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Review Article

Migraine with Aura and Its Association with MTHFR Gene Mutations

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Abstract

Migraine with aura (MA) affects one-third of people who suffer from it and is characterized by the presence of transient neurological symptoms, such as visual, sensory, or language disturbances, that precede or accompany the headache. Various studies have highlighted the relationship between migraine with aura and mutations in the MTHFR gene, which encodes the enzyme methylenetetrahydrofolate reductase, responsible for folate metabolism and the regulation of homocysteine levels. Two main mutations, C677T and A1298C, have been implicated in the risk of developing migraine with aura. The C677T mutation in the MTHFR gene can reduce enzymatic activity by up to 30% in homozygous individuals, which increases homocysteine levels, especially in those with low folate intake. Elevated homocysteine has been associated with endothelial dysfunction and inflammatory processes, both factors involved in the pathophysiology of migraine. Additionally, the A1298C mutation has also been linked to a decrease in enzymatic activity, although its impact on homocysteine levels is less significant. Genetic studies have linked these mutations to a higher susceptibility to migraine with aura. For instance, individuals with the TT genotype of the C677T mutation have a significantly higher risk of suffering from MA compared to those without the mutation. This review article discusses the pathophysiological implications of these mutations, the relationship between hyperhomocysteinemia and migraine with aura, and the possible underlying mechanisms, including oxidative stress and mitochondrial dysfunction, which may contribute to the development and severity of migraine with aura.

***Keywords:** Migraine with aura, MTHFR, Hyperhomocysteinemia, C677T mutation, Oxidative stress.*

Introduction

Migraine affects more than one billion people worldwide, with one-third experiencing migraine with aura (MA). The most common manifestation of aura is visual, reported by over 90% of patients. Somatosensory aura, characterized by sensations such as paresthesia, occurs in only 30% of cases, while other, less frequent manifestations include speech disturbances, motor involvement, and other neurological symptoms. ,[1].

Among the causes associated with this type of migraine are the C677T and A1298C mutations in the gene that encodes the enzyme methylenetetrahydrofolate reductase (MTHFR). ,[2]. This enzyme is involved in folate metabolism and the regulation of homocysteine levels. These mutations are not only significant in the context of migraine but also in other neurological and vascular conditions.

1. Definition and Classification of Migraine

1.1 Definition of Migraine

Migraine is defined as a frequent and debilitating primary headache. It is classified into two main types:

Migraine without aura, characterized by recurrent episodes of moderate to severe headache, typically unilateral and pulsating in nature, lasting from 4 to 72 hours. Clinically, migraine without aura is associated with at least two of the following criteria: unilateral headache, pulsating pain, aggravation by routine physical activity or inability to perform such activity, and moderate to severe intensity. Additionally, it must be accompanied by at least one of the following symptoms: nausea, vomiting, photophobia, or phonophobia.

Migraine with aura includes transient focal neurological symptoms that precede or accompany the headache. Some patients experience prodromal (before the headache) and resolution (after the headache) phases, which may include symptoms such as hyperactivity, depression, food cravings, and neck pain. If a patient meets the criteria for more than one type of migraine, all present types should be diagnosed and classified. However, if chronic migraine is diagnosed, which includes episodes of all subtypes, it is not necessary to classify the episodic subtypes separately.

To establish the diagnosis of migraine with aura, a detailed description of the symptoms is essential, and a series of specific diagnostic criteria must be met. The characteristics of these episodes include recurrent episodes lasting several minutes, featuring visual, sensory, or central nervous system symptoms that are unilateral and completely reversible. These symptoms typically develop gradually and precede the headache [3].

***Diagnostic criteria**:*

A. At least five attacks fulfilling criteria B and C.

B. One or more of the following fully reversible aura symptoms:

1. Visual
2. Sensory
3. Speech or language
4. Motor
5. Brainstem
6. Retinal

C. At least three of the following six characteristics:

7. Gradual spread of at least one aura symptom over ≥5 minutes
8. Two or more aura symptoms occur in succession
9. Each aura symptom lasts 5-60 minutes
10. At least one aura symptom is unilateral
11. At least one aura symptom is positive
12. The aura is accompanied by, or followed within 60 minutes by, a headache

D. Not attributable to another ICHD-III diagnosis [4].

This article describes the relationship between MTHFR mutations and MA, as well as their involvement in migraine pathophysiology, the prevalence of these mutations in patients with migraine, and the therapeutic implications derived from their identification.

1.2 Epidemiological Data

A study conducted by Burch et al. observed that the prevalence of migraines and severe headaches in the adult population of the U.S. is high, affecting 1 in 6 people and 1 in 5 women over a three-month period. Overall, the prevalence is 15.3%, being higher in women (20.7%) than in men (9.7%). This prevalence has remained stable for 19 years. In 2015, Native Americans or Alaska Natives had the highest prevalence (18.4%), while Asians had the lowest (11.3%). Incidence is higher in individuals aged 18 to 44 years (17.9%), the unemployed (21.4%), those with family incomes below $35,000 (19.9%), and elderly or disabled individuals (16.4%). Headaches are one of the leading causes of emergency department visits, accounting for 3% of the total, and are the third leading cause in women of reproductive age [5].

The 2019 Global Burden of Disease Study analyzed the prevalence, incidence, and years lived with disability (YLD) due to migraine in 204 countries from 1990 to 2019. In 2019, the age-standardized global prevalence was 14,107 per 100,000 people, with an annual incidence of 1,143 per 100,000. The burden of migraine, measured in YLD, slightly increased since 1990. Belgium, Italy, and Germany had the highest prevalence rates [6].

2. Migraine Pathophysiology

Cortical spreading depression and the activation of the trigeminovascular system is a phenomenon that involves the depolarization of neurons and glial cells. This process spreads across the cerebral cortex, activating the trigeminal nerve and triggering migraine aura. It increases the permeability of the blood-brain barrier, promoting meningeal inflammation. Additionally, pro-inflammatory mediators are activated, intensifying the pain. [7].

This cortical spreading depression causes the opening of pannexin-1 megachannels, which leads to the activation of caspase-1 [8]. Triggering the release of pro-inflammatory mediators, the activation of nuclear factor kappa-B in astrocytes [9], and the transduction of inflammatory signals to the trigeminal nerve fibers surrounding pial vessels [10].

Meningeal vasodilation and inflammation are caused by the activation of vascular networks, resulting in headache, along with the sensitization of both afferent and efferent neurons of the trigeminovascular system, responsible for pain perception.

Additionally, neurotransmitters like serotonin play a crucial role in headache pathophysiology, as serotonin has both inhibitory and excitatory actions through its receptors located in the brain and vascular system. This makes it a key target for therapies aimed at modulating its effects by inducing vasoconstriction and inhibiting peptides such as substance P and CGRP [11].

2.1 Stages of Migraine with Aura

Prodromal Phase: Occurs 24-72 hours before the headache, with symptoms such as irritability, euphoria, food cravings, mood changes, fatigue, and phonophobia. These symptoms can persist, including during the headache phase [12].

Aura: Present in 25% of patients, it lasts up to 60 minutes. Up to 99% of patients with migraine with aura experience visual phenomena such as flashes of light, zigzags, colored spots, or more complex perceptions like fractured vision or Lilliputian hallucinations. Auras may also include sensory alterations, such as paresthesias, or language disturbances, such as paraphasia and aphasia. When the aura involves motor weakness, it is classified as hemiplegic migraine. The symptoms can vary in form, severity, and duration, affecting different cortical areas over the course of several minutes, showing great variability between patients and attacks [13].

Headache: Typically unilateral, pulsatile, and accompanied by nausea, vomiting, and photophobia. It can last for hours or days. According to the neurovascular theory, this pain is caused by the activation of the trigeminovascular system, which is initiated in higher centers such as the hypothalamus and thalamus. The nociceptive fibers of the trigeminal ganglion, which innervate the dura mater, become sensitized and release inflammatory mediators such as CGRP, substance P, and VIP. These signals are transmitted through the trigeminovascular pathway and reach multiple cortical areas, passing through the brainstem, hypothalamus, thalamus, and basal ganglia [14].

Postdrome: After the headache subsides, patients may feel fatigue or euphoria, and the pain can briefly reappear with sudden head movements. In the pathophysiology of the postdrome, there is a global reduction in regional cerebral blood flow, which may be caused by generalized vasoconstriction secondary to the activation of brainstem nuclei through α2-adrenergic receptors, including the locus coeruleus, or secondary to cortical spreading depression [15].

3. Migraine with Aura and the Association with Methylenetetrahydrofolate Reductase Mutations

3.1 The MTHFR Gene and Its Function

5,10-Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of folate and homocysteine (Hcy). The gene encoding this enzyme is located on the short arm of chromosome 1 (1p36.3) and produces dimeric proteins. The main product of the MTHFR gene is a 77 kDa protein, with a second isoform of 70 kDa [16].

During the transcription of the MTHFR gene, alternative splicing occurs, generating three mRNA variants (7074, 7018, and 7071 bp), which encode polypeptides of 697, 656, and 696 amino acids, respectively. MTHFR catalyzes the irreversible reduction of 5,10-MTHF to 5-methylTHF, the circulating form of folate used for the remethylation of Hcy to methionine. Methionine is then transformed into S-adenosylmethionine (SAM), an important methyl group donor for various reactions such as the methylation of histones, choline, sphingomyelin, acetylcholine, phospholipids, DNA, RNA, and other neurotransmitters. Hcy can also be converted into cysteine via transsulfuration, a process dependent on vitamin B6 [17]. Table 1.

Deficiency in 5,10-methylenetetrahydrofolate reductase (MTHFR) leads to hyperhomocysteinemia. To date, 109 mutations of MTHFR have been reported in 171 families, including 70 missense mutations, 17 splice-site mutations, 11 nonsense mutations, 7 small deletions, 2 no-stop mutations, 1 small duplication, and 1 large duplication [18].

3.2 Prevalence of MTHFR C677T/A1298C Mutations

The C677T mutation (rs1801133) is the most common mutation. In the United States, between 20% and 40% of white and Hispanic individuals are heterozygous for MTHFR C677T, while it is present in only 1% to 2% of Black individuals. In North America, Europe, and Australia, between 8% and 20% of the population has two MTHFR C677T mutations, meaning they are homozygous [19]. This mutation involves the substitution of cytosine (C) for thymine (T) at position 677 of the MTHFR gene. This causes an amino acid change from alanine to valine at position 222 of the enzyme. Individuals with this mutation may experience a significant reduction in enzymatic activity. In heterozygous individuals (CT), enzymatic activity is approximately 65% of normal, while in homozygous individuals (TT), it is approximately 30% of normal. This mutation leads to elevated blood homocysteine levels, especially in individuals with low folate intake [20].

The MTHFR A1298C polymorphism is present in 7-12% of North American, European, and Australian populations, but its prevalence is lower among Hispanics (4-5%), Chinese (1-4%), and other Asian populations (1-4%). Homozygosity for this polymorphism results in approximately 60% of normal enzyme function. [21]. This mutation involves the substitution of adenine (A) for cytosine (C) at position 1298 of the MTHFR gene, causing an amino acid change from glutamine to alanine at position 429 of the enzyme. Although this mutation also reduces enzyme activity, its impact on homocysteine levels is not as pronounced as the C677T mutation. Individuals with the A1298C mutation may experience greater symptoms when it is combined with the C677T mutation [22].

