Folate and Migraines

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Migraines are a common disease with limited treatment options and some dietary factors are recognized to trigger headaches. Although migraine pathogenesis is not completely known, aberrant DNA methylation has been reported to be associated with its occurrence. Folate, an essential micronutrient involved in one-carbon metabolism and DNA methylation, was shown to have beneficial effects on migraines.

epigenetic diet DNA methylation folate migraine valproic acid

1. Introduction

The role of diet in the prevention and treatment of human disorders is still controversial, but many dietary compounds that can contribute to disease pathogenesis have been identified [1]. It is estimated that most human cancers in the USA are caused by external factors and diet (excluding alcohol and food additives) is the main causal external factor responsible for about 35% of cancer-related deaths [2]. Some “familial cancers” are, in fact, not attributed to the same genetic constitution of family members, but rather their similar dietary habits. Therefore, diet should be considered as a possible factor or confounder in the pathogenesis of many diseases. This raises the question of whether diet modification can be important in the prevention and therapy of diseases, not only by the avoidance of dietary elements with recognized detrimental roles in pathophysiology (e.g., an elimination diet), but also by the addition of compounds with specific mechanisms of action.

Headache disorders including migraines, seem to be especially prone to diet as it is generally believed that some dietary ingredients and additives may trigger headache attacks [3][4]. Therefore, using an elimination diet to avoid a migraine trigger may be effective in migraine prevention, but few rigorous studies on the role of diet in headache prevention have been performed and most of them lack appropriate controls (reviewed in [5]). On the other hand, a more comprehensive diet containing specific ingredients can prevent headaches, but this is even more controversial and less studied than the elimination diet (reviewed in [6]).

Many kinds of diet are recommended to reduce risk and attenuate the detrimental syndromes of many diseases. Some diets target specific organs and some address mental and physical well-being [7]. A Mediterranean-style diet and ketogenic diet are some of the most common diets recommended to be beneficial for many human disorders [8][9][10]. However, there are no solid reports on the effect of the Mediterranean diet on migraines, but the ketogenic diet as well as high folate, low fat, modified Atkins, and high omega-3/low omega-6 diets have been reported to have some beneficial effects in the prevention of headaches including those occurring from migraines (reviewed in [6]).

Apart from diets composed of specific food or avoiding specific ingredients, diets targeting specific cellular structures and macromolecules such as mitochondria or DNA have been proposed [11][12]. The epigenetic diet, a term introduced by Hardy and Tollefsbol in 2011, is intended to target the cellular epigenetic profile and specifically mediate its changes induced by environmental factors [13]. The epigenetic diet is mainly considered in cancer prevention [14][15]. However, its rationale is based on the assumptions that diet can modify the cellular epigenetic profile and that changes in the epigenetic profile are important in cancer transformation. Both assumptions are true, but this does not necessarily mean that it is possible to compose a balanced diet specifically addressing a cancer-related, epigenetically aberrant element. Nutrition can change one's epigenetic profile, but how to specifically regulate one's profile with this diet is still open as it is also an important question for epigenetic drugs [16].

2. Epigenetic Regulation of Gene Expression

The Human Genome Project has provided information on the sequence of our genome and mapped most of our genes, but now in the post-genomic era, studies aim to understand how information contained in the gene sequence is turned into a phenotype. As all our nucleated cells contain essentially the same DNA, the control of its expression in different tissues is critical for the development and functioning of our body, and deviation from it may result in disorders including serious diseases. Maintaining cellular identity and function is mostly executed by epigenetic mechanisms that include covalent modifications of genes and associated proteins and do not include changes in DNA sequences. These modifications include DNA methylation/demethylation, post-translational histone modifications, and changes mediated by non-coding RNAs (ncRNAs). The epigenome can be understood as the complement of chemical compounds that modify the expression and function of the genome [17] This complement is referred to as the cellular epigenetic profile and its changes can be considered as epimutations.

3. Migraine and Diet

Migraines are a common (2013 estimated global prevalence 14.7%) brain disorder with severe headaches and associated neurological and systemic symptoms [18]. Based on the frequency of occurrence, the International Headache Society classifies migraines as episodic or chronic migraines. Migraines may occur in two main clinical subtypes: migraine with aura (MA) and without aura (MO). A migraine aura may precede a headache attack, occur during the attack, or appear without a headache [19].

The aura may include several visual and mental syndromes and is believed to relate to cortical spreading depression (CSD), an important effect in migraine. However, the exact mechanism whereby CSD is initiated is not exactly known, nor is it known how CSD initiates the subsequent phases of migraine. Some possible mechanisms including the activation of the trigeminal nerve and the induction of neurogenic inflammation are presented in Figure 1 [20]. A trigger may be an environmental or lifestyle factor such as stress, a light flash, physical effort, noise, sleep disturbance, or diet [21].

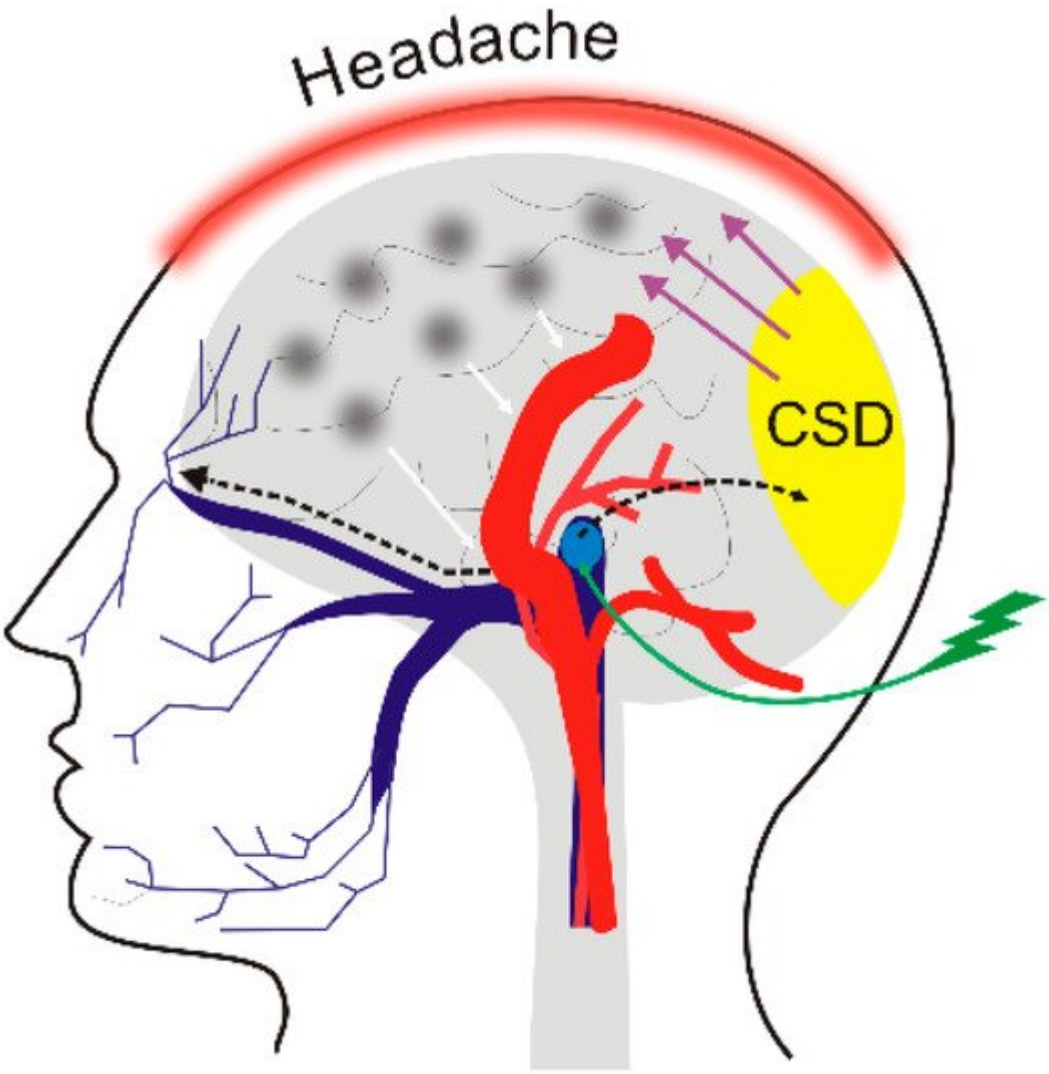

Figure 1. A putative mechanism for migraine headaches induced by a trigger. A migraine trigger (green thunder) affects the nucleus (light blue oval) of the trigeminal nerve (dark blue) and activates it. This results in waves of depolarization (black broken arrows) moving along the nerve and reaching the cortex and evoking cortical spreading depression (CSD). This results in neurogenic inflammation (black clouds) and release of inflammatory neurotransmitters (white arrows), which induce dilation of the brain blood vessels (red), which causes the release of pain-producing prostaglandins that in turn evoke a migraine headache. The specific order of events presented here is hypothetical and requires validation.

Although the prevention and treatment of migraines remain challenging [22], migraine drugs approved by the FDA have lately produced hope for a breakthrough [23] These drugs include erenumab (Aimovig), fremanezumab (Ajovy), and galcanezumab (Emgality), which are all monoclonal antibodies and GRPC antagonists. It is too early to draw a definite conclusion on the general role these drugs may play in migraine treatment, but the first observations are prospective, despite the relatively high cost of therapy with these drugs, estimated at about $575 per month [24].

The pathogenesis of migraine is largely unknown, but both genetic and environmental factors may be involved. These factors can modulate the threshold for a migraine trigger that precedes and evokes a migraine attack [25]. Many potential migraine triggers have been identified and a substantial fraction of them is associated with food (Figure 2). Female sex hormones, the menstrual cycle, and pregnancy modulate migraine attacks, so they may contribute to the approximately three times higher prevalence of migraines in women than in men [26]. This relationship may also be underlined by the X-linked form of this disease or the mitochondrial transmission of its other form or both [27].

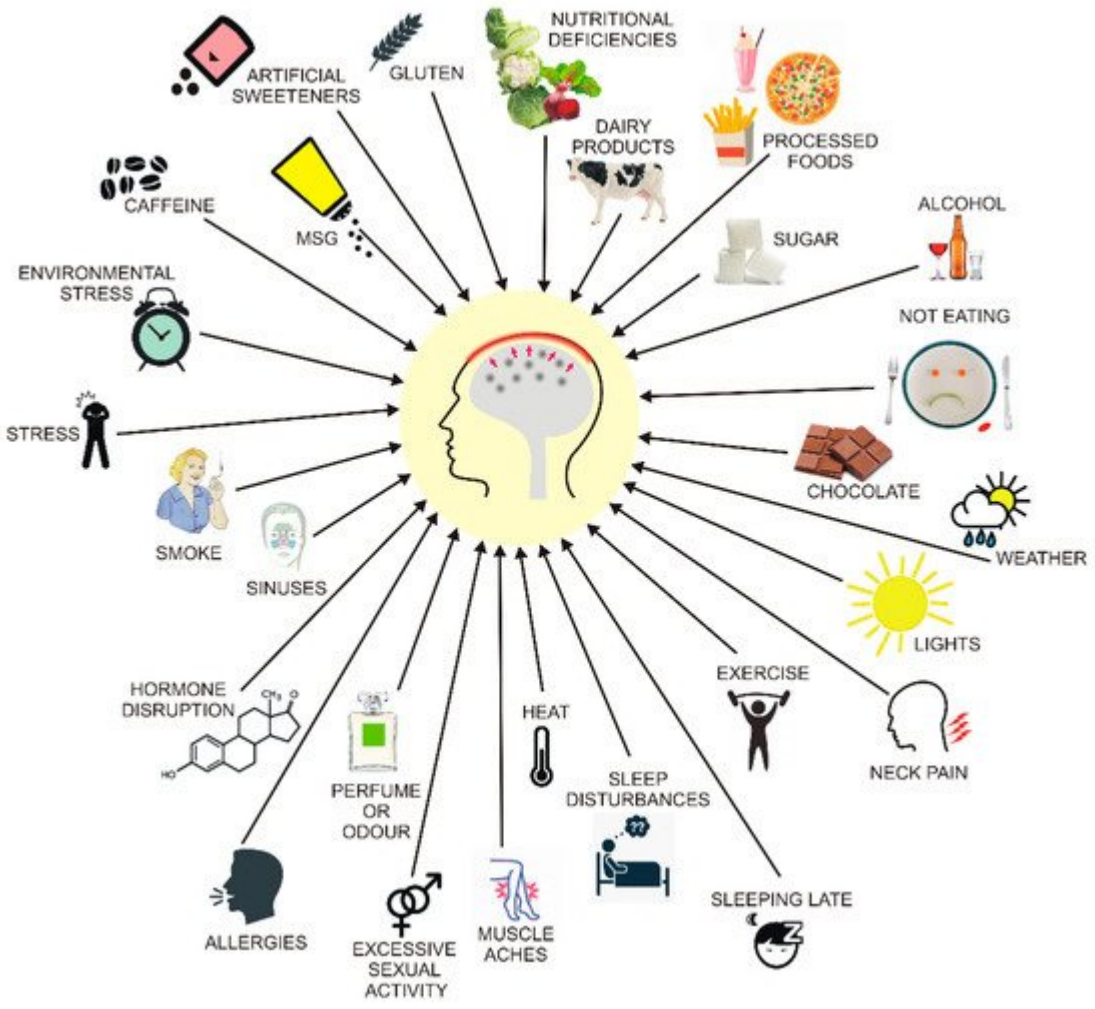

Figure 2. Main migraine triggers. Some are well established and confirmed by reports on large cohorts, but others are problematic and require further research. Recent research suggests that some food triggers are actually food cravings experienced as the first phase of migraine before pain onset. Their action and threshold can be modulated by several environmental and genetic factors that act synergistically.

The genetic basis of migraine is supported by the association of migraine with mutations in a single gene (monogenic migraine) or clusters of genes (polygenic migraine) (reviewed in [28]). Mutations in the three ion channels genes, *CACNA1A* (calcium voltage-gated channel subunit alpha 1 A), *ATP1A2* (ATPase Na^+/K^+ transporting subunit alpha 2), and *SCN1A* (sodium voltage-gated channel alpha subunit 1) were identified as specifically causal for hemiplegic migraines, a rare variant of MA, and genome-wide association studies have

identified 38 loci associated with increased risk of migraines [29]. Many other genes are candidates of importance in migraine pathogenesis, but a substantial majority of them have not been convincingly replicated [30]. However, these are not genes themselves, but their expression directly determines the migraine's phenotype. As mentioned, the cellular epigenetic profile is an important element of the regulation of gene expression. Epigenetics is also a significant element of pathogenesis in many human diseases including behavioral and brain disorders [31]. Several chemicals targeting the epigenome have been accepted as drugs or are under clinical trials [32]. Valproic acid (VPA), a histone modifier, has been applied for more than 50 years in epilepsy treatment and is currently used in the therapy of bipolar disease and the prophylaxis of migraines [33][34]. The role of epigenetic modifications in migraine is not completely known, but epigenetics is considered to be a promising avenue in the prophylactic treatment of this disease [35].

The cellular epigenetic profile is more prone to nutritional modifications than corresponding DNA sequence [36]. Therefore, epigenetically active nutrients can affect the pathogenesis of human disorders and nutriepigenomics is also a promising avenue in the prevention and therapy of human complex diseases [1]. This issue seems to be especially important in migraines, as it is frequently related to improper diet, and the avoidance of certain nutrients in the diet is an important element of its prophylaxis and often results in a decreased severity of headaches [37]. Much less is known about the prevention of migraine and the attenuation of its symptoms via the active supplementation of the diet. The ketogenic diet is considered to be a rapid onset effective prophylaxis for episodic and chronic migraines, and ketosis was recently suggested to regulate cellular functions through interactions with the epigenome, but our knowledge of the mechanisms of this interaction is far from complete [38][39]. However, a ketogenic diet is not the only diet that may affect the epigenome as many compounds not included in such a diet are reported to do so [13].

