourthly, the efficient implementation of personalized nutrition requires accurate intervention of health professionals and good compliance from individuals, thus requiring novel digital tools or tracking devices to bridge the gap between them (98).

In conclusion, genotype-based nutritional studies have highlighted the critical role of SNPs in the regulation of macronutrient and micronutrient levels, which are fundamental for health. Although further studies are required for the adequate implementation of personalized nutrition into healthcare research and practice, current evidence indicates the necessity of incorporating more genetic variants into personalized nutritional interventions to achieve improved nutrient levels and health outcomes and reduce the burdens of nutritional disorders on healthcare services.

Author contributions

JK, YY, YL, and JD designed the manuscript. FeiW, JZ, HZ, ML, BD, RL, FenW, DH, and GL performed the literature review. FeiW and JZ wrote the manuscript. JC, RZ, and XD revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

Authors HZ and YL are employed by Sequanta Technologies Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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