Personalized Nutrition for Management of Micronutrient Deficiency—Literature Review in Non-bariatric Populations and Possible Utility in Bariatric Cohort

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Abstract
Background Bariatric surgery can effectively treat morbid obesity; however, micronutrient deficiencies are common despite recommendations for high-dose supplements. Genetic predisposition to deficiencies underscores necessary identification of high-risk candidates. Personalized nutrition (PN) can be a tool to manage these deficiencies.

Methods Medline, PubMed, and Google Scholar were searched. Articles involving genetic testing, micronutrient metabolism, and bariatric surgery were included.

Results Studies show associations between genetic variants and micronutrient metabolism. Research demonstrates genetic testing to be a predictor for outcomes among obesity and bariatric surgery populations. There is limited research in bariatric surgery and micronutrient genetic variants.

Conclusion Genotype-based PN is becoming feasible to provide an effective treatment of micronutrient deficiencies associated with bariatric surgery. The role of genomic technology in micronutrient recommendations needs further investigation.

Keywords Obesity · Gene · Polymorphism · Gene expression · Nutrients · Supplementation · Deficiency

Background

The prevalence of obesity is consistent with more than one third of adults having the disease of obesity [1]. Obesity is the focus for many public health efforts in the USA with one treatment option being bariatric surgery [1, 2]. Achieving weight loss is a benefit from bariatric surgery; however, micronutrient deficiencies can occur [2]. Micronutrient deficiencies are associated with serious consequences due to the negative effects on metabolic and cellular signaling pathways. Possible causes of micronutrient deficiencies after bariatric surgery are decreased food intake, food intolerance, reduced gastric secretions, bypass of intestinal surface area for absorption, as well as failure to comply with recommended vitamin regimens [3, 4]. Multiple case series have reported postoperative, malabsorptive procedures to increase prevalence of iron deficiency to 20–49%, calcium and vitamin D deficiency 25–50%, vitamin B12 deficiency about 33%, and folate deficiency as high as 45% [3]. For malabsorptive procedures, patients are recommended to take at least double the recommended daily dose of a multivitamin plus mineral supplement and additional 1200–2400 mg calcium, 3000 IU vitamin D to reach levels > 30 ng/mL, and vitamin B12 as needed for normal levels [5]. In a cohort of adults who underwent bariatric surgery, 73% of the patients had at least one nutritional deficiency 5 years later even though they reported taking a dietary supplement [6]. However, there are some patients, up to 47%, that may be non-responders to supplements even with compliance rates of about 86–93% [7]. Indeed, individuals respond differently to dietary interventions. Genetic variation among individuals could be the root cause for varying responses to the same regimen and explains why some individuals respond better to a certain regimen than others in the same environmental conditions [8].

Introduction

Genetic testing can be a critical tool for health and medical diagnosis, treatment, and prevention. Predictive testing may
be among the most useful tests regarding medical nutrition therapy (MNT). Genetics along with environment and behavior are the key to providing the best assessment, intervention, and tailored changes for an individual [9]. MNT should follow an appropriate paradigm that encompasses prediction (early diagnosis), prevention (intervention on healthy persons), and a tailored therapy for patients [9]. Identifying ways for early intervention may help develop strategies for preventing poor nutritional status and maximizing surgery-induced metabolic benefits later.

Sequencing of the human genome and identifying gene-nutrient interactions are the underlying concept of PN [10]. Nutrigenomics is the study of the effect of specific nutrients on gene expression [10], while nutrigenetics refers to the study of genetic variations of an individual that can provide some prediction to help prevent as well as contribute to personalized dietary management [11]. Both nutrigenomics and nutrigenetics may be a strategy to improve understanding of the gene-diet interaction and deliver individualized MNT to prevent chronic nutrition-related diseases [(10), (11)]. The usefulness and validity of this type of PN are in their infancy, although some studies have shown that individuals find dietary recommendations based on genetics more beneficial than general dietary advice [12]. A survey conducted by the publisher Nature showed that 27% of respondents who had their genomes analyzed changed their diet, lifestyle, or medication based on their genetic information [13]. However, another study reported that genetic testing led to no short-term changes in specific dietary or exercise behaviors [14]. Thus, increased understanding and awareness of these tests is required to effectively use them among public and healthcare providers [12].

Since many micronutrients control energy metabolism, their deficiencies can result in an array of symptoms, ranging from anemia to neurological dysfunction [15, 16]. Additionally, subclinical micronutrient deficiency can lead to increased risks for coronary artery disease, infections, age-related macular degeneration, and oxidative damage [17, 18]. Therefore, measuring nutritional status in the context of pathophysiology is critical, but this is a major challenge because it is influenced by a number of factors including dietary consumption, physical/social stressors, and infections [19]. Furthermore, the impact of nutrition could vary among individuals and specific population subgroups based on their molecular and genetic make-up [19]. Studying this complex nutrient-gene relationship to understand the metabolic networks in context of health and disease should be a focus. It can provide information on potential biomarkers of nutritional status, disease progression, and response to interventions. This literature review aims to summarize data from studies of genes involved in micronutrient metabolism. Identifying these nutrient-gene pathways and their variants can help predict those at risk for deficiencies. This may recognize the need for increasing consumption of essential nutrients to intervene prior to bariatric surgery and develop strategies to prevent micronutrient deficiency postoperatively.

Methods

Due to the limited amount of literature published on micronutrient deficiencies, micronutrient genetic variants, and bariatric surgery, the authors conducted a narrative review. A comprehensive search of the literature from 1975 to 2020 was conducted to identify articles examining the association between genetic variants of micronutrient metabolic pathways and serum levels of micronutrients. Searches were conducted in databases that contain research related to health and metabolic outcomes, including PubMed, Medline, and Google Scholar. The search terms that were used included genetic variants, micronutrient metabolism, treatment of genetic defects of micronutrients, precision nutrition, nutrigenomics, and bariatric surgery. Additionally, review articles produced through the database searches were examined for further articles that fit within the inclusion criteria and thus were included in the results.

Inclusion/Exclusion Criteria

Criteria for inclusion in the review were [1] peer-reviewed articles, [2] articles that included empirical data, [3] articles published or available in English, [4] articles that included people with low micronutrient levels, [5] articles that included people that had micronutrient genetic variants, [6] supplementation/treatment regimens for people with genetic variants and low micronutrient levels, and [7] articles that included genetic testing among obesity and bariatric surgery patients were found. Due to this limitation, studies involving non-surgical patients and micronutrient genetic variants were included. Other studies involving genetic testing and bariatric surgery were included to demonstrate its potential as a tool for this patient population. There were also limitations on studies involving treatment and supplementation according to genetic variants. Ideally, inclusion criteria would comprise of studies with a high number of participants, a control group, and that used similar measures and procedures across studies for comparison; however, using the search methods and criteria described above, 80 articles met the inclusion criteria. All the authors confirmed that the articles met the inclusion criteria and were appropriate for the review. The articles that met the inclusion criteria focused on micronutrient...
genetic variants and genetic testing in diverse populations shifting to describe the findings.

**Results**

Of the 80 articles included, 2 were published between 1975 and 1990, 5 were published between 1991 and 2000, 25 were published between 2001 and 2010, and 48 were published between 2011 and 2020. Twenty-two of these studies took place in the USA, and the rest were conducted in other countries. The articles were divided into four categories which are used to organize the results: [1] micronutrient deficiencies prevalent among bariatric surgery patients (19 articles), [2] micronutrient genetic variants prevalence among different populations (29 articles), [3] clinical trials involving supplementation for micronutrient genetic variants (26 articles), and [4] genetic testing studies in persons with obesity and bariatric surgery populations (6 articles).

**Genetic Variants and Their Effect on Vitamin and Mineral Pathways and Response to Supplementation**

Genetic variations in specific genes among vitamin and mineral metabolic pathways are associated with altered nutrient homeostasis and adverse health outcomes [19]. SNPs are the most common type of genetic variations among people [20]. In the human genome, SNPs may occur at every 1000 nucleotides, which means that a person may have 4–5 million SNPs [20]. SNPs are known to impact micronutrient status or chronic diseases related to micronutrient metabolism [19, 21–23]. The ability to identify a person having genetic variants involved in vitamin and mineral metabolism may reduce the chance of developing micronutrient deficiencies that can lead to various diseases [19]. GWAS have shown that several genetic variants associated with vitamin metabolism can affect circulating vitamin levels, which could lead to abnormal vitamin function [24]. Most GWAS have been conducted among healthy, Caucasian populations, which is a limitation in this research [24]. Table 1 demonstrates recent studies that associate genetic variants and micronutrient metabolism.

**Vitamin D**

Vitamin D is essential for many functions of the body. Deficiency of vitamin D is associated with many cancers, autoimmune disorders, and cardiovascular disease as well as significantly affects musculoskeletal function [39–41]. Obesity has been identified as a risk factor of vitamin D deficiency prevalence to range from 13 to 90% preoperatively which was maintained after surgery [43].

The heritability of vitamin D status is estimated to be 30% and common variants group-specific component (GC) (also known as vitamin D–binding protein); 7-dehydrocholesterol reductase (DHCR7) and CYP2R1 (involved in 25-hydroxylase production) are associated with fasting plasma 25(OH) D concentrations [25, 44, 45]. Nissen and colleagues have shown that 7 prominent variants in CYP2R1 and GC genes were significantly associated with low serum 25(OH) D concentrations [26]. People who have these common genetic variations could be treated on a more individualized basis to correct deficiencies that occur.

One randomized controlled trial looked at older Australians randomly assigned to monthly doses of 30,000 IU or 60,000 IU vitamin D3 for 12 months and found that genetic variability is associated with response to supplementation, perhaps suggesting that some people might need a higher dose to reach optimal 25(OH) D levels [46]. Another study investigated 41 candidate single nucleotide polymorphisms (SNPs) in vitamin D and calcium pathway genes among healthy non-Hispanic white participants and stated that the increase in [25(OH)D] attributable to vitamin D3 supplementation may vary according to common genetic differences in CYP2R1, 24-hydroxylase (CYP24A1), and vitamin D receptor (VDR) genes [27]. There is evidence from three randomized controlled trials that indicate a strong association between genetic polymorphisms and levels of serum 25(OH) D in response to 40,000 IU vitamin D/week given for 6 months [47]. However, there is a wide variation in the response of blood 25(OH) D to vitamin D supplementation that is associated with genetic variants in vitamin D metabolism [25].

**Vitamin B12**

Vitamin B12 is a coenzyme, cofactor, and essential component in vitamin B complex. It is essential for cardiac health [48] and cognitive function [49, 50]. Deficiency of vitamin B12 can lead to deleterious consequences including macrocytic anemia, neuropsychiatric symptoms [51], cardiovascular diseases [52, 53], and onset of different forms of cancer [54, 55]. The most common cause of vitamin B12 deficiency is loss of intrinsic factor (IF) as absorption depends on it [56]. People who have bariatric surgery, short gut syndrome, long-term vegetarian, or vegan diets can potentially develop vitamin B12 deficiency [56]. While vitamin B12 level can be normal at baseline, it is often found to be lower in individuals after bariatric surgery [57, 58].
Nutritional parameters were compared preoperatively and at similar periods postoperatively among patients undergoing malabsorptive procedures [59]. Vitamin B12 abnormalities prior to surgery ranged from 3.2–8.3% to 24–25% at 1 year post-op [59]. In a study of gastric bypass surgery subjects, vitamin B12 deficiency was observed in 33.3% at 2 years and in 27.2% at 3 years postoperatively [60].

Genetic variants may impact the proteins involved in vitamin B12 absorption, cellular uptake, and intracellular metabolism [61–63]. Genetic influence for B12 levels is estimated to be 59% in a study using monozygotic and dizygotic twins [64] and 27% in another study among Icelandic sibling pairs [65]. Variants of the transcobalamin 1 (TCN1) gene (vitamin B12 binding protein, transcobalamin I (TCI)) have been associated with circulating B12 concentrations [29, 66]. Genetic variants of fucosyltransferase 2 (FUT2 gene) that codes for an enzyme in the vitamin B12 pathway are associated with B12 levels [29]. Transcobalamin 2 (TCN2) gene is responsible for making a B12-binding protein called transcobalamin II (TC) that carries B12 from the intestine to blood and liver. Although TC represents approximately 10–20% of circulating B12, the most common variant of this gene among Caucasian

### Table 1: Relevance of genetic variants associated with micronutrient metabolism

| Micronutrients | Genes identified with micronutrients | Relevance in micronutrient status | Reference |
|----------------|-------------------------------------|----------------------------------|-----------|
| Vitamin D      | 1. GC                               | 1. GC gene encodes Vitamin D Binding Protein (DBP) which is a glycosylated alpha-globulin that transports vitamin D metabolites from gut and skin to target end-organs. | [25–28] |
|                | 2. CYP2R                            | 2. CYP2R1 gene encodes 25-hydroxylase, which converts Vitamin D to 25(OH)D. | |
|                | 3. DHCR7                            | 3. DHCR7 gene provides instructions for making 7-dehydrocholesterol reductase, an enzyme involved in the final step of cholesterol production. | |
|                | 4. CYP24A                           | 4. CYP24A gene provides instructions for making 24-hydroxylase, an enzyme that controls the amount of active vitamin D in the body. | |
|                | 5. VDR                              | 5. VDR gene provides instructions for making vitamin D receptor (VDR) protein, which allows the body to respond appropriately to vitamin D. | |
|                |                                     | >A variation in these genes may impact body vitamin D levels. | |
| B12            | 1. FUT2                             | 1. FUT2 gene encodes fucosyltransferase 2 gene and is involved in Vit B12 absorption and transport. | [28–31] |
|                | 2. CUBN                             | 2. CUBN gene provides instructions for making cubilin protein which is involved in the uptake of vitamin B12. | |
|                | 3. TCN1                             | 3. TCN1 gene encodes B12-binding protein family which facilitates the transport of cobalamin into cells. | |
|                | 4. MTRR                             | 4. MTRR gene is responsible for maintaining adequate levels of activated vitamin B12, which maintains methionine synthase enzyme in its active state. | |
|                | 5. TCN2                             | 5. TCN2 provides instructions for making transcobalamin. | |
|                | 6. MTR                              | 6. MTR gene provides instructions for making methionine synthase enzyme which needs B12 and is involved in the formation of the amino acid methionine | |
|                | 7. MMAAA                            | 7. The protein encoded by MMAAA gene is involved in the translocation of cobalamin into the mitochondrion. | |
|                | 8. MMACHC                           | 8. It is postulated that the protein encoded by MMACHC gene may have a role in the binding and intracellular trafficking of cobalamin. | |
|                |                                     | >SNP related to these genes can lead to insufficient B12 levels in the body. | |
| Folic acid     | 1. MTHFR                            | 1. MTHFR gene produces Methylenetetrahydrofolate reductase (MTHFR) which is a vital enzyme for the folate pathway. | [28, 32–34] |
|                |                                     | >SNP related to this gene may be an important marker to identify people at risk for lower plasma folate concentrations, changes in folate form distribution, and elevated plasma homocysteine concentrations. | |
| Thiamine       | 1. SLC19A2                          | SLC19A2, SLC19A3 and SLC35F3 genes code for thiamine transporter protein which allow thiamine to move into the cells. | [28, 35, 36] |
|                | 2. SLC19A3                          | >Mutations in these gene can cause thiamine deficiency leading to thiamine responsive megaloblastic anemia. | |
|                | 3. SLC35F3                          | | |
| Iron           | 1. TMPRSS6                          | 1. TMPRSS6 gene codes for the protein matriptase-2 which helps in regulation of iron balance. | [28, 37, 38] |
|                | 2. TFR2                             | 2. TFR2 gene codes for TFR2 protein which facilitates entry of iron into the cells. | |
|                | 3. TF                               | 3. TF gene codes for protein transferrin which is a transport protein for iron in the body. | |
|                | 4. HFE                              | 4. HFE gene provides instruction for production of HFE protein which determines iron absorption from diet and iron release from body stores. | |
|                |                                     | >A variation in these genes together has an impact on the risk of insufficient iron levels in the body. | |
populations has been associated with B12 levels [29]. In a study among Irish men, having this SNP and homozygous CC genotype had lower vitamin B12 levels than those with GG genotype [67]. This demonstrates that different genotypes of transcobalamin impact the distribution of vitamin B12 and shows an association between this genetic variant and B12 levels [67].

Vitamin B12 along with folate influences one-carbon metabolism. Cubulin (CUBN) is the intestinal (IF) and polymorphisms of this gene have been associated with chronic diseases in individuals with low B12 status [29]. A study involving a Canadian population found that many SNPs in genes related to folate, B12, and homocysteine metabolism—CUBN, TCN1, TCN2, methylenetetrahydrofolate reductase (MTHFR), MUT (methylmalonyl coenzyme A mutase), and FUT2—are possibly correlated with B vitamin-related diseases [30]. Genetic polymorphisms of MTHFR, MTR, MTRR, MMAA (methylmalonic aciduria (cobalamin deficiency) cb1A type), MMACHC (methylmalonic aciduria and homocystinuria, cb1C type), and MUT have been analyzed. This research has failed to show an association between MTHFR gene polymorphisms and B12 concentrations [29]. However, a study using a classic twin model found that common gene variants—MMAA, MMACHC, MTRR, and MUT—were significantly associated with B12 levels and could explain the variation in B12 levels, which might facilitate the prevention and treatment of B12 insufficiency/deficiency in individuals at a higher risk of associated diseases [68]. A cross sectional study looking at 56 SNPs of the B12 pathway among an older female population and found TCN2 to be significantly associated with elevated serum methylmalonic acid (MMA) levels, a marker for available B12 [69]. When using MMA levels as a marker for B12, it is suggested that TCN2 gene variants may lead to decreased vitamin B12 availability [69]. This review spotlights the complex nature of nutrigenomics and vitamin B12. Identifying these gene variants among people having bariatric surgery could contribute to a more personalized nutrition plan.

### Folate

Folate plays a role in one-carbon metabolism, methylation and DNA synthesis, and methionine regeneration [70–72]. Folate deficiency is associated with elevated homocysteine, cardiovascular diseases, neural tube defects, cleft lip and palate, late pregnancy complications, neurodegenerative and psychiatric disorders [73–75]. Elevated homocysteine levels are a risk marker for dementia, Alzheimer’s disease, bone fractures, cancers, and cardiovascular diseases [76–78]. Many studies show folate deficiency to be low due to food fortification in America [39, 79–81]. Although preoperative deficiencies are not alarming, prevalence of folate deficiency and elevated homocysteine have shown to persist or worsen after bariatric surgery despite supplementation [82, 83]. The prevalence of abnormalities 1 year after gastric bypass were higher compared to preoperative levels in 232 patients with elevated homocysteine as high as 29% and low RBC folate in 12% of 149 postoperative subjects [82]. Another study found similar results among patients undergoing bariatric surgery with 13% having folate deficiency postoperatively [84].

