Folate and homocysteine metabolism and gene polymorphisms in the etiology of Down syndrome1,2

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One of the major advances in preventing malformations in the past few decades had its origin in the observation by Smithells et al (1) that multivitamin preparations are protective against neural tube defects. This observation was followed by confirmation that consumption of folic acid in the periconceptional period could prevent both the occurrence and recurrence of this common birth defect (2, 3). The mechanism by which folic acid exerts its protective effect against neural tube defects is unclear. Over the past 2 decades, the importance of elevated total plasma homocysteine concentrations as a risk factor for vascular disease has been clearly shown (4, 5). Several clinical trials are in progress to determine whether lowering total homocysteine concentrations with vitamins will prevent vascular disease.

Several autosomal recessive inborn errors of metabolism, including cystathionine β-synthase (CBS) deficiency, methyltetrahydrofolate reductase (MTHFR) deficiency, methionine synthase deficiency (cblG), and methionine synthase reductase deficiency (cblE), are associated with elevated homocysteine concentrations. Although heterozygosity for CBS deficiency has been proposed as a common cause of elevated homocysteine concentrations in the general population, it is no longer thought to play a major role. Severe MTHFR deficiency is associated with elevated homocysteine concentrations and low methionine concentrations; most patients have developmental delay and vascular disease. We showed originally that fibroblast extracts from some patients with severe MTHFR deficiency had residual enