Methylenetetrahydrofolate reductase and psychiatric diseases

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Abstract
Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme for the critical process of one-carbon metabolism involving folate and homocysteine metabolism. It is known that some polymorphism of MTHFR would result in reduction of MTHFR enzyme activity as well as DNA methylation process, later shown to have significant impacts in various psychiatric diseases. However, it is unclear whether the polymorphism of MTHFR could be an independent or an add-on risk factor for specific psychiatric symptoms, such as anxiety, depression, positive, or negative symptoms of schizophrenia, or acts as risk factor for specific psychiatric disorders, such as schizophrenia, major depression, autisms, and bipolar disorders. It is also understudied on whether folate supplements could be an effective treatment for psychiatric patients with defect MTHFR activity. In this review, we not only gathered the most recent discoveries on MTHFR polymorphism and related DNA methylation in various psychiatric disorders, but also highlighted the potential relationships between MTHFR activity and implication of folate-related function in specific mental diseases.

Introduction
Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme of folate metabolism in the process of one-carbon metabolism. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and participate in folate and homocysteine conversion correlated to DNA methylation. As consequences of polymorphism of MTHFR, reduction of MTHFR enzymatic activity would cause impaired methylation as well as deficiency of folate. There are plenty of relevant studies on linkage between MTHFR and human diseases including cardiovascular diseases, tumors, neurologic diseases, and psychiatric disorders. Moreover, there are stratified factors that have been identified to be involved in the relationship between MTHFR and diseases, such as gender, age, and ethnicity. As both DNA methylation and folate are important in mental health, reduction of MTHFR activity or folate deficiency have been associated with an onset of several psychiatric diseases, schizophrenia, bipolar disorder, depression, autism, and ADHD. In this review, we specifically focus on the MTHFR polymorphism and related methylation and folate effects on psychiatric diseases as well as the possibility of relationship between clinical phenotypes of MTHFR-related diseases and effectiveness of clinical treatment in psychiatric patients.

MTHFR
MTHFR gene
In humans, the MTHFR resides on chromosome 1 location p36.3 and was originally described as containing 12 exons as shown in Fig. 1. Human MTHFR transcripts are respectively at 2.2 kb, 7.5 kb, and 9.5 kb. The cDNA of 2.2 kb-fragment sequence codes for a 656 residue and 70–77 kDa protein. The cDNA of 7.5 kb and 9.5 kb sequence code a second isoform of 77 kDa protein. Among the exons of MTHFR, the first one is noncoding. Apart from the coding region, variable 5’ and 3’ non-coding regions (UTR) were identified, resulting in transcript heterogeneity. The 5’ and 3’ termini of the MTHFR cDNA overlap with the 5’ terminus of a chloride ion.
channel gene and the 3’ terminus of an unidentified gene, respectively. The MTHFR gene has multiple promoters and several polyadenylation sites creating 3’UTR lengths of 0.2 kb ± 5.0 kb or 0.6 kb ± 4.0 kb in human12. The MTHFR gene has been identified to possess 14 common or rare single nucleotide polymorphism that are associated with enzymatic deficiency14. Among them rs1801133(C677T) and rs1801131(A1298C) are most reported that may reduce the MTHFR activity in various degrees. For C677T, the enzyme activity of heterozygous and homozygous mutant individuals are respectively 67 and 25% of the wild-type ones. And for A1298C, the enzyme activity of heterozygous and homozygous mutant individuals are respectively 83 and 61% of the wild-type subjects15, as shown in Fig. 1.

**MTHFR and its activity**

While MTHFR gene codes for different variants, the most common form of MTHFR in human is a 656 amino acids protein. Human MTHFR consists of an N-terminal catalytic domain (amino acids 1–356) which binds 5,10-methylenetetrahydrofolate (5,10-methylene THF), and a C-terminal regulatory domain (amino acids 363–656) which binds S-adenosylmethionine (AdoMet, SAM)16,17. As shown in Fig. 2, MTHFR catalyzes the physiologically irreversible reduction of 5,10-methylene THF to 5-methyltetrahydrofolate (5-methyl THF), and plays a critical role in one-carbon metabolism for the reaction of producing methyl groups to participate in epigenetic regulation18. The properties and crystal structure of MTHFR from the bacterium Thermus thermophilus HB8 have been determined19. While the regulation of MTHFR activity is closely controlled by SAM at C-terminal regulatory domain, more studies indicated that the human MTHFR enzyme activity is also regulated by multiple phosphorylated sites on a serine-rich N-terminal extension region20. The phosphorylation leads down-regulation of MTHFR activity and upregulation of allosteric inhibition by SAM. It is suggested that phosphorylation impacts on the allosteric regulation of MTHFR via altering the equilibrium of active and inactive states of the enzyme, favoring the inactive state which SAM preferentially binds21. The active form of MTHFR could impact on the generation of 5-methyl THF, which is the active form of folate in vivo. Then methionine level increases and related methyl group donation is driven which successively exert potential mechanism on psychiatric diseases, as shown in Fig. 3.

**MTHFR and DNA methylation**

Another important role of MTFHR is to participate in donating methyl group to regulate epigenetic modification in the one-carbon metabolism. Methylation is a common regulation process of gene expression that influences cellular development and function22, which is dependent on SAM as a methyl donor. SAM originated from methionine cycle in which 5-methyl THF transfers methyl groups to homocysteine in a reaction catalyzed by methionine synthase to produce methionine. In this process, 5,10-methylene THF play a critical role in methionine regeneration and methyl donation, meanwhile MTHFR catalyzes the irreversible conversion of 5,10-methylene THF to 5-methyl THF that participate in generation of SAM in methionine cycle and offer methyl group23.

**MTHFR polymorphism**

**MTHFR polymorphisms and enzymatic activity**

There are several sites of MTHFR polymorphism that have been reported including 2 enzyme activity associated locuses C677T and A1298C and 6 enzyme activity unassociated locuses6. As shown in Table 1, with regard to the
The association of MTHFR gene and its enzyme products, some of the studies revealed severe enzymatic deficiency. The encoding of MTHFR appears to be polymorphic such as the gene site C677T, one of the most studied and clinically important variant in exon 4. The C677T variant results from a single nucleotide substitution at this position, in which cytosine is replaced by thymine resulting a conversion of alanine to valine residue. The substitution lowers the affinity of MTHFR and its cofactor, which promotes the thermolability and diminishes the enzyme activity. Comparing with wild genotype (CC), the heterozygote (CT) and mutation homozygote (TT) lead to the decline of enzyme activity by about 34 and 75%, and increased thermolability in lymphocyte extracts. In 2001, the Ala222Val mutation was created in human MTHFR, and the mutant protein was successfully purified and its properties were determined. Different from the former studies, the Ala222Val variant exhibits identical catalytic properties as the wild-type enzyme, but it is thermolabile.

Another common polymorphism is A1298C, in which adenine is replaced by cytosine resulting a conversion of glutamate to alanine at 429 residue, which also diminishes the enzyme activity. Lymphocyte extracts from

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**Fig. 2 One-carbon metabolism.** MTHFR is a key enzyme to catalyze conversion of 5,10-methylene THF to 5-methyl THF and contribute to generation of SAM, which is the direct donor of methyl group. DHF, dihydrofolate acid; THF, tetrahydrofolate acid; MTHFR, methylenetetrahydrofolate reductase; dTMP, deoxymethylcytosine monophosphate; dUMP, deoxuridine monophosphate; NADPH, nicotinamide adenine dinucleotide phosphate; FAD, flavine adenine dinucleotide; Met, methionine; Hcy, homocysteine; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine

**Fig. 3 Potential mechanisms of MTHFR in psychiatric diseases.** Methyl group supply in one-carbon metabolism is affected by MTHFR enzyme catalytic process. MTHFR polymorphism affects downstream methylation of schizophrenia-related proteins. DA, glutamate and so on. BH4, tetrahydrobiopterin; DA, dopamine; NE, norepinephrine; 5-HT, 5-hydroxytryptamine
| Gene locus | Diagnosis | Subjects (F/M) | Mean age (F/M) | Genotype number | Allele number | Comments | Country | Year [Ref.] |
|------------|-----------|----------------|----------------|----------------|---------------|-----------|---------|------------|
| C677T     | SCZ       | 32.7/9.6       | CC 113, CT 68, TT 19 | C 294, T 106 | 5 and 1.7-fold times higher distribution of T allele in SCZ and BD patients, SCZ patients TT was 3.5 times higher than controls. | Poland | 2006 | 46 |
|           | BPD       | 46.0/3.5       | CC 108, CT 73, TT 19 | C 269, T 111 | TT genotype associated with an increased of schizophrenia compared to CC subjects accounted for an increased of schizophrenia | Netherland | 2005 | 45 |
| C677T     | SCZ       | 41 ± 14        | CC 111, CT 11, TT 31 | C 358, T 173 | Increased 677T allele load confers risk for negative symptoms in SCZ | USA | 2006 | 47 |
|           | SCZ       | 52 ± 11        | CC 123, CT 66, TT 36 | C 109, T 288 | TT exhibited significantly greater deficits on VFT, had more difficulty achieving the first category on the WCST and did not differ in CVLT | China | 2006 | 48 |
| C677T     | SCZ       | 43.4           | CC 97, CT 21, TT 21 | C 726, T 214 | SCZ Patients TT was 2.5 times higher than controls. | Poland | 2006 | 46 |
|           | BPD       | 48.5/10.9      | CC 97, CT 21, TT 21 | C 726, T 214 | SCZ Patients TT was 2.5 times higher than controls. | Poland | 2006 | 46 |
| C677T     | SCZ       | 37 ± 10        | CC 47, CT 12, TT 12 | C 120, T 99 | A significant association for MTHFR 677TT in the male, and 677CT genotype significantly affected age at onset of schizophrenia | Syria | 2012 | 49 |
|           | SCZ       | 50 ± 15        | CC 58, CT 19, TT 10 | C 209, T 39 | A significant association for MTHFR 677TT in the male, and 677CT genotype significantly affected age at onset of schizophrenia | China | 2013 | 50 |
| C677T     | SCZ       | 3 ± 18         | CC 147, CT 30, TT 14 | C 316, T 93 | A significant association between the MTHFR T-allele and schizophrenia risk | Japan | 2014 | 51 |
|           | SCZ       | 38.8 ± 11.6    | CC 120, CT 45, TT 35 | C 687, T 363 | MTHFR polymorphisms interacted on cognition, and the MTHFR T-allele attenuated the cognitive effects. | Greece | 2015 | 52 |
| C677T     | SCZ       | 46.5 ± 13.8    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms do not influence age of onset in schizophrenia and bipolar disorder. | East Asia & Caucasus | 2010 | 53 |
|           | SCZ       | 34.5 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms do not influence age of onset in schizophrenia and bipolar disorder. | East Asia & Caucasus | 2010 | 53 |
| C677T     | SCZ       | 37.8 ± 12.7    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms do not influence age of onset in schizophrenia and bipolar disorder. | East Asia & Caucasus | 2010 | 53 |
|           | SCZ       | 38.8 ± 11.6    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms do not influence age of onset in schizophrenia and bipolar disorder. | East Asia & Caucasus | 2010 | 53 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | Netherland | 2006 | 54 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | Egypt | 2006 | 55 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | China | 2009 | 56 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | China | 2009 | 56 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | Australia | 2013 | 57 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | Australia | 2013 | 57 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | Iran | 2012 | 58 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | Iran | 2012 | 58 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | Iran | 2012 | 58 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | Iran | 2012 | 58 |