3.3 Studies on MTHFR and Migraine with Aura

Mutations in the methylenetetrahydrofolate reductase (MTHFR) gene have been linked to various neurological conditions, with a particular focus on migraines, especially migraine with aura. The C677T variant of the MTHFR gene results in the substitution of alanine (Ala) with valine (Val) at position 222. This alteration leads to a significant reduction in MTHFR enzyme activity—approximately 65% in Ala/Val heterozygotes and as low as 30% in Val/Val homozygotes. This decrease in enzymatic activity can cause a moderate increase in plasma homocysteine levels, particularly when folate intake is insufficient. The T allele of the MTHFR C677T polymorphism has been specifically associated with an increased risk of migraine, particularly with aura [23].

A study by Scher et al. compared adults with migraine with aura (MA; n = 187), without aura (MO; n = 226), and non-migraine controls (n = 1212). The findings indicated that individuals with the T/T genotype had significantly higher odds of having MA (OR: 2.05; 95% CI: 1.2-3.4; $p < 0.006$), with a trend toward increased risk as the number of T alleles increased (OR: 1.40; 95% CI: 1.1-1.8; $p < 0.007$) [24].

In a meta-analysis of 17 case-control studies, comprising 8,903 cases and 27,637 controls, the association between the MTHFR C677T polymorphism and migraine was explored. The analysis revealed that the 677T allele is associated with a higher risk of migraine with aura, particularly in individuals of Asian descent [25].

Another case-control study examined the relationship between MTHFR gene polymorphisms (C667T and A1298C) and migraine susceptibility in 100 patients (23 with MA and 77 with MO) compared to 100 healthy controls. Genotyping was performed using PCR-RFLP, and the data were analyzed with SPSS. Although there was a non-significant increase in the CT and TT genotypes for C667T among migraine patients compared to controls (52% and 10% vs. 42% and 7%; $p > 0.05$), the CC genotype in A1298C was significantly associated with a higher risk of migraine (30% vs. 17%; $p < 0.05$). Specifically, the 677CT genotype and T allele in C667T were associated with a higher susceptibility to MA ($p < 0.05$), while the CC genotype in A1298C was a risk factor for MO ($p < 0.05$) [26].

In a meta-analysis by Rubino et al., no significant difference was observed between the 2,961 migraine patients and controls. However, in the case of migraine with aura, the TT genotype was associated with a higher risk compared to the CC genotype (OR: 1.30 to 1.66). A significant difference was also noted when comparing the TT genotype with the CT + CC genotypes in this subgroup. This study suggests a specific association between the MTHFR gene and migraine with aura [27].

4. Pathophysiological Mechanisms Associated with MTHFR Mutations

4.1 Hyperhomocysteinemia and Migraine with Aura

Pathophysiology of Migraine with Aura Associated with Methylenetetrahydrofolate Reductase Mutations

Elevated levels of homocysteine can exert toxic effects on the endothelium, promoting the proliferation of vascular smooth muscle cells, increasing platelet aggregation, and disrupting both the coagulation and fibrinolysis pathways. These alterations may create or exacerbate a prothrombotic state, especially when combined with other risk factors. Additionally, excess homocysteine activates coagulation factors V, X, and XII, inhibits the activation of protein C and thrombomodulin on the cell surface, and interferes with the binding of tissue plasminogen activator to its endothelial receptor, annexin II [28].

Moreover, the accumulation of homocysteine induces a series of pathophysiological changes that may contribute to the development of migraines and other neurological disorders. It notably increases oxidative stress, leading to the accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS). ADMA impairs the activity of both endothelial (eNOS) and inducible (iNOS) NOS enzymes, disrupting nitric oxide homeostasis and potentially compromising vascular function [29].

This condition also promotes mitochondrial dysfunction, a key factor in increasing neuronal excitability, making the brain more susceptible to migraines. The energy deficits in brain mitochondria triggered by this dysfunction are likely associated with the onset of migraine episodes [30]. When combined with Cu^{2+}, which generates hydrogen peroxide, homocysteine further impacts mitochondrial RNA levels, induces morphological changes, and reduces cell growth and mitochondrial respiration. An increase in mitochondrial mass in endothelial cells has also been observed, along with enhanced expression of (Nuclear respiratory factor-1 (NRF-1) and mitochondrial transcription factor A (Tfam A), key regulators of mitochondrial biogenesis [31].

Homocysteine also induces glial and astrocytic dysfunction, which has been linked to various neuropathological events associated with its abnormal metabolism. Experimental studies have shown that cortical astrocytes exposed to homocysteine exhibit actin cytoskeleton alterations and disruption of glial fibrillary acidic protein (GFAP), resulting in morphological changes. This cytoskeletal alteration is also observed in astrocyte-like cells, such as the C6 cell line, where homocysteine induces GFAP and vimentin hypophosphorylation, suggesting cytoskeletal reorganization [32].

Another significant effect is the disruption of the blood-brain barrier (BBB) through an imbalance in the activity of matrix metalloproteinase 9 (MMP-9) and its tissue inhibitor, Tissue Inhibitor Of Metalloproteinases 4 (TIMP-4). Increased MMP-9 activity and reduced TIMP-4 facilitate BBB disruption, allowing inflammatory cells and molecules to enter the brain parenchyma, exacerbating neuroinflammation and triggering migraine attacks [33]. Additionally, homocysteine acts as an excitatory neurotransmitter, affecting gamma-aminobutyric acid receptor type A (GABA-A) and N-methyl-D-aspartate receptor (NMDA receptors), which increases vascular permeability and further contributes to BBB disruption. Cerebral endothelial cells, which also express NMDA receptors, become more susceptible to excitatory amino acids under the action of free radicals, aggravating this disruption even further [34].

Finally, homocysteine also plays a role in vasodilation and secondary metabolic changes, acting as an excitatory amino acid in the pathophysiology of migraine [35].

4.2 Conversion of Homocysteine to Methionine and S-Adenosylmethionine (SAM)

5-MTHF is necessary to convert homocysteine into methionine, a reaction catalyzed by methionine synthase, with vitamin B12 as a cofactor. Methionine is a sulfur-containing essential glucogenic amino acid that is converted into S-adenosylmethionine (SAMe) by the enzyme methionine adenosyltransferase (MAT), using ATP as a cosubstrate. The methyl group of SAMe is then transferred to a wide range of substrates, such as DNA, RNA, proteins, and phosphatidylethanolamine (PE).

These reactions are generally known as transmethylation reactions and are catalyzed by specific methyltransferases (MT). There are more than 200 SAMe-dependent proteins in the human genome. The byproduct of these reactions, S-adenosylhomocysteine (SAH), is hydrolyzed to form homocysteine and adenosine by the enzyme SAH hydrolase [36]. Figure 1. If SAM production is impaired, the ability of cells to add methyl groups to DNA is limited, which can alter gene regulation, including neuronal and vascular pathways, and potentially contribute to diseases like migraine. When methylation capacity is reduced, the following mechanisms may contribute to the development of migraines:

1. Altered neurotransmitter synthesis: Catecholamines such as dopamine, norepinephrine, and epinephrine are critical neurotransmitters that depend on SAMe for their synthesis and regulation. The enzyme phenylethanolamine N-methyltransferase (PNMT), which converts norepinephrine into epinephrine, uses SAMe as a methyl group donor. A decrease in SAMe levels affects the activity of this enzyme, reducing epinephrine levels and altering the balance of catecholamines [37].

2. Serotonin: Between migraine attacks, serotonin levels are typically low, but increase during episodes [38]. During an attack, serotonin released into the bloodstream raises brain levels, causing vasoconstriction in intracerebral arteries, triggering the aura phase and cerebral ischemia. Subsequently, serotonin levels drop, leading to extracerebral vasodilation, which causes the headache. Migraine is considered a low-serotonin syndrome, which is also seen in other conditions such as chronic tension-type headaches and depression. Tricyclic antidepressants reduce migraine attacks by increasing serotonin levels, and serotonin depletion in experiments increases trigeminovascular activity and susceptibility to cortical spreading depression (CSD) [39].

