

# Methylenetetrahydrofolatereductase C677T polymorphism and folate metabolism in human health

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Folate is an essential B vitamin that provides one-carbon molecules for DNA synthesis, protein synthesis, and methylation of DNA and proteins. The folate pathway plays a critical role in cellular function and human development, as evidenced by the association between maternal folic acid intake and the risk of neural tube defects, cardiovascular disease, and cancer.<sup>[1]</sup> Both nutrient status and genetic background are independent but interacting risk factors for these disorders. However, the biochemical and developmental mechanisms that lead to pathology or the mechanisms whereby folate prevents the occurrence and recurrence of these disorders are unknown. The methylenetetrahydrofolatereductase (MTHFR) gene (677C → T) is a common polymorphism which results in reduced MTHFR enzyme activity that leads to reduced capacity to remethylate homocysteine and generate S-adenosyl methionine and hypomethylated lymphocytic DNA. Two studies in this issue found no association of MTHFR C677T polymorphism with the disease condition. Pandey *et al.*<sup>[2]</sup> studied MTHFR 677CT polymorphism in craniosynostosis and found no association with the disease. The other study in this issue found no association of MTHFR 677CT polymorphism in Down syndrome (DS) children, however, it was linked to clinical severity such as low IQ.<sup>[3]</sup> In general, maternal

folate metabolism associated with fetal disease condition. Several studies were carried out on maternal MTHFR 677CT polymorphism and nondisjunction of trisomy 21. James *et al.*<sup>[4]</sup> were the first to suggest a role of the folate pathway in chromosome 21 nondisjunction as the major cause of DS. They showed that the C677T polymorphism associated biochemical changes in folate pathway metabolites in mothers, were associated with a 2.6-fold increased chance of having a child with trisomy 21. Some subsequent studies examining the relationship between maternal folate metabolism and delivering a child with DS found no link with genetic variants in single folate pathway genes, whereas others pointed to an additive effect with variants in multiple genes.<sup>[5]</sup> Since maternal folic acid supplementation can modify the effect of genetic variants in the folate pathway, a lack of maternal folic acid supplementation is a potential risk factor for chromosome 21 nondisjunction.

The studies on intake of folic acid and risk of DS are contradictory. The research groups observed a significantly reduced association between trisomy 21 and maternal folic acid supplement intake three or more times a week at least 1 week before conception. It was hypothesized that the environmental factors, like maternal exposure to folic acid, may influence chromosome segregation at different times during oocyte development. In females, the formation of oocytes is initiated during fetal life and is not completed until decades later. Meiosis I (MI) begins at around 12 weeks of gestation in the mother's fetal life, at which time chromosomes replicate, and homologs pair and undergo recombination. At approximately 20 weeks in maternal fetal life, MI arrests in prophase, and this arrest is not released until ovulation,

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some 10-50 years later. Upon ovulation, MI is completed, MII begins immediately, then arrests at metaphase and is completed after fertilization. Thus, studies examining the association between lack of maternal folic acid supplementation and DS in their offspring examine only the time period between the resumption of MI and the completion of MII. To date, there have been no studies of maternal folic acid supplementation and chromosome 21 nondisjunction that consider the type of meiotic error. Over 95% of DS results from the failure of chromosomes 21 to properly segregate during meiosis. The maternal meiotic origin accounts for more than 90% cases, that is, they occur during the formation of oocytes. Though frequency of MI and MII errors differs, both are associated with advanced maternal age and MII error frequency is more in older (40-45 years) mothers of DS. The MTHFR C677T polymorphism has been shown to be associated with maternal MII errors.<sup>[6]</sup> The studies also showed the influence of MTHFR genotypes on the occurrence of associated morphological anomalies specifically congenital heart disease.<sup>[7]</sup> The MTHFR C677T polymorphism frequency varies in different populations. Studies conducted from north and south India showed varied frequencies of MTHFR polymorphisms. This clearly indicates the role of environmental factors. As folate metabolism plays an important role in the fetal development, maternal intake of folate is important to reduce the risk of developmental anomalies particularly trisomy 21 (DS). However, population-based case-control studies are important

to know the effect of preconception intake of folate and MTHFR 677CT polymorphism.

## References

1. Stover PJ. Physiology of folate and vitamin B12 in health and disease. *Nutr Rev* 2004;62:S3-12.
2. Pandey RK, Ali A, Singh A, Gayan S, Bajpai M. Methylenetetrahydrofolate reductase C677T variant in Indian children with craniosynostosis: Its role in the pathogenesis, risk of craniosynostosis. *Indian J Hum Genet* 2014;20:100.
3. Rai V, Yadav U, Kumar P, Yadav SK. Methylenetetrahydrofolate reductase polymorphism is not risk factor for Down syndrome in North India. *Indian J Hum Genet* 2014;20:100.
4. James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, *et al*. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. *Am J Clin Nutr* 1999;70:495-501.
5. Coppède F. The complex relationship between folate/homocysteine metabolism and risk of Down syndrome. *Mutat Res* 2009;682:54-70.
6. Hollis ND, Allen EG, Oliver TR, Tinker SW, Druschel C, Hobbs CA, *et al*. Preconception folic acid supplementation and risk for chromosome 21 nondisjunction: A report from the National Down Syndrome Project. *Am J Med Genet A* 2013;161A: 438-44.
7. Brandalize AP, Bandinelli E, dos Santos PA, Roisenberg I, Schüler-Faccini L. Evaluation of C677T and A1298C polymorphisms of the MTHFR gene as maternal risk factors for Down syndrome and congenital heart defects. *Am J Med Genet A* 2009;149A: 2080-7.

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