Several studies have shown an association between SNPs related to folate metabolism, folate deficiency, and elevated homocysteine [70]. A common genetic variant in MTHFR is known to influence blood folate and prevalent in 10% of the population worldwide [85, 86]. Stelutti and colleagues studied polymorphism frequencies and differences in homocysteine concentrations even in the presence of folic acid fortification and found that homocysteine levels increased in those carrying genetic variants in folate metabolism, specifically in the MTHFR gene [87]. The prevalence of variant MTHFR TT has been found in 25% of Americans of Hispanic origin, 10–15% among white Americans, and only 0–1% for African Americans [77, 87–89]. A review examining the nutritional deficiencies, bariatric surgery, and serum homocysteine levels found that the mutations of the MTHFR gene can be one of the reasons for persistent elevated serum homocysteine after surgery despite supplementation with B-group vitamins [76]. Knowing the presence of genetic variants of folate metabolism would provide a critical personalized care to those that might benefit from the methylated form of folic acid to prevent elevated homocysteine levels [76].

### Thiamine

Thiamine is essential for glucose, amino acid, and energy metabolisms [90–92]. Deficiency of thiamine can cause complications including cardiovascular and neurological diseases, including Wernicke-Korsakoff syndrome [90, 93]. Preoperative thiamine deficiency is prevalent in about 29% of patients undergoing bariatric surgery [57]. Studies have found that preexisting thiamine deficiency can be present in 15.5% and as high as 47% of patients; however, race plays a role showing Hispanic patients with the highest level of prevalence followed by African Americans (31%) and Caucasians (7%) [57, 79, 94]. Similarly, a retrospective study showed 33.6% of patients having thiamine deficiency pre-operatively, suggesting that people with obesity, especially those with many weight loss attempts, may have different needs to maintain adequate thiamine levels [95].

Mutations in thiamine transporter genes, SLC19A2 and SLC19A3, have been observed in cases of thiamine deficiency due to decreased absorption of thiamine that leads to neurological dysfunction [91]. SLC35F3 is another thiamine transporter gene that plays a role in cardiac health and blood pressure. Genetic variants have been associated with thiamine deficiency as well as hypertension [35]. Prevalence of
mutations in these genes is largely unaccounted for despite recent advances in GWA studies. However, studies show that thiamine deficiency and cardiac dysfunction associated with these genetic variants are alleviated with thiamine supplementation [96–99]. Literature reviews have shown that treatment for thiamine deficiency vary according to the genetic defect of thiamine metabolism and that supplementation results in adequate thiamine levels and improved clinical outcomes [100, 101]. The best responses to thiamine therapy were associated with early referral for genetic testing and early initiation of thiamine treatment. This evidence demonstrates that early diagnosis of these mutations can be beneficial. It may also implicate the hereditability of thiamine deficiency and that therapeutic doses of thiamine vary according to the genetic defect.

Iron

Iron is essential for metabolic processes like oxygen transport, deoxyribonucleic acid (DNA) synthesis, electron transport, as well as cellular functions can affect one’s well-being [102]. In individuals with obesity, the chronic inflammatory state related to obesity might be a possible risk factor for iron deficiency, which is also called the anemia of inflammation [57, 103–105]. Studies have shown that the prevalence of iron deficiency in adults with obesity is remarkable, and a decrease in serum iron and transferrin saturation levels is inversely associated with an increase in body mass index [103, 106–108]. A study involving bariatric surgery candidates showed 86.2% of females and 80% of males to be iron deficient prior to surgery [109]. A retrospective analysis of patients undergoing RYGB surgery showed that 43.9% were iron-deficient pre-operatively, which may be associated with higher complication rates as well as worsening of iron deficiency after surgery [57, 110, 111]. These findings reaffirm the need to assess and possibly intervene to manage deficiency in bariatric surgery candidates preoperatively.

Considering the results of several GWAS, there is strong evidence of genetic regulation of iron metabolism, and mutations in transmembrane serine protease 6 (TMPRSS6) gene that encodes for an enzyme that regulates hepcidin involved in iron homeostasis, iron carrier transferrin (TF), and transferrin receptor-2 (TFR2) genes have been associated with iron deficiency [112]. A GWAS concluded that identifying mutations in the TMPRSS6 gene has broad applications in understanding clinical disorders of iron metabolism, and polymorphisms in TMPRSS6 gene may contribute to iron deficiency anemia (IDA) in individuals even in absence of other predisposing factors for IDA [112]. Studies have shown a common TMPRSS6 gene variant to be prevalent in 45% of the individuals without iron deficiency and clinically relevant inflammatory conditions [104] and 36.5–41.7% in a group of non-pregnant women [113]. TF and human hemochromatosis (HFE) genes are involved in genetic regulation of maintenance of iron homeostasis [37]. Mutations in the HFE gene can lead to hereditary hemochromatosis, an iron overload disorder [114]. These factors should be considered to possibly affect iron absorption and thus response to treatment.

TMPRSS6 mutations have been associated with refractoriness to oral iron and studies confirm the role of TMPRSS6 in predicting oral iron response [114, 115]. One study evaluated subjects with persistent IDA to poorly respond to oral iron, indicating that TMPRSS6 polymorphisms are more frequent in subjects with persistent IDA [115]. Identifying mutations of these iron-related genes can help with providing personalized iron supplementation for a common deficiency post bariatric surgery.

Association Between Genetic Defects and Micronutrient Supplementation

The vitamin and mineral supplementation studies that focus on treating genetic disorders are mainly case studies. Supplementation studies for vitamin D-related genetic variants have been conducted in populations that are overweight and have obesity. Limited data is available on micronutrient supplementation according to genetic variants in bariatric surgery populations. Table 2 shows studies involving micronutrient supplementation according to genetic defect in diverse populations.

