

# Evaluation of C677T Polymorphism of the Methylene tetrahydrofolate Reductase (MTHFR) Gene in various Neurological Disorders

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## Abstract

**Background:** Genetic risk factors play an important role in neurological disorders. In this case-control study, we examined the C677T polymorphism (*rs1801133*) in the Methylene tetrahydrofolate reductase (MTHFR) gene and its association with three neurodegenerative disorders: The late onset pathology, Alzheimer disease and two early onset ones, Autism and Down syndrome. New evidence suggests that autism may be associated with varied behavioural responses to folate therapy and metabolic anomalies, including those in folate metabolism, that contribute to hypomethylation of DNA. We hypothesize that, MTHFR C677T mutation may be the underlying common risk factor in various neurological disorders leading to impaired one carbon metabolism resulting in similar and severe neuropsychological symptoms. Hence our objective was to evaluate MTHFR C677T polymorphism in different Neurological disorders and compare it with age-matched healthy controls.

**Method:** This case-control study was carried out on 200 samples which included 100 patients with different neurological disorders and 100 healthy individuals without any neurological problems taken as the control group. MTHFR polymorphism was assessed by PCR-RFLP.

**Results:** Results indicated that the C677T MTHFR polymorphism was not significantly different between controls of younger and older age groups. Among the three neurological disorders studied the T allele was associated with autism (TT+CT vs. CC; OR=4.472, 95% CI: 1.605-12.799,  $p < 0.002$ ), but not with the other two conditions.

**Conclusion:** In conclusion, despite the smaller sample size, the C677T polymorphism of MTHFR plays a role in some complex neurodevelopmental disorders and not in others.

**Keywords:** Alzheimer disease; Autism; Down syndrome; 5, 10-Methylene tetrahydrofolate Reductase; Polymorphism; Total homocysteine

**Abbreviations:** Alzheimer Disease: AD; Down Syndrome: DS; 5, 10-Methylene tetrahydrofolate Reductase (MTHFR); Total Homocysteine: T-Hcys

## Introduction

Over the past few decades, various studies have shown an increased incidence of folate deficiency and a significant correlation with neuropsychological symptoms, especially cognitive decline, in psychogeriatric and psychiatric populations [1,2]. Both animal and human studies have shown the essential role of folate during nervous system and brain development [3]. Folates, especially in the form of methyl folate, are important for the nervous system at all ages. *In vivo* and *in vitro* studies suggest that chronic folate/methyl deficiency has been associated with abnormal DNA methylation [4-7].

Methylene tetrahydrofolate reductase (MTHFR) enzyme plays a key role in the folate metabolism pathway and regulates the intracellular folate pool for synthesis and methylation of DNA [8,9]. It catalyzes the conversion of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the methyl donor for the remethylation of homocysteine to methionine. The MTHFR gene is located at chromosome 1p36.3 and is 2.2 kb in length with a total of 11 exons [10]. Several single nucleotide polymorphisms in the MTHFR gene have been characterised, with C677T polymorphism being the most commonly studied [11]. The C to T mutation at position 677 causes an alanine to valine substitution in the MTHFR gene (677C>T) [12] which make the enzyme thermo-labile [13]. Reduced MTHFR activity raises

the dietary requirement for folic acid, which is required to maintain normal homocysteine remethylation to methionine.

MTHFR C677T mutation has been associated with seizures, neurological impairment, and diabetic complications and has also been considered as a risk factor for birth defects and cancers [14-16]. Low blood levels of folate and vitamin B12, and elevated homocysteine levels were associated with poor cognitive performance in elderly people [2,17-20]. Insufficient one-carbon metabolism has been suggested to have a contributory role in the development of dementia and has been found to be significant in Alzheimer disease (AD) patient [21]. AD is the leading cause of dementia in the elderly. It is a multifactorial pathology marked with presence of plaques in the brain resulting from the interaction of both genetics and environmental factors. Some studies have implicated MTHFR polymorphism a risk factor for AD [22].

Autism is a neurodevelopmental disorder that is diagnosed in

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early paediatric group. Several studies indicate that defects in the folate pathway may play an important role in the pathophysiology of Autism and that MTHFR C677T polymorphism may be an independent risk factor for this neurodevelopmental disorder [23].

James et al. [24] proposed the possibility that gene nutrient interactions associated with abnormal folate metabolism and DNA hypomethylation might increase the risk of maternal meiotic chromosome non disjunction, e.g., Down syndrome (DS), which usually results due to malsegregation (non disjunction) of chromosomes 21. Mothers with the MTHFR677C>T mutation had a 2.6-fold higher risk of having a child with Down syndrome than did mothers without the T substitution. Guéant et al. [25] found evidence of an association between total homocysteine (t-Hcys) and MTHFR 677 T with low IQ in DS.

MTHFR C677T mutation has also been associated with neuropsychiatric conditions like schizophrenia-like syndromes, bipolar disorder, Parkinson's disease, and vascular dementia [26]. Hence in this study we have assessed C677T MTHFR polymorphism in three neurological disorders Alzheimer disease (AD), Autism and Down syndrome (DS), and compared it with that in age-matched children and adult controls.

## Materials and Methods

### Sample collection

This case/control study included 100 subjects with different neurological disorders like Alzheimer disease (n=25), Autism (n=50), Down syndrome (n=25), with age-matched controls (100) i.e. 50 adult volunteers with age greater than 50 years and 50 healthy children between the ages of 2 years to 17 years with no neurological defects or family history of AD. The patients of AD were clinically identified by a neurologist based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association for probable AD (NINCDS-ADRDA) [27]. DS was diagnosed by the presence of trisomy 21 after karyotyping, while autistic children were selected on the basis of Indian Scale for Autism Assessment (ISAA) which is based on the criteria laid down in "Diagnostic & Statistical Manual of Mental Disorders-IV" and

Childhood Autism Rating Scale (CARS). The study was approved by Institutional Ethics Committee.

### Isolation of genomic DNA

Blood samples were collected in EDTA vacutainers and DNA was isolated from 300 µl of venous blood, by the procedure routinely used in our lab [28]. DNA samples were stored at -20°C till analysis.

### Polymerase Chain Reaction (PCR) & Restriction Fragment Length Polymorphism (RFLP)

MTHFR genotypes were determined by PCR using specific primers, followed by RFLP and gel analysis as reported earlier by our group [14,16]. HinfI restriction enzyme was used to generate two fragments of 175bp and 23bp. The PCR products and the enzyme digested PCR products were visualized on 2% agarose gel stained with ethidium bromide and their band images were analyzed with UVI TECH gel documentation system (Cambridge, UK).

### Statistics

The statistical analysis of data was performed by using 2-way contingency table analysis on stat pages which is available online. Outcomes were assessed with Fisher exact test which was utilized to compare ratios and p<0.05 was accepted as statistically meaningful.

### Results

A total of 100 cases with three neurological disorders and 100 controls participated in the study. The demographic details are mentioned in the Table 1.

The genotype frequencies of CC, CT and TT in controls belonging to both young and old age groups were the same and did not follow the Hardy Weinberg equilibrium. We did not find individuals with TT either in cases or in controls. This is not surprising, given the low incidence of T allele in Asians as well as the small sample size [29]. Our results were similar to a study done by Kohli et al. [30] who did not find any homozygous TT genotype in DS cases as well as controls.

The frequency of C and T alleles were the same in Down syndrome and controls (Figure 1), the T allele was present at a slightly increased

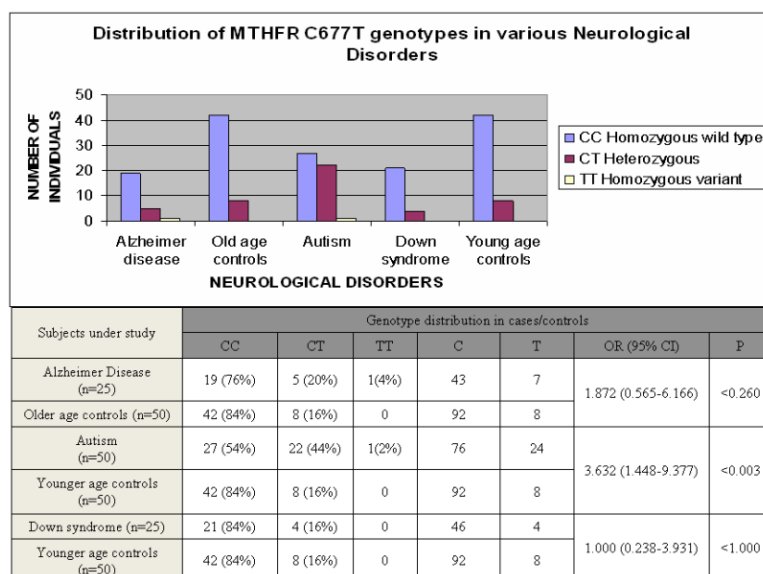


Figure 1: Genotype and allele frequency distribution in cases and controls.

	Total cases	Male (♂)	Female (♀)	Age range (yrs)	Mean ± SD
Alzheimer Disease	25	15	10	52-87	70.2 ± 10.3
Older age controls >50yrs	50	21	29	50-86	63.42 ± 8.8
Autism	50	42	8	3-17	11.74 ± 3.7
Down syndrome	25	16	9	3-17	6.3 ± 3.4
Younger age controls <18yrs	50	23	27	2-17	8.76 ± 3.19

**Table 1:** Neurodegenerative cases and controls.

		P-value	OR (95% CI)	95%CI
Dominant model	TT+CT vs. CC	P<0.002	4.472	1.605-12.799
Co-dominant model	CT vs. CC+TT	P<0.004	4.125	1.478-11.817
Recessive model	TT vs. CC+CT	P<1.000	0.490	0.017-7.225

**Table 2:** Statistical analysis of the Genotype Distribution in Autism cases.

frequency in AD, but this was not statistically significant ( $p < 0.260$ )

MTHFR C677T allele frequency was found to be higher in autistic children compared with non-autistic children with a 4.47-fold increased risk for autism [95% confidence interval (CI): 1.605-12.799] (Table 2). MTHFR 677T allele appears to be a risk factor for autism.

## Discussion

5,10-Methylenetetrahydrofolatereductase, a key enzyme in methionine-homocysteine metabolism, maintains the folate pool between the DNA synthesis and methylation pathways [31-33]. MTHFR C677T (*rs1801133*), particularly in the homozygous state, is a risk factor for multifactorial disorders such as cardiovascular disease, spina bifida (NTD), infertility and several other pathologies [34]. C677T polymorphism of the MTHFR gene is important in determining the activity of the enzyme.

One of the neurobehavioral disorders included in our study AD showed that 20% of the population was heterozygous (CT), 4% were homozygous (TT), and 76% were wild type (CC). 20% of the cases were heterozygous for this polymorphism (CT) and T allele was higher in cases compared to controls. However, the data was not statistically significant and this may be because of the small sample size. But earlier studies with a much larger sample (i.e.,  $n=100$  and  $n=140$ ) also did not show association with AD in Polish and Swedish populations. Our results are in accordance with other studies [21,35] which also failed to find an association between AD and the C/T polymorphism in the MTHFR gene. Results from Japanese, Canadian, Italian and US population were also similar [36-39].

There are several studies which have evaluated the C677T polymorphism in mothers having DS children. Various studies have shown that the C677T polymorphism is a maternal risk factor for DS [40-44]. However, there are few studies in patients with DS *per se*, as has been evaluated in our present study. Our study does not show association of this polymorphism with either the syndrome or any of its specific clinical characteristics.

Previous studies have reported that perturbations in folate metabolic pathway and polymorphism at C677T of MTHFR gene are associated with autism. There are conflicting reports suggesting both a positive and negative association of MTHFR C677T polymorphism with autism [45,46]. In our study, a positive association was observed

between MTHFR C677T variant allele and autism risk. Our observation supports the meta-analysis data reported by Pu et al. [47]. Another study by Mohammad et al. [23] of the MTHFR C677T polymorphism in Indian patients with specific neurological pathologies has indicated that there was significant association with children associated with Autism.

## Conclusion

In conclusion, it can be commented that despite the small sample size the C677T polymorphism of MTHFR plays a role in some complex neurodevelopmental disorders and not in others. Supplementing folic acid B6, B12 in mother or children may be a recommended strategy for management of Autism [48,49].

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