



# Gene-wide association study between the methylenetetrahydrofolate reductase gene (*MTHFR*) and schizophrenia in the Japanese population, with an updated meta-analysis on currently available data

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## ARTICLE INFO

### Article history:

Received 9 March 2010

Accepted 14 July 2010

Available online 7 August 2010

### Keywords:

Gene-wide association

Japanese population

Meta-analysis

Methylenetetrahydrofolate reductase

Schizophrenia

## ABSTRACT

Methylenetetrahydrofolate reductase (*MTHFR*) is a critical molecule for single-carbon transfer reactions. Recent evidence suggests that polymorphisms of *MTHFR* are related to neural tube deficits and the pathogenesis of schizophrenia. While several studies have demonstrated associations between the gene encoding the *MTHFR* (*MTHFR*) polymorphisms and schizophrenia, these studies lack consistency. Therefore, we conducted a gene-wide association study (patients with schizophrenia = 696, control subjects = 747) and performed imputation analysis. Additionally, we performed meta-analysis on currently available data from 18 studies for two common functional polymorphisms (rs1801131 and rs1801133).

There were no significant associations with schizophrenia in the single marker analysis for the seven tagging SNPs of *MTHFR*. In the haplotypic analysis, a nominally significant association was observed between the haplotypes, which included four SNPs (rs1801133, rs17421511, rs17037396, and rs9651118) and the schizophrenic patients. Additionally, the imputation analysis demonstrated there were several associated markers on the *MTHFR* chromosomal region. However, confirmatory analyses of three tagging SNPs (rs1801133, rs17037396, and rs9651118) and the top SNP (rs17421511) for the imputation results (patients with schizophrenia = 797, control subjects = 1025) failed to replicate the haplotypic analysis and the imputation results. These findings suggest that *MTHFR* polymorphisms are unlikely to be related to the development of schizophrenia in the Japanese population. However, since our meta-analysis results demonstrated strong support for association of rs1801133 with schizophrenia, further replication studies based on a gene-wide approach need to be considered.

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## 1. Introduction

Schizophrenia is a chronic and disabling mental disorder with a lifetime prevalence of approximately 1% in the global population (Freedman, 2003). Accumulating evidence suggests that both genetic and environmental factors contribute to the

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etiology of schizophrenia (Burmeister et al., 2008). Although schizophrenia has a high heritability with rates estimated at 80% (Sullivan et al., 2003), there has been no consistent replication found for the schizophrenia candidate genes (Harrison and Weinberger, 2005). Recent genome-wide association (GWA) studies have demonstrated new promising susceptibility genes for schizophrenia (O'Donovan et al., 2008), as well as for other common diseases (Rioux et al., 2007; The Wellcome Trust Case Control Consortium, 2007; Zeggini et al., 2007). Therefore, use of this methodology can be advantageous when trying to detect potential genetic factors responsible for the development of these disorders. In addition, by focusing on the specific molecular pathway related to the pathophysiology of schizophrenia, this may also be useful when trying to identify susceptibility genes that have a mild contribution to the development of the disease (Kirov et al., 2005).

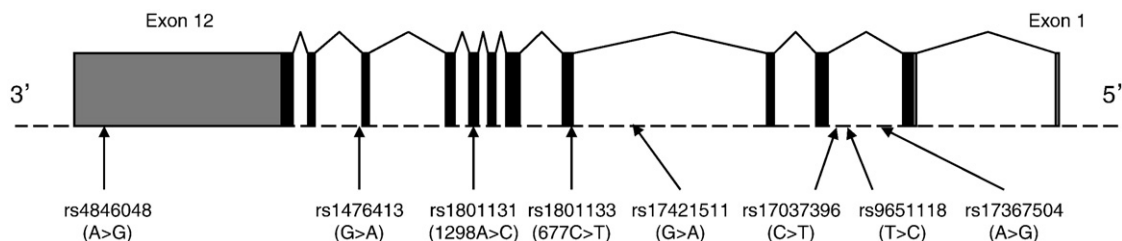
Dysfunction of homocysteine metabolism has been linked to neurodevelopmental disorders, including neural tube defects (NTDs) (Blom et al., 2006; van der Put et al., 1995), schizophrenia (Allen et al., 2008; Muntjewerff et al., 2006), and depression (Lewis et al., 2006), in addition to other diseases and syndromes (Hobbs et al., 2000; Kluijtmans et al., 1996; Qian et al., 2007). Recent studies have also suggested that elevated plasma homocysteine levels are observed in major psychiatric disorders such as schizophrenia and bipolar disorder (Levine et al., 2005). Plasma homocysteine levels affect the intracellular methylation process of DNA, lipids, proteins, and neurotransmitters (Scott and Weir, 1998). Both elevated homocysteine levels along with physiological levels of its oxidized derivatives, such as homocysteic acid and homocysteine sulfinic acid, have been shown to be toxic for neurons and vascular endothelial cells (Zou and Banerjee, 2005). While levels of homocysteine are affected by various genes involved in the homocysteine metabolic pathway and by environmental factors such as folate or vitamin B<sub>12</sub> intake (Refsum et al., 2004), methylenetetrahydrofolate reductase (MTHFR) also plays a major role in this pathway. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which serves as a carbon donor for the methylation of homocysteine, leading to the generation of S-adenosylmethionine (SAM) (Andreoli and Maffei, 1975). SAM is a major source of methyl groups in the brain (Godfrey et al., 1990) and is involved in catechol-O-methyltransferase (COMT) reactions such as the catabolism of serotonin and other catecholamines (Anguelova et al., 2003; Chen et al., 2004). Freeman et al. (1975) reported there is direct evidence linking decreased MTHFR activity to schizophrenia (Freeman et al., 1975). These findings have led to multiple genetic analyses examining the link between the MTHFR gene (gene symbol:

*MTHFR*, GenBank accession number: NM\_005957) and schizophrenia.

*MTHFR* is composed of twelve exons (Fig. 1) and is localized on chromosome 1p36.3 (Goyette et al., 1994). It has been suggested that this may be a susceptibility locus for schizophrenia, bipolar disorder (Kempisty et al., 2007) and major depressive disorder (McGuffin et al., 2005). Two common functional polymorphisms of *MTHFR*, C677T (rs1801133) and A1298C (rs1801131), are known to cause a decrease of enzyme activity and affect nucleic synthesis and DNA methylation (van der Put et al., 1998). Several studies have confirmed the possible involvement of these SNPs in psychiatric conditions such as schizophrenia (Regland, 2005) and affective disorders (Arinami et al., 1997). Subjects with homozygosity for the 677 T allele have a mild increase in their plasma homocysteine levels, and these subjects have a higher frequency of neural tube deficits and premature cardiovascular disease as compared to other similar genotype carriers (Bakker and Brandjes, 1997; Matsushita et al., 1997). The impact of this polymorphism varies according to environmental factors, such as folate, vitamin B<sub>2</sub> or vitamin B<sub>12</sub> (Hustad et al., 2000; Refsum et al., 2004; van der Put et al., 1995). Although some studies have reported that carriers of the 677 T allele in *MTHFR* are associated with an increased risk of schizophrenia (Arinami et al., 1997; Muntjewerff et al., 2005; Sazci et al., 2003), others have shown contradictory results (Kunugi et al., 1998; Vilella et al., 2005; Yu et al., 2004). The association of the *MTHFR* C677T variant with schizophrenia may be linked to the excitatory amino acids hypothesis or to decreased plasma concentrations of SAM that have been reported in psychiatric disorders (Andreoli and Maffei, 1975). Another functional polymorphism, A1298C, also has been shown to decrease MTHFR activity, although van der Put et al. (1998) have reported finding no significant effect of this variant on the plasma homocysteine levels.

A recent meta-analysis demonstrated an association between elevated homocysteine levels or carriers of the 677 T allele and an increased risk of developing schizophrenia (Allen et al., 2008; Muntjewerff et al., 2006). It has been suggested that potential associations between genetic variation in folate metabolism and psychiatric disorders could be plausible biological explanations for these disorders (Coppin and Bolander-Gouaille, 2005).

Taken together, *MTHFR* may be related to the development of schizophrenia. Although a number of studies have demonstrated associations between specific polymorphisms of *MTHFR* and schizophrenia, there have been no gene-based analysis studies. Therefore, it is still difficult to interpret these types of studies due to the inconsistent results that have been derived from some of the confounding factors, such as population



**Fig. 1.** Genomic structure of *MTHFR*. Black boxes indicate protein-coding regions, while the gray boxes represent the untranslated regions (UTRs). Each box represents *MTHFR* exons. Numbers under the arrows represent the SNP IDs, the tagging SNPs (pairwise tagger:  $r^2 > 0.8$ ; Haploview 3.32), and the top SNP (rs17421511) of imputation results.

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