In a large (8042 men and 23,728 women) cross-sectional study on subjects from a population-based NutriNet-Santé e-cohort, Andreeva et al. observed migraine occurrence in 9.2% of men and 25% of women [40]. They also observed lower protein and higher fat consumption in male migraineurs than in males without headaches and those with non-migraine headaches and higher fat and carbohydrate intake in female migraineurs than females without headaches and those with non-migraine headaches. These results indicate a gender-specific difference in the consumption of macronutrients among migraineurs. However, whether this difference contributes to different prevalence of migraine between men and women should be confirmed by further research, as the differences observed in these large cross-sectional studies were not very pronounced. These and other studies show that nutrition may be important in migraine pathogenesis, and this problem should be considered along with other genetic and environmental migraine-related factors. Further details on the role of diet in migraine pathogenesis are provided in the next sections.

In summary, the use of the term "epigenetic diet" is, at present, not fully justified and should not be understood in a similar way to other relatively well established kinds of diets including the Mediterranean diet or ketogenic diet.

4. DNA Methylation in Migraine

A migraine trigger must reach a threshold to induce headaches and this threshold may be lowered by frequent headache attacks through epigenetic mechanisms [35]. Several genes have been reported to change their methylation profile with migraine occurrence or progression, and some of them were previously associated with migraine pathogenesis (**Table 1**).

Table 1. Genes whose methylation can be associated with migraine occurrence.

	Full Name	Reference
SH2D5	SH2 domain containing 5	[41]
COMT *	catechol-O-methyltransferase	[42]
ZNF234	zinc finger protein 234	[42]
SOCS1	suppressor of cytokine signaling 1	[42]
SLC2A9, SLC38A4, SLC6A5	solute carrier family 2,38A,6A member 9,4,5	[43]
DGKG	diacylglycerol kinase gamma	[43]
KIF26A	kinesin family member 26A	[43]
DOCK6	dedicator of cytokinesis 6	[43]
CFD	complement factor D	[43]
RAMP1 *	receptor activity modifying protein 1	[44]
CGRP *	calcitonin gene related peptide	[45]
CRCP *[1)]	CGRP receptor component	[45]

	Full Name	Reference
CALCRL *[1)]	calcitonin receptor like receptor	[45]
ESR1 *[1)]	estrogen receptor 1	[45]
NOS3 *[1)]	nitric oxide synthase 3	[45]

[1)]

5. Folate and Its Role in DNA Methylation and Migraine Pathogenesis

Folate (folacin, vitamin B9) is one of the B vitamins and an essential micronutrient that plays a critical role in one-carbon cellular metabolism [46][47]. Humans, as mammals, cannot synthesize folate and must intake it with food either as a component of a natural diet, or as a fortified food or diet supplement. Folate supplementation, recommended in many countries, can come in the form of folic acid, folinic acid, or 5-methyltetrahydrofolate (5-MTHF). 5-MTHF occurs naturally and has some advantage over synthetic forms of folate including its higher bioavailability [48]. Folate is essential for many cellular effects such as nucleoside synthesis and the methylation of biomolecules including DNA (**Figure 3**).

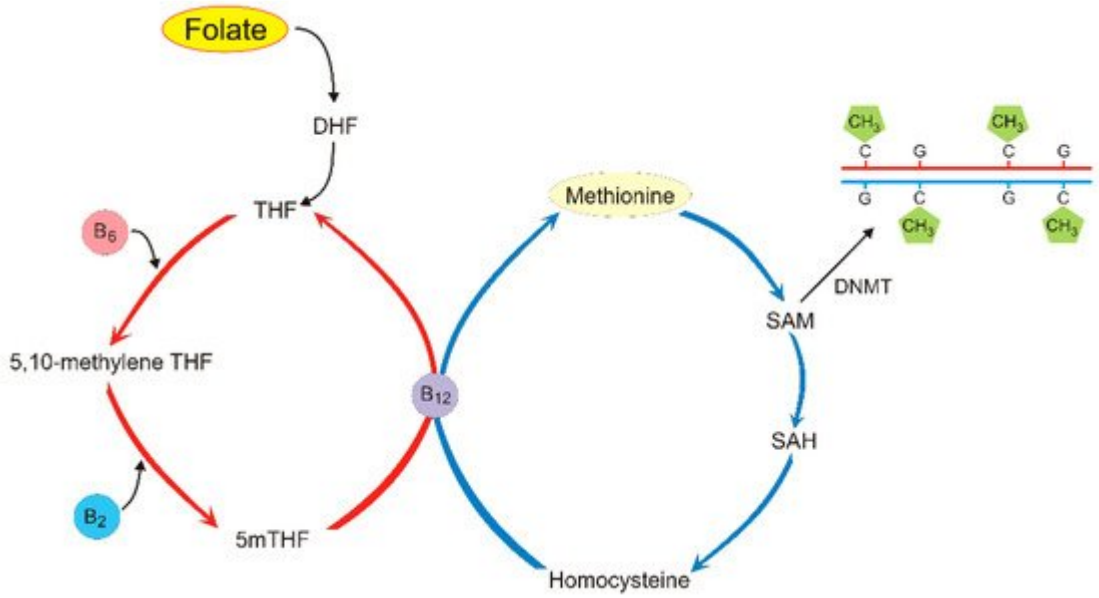

Figure 3. DNA methylation in one-carbon metabolism centered around the folate (**left**) and methionine (**right**) cycles. Folate is reduced to dihydrofolate (DHF) and tetrahydrofolate (THF). THF is changed into 5,10-methylene THF with the possible involvement of vitamin B6; 5,10-methylene THF is converted to 5mTHF, which is demethylated to complete the folate cycle. Vitamin B2 can also be involved in these steps. Carbon from the 5mTHF demethylation enters the methionine cycle through the methylation of homocysteine to produce methionine

by methionine synthase with vitamin B12 as a cofactor. Methionine may generate S-adenosyl-methionine (SAM), which provides methyl groups for DNA methyltransferases (DNMTs) that methylate DNA. SAM is then demethylated to S-adenosylhomocysteine (SAH), which is converted back to homocysteine.

Dietary folate is metabolized to 5-methyltetrahydrofolate (5mTHF, monoglutamyl form) by methylenetetrahydrofolate reductase (MTHFR). This reaction is important for the remethylation of homocysteine to methionine, which is a substrate for SAM, providing methyl groups for DNA methyltransferases to methylate DNA [49]. Several other dietary nutrients are required to maintain the one-carbon flux needed for DNA methylation including vitamins B2, B6, and B12, riboflavin, and choline (**Figure 3**) [50].

Low folate status is associated with an increased risk of several disorders including cardiovascular diseases (CVD) and cancer, but the mechanisms underlying these associations are not exactly known, and several pathways may be involved [51][52]. However, the results of some folate intervention trials suggest that excessively high folate supplementation may be detrimental for a person with an elevated risk of cancer and CVD (reviewed in [53]). That review summarized studies with the supplementation of both folate and folic acid, which were not adequate due to inter-individual variability in the activity of the 5,10-methylene THF reductase. Therefore, the dose-effect relationship for folate in CVD may be nonlinear.

Folate deficiency could be also involved in disorders of the nervous system [54][55]. Folate is an important factor in the functioning of the blood–brain barrier and brain development [56]. Variability of the *MTHFR* gene could result in phenotypic differences: the T allele of the 677C > T polymorphism of this gene is associated with elevated levels of plasma homocysteine [57]. An excess of homocysteine can be detrimental for vessels and result in endothelial cell injury and changes in blood properties that can be important in CVD and migraine pathogenesis [58][59].

Novel epigenomic loci associated with dietary folate and vitamin B12 intake were identified in a large-scale epigenome-wide association study on 5841 individuals [60]. These studies identified significant differentially methylated positions (DMPs) and regions (DMRs) in the genome, and a pathway analysis was performed on DMR annotated genes. Vitamin B12 intake was associated with 29 DMRs annotated with 48 genes. Folate intake was negatively associated with six DMPs annotated with five genes involved in cellular processes including centrosome localization, cell proliferation, and tumorigenesis. In these studies, vitamin intake was assessed on the basis of a questionnaire.