| C677T     | SCZ       | 39.0 ± 14      | CC 334, CT 32, TT 86 | C 900, T 494 | Neither winter birth nor MTHFR were significantly associated with increased schizophrenia risk | Iran | 2012 | 58 |
|           | BPD       | 45.0 ± 11.2    | CC 45, CT 38, TT 13 | C 726, T 214 | MTHFR polymorphisms are associated with the risk of developing BD and schizophrenia and influence the age at onset of BD but not schizophrenia | Iran | 2012 | 58 |
| Gene locus | Diagnosis | Subjects (F/M) | Mean age (F/M) | Genotype number | Allele number | Comments | Country | Year [Ref.] |
|-----------|-----------|---------------|---------------|----------------|---------------|----------|---------|------------|
| Anxiety   | Cases 621(431/190) | CC 308, CT 263, TT 50 | C 879, T 363 | TT genotype was significantly related to depression without comorbid anxiety and no significant association to anxiety. | Norway | 2003 [95] |
| DD        | Cases 621(431/190) | CC 308, CT 263, TT 50 | C 879, T 363 | TT genotype displayed a 4.831-fold increased risk of moderate and severe depression. | Poland | 2013 [79] |
| DD (postmenopausal) | Cases 83 | 54.2 ± 4.7 (cases + controls) | CC 22, CT 38, TT 19 | C 90, T 76 | UK | 2011 [76] |
| ASD      | Cases 431 | CC 46, CT 36, TT 77 | C 28 ± 6.4 | a normal distribution of polymorphism in ASDs, but the frequency of T allele was more prevalent. | Romania | 2009 [80] |
| ASD      | Controls 74 | CC 13, CT 4, TT 17 | C 20, T 9 | No significant differences were found in frequency of the T allele or the MTHFR C677T TT genotype between the depressed and controls. | USA | 2011 [77] |
| DLD/Anxiety | Cases 240 | CC 98, CT 113, TT 29 | C 309, T 171 | ASD as a genetic variant does not play a role in the modulation of mood and cognitive performance. | Australia | 2009 [78] |
| MDD      | Cases 1222(641/581) | CC 545, CT 513, TT 164 | C 1603, T 841 | no significant differences in C677T or T allele frequencies between DD patients and controls. | UK | 2008 [74] |
| ASO      | Cases 308(131) | CC 21, CT 14, TT 4 | C 56, T 22 | Four behaviors were more common and at least one copy of T allele as compared to homozygous wildtype individuals. No differences existed among genotypes for level of functioning. | Romania | 2009 [80] |
| ASD      | Controls 43(14/29) | CC 25, CT 15, TT 3 | C 68, T 21 | ADHD as a genetic variant does not play a role in the modulation of mood and cognitive performance. | Australia | 2009 [78] |
| MDH      | Cases 1377(737/640) | CC 67, CT 43, TT 207 | C 237, T 102 | The TT frequency in children with autism was significantly higher than those in controls. | USA | 2012 [75] |
| ASO      | Cases 186(86/98) | CC 79, CT 77, TT 30 | C 235, T 137 | The TT frequency in children with autism was significantly higher than those in controls. | China | 2012 [75] |
| ASD      | Controls 280(65/215) | CC 87, CT 83, TT 16 | C 257, T 115 | 677C/T1298A was significantly associated with an risk of ASD by 2.11-fold to 677CC/1298AA in males but not females. | Korea | 2014 [84] |
| ASO      | Cases 283(150/133) | CC 60, CT 48, TT 35 | C 188, T 114 | The TT allele frequency was higher in autistic children compared with controls, not significantly. | Turkey | 2014 [81] |
| ADHD     | Controls 46(16/30) | CC 23, CT + TT 25 | C 107, T 33 | 677T-allele frequency was significantly higher in autistic children compared with controls. | Turkey | 2014 [81] |
| ADHD     | Cases 240(107/133) | CC 44, CT 47, TT 9 | C 135, T 65 | ADHD, which was not significantly associated. | USA | 2008 [90] |
| ADHD     | Controls 300(153/147) | CC 154, CT 125, TT 21 | C 438, T 167 | no significant differences in genotype distributions of the 677T allele between ADHD and controls. | Turkey | 2011 [79] |
| ADHD     | Cases 100(50/50) | CC 44, CT 47, TT 9 | C 135, T 65 | The folate-homocysteine pathway gene variants may affect ADHD through mild hyperhomocysteinemia and vitamin B12 deficiency. | India | 2017 [72] |

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homzygous 1298CC individuals showed 61% of wild-type enzyme activity. The Ala177Val was established in the MTHFR of E. coli to study the biochemical phenotype of the Ala222Val variant. Then literatures reported the Ala177Val mutation has no influence on the kinetic parameters of bacterial MTHFR, but rather reduces enzyme stability and affinity for cofactor, and thus increases the tendency to form inactive enzyme via flavin dissociation, compared to the wild-type enzyme.

**MTHFR polymorphism and methylation**

*MTHFR* polymorphism is also associated with global methylation activity. For example, a study of coronary artery patients indicated that genomic DNA methylation directly correlates with folate status and inversely with plasma homocysteine levels. After genotype analysis, TT genotypes had a diminished level of global DNA methylation compared with those with CC wild type. Such a change was also found in healthy individuals which showed reduction of DNA methylation in individuals with the TT *MTHFR* genotype compared to subjects with CC *MTHFR* genotypes. While DNA methylation may be age, gender, and cell-type specific, *MTHFR* polymorphism might not always be associated with hypomethylation of DNA. For example, a study of aging-related DNA methylation found hypomethylation in aged individuals compared to young populations without significant association with C677T *MTHFR* genotypes. Studies also demonstrated no significant inference of *MTHFR* C677T polymorphism in global DNA methylation in oral epithelial cell samples or lymphocytes of healthy individuals, as well as cutaneous squamous cell carcinoma in renal transplant patients. Those reports suggested a *MTHFR* polymorphism independent mechanism in aging and cell-type specific global DNA methylation. Furthermore, a similar results were reported in a study of individuals with or without oligozoospermic which showed no significant association between DNA methylation in spermatozoa and the *MTHFR* C677T genotypes although a trend for higher incidence of methylation alterations in severe oligozoospermic infertile men with CT genotypes were observed, suggesting that a much more complicated or indirect interactions between *MTHFR* polymorphism and methylation are involved.

As global DNA methylation refers to the average methylation status that occurs across the whole genome, *MTHFR* polymorphism could also destruct gene-specific methylation process which refers the methylation status of specific genes. For example, a study of *MTHFR* polymorphism genotypes in colorectal cancer patients reported that the frequency of methylated Bcl-2 promoter was significantly higher in individuals with CC genotype than that of those with CT and TT genotypes, and a significant difference of C and T alleles distribution were observed.
between patients with methylated and unmethylated Bcl-2 promoter. Furthermore, studies of IGF-2 gene in transitional cell carcinoma of the bladder and MGMT gene in gastric cancer showed that patients with CT or TT MTHFR genotypes had reduced methylation of IGF-2 or MGMT compared those with CC genotype. Together, as MTHFR is an important enzyme for folate metabolism which plays critical role in epigenetic as DNA methylation, accumulated evidence showed that global DNA methylation can be associated with MTHFR polymorphism genotypes in both healthy populations and individuals with various diseases. However, some cell type- and age-related global DNA methylation showed independent of MTHFR genotypes. While the underlying mechanism of MTHFR independent global DNA methylation remains unknown, the MTHFR polymorphisms related gene-specific DNA methylations were commonly reported in various pathological conditions.

**Mouse models of MTHFR deficiency**

The Mthfr of mice were knockout to investigate MTHFR deficient by animal models. The Mthfr<sup>+/−</sup> mice showed normal growth and similar survival to that of wild-type mice. The Mthfr<sup>−/−</sup> mice were with none MTHFR enzyme activity in all tissues, whereas the Mthfr<sup>+/−</sup> showed 60% residual activity, similar to the value observed in patients homozygous for the C677T polymorphism. In the Mthfr<sup>+/−</sup> and Mthfr<sup>−/−</sup> mice, the plasma total homocysteine levels were 1.6- and 10-fold higher, respectively, than the wildtype controls. SAM levels were decreased, but S-adenosylhomocysteine (AdoHcy, SAH) levels were elevated considerably, with global DNA hypomethylation observed in both heterozygotes and homozygotes. Then researchers proposed that heterozygous knockout mice appeared to be a good animal model for individuals homozygous for the C677T polymorphism, whereas the homozygous null mice were a better one for severely MTHFR-deficient individuals. Apart from human studies, mice with heterozygous and homozygous mutation in Mthfr C677T still accompany with global DNA hypomethylation, decreased SAM and increased SAH levels.

**MTHFR polymorphism and psychiatric diseases**

Extensive clinical studies demonstrated a significant linkage between MTHFR polymorphism and various diseases, such as cardiovascular diseases, neuronal developmental diseases, cancers as well as psychiatric disorders. Among which, C677T and A1298C polymorphisms of MTHFR have been studied the most in psychiatric diseases and showed significant association with reduction of MTHFR enzymatic activity and methylation. In this session, we will focus on the polymorphisms in the gene encoding for MTHFR in schizophrenia (SZ), bipolar disorder (BPD), depression, autism disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Table summarizes studies including MTHFR polymorphism and psychiatric diseases involved in this review.

**Schizophrenia**

For decades ago, there was a report of MTHFR enzymatic activity reduction in two schizophrenia patients which were 18 and 21% percent of the normal level, respectively, while homocysteine remethylation was also defected. Later, a regression model was created in a study of MTHFR C677T genotype and DNA methylation in schizophrenia subjects, which found females with TT genotype were associated with the lowest global methylation.

Amounts of studies have demonstrated that the level of MTHFR polymorphism in C677T locus is associated with the risk of schizophrenia. As indicated in a meta-analysis of MTHFR consisted of 7 studies, individuals carried with TT homozygotes had the greatest risk of schizophrenia, compared to the subjects with CC wild type and CT heterozygous genotypes. An allele study with well-defined patients and healthy controls indicated that people with CT heterozygotes had the higher risk of schizophrenia than CC carriers. Furthermore, a genotype study also reported that homozygous TT genotype of MTHFR was also associated with risk of schizophrenic patients accompanying with bipolar disorder.

It is interesting to mention that the C677T polymorphisms of MTHFR also has an influence on symptoms of schizophrenia. For example, an increased T allele load is linked to the increase severity of negative symptoms in schizophrenia, while reducing severity of positive symptoms were also noticed. However, the effect of T allele on the negative symptoms of schizophrenia could be further enhanced by folate deficiency. Furthermore, comparing with CC and CT, schizophrenia patients with TT genotype exhibited greater deficits on the verbal fluency test (VFT) and more difficulties on the Wisconsin Card Sorting Test (WCST), but not in California Verbal Learning Test (CVLT) performance. However, the effect of C677T polymorphisms of MTHFR on cognitive function was not significant in normal subjects as a longitudinal cognitive study showed that the MTHFR C677T polymorphism was not associated with cognitive performance at baseline or over 12 years. In addition, studies also demonstrated that the C677T polymorphism of MTHFR is associated with onset age of schizophrenia in a dose-dependent manner, such as increasing numbers of the mutant T allele is linked with early onset.

The relationship between MTHFR polymorphism and schizophrenia in different ethnic population were also investigated. Study of schizophrenic patients and healthy controls in the Arab population from Syria found a strong
association between C677T and schizophrenia, which showed higher variant T allele frequency in the patients group. Interestingly, a statistically significant association was found for 677TT genotype under the recessive model in the male patients subgroup, and CT genotype under the overdominant model in the total patients group. Studies of Chinese Han population indicated that the T allele shown associated with schizophrenia as a risk allele, while a case–control association between the MTHFR C677T polymorphism and schizophrenia in a Japanese subjects research also demonstrated a strong linkage between the MTHFR C677T polymorphism and schizophrenia. Furthermore, a meta-analysis including 38 studies with schizophrenia cases and controls showed the association between C677T polymorphism and risk of schizophrenia in all three ethnic populations—African, Asian, and Caucasian.

Studies of sex differences in MTHFR polymorphism might provide some insights for the divergent results from various studies of psychiatric disorders. A strong association between 677T allele and male patients with schizophrenia compared female patients suggest that 677T allele might represent different liability in genders. While little is known on the sex differences in MTHFR polymorphisms, sex hormones, such as estrogen is known to play a protective effect in female patients with schizophrenia as for the impact of neurodevelopment and social maturation. On the other hand, testosterone may increase male vulnerability to an adverse illness course compared to estrogen, attributed to its narrower and sometimes unfavorable neuroprotection and neurotransmitter modulation profile. Furthermore, progesterone is reported to benefit neurocognition though enhancement of dopamine release in human males and may also have relevance in male physical and mental health while enhancing the benefits of estrogen through potentiation of estrogen-primed effects on dopamine receptors in male schizophrenic patients.

Except for the C677T, there is another site of MTHFR polymorphisms associated with psychiatric disorders. A study with patients of schizophrenia and control subjects showed an association between the A1298C allele and schizophrenia. Another research including 111 families, demonstrated that deficient MTHFR enzyme activity in pregnant women was related to the A1298C variant, which was associated with a higher risk of schizophrenia in the offsprings. Studies of individual with both SNPs (C677T and A1298C) showed that subjects with heterozygosity for both mutations resulted in an even lower MTHFR activity than heterozygosity for single MTHFR mutations, while no subjects carry both homozygote for MTHFR mutations regardless which SNPs. Furthermore, There were studies of multiple polymorphisms of one-carbon metabolism and schizophrenia symptoms showed an increase negative symptoms severity with increase of risk alleles, suggesting a cumulative effects of risk SNPs in one-carbon metabolism.

### Bipolar disorder

In addition to schizophrenia, study demonstrated an association between homozygous 677TT genotype of MTHFR gene and bipolar disorder with stronger linkage in male patients than female patients. Another study found a higher prevalence of C677T polymorphism in BD patients than healthy subjects, while patients with BD with early onset carried one copy of the T allele. A meta-analysis of 56 studies examining MTHFR C677T in patients and control subjects indicated that the T allele and TT genotype carriers showed significant increased risk of major psychiatric disorders including schizophrenia and bipolar disorder. At the same time, some studies found disparate results. For instance, a study reported no significant association between C677T and bipolar disorder, while another study found no evidence for C677T genotypic or allelic association with BD regardless of type I or II. A study with bipolar patients and schizophrenia subjects also observed no robust differences between patients and controls either for allele frequencies or genotype distribution of C677T polymorphism. These discrepancies may result from population stratifications, explicitly, socio-economic status. On the other hand, the included sample size may play a critical role in divergent results.

### Depression

Depression is another major psychiatric disease. MTHFR polymorphism is also noticed in patients with depression. Studies found that MTHFR polymorphisms might be related to the episode and prognosis of depressive disorder, not the stage of the disease. For example, a cohort study of depressive patients and healthy controls found that MTHFR polymorphism were more common in the individuals with depression history compared to controls, while a study over a 60-month follow-up with depressed subjects indicated that the CC genotype of MTHFR C677T were more likely to have more severe symptoms compared to TT genotype carriers. Another study showed that hyperhomocysteinemia and TT MTHFR genotype were significantly related to depression only, not comorbid anxiety disorder. More studies reported that MTHFR C677T is associated with risk of depression, such as postmenopausal depression and childhood trauma related major depression disorder (MDD). It is important to point out the interaction between MTHFR polymorphisms and environmental risks for MDD, such as dietary and stress. For example, a study of inter-relationship between MTHFR polymorphism and
MDD found that the minor T-allele of MTHFR C677T was associated with increased folate deficiency-related body mass index and homocysteine levels in MDD patients only. Another stress-related MTHFR polymorphism in MDD study showed that traumatic stress in childhood could increase risk of MDD recurrence as well as the development of more severe depressive symptoms in MTHFR TT genotype carriers. This study suggests that the increase of mutant allele number of T in C677T locus will enhance stress risk for depression. Both above studies suggest that MTHFR polymorphisms might enhance the environmental risks (low folate intake, traumatic stress at childhood) for MDD via the interaction between genetic and environmental factors. Such a risk was confirmed by a meta-analysis recruiting 26 published studies which showed an association between MTHFR C677T polymorphism and increased risk of depression. However, some studies showed no association between MTHFR and MDD or antidepressant treatment response.

Similarly, diverse situation existed in other researches as a study did not find evidence of an association between the MTHFR TT genotype and depression in a depression cohort. Another study including depressed subjects indicated no significant differences in frequency of the T allele or TT genotype between the depressed and healthy controls. A research of TT genotype and depression scores revealed that the C677T gene variation does not play an important role in the depression scores. In a meta-analysis, no significant differences in genotype or allele frequencies between depressive patients and controls were observed.

A possible reason for divergent consequences is population stratification as the frequency of the T allele is subject to considerable ethnic and geographic variation. Another possibility is that there is an association of this SNP with another disease that is highly correlated with depression. Indeed it has been hypothesized that depression and vascular disease may be different manifestations of the same genetic substrates. Both of these conditions are a result of the interaction of multiple genetic factors and environment, involving multiple genes with small interactive and additive effects.

**Autism disorder**

Comparing to Schizophrenia and depression, relatively limited studies of MTHFR in autism have been conducted. Some studies showed higher frequency of C677T polymorphism in children with ASD than in healthy controls, or associated with ASD behavior phenotypes. A risk study of ASD with typical development indicated significant interaction effects between maternal TT genotype and greater risk for ASD, suggesting MTHFR polymorphism might involve the early development of ASD. Other studies in the Chinese Han and Korean population also found that MTHFR C677T and A1298C mutation genes were risk factors for autism in Chinese Han children and Korean population, respectively.

**Attention deficit hyperactivity disorder (ADHD)**

In terms of the relationship between MTHFR and ADHD, only very few studies have been reported, even with controversial findings. For example, studies demonstrated that A1298C genotype appeared to be the predominant linkage to the inattentive symptoms, leading to a 7.4-fold increase in ADHD, compared with a 1.3-fold increase for the C677T genotype, individuals with ADHD seem to be related to A1298C polymorphisms. However, a research with ADHD and healthy controls reported no association between C677T or A1298C polymorphism and ADHD in Turkish children. Further studies with large sample size or better controls are needed.

In conclusion, MTHFR polymorphism not only increase risks for diabetes, cardiovascular diseases, and various cancers, but also increase the risk for various psychiatric diseases. For example, as we described above that MTHFR polymorphism is associated with early onset of schizophrenia and the severity of depressive symptoms in MDD. This is important since neurotransmitter imbalances hypotheses are still the main streams for schizophrenia and MDD. Understanding alternative mechanisms of psychiatric diseases will not only provide potential biomarkers for specific psychiatric diseases, but also new targets for antipsychotic drug development. Due to significant controversial findings in MTHFR mutation and DNA methylation in both healthy populations and psychiatric patients, investigation of MTHFR activity in peripheral samples might be important. As yet, the relationships between enzymatic activity and mutation of MTHFR have been reported in general healthy and mental retardation populations as well as in animals, no studies have been found in clinical test of MTHFR activity in psychiatric patients. In addition, there are still some shortages on MTHFR mutation and psychiatric disease studies. Except for C677T and A1298C, there were little studies on other SNPs as well as the effect of multiple SNPs on the diseases which may also affect MTHFR activity.

**Clinical treatment strategy for MTHFR-related psychiatric disorders**

As MTHFR plays a critical role in one-carbon metabolism, which is composed of folate, homocysteine, vitamin B12, and methylation of DNA, mutation of specific gene locus on MTHFR and correlative enzyme activity decline will affect various of physiological events as well as some pathology states, including psychiatric disorders. Whether we could cope with gene mutation and enzyme
activity damage using folate one-carbon metabolism strategy as clinical treatment for MTHFR-related psychiatric disease? Some studies showed some interesting possibilities. For example, studies of healthy females found that the low level of serum folate in 677TT genotype is associated with an increase in homocysteine concentration and DNA hypomethylation, which reveals the association between MTHFR C677T polymorphisms and nutrient status. As food is a major resource for folate, studies reported that low folate level due to unbalanced diet is associated with higher prevalence on schizophrenia, particularly in infants with maternal nutritional deficiency. Another study exploring the association between folate and symptoms of schizophrenia indicated that low folate was associated with negative symptoms severity in schizophrenia subjects. One possible role of folate in mental health is its action on DNA methylation and gene expression which have been wildly reported in human psychiatric disorders.

As MTHFR polymorphisms-induced MTHFR activity decline is irreversible, clinicians tried to use supplement of folate to help methylation process and change the pathogenesis state. For instance, methylfolate supplement was used for the improvement of psychiatric symptoms, while folate supplementation showed reduction of the incidence of neural tube defects which reduces the incidence of schizophrenia. Although there is no evidence that supplements are helpful in the treatment of psychosis in general, based on the published studies, we believe that if we can detect MTHFR polymorphism in individuals with various psychiatric diseases, we might be able to differentiate those MTHFR-related psychiatric patients from non-MTHFR deficient patients and develop specific clinical treatment strategies, such as folate or methylfolate supplement to reverse the symptoms. In summary, due to the higher frequency of MTHFR polymorphism in various psychiatric disease, supplement of folate and cobalamin might be critical when patients with MTHFR deficiency. MTHFR deficiency-related psychiatric diseases should be identified and might be able to be treated with targeted supplement for the diseases and related symptoms.

Conclusions

Increasing evidence demonstrated that MTHFR polymorphism including C677T and A1298C is associated with psychiatric diseases. The MTHFR gene polymorphism is linked to onset, clinical symptoms, prevalence as well as response to treatments. The influence of MTHFR on psychiatric diseases is mainly through reduction of MTHFR activity which results in elevation of homocysteine, reduction of DNA methylation-dependent methyl donor, finally induces hypomethylation, and then active disease-related genes. However, some age- and cell type-specific methylation seems independent from MTHFR polymorphism. MTHFR mutation also can increase environmental risks for psychiatric disorders, such as MDD through interaction between genetic and epigenetic factors. Investigation of MTHFR in psychiatric diseases has important clinical implications, such as identification role of MTHFR and its genotypes in the psychiatric patients who respond or not respond to traditional pharmacological treatment for personalized treatment management of psychiatric diseases.

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Competing interests

The authors declare that they have no conflict of interest.

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