Serotonin (5-HT) is a monoamine neurotransmitter present in both the central and peripheral nervous systems, with multiple and complex biological functions depending on the type of receptor it binds to. Seven main types of 5-HT receptors have been identified (5-HT1 to 5-HT7), some with additional subtypes, such as 5-HT1A, 5-HT1B, and 5-HT1D. 5-HT1 receptors are coupled to G-proteins and, by inhibiting adenylate cyclase, reduce neurotransmitter release and neuronal activity [40].

3. Oxidative Stress: A reduced methylation capacity can lead to increased oxidative stress. Oxidative stress is a key facilitating factor in the pathogenesis of migraine, occurring when oxidant levels, such as free radicals and non-radical oxidants, exceed the body's ability to neutralize them through antioxidant defenses. Oxidants include peroxynitrite, hydroxyl radicals, and hydrogen peroxide, which can damage important biomolecules such as DNA, membrane lipids, and structural proteins. This oxidative damage can disrupt cellular functions in the brain, contributing to the onset and perpetuation of migraine attacks [41]. The main sources of oxidants in the brain that contribute to oxidative stress include:

- **Mitochondria**: where electron leakage in the respiratory chain generates superoxide anions. Mitochondrial dysfunctions, such as structural damage or the accumulation of mutations in mitochondrial DNA, increase oxidant production, which can facilitate neuronal hyperexcitability, a state associated with migraines [42].
- **NADPH oxidase (NOX)**, which produces superoxide radicals in response to threats such as bacteria or toxins. In the brain, activation of the NOX2 enzyme in neurons, astrocytes, and microglia generates an excess of oxidants, which can activate the trigeminovascular pathway, linked to the pain mechanisms in migraine [43].
- **Enzymes such as monoamine oxidase (MAO**), which metabolizes neurotransmitters like dopamine and serotonin, generate hydrogen peroxide as a byproduct. This process can increase vulnerability to oxidative stress and trigger migraine attacks in predisposed individuals [44].

4. Vascular Dysfunction: Methylation is essential for the health of the vascular endothelium. Reduced methylation may compromise endothelial function, favoring dysfunction in vasodilation and vasoconstriction in cerebral blood vessels, a central process in the pathophysiology of migraine [45].

5. Chronic Inflammation: Chronic inflammation promotes the release of proinflammatory molecules such as cytokines, chemokines, and growth factors, sensitizing nerve fibers and activating pain pathways, particularly affecting the trigeminovascular system, a key component in the development and persistence of migraine. Additionally, the release of inflammatory mediators such as substance P, CGRP (calcitonin gene-related peptide), and other prostaglandins during migraine may be exacerbated by the epigenetic dysregulation of genes that would normally restrict this response.

Under normal conditions, DNA methylation helps control the expression of genes that promote inflammation, but an alteration in this system may favor the overexpression of proinflammatory genes [46].