That work can be considered in the context of the study by Illingworth et al., which assayed 1.9 million CpG islands in each of the 43 brain samples and showed over 16,000 DMRs [61]. These authors concluded that except for the cerebellum, patterns of DNA methylation in different brain regions were more similar than the patterns for those regions in different individuals. Therefore, human brain methylome is primarily determined by DNA sequence and not developmental status. Although it is assumed and supported by many studies that the DNA methylation pattern is stable and retains in isolated genomic DNA, it is not completely known as to which changes in the epigenome are associated with death.

The 677C > T polymorphism of the *MTHFR* gene is likely the most frequently addressed genetic aspect of migraine pathophysiology, but the results obtained so far are not conclusive [62]. This polymorphism is claimed to be both an independent and combined marker for migraines, especially MA. Several meta-analyses addressing this polymorphism in migraines have been performed. Liu et al. concluded that the 677T allele was associated with an increased risk of total migraine and MA in Asians [63]. Similar results were obtained in other analyses with the general conclusions supporting the use of folate in migraine patients, especially those with auras, but further replication studies are needed, particularly large randomized clinical trials [62].

Menon et al. observed an inverted relationship between folic acid consumption and migraine frequency in 141 females [64]. This relationship was modulated by the 677C > T polymorphism of the *MTHFR* gene. Similar effects were noted in children with migraines and hyperhomocysteinemia [65]. Vitamin supplementation including 2 mg/day of folic acid reduced the prevalence of MA disability from 60% to 30% after six months [66]. A randomized, double-bind, placebo-controlled study (n = 95) showed that folic acid at 5 mg and vitamin B6 at 80 mg decreased headache frequency and headache severity [67].

A case-control study performed on 124 migraine patients and 130 non-migraine subjects revealed a lower level of dietary folate intake in migraineurs [68].

No association was found between the 134R > K and 653R > Q polymorphisms of the *MTHFD1* (methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1) gene, whose product is important in folate metabolism and migraine occurrence in 162 MO and 358 MA Australian patients [69]. Moreover, these two polymorphisms did not change the increased migraine risk associated with the 677T allele of the *MTHFR* gene.

Although the exact mechanism connecting the 677C > T polymorphism of the *MTHFR* gene with migraine pathophysiology is not completely known, some pathways can be considered. The C→T transition at 677 leads to the substitution of alanine to valine, thereby resulting in reduced activity of the MTHFR enzyme compared to its wild-type counterpart [70]. Consequently, individuals homozygous for the T variant have higher homocysteine levels than the C homozygotes [71]. As stated previously, an excess of homocysteine can be destructive for vessels and play a role in migraine pathogenesis, especially in migraine with an aura [72]. However, the direct link between homocysteine level and migraines is still a matter of debate, especially since only one study so far has evaluated the level of homocysteine in the cerebral fluid of migraineurs [73]. Nevertheless, elevated homocysteine may cause injury to endothelial cells, reduced flexibility of the vessels, and changes in hemostasis, which may contribute to headaches and the many associated effects and even vascular comorbidity of migraines, especially MA [74]. Homocysteine and its related compounds may act as excitatory agonists of the NMDA (*N*-methyl-d-aspartate) subtype of glutamate receptors, which are important for CSD [75][76]. Other potential aspects of the significance of the 677T > C polymorphism in the *MTHFR* gene such as its association with calcitonin gene related peptide or migraine triggers have not been investigated so far and require further research. Several cross-sectional, prospective, or interventional studies suggest that elevated plasma levels of homocysteine are associated with an increased risk of migraines (reviewed in [77]). The production of homocysteine requires folate and vitamins B6 and

B12 whose deficiency results in DNA hypomethylation, which was hypothesized to trigger migraine resulting from an interplay with MTHFR and variants of estrogen receptor 1 [78].

In summary, folate is essential for DNA methylation and its presence in the diet was reported to exert a beneficial effect on migraines. However, these profitable effects of dietary folate have not been attributed to changes in DNA methylation or other alterations in the epigenetic profile.

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