Bariatric Surgery, Genetic Testing, and Gene Expression Profiles

Genetic expression patterns can be a predictive tool for responsiveness to nutritional treatments. Some studies have indicated that surgery-induced weight loss was associated with remodeling of the epigenome that helps regulate metabolic gene expression [125, 126]. One study found that 1366 genes were differentially expressed after bariatric surgery and subsequent weight loss, which are associated with gene transcription and energy metabolism [127]. Knowing the impact of bariatric surgery on the vitamin/mineral metabolic pathways can lead to successful prevention and treatment of micronutrient deficiencies. A study that specifically assessed the mRNA of genes within B12 degradation pathway after gastric bypass found that the intestine reprogrammed its genetic phenotype to compensate for the changes in B12 metabolism. The authors also found decreased expression of TCN1 but an increased production of CUBN, which reflects adaptive genetic reprogramming [128]. However, research on the role of vitamin metabolism genes and their adaptation after bariatric surgery is scarce. We do know that healthy individuals and people with obesity have different gene expression profiles and bariatric surgery further modifies the epigenome [129, 130]. Genetic testing is a useful tool for applying personalized medicine in bariatric surgery patients as demonstrated by
| Reference | Micronutrient Defective or mutated gene | Dosage and monitoring | No. of patients | Summary |
|-----------|----------------------------------------|-----------------------|----------------|---------|
| [116]     | Thiamine SLC19A2                        | 75 mg thiamine/day    | Case study of 1 female patient | Patients with this defect present with diabetes mellitus, megaloblastic anemia, and sensorineural deafness. Thiamine supplementation improved blood glucose and insulin requirements decreased. |
| [117]     | SLC19A3                                | 100 mg thiamine 2×/day along with 10 mg biotin 2×/day for 5 months | Case study of 1 female patient | This genetic defect causes ophthalmoplegia, ataxia and confusion. Oral biotin and thiamine improved the symptoms dramatically the next day. |
| [100, 118]| TPK1                                   | 500 mg thiamine/day   | 2 patients with homozygous TPK1/ mutation- s | Early thiamine supplementation prevented encephalopathic episodes and improved developmental progression. Evidence suggests that thiamine supplementation may rescue TPK enzyme activity. |
| [119]     | Vitamin D GC                           | 50,000 IU vitamin D3 per week for 8 weeks, followed by daily maintenance of 1000 IU vitamin D3 for 4 months | 234 participants with vitamin D deficiency | Carriers of GC mutation showed the lowest baseline 25(OH)D levels and lowest response to vitamin D supplementation. Mutations in GC gene can predict response to vitamin D supplementation. |
| [27]      | CYP2R1, CYP24-A1, VDR                  | Vitamin D3 (1000 IU/day) and/or calcium carbonate (1200 mg/day elemental calcium) | 1787 healthy participants | The increase in [25(OH)D] attributable to vitamin D3 supplementation may vary according to common genetic differences in CYP2R1, CYP24A1, and VDR genes. |
| [120]     | Folic acid (FA) MTHFR                  | Each treatment taken once daily for 8 weeks: 1. Enalapril only (10 mg, control group) 2. Enalapril-FA tablet (10 mg enalapril combined with 0.4 mg of FA) 3. Enalapril-FA tablet (10 mg enalapril combined with 0.8 mg of FA) | 480 subjects with mild or moderate essential hypertension | MTHFR mutation can affect homocysteine concentration at baseline and post-FA treatment as well as can modify therapeutic responses to various dosages of FA supplementation. |
| [121]     | MTHFR 677C → T genotype                | 3 random dietary interventions (4 months each): 1. Exclusion diet (avoidance of FA–fortified foods) 2. Folate-rich diet (folate-rich foods to achieve 400 mcg folate/d) 3. Supplement (exclusion diet plus a folate supplement of 400 mcg/day) | 126 healthy subjects (42 TT, 42 CT, and 42 CC genotypes) | The TT homozygotes tended to have low plasma folate and high plasma homocysteine levels. Folate intervention on plasma folate was observed across genotypes. However, the TT homozygotes required higher supplement intervention to achieve similar effects observed in other genotypes suggesting a need for supplementation with at least 400–600 mcg/day for individuals with the TT genotype. |
| [122]     | Vitamin B12 MTHFR 677C→T genotype      | One vitamin tablet consisting of 2 mg of folic acid, 25 mg vitamin B6, and 400 μg of vitamin B12 daily for 6 months | 52 patients with migraine with aura. | Vitamin supplementation lowered homocysteine and reduced migraine disability in a subgroup of patients. In this patient group the treatment effect on both homocysteine levels and migraine disability was associated with MTHFR C677T genotype; carriers of the C allele experienced a greater response compared to TT genotypes concluding that TT genotypes require a larger dosage of vitamins to exhibit the same effect as C alleles. |
| [123]     | Iron HFE, TMPRSS6, TF                   | Iron supplementation with aspirin capsules (ferrous fumarate; 98.6 mg elemental iron) once a day for 20 weeks from the time of diagnosis | 181 pregnant women with anemia | The HFE variant had a positive effect with significant improvement in hemoglobin, iron and ferritin. This shows an association of genetic variants and iron absorption and thus response to treatment. The TMPRSS6 variant also showed a positive effect. |
Bandstein et al. that showed presurgery vitamin D levels may impact the size of genotype effects of FTO rs9939609 on weight loss among gastric bypass surgery patients [131]. Nutritional genomics may provide the path for precise nutrition recommendations to provide high-risk individuals with personalized treatment and to prevent micronutrient deficiencies.

**Discussion**

From the review, it is evident that the deficiencies of the studied micronutrients are influenced by genetic mutations. Postbariatric surgery, patients frequently have these deficiencies and knowledge of these mutations may have bearing on its management. Additional research is needed to establish this association. This review confirmed the scarcity of research that has been conducted in the area of bariatric surgery and micronutrient genetic variants, with only two articles being found in this search. This limitation should be considered when interpreting the findings in this discussion. Furthermore, the treatment regimen for those who have micronutrient genetic variants and undergoing bariatric surgery should be an area of future research.

Personalized dietary and supplement advice derived from genetic testing should be based on appropriately designed studies. Utility of data from GWAS in providing dietary advice is limited because it is not known what diet and supplement intakes are required to prevent and treat the deficiencies that might be caused by micronutrient genetic variants. Identifying how a genetic variant modifies the response to supplementation on the micronutrient status and possibly identify responders and non-responders will be required to understand this population and area of research. Genotype along with micronutrient blood levels would be the initial step in applying PN among bariatric surgery patients. Genetic marker is only one factor that influences improvements related to micronutrient status [132].

Future work should focus on genotyping for multiple variants in the micronutrient metabolic pathways and their additive and interactive effects to get a complete understanding of the influence of genetic factors on micronutrient metabolism. Then, utilizing genomic technology to understand this influence on the responses to micronutrient supplementation is also important. This would involve micronutrient status, genetic variations, and genetic interactions within metabolic pathways involving the micronutrient, its molecular targets, and environmental stressors [133].

Furthermore, studies should focus to understand the role of the gut microbiome and its influence on metabolism and physiology. The human gut microbiota (which has its own genome) can modulate signaling pathways and regulate gene expression [134]. Diet, lifestyle, medications, and environmental exposure can increase inflammation within the gut, causing dysbiosis, which can contribute to chronic diseases and other illnesses [135]. Interestingly, gut microbial contribution to vitamin metabolism has been recognized in whole-genome metagenomic studies, suggesting microbe-mediated vitamin metabolism [136, 137]. Pre- and probiotics as well as diet can alter the gut microbiome in a manner that improves human health [138]. Investigating how the gut microbes can positively influence vitamin metabolism is warranted.

Techniques used for genetic testing will determine the cost. Methods being used in healthcare and research to identify genetic variations are known as next-generation sequencing.