Figure 1

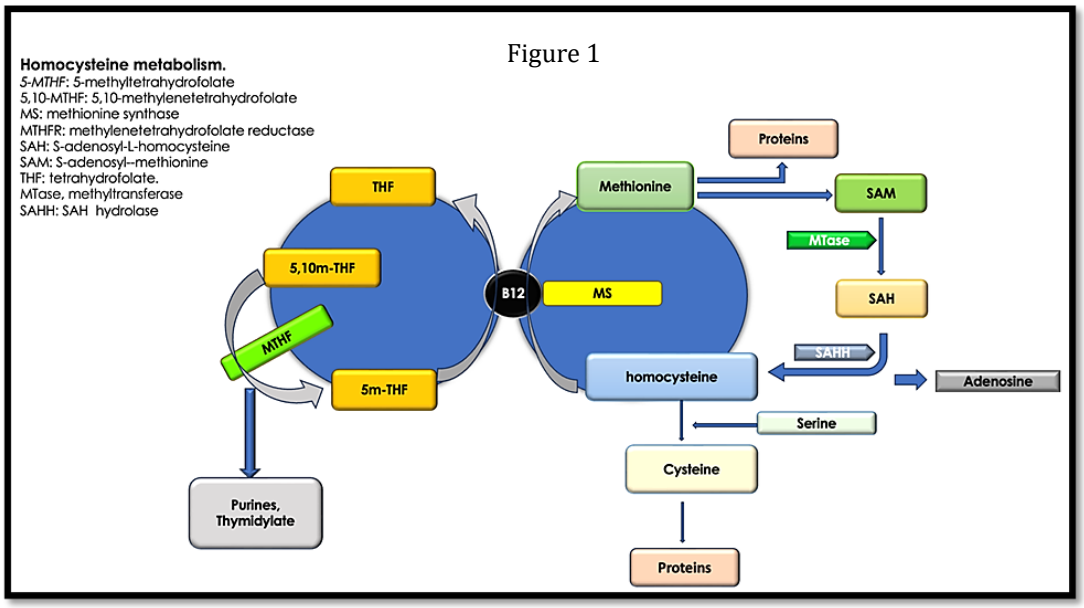

Table 1: Homocysteine and Methionine Metabolism

Element	Pathway or Process	Description	Outcome/Consequence
Homocysteine	Trans-sulfuration	Homocysteine is converted to cysteine through trans-sulfuration, which involves enzymes such as CBS (cystathionine beta-synthase) and CGL (cystathionine gamma-lyase), with vitamin B6 as a cofactor.	**Reduces homocysteine levels and forms cysteine, important for proteins** .
Homocysteine	Methylation (Remethylation)	Homocysteine can be reconverted to methionine through the addition of a methyl group, facilitated by MS (methionine synthase) and 5-MTHF (5-methyltetrahydrofolate), with vitamin B12 as a cofactor.	**Forms methionine, necessary for SAM synthesis.**
MTHFR	Folate Cycle	The MTHFR enzyme (methylenetetrahydrofolate reductase) converts 5,10-MTHF to 5-MTHF, a key step in the remethylation of homocysteine to methionine.	**Provides 5-MTHF for homocysteine remethylation.**
SAM (S-adenosylmethionine)	Methyl Donor	Methionine is converted into SAM, the main methyl donor in methylation reactions. It participates in the regulation of gene expression and other vital cellular reactions.	**Participates in methylation of DNA, RNA, proteins, and lipids.**
SAH (S-adenosylhomocysteine)	Methylation Product	After donating its methyl group, SAM is converted into SAH, which is then hydrolyzed to form homocysteine. The balance between SAM and SAH is crucial for maintaining cellular methylation homeostasis.	**Reconverts to homocysteine.**
5,10-MTHF	Part of the Folate Cycle	5,10-MTHF is converted into 5-MTHF by MTHFR. This is an active form of folate that facilitates the remethylation of homocysteine to methionine.	**Precursor to 5-MTHF.**
Methionine Cycle	Metabolic Cycle	**Involves the cyclical conversion of homocysteine into methionine, followed by SAM synthesis and SAH formation.**	**Maintains availability of methionine and SAM.**

Discussion and Conclusion

Mutations in the MTHFR gene, particularly the C677T polymorphism, have been consistently associated with an increased risk of migraine with aura, while their role in migraine without aura remains less clear. The reduction in MTHFR enzyme activity due to the C677T variant leads to elevated homocysteine levels, contributing to a pro-inflammatory and pro-thrombotic state, which may underlie the pathophysiology of migraine with aura. The T/T genotype, in particular, appears to confer a higher risk, with population-specific variations in the strength of this association. Further research is needed to better understand the differential effects of various MTHFR polymorphisms on migraine subtypes and to explore the potential for personalized interventions, such as folate supplementation, aimed at reducing homocysteine levels in genetically predisposed individuals. Given the increasing body of evidence, genetic screening for MTHFR mutations could become a valuable tool in identifying individuals at higher risk for migraine with aura, enabling more targeted prevention and treatment strategies.

Conflict of Interest

The authors declare no conflict of interest.

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