### Table 2 (continued)

| Reference | Micronutrient | Defective or mutated gene | Dosage and monitoring | No. of patients | Summary |
|-----------|---------------|---------------------------|----------------------|----------------|---------|
| [124]     | TMPRSS6       | Intravenous iron gluconate (1.3 mg/kg/day) for 5 days as first course and same dose was repeated after 5 months | Case study of 1 female patient | A comprehensive assessment that includes sequence analysis of TMPRSS6 can help to confirm the genotype-phenotype association of genes involved in iron metabolism and may also be useful for predicting the patient’s response to iron treatment. |

Mutation was significantly associated with higher serum iron and hemoglobin. The presence of variants in STEAP3, TMPRSS6, SLC11A2, SLC40A1, HAMP and TF genes indicate a probable genetic association with iron status.
Examined the evidence for genotype-based personalized information on micronutrient metabolism may affect the impact of genotype-based personalized advice. The researchers reported that PN advice resulted in greater dietary changes compared with general healthy eating advice. Analyzing biochemical markers for vitamins/minerals as well as defining a person’s “nutrigenomic profile” for those undergoing bariatric surgery will open the door to implement more personalized recommendations for micronutrient supplementation.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Ethical Approval** For this type of study, ethical approval and informed consent do not apply as it is a narrative review.

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### References

1. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311(8):806–14. https://doi.org/10.1001/jama.2014.732.
2. Bloomberg RD, Fleishman A, Nalle JE, et al. Nutritional deficiencies following bariatric surgery: What can we do about it? Am J Case Rep. 2012;13(9):1345–55. https://doi.org/10.1381/0960892053268264.
3. Sawaya RA, Jaffe J, Friedenberg L, et al. Vitamin, mineral, and drug absorption following bariatric surgery. Curr Drug Metab. 2012;13(9):1345–55.
4. Ahmad DS, Esmadi M, Hammad H. Malnutrition secondary to non-compliance with vitamin and mineral supplements after gastric bypass surgery: What can we do about it? Am J Case Rep. 2012;13:209–13. https://doi.org/10.12695/AJCR.883335.
5. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists - Executive Summary. Endocr Pract. 2019;25(12):1346–59. https://doi.org/10.4158/GL-2019-0406.
6. Lombardo M, Franchi A, Padua E, et al. Potential nutritional deficiencies in obese subjects 5 years after bariatric surgery. Bariatric Surgical Practice and Patient Care. 2019;14(3):125–30.
7. Mahlay NF, Verka LG, Thomsen K, et al. Vitamin D status before Roux-en-Y and efficacy of prophylactic and therapeutic doses of
vitamin D in patients after Roux-en-Y gastric bypass surgery. Obes Surg. 2009;19(5):590–4. https://doi.org/10.1007/s11695-008-9698-1.

8. Ferguson LR, De Caterina R, Gümän U, et al. Guide and knowledge of the International Society of Nutrigenetics/Nutrigenomics on personalised nutrition: part 1 - fields of precision nutrition. J Nutrigenet Nutrigenomics. 2016;9(1):12–27. https://doi.org/10.1159/000443530.

9. Trovato GM. Behavior, nutrition and lifestyle in a comprehensive health and disease paradigm: skills and knowledge for a predictive, preventive and personalized medicine. EPMA J. 2012;3(1):8. https://doi.org/10.1007/s12263-012-0142-1.

10. Fallaize R, Macready AL, Butler LT, et al. An insight into the public acceptance of nutrigenomic-based personalised nutrition. Nutr Res Rev. 2013;26(1):39–48. https://doi.org/10.1017/S0954424413000024.

11. Croyes L, Rosado EL. Interaction between genes involved in energy intake regulation and diet in obesity. Nutrition. 2019;67–68:110547. https://doi.org/10.1016/j.nut.2019.06.027.

12. Nielsen DE, El-Sohemy A. A randomized trial of genetic information for personalized nutrition. Genes Nutr. 2012;7(4):559–66. https://doi.org/10.1007/s12263-012-0290-x.

13. Maher B. Nature readers flirt with personal genomics. Nature. 2008;411(6835):578. https://doi.org/10.1038/48019a.

14. Blom CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. N Engl J Med. 2011;364(6):524–34. https://doi.org/10.1056/NEJMoa1011893.

15. Brolin RE, LaMarca LB, Kenler HA, et al. Malabsorptive gastric bypass in patients with superobesity. J Gastrointest Surg. 2002;6(2):195–203. discussion 4-5

16. Berger JR. The neurological complications of bariatric surgery. Arch Neurol. 2004;61(8):1185–9. https://doi.org/10.1001/archneur.61.8.1185.

17. Shenkin A. Micronutrients in health and disease. Postgrad Med J. 2006;82(971):559–67. https://doi.org/10.1136/pgmj.2006.047670.

18. Geissler C, Powers H. Fundamentals of human nutrition E-book: for students and practitioners in health sciences: Churchill Livingstone Elsevier; 2009. 324 p.

19. Reddy VS, Palika R, Ismail A, et al. Nutrigenomics: Opportunities & challenges for public health nutrition. Indian J Med Res. 2018;148(5):632–38. https://doi.org/10.4103/ijmr.IJMR_1734_17.

20. Lister Hill National Center for Biomedical Communications. Genetics home reference [unspecified]. Bethesda, MD: National Library of Medicine, National Institutes of Health; 2003. Available from: http://ghr.nlm.nih.gov/.

21. Sharp P, Srai SK. Molecular mechanisms involved in intestinal iron absorption. World J Gastroenterol. 2007;13(35):4716–24. https://doi.org/10.3748/wjg.v13.i35.4716.

22. Klujtmans LA, van den Heuvel LP, Boers GH, et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. Am J Hum Genet. 1996;58(1):35–41.

23. Borel P, Desmarchelier C. Bioavailability of fat-soluble vitamins and phytochemicals in humans: effects of genetic variation. Annu Rev Nutr. 2018;38:69–96. https://doi.org/10.1146/annurev-nutr-082217-051628.

24. Dib MJ, Elliott R, Ahmadi KR. A critical evaluation of results from genome-wide association studies of micronutrient status and their utility in the practice of precision nutrition. Br J Nutr. 2019;122(2):121–30. https://doi.org/10.1017/S0007114519001119.

25. Desmarchelier C, Borel P, Goncalves A, et al. A combination of single-nucleotide polymorphisms is associated with interindividual variability in cholecalciferol bioavailability in healthy men. J Nutr. 2016;146(12):2421–8. https://doi.org/10.3945/jn.116.237115.

26. Nissen J, Rasmussen LB, Ravn-Haren G, et al. Common variants in CYP2R1 and GC genes predict vitamin D concentrations in healthy Danish children and adults. PLoS One. 2014;9(2):e89907. https://doi.org/10.1371/journal.pone.0089907.

27. Barry EL, Rees JR, Peacock JL, et al. Genetic variants in CYP2R1, CYP24A1, and VDR modify the efficacy of vitamin D3 supplementation for increasing serum 25-hydroxyvitamin D levels in a randomized controlled trial. J Clin Endocrinol Metab. 2014;99(10):E2133–7. https://doi.org/10.1210/jc.2014-1389.

28. NIH. Genes Home Reference [cited 2019]. Available from: https://ghr.nlm.nih.gov/.

29. Surendran S, Adaikalakoteswari A, Saravanan P, et al. An update on vitamin B12-related gene polymorphisms and B12 status. Genes Nutr. 2018;13:2. Epub 2018/02/06. https://doi.org/10.1186/s12263-018-0591-9.

30. Zinck JW, de Groh M, MacFarlane AJ. Genetic modifiers of folate, vitamin B-12, and homocysteine status in a cross-sectional study of the Canadian population. Am J Clin Nutr. 2015;101(6):1295–304. Epub 2015/05/06. https://doi.org/10.3945/ajcn.115.107219.

31. Hazra A, Kraft P, Selhub J, et al. Common variants of FUT2 are associated with plasma vitamin B12 levels. Nat Genet. 2008;40(10):1160–2. https://doi.org/10.1038/ng.210.

32. Tanaka T, Scheet P, Giusti B, et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. Am J Hum Genet. 2009;84(4):477–82. https://doi.org/10.1016/j.ajhg.2009.02.011.

33. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet. 1995;10(1):111–3. Epub 1995/05/01. https://doi.org/10.1038/ng0595-111.

34. Bagley PJ, Selhub J. A common mutation in the methylenetetrahydrofolate reductase gene is associated with an accumulation of formylated tetrahydrofolic acids in red blood cells. Proc Natl Acad Sci U S A. 1998;95(22):13217–20. https://doi.org/10.1073/pnas.95.22.13217.

35. Zhang K, Huettelman MJ, Rao F, et al. Genetic implication of a novel thiamine transporter in human hypertension. J Am Coll Cardiol. 2014;63(15):1542–55. Epub 2014/02/05. https://doi.org/10.1016/j.jacc.2014.01.007.

36. Mikstiene V, Songailiene J, Byckova J, et al. Thiamine responsive megaloblastic anemia syndrome: a novel homozygous SLC19A2 gene mutation identified. Am J Med Genet A. 2015;167(7):1605–9. Epub 2015/02/23. https://doi.org/10.1002/ajmg.a.37015.

37. Pichler I, Minelli C, Sanna S, et al. Identification of a common variant in the TFR2 gene implicated in the physiological regulation of serum iron levels. Hum Mol Genet. 2011;20(6):1232–40. https://doi.org/10.1093/hmg/ddq552.

38. Blanco-Rojo R, Baeza-Richer C, López-Parrá AM, et al. Four variants in transferrin and HFE genes as potential markers of iron deficiency anemia risk: an association study in menstruating women. Nutr Metab (Lond). 2011;8:69. https://doi.org/10.1186/1743-7075-8-69.

39. Gemmel K, Santry HP, Prachand VN, et al. Vitamin D deficiency in preoperative bariatric surgery patients. Surg Obes Relat Dis. 2009;5(1):54–9. https://doi.org/10.1016/j.soard.2008.07.008.

40. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293(18):2257–64. https://doi.org/10.1001/jama.293.18.2257.

41. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81(3):353–73. https://doi.org/10.4065/81.3.353.
42. Chakhtoura MT, Nakhoul NN, Shawwa K, et al. Hypovitaminosis D in bariatric surgery: A systematic review of observational studies. Metabolism. 2016;65(4):574–85. https://doi.org/10.1016/j.metabol.2015.12.004.

43. Peterson LA, Zeng X, Caulfield-Noll CP, et al. Vitamin D status and supplementation before and after bariatric surgery: a comprehensive literature review. Surg Obes Relat Dis. 2016;12(3):693–702. https://doi.org/10.1016/j.soard.2016.01.001.

44. Afzal S, Brandum-Jacobsen P, Bojesen SE, et al. Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. BMJ. 2014;349:g6330. https://doi.org/10.1136/bmj.g6330.

45. Shea MK, Benjamin EJ, Dupuis J, et al. Genetic and non-genetic correlates of vitamins K and D. Eur J Clin Nutr. 2009;63(4):458–64. https://doi.org/10.1038/sj.ejcn.1602959.

46. Wadsworth M, Tran B, Armstrong BK, et al. Environmental, personal, and genetic determinants of response to vitamin D supplementation in older adults. J Clin Endocrinol Metab. 2014;99(7):E1332–40. https://doi.org/10.1210/jc.2013-4101.

47. Didriksen A, Grimnes G, Hutchinson MS, et al. The serum 25-hydroxyvitamin D response to vitamin D supplementation is related to genetic factors, BMI, and baseline levels. Eur J Endocrinol. 2013;169(5):559–67. https://doi.org/10.1530/EJE-13-0323.

48. Quinlivan EP, McPartlin J, McNulty H, et al. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet. 2002;359(9202):227–8. https://doi.org/10.1016/s0140-6736(02)07439-1.

49. Hin H, Clarke R, Shertliper K, et al. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Ageing. 2006;35(4):416–22. https://doi.org/10.1093/ageing/afl033.

50. O’Leary F, Samman S. Vitamin B12 in health and disease. Br J Nutr. 2003;90(3):279–86. https://doi.org/10.1079/BJN2003702.

51. Lechner K, Födinger M, Grisold W, et al. Vitamin B12 deficiency. Wien Klin Wochenschr. 2005;117(17):759–91. https://doi.org/10.1002/s0040-6736(05)00406-7.

52. Collaboration HLT. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. Am J Clin Nutr. 2005;82(4):806–12. https://doi.org/10.1093/ajcn/82.4.806.

53. Spence JD, Bang H, Chambless LE, et al. Vitamin intervention for stroke prevention trial: an efficacy analysis. Stroke. 2005;36(11):2404–9. https://doi.org/10.1161/01.STR.0000185929.38534.f3.

54. Arendt JF, Nexo E. Unexpected high plasma cobalamin: proposal for a diagnostic strategy. Clin Chem Lab Med. 2013;51(3):489–96. https://doi.org/10.1515/cclm-2012-0545.

55. Arendt JF, Pedersen L, Nexo E, et al. Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study. J Natl Cancer Inst. 2013;105(23):1799–805. https://doi.org/10.1093/jnci/djt315.

56. Stabler SP. Vitamin B12 deficiency. N Engl J Med. 2013;368(21):2041–2. https://doi.org/10.1056/NEJMc1304350.

57. Flanchbaum L, Belsky S, Drake V, et al. Preoperative nutritional status of patients undergoing Roux-en-Y gastric bypass for morbid obesity. J Gastrointest Surg. 2006;10(7):1033–7. https://doi.org/10.1016/j.gassur.2006.03.004.

58. Mehaffey JH, Mehaffey RL, Mullen MG, et al. Nutrient deficiency 10 years following Roux-en-Y gastric bypass: who’s responsible? Obes Surg. 2017;27(5):1131–6. https://doi.org/10.1007/s11695-016-2364-0.

59. Skroubis G, Sakellaropoulos G, Pougouras K, et al. Comparison of nutritional deficiencies after Roux-en-Y gastric bypass and after biliopancreatic diversion with Roux-en-Y gastric bypass. Obes Surg. 2002;12(4):551–8. https://doi.org/10.1381/096089202762252334.
involving 37 485 individuals. Arch Intern Med. 2010;170(18): 1622–31. https://doi.org/10.1001/archinternmed.2010.348.

79. Xanthokos SA. Nutritional deficiencies in obesity and after bariatric surgery. Pediatr Clin N Am. 2009;56(5):1105–21. https://doi.org/10.1016/j.pcl.2009.07.002.

80. de Luis DA, Pacheco D, Izaola O, et al. Clinical results and nutritional consequences of bilipancreatic diversion: three years of follow-up. Ann Nutr Metab. 2008;53(3–4):234–9. Epub 2008/12/16. https://doi.org/10.1159/000185641.

81. Mallory GN, Macgregor AM. Folate status following gastric by-pass surgery (the great Folate mystery). Obes Surg. 1991;1(1):69–72. https://doi.org/10.1007/BF00382917.

82. Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. Nutrition. 2009;25(11–12):1150–6. Epub 2009/05/31. https://doi.org/10.1016/j.nut.2009.03.012.

83. Bal BS, Finelli FC, Shope TR, et al. Nutritional deficiencies after bariatric surgery. Nat Rev Endocrinol. 2012;8(9):544–56. Epub 2012/04/24. https://doi.org/10.1038/nrendo.2012.48.

84. Gudzune KA, Huizenga MM, Chang HY, et al. Screening and diagnosis of micronutrient deficiencies before and after bariatric surgery. Obes Surg. 2013;23(10):1581–9. https://doi.org/10.1007/s11695-013-0919-x.

85. Wilcken B, Bamforth F, Li Z, et al. Geographical and ethnic variation of the 677C>T allele of the 10 methyltetrahydrofolate reductase (MTHFR): findings from over 7000 newborns from 16 areas worldwide. J Med Genet. 2003;40(8):619–25. https://doi.org/10.1136/jmg.40.8.619.

86. Hiraoka M, Kagawa Y. Genetic polymorphisms and folate status. Congenit Anom (Kyoto). 2017;57(5):142–9. Epub 2017/07/20. https://doi.org/10.1111/ benefits of lifestyle interventions. Eur J Clin Nutr. 2009;63(8):892–9. https://doi.org/10.1111/j.1365-2699.2008.02770.x.
Barres R, Kirchner H, Rasmussen M, et al. Weight loss after
Donkin I, Versteyhe S, Ingerslev LR, et al. Obesity and bariatric
Qin X, Li J, Cui Y, et al. MTHFR C677T and MTR A2756G
Athiyarath R, Shaktivel K, Abraham V, et al. Association of genetic
Ashfield-Watt PA, Pullin CH, Whiting JM, et al. Methionylthreonofolate reductase 677C–>T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: a randomized controlled trial. Am J Clin Nutr. 2002;76(1):180–6. https://doi.org/10.1093/ajcn/76.1.180.
Al-Daghri NM, Mohammed AK, Bukhari I, et al. Efficacy of vitamin D supplementation according to vitamin D-binding protein polymorphisms. Nutrition. 2019;63–64:148–54. https://doi.org/10.1016/j.nut.2019.02.003. 2
Qin X, Li J, Cui Y, et al. MTHFR C677T and MTR A2756G polymorphisms and the homocysteine lowering efficacy of different doses of folic acid in hypertensive Chinese adults. Nutr J. 2012;11(2) https://doi.org/10.1186/1475-2891-11-2. 12
Ashfield-Watt PA, Pullin CH, Whiting JM, et al. Methylenetetrahydrofolate reductase 677C–>T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: a randomized controlled trial. Am J Clin Nutr. 2002;76(1):180–6. https://doi.org/10.1093/ajcn/76.1.180. 12
Lea R, Colson N, Quinlan S, et al. The effects of vitamin supplementation and MTHFR C677T genotype on homocysteine-lowering and migraine disability. Pharmacogenet Genomics. 2009;19(6):422–8. https://doi.org/10.1097/FCG.0b013e3282a5d93.
Ahiyarath R, Shaktivel K, Abraham V, et al. Association of genetic variants with response to iron supplements in pregnancy. Genes Nutr. 2015;10(4):474. https://doi.org/10.1007/s11695-015-0474-2.
Capra AF, Ferro E, Cannavò L, et al. A child with severe iron-deficiency anaemia and a complex TMRPS6 genotype. Hematology. 2017;22(9):559–64. https://doi.org/10.1080/10245332.2017.1317990.
Donkín I, Versteyhe S, Ingerslev LR, et al. Obesity and bariatric surgery drive epigenetic variation of spermatozoa in humans. Cell Metab. 2016;23(2):369–78. Epub 2015/12/06. https://doi.org/10.1016/j.cmet.2015.11.004. 24
Barres R, Kirchner H, Rasmussen M, et al. Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. Cell Rep. 2013;3(4):1020–7. Epub 2013/04/11. https://doi.org/10.1016/j.celrep.2013.03.018.
Pintel MAS, Nornoha NY, Nicoletti CF, et al. Changes in global transcriptional profiling of women following obesity surgery by-pass. Obes Surg. 2018;28(1):176–86. https://doi.org/10.1007/s11695-017-2828-x. 27
Sala P, Belarmino G, Torrinhas RS, et al. Gastrointestinal transcriptomic response of metabolic vitamin B12 pathways in Roux-en-Y gastric bypass. Clin Transl Gastroenterol. 2017;8(1):e212. https://doi.org/10.1038/cg.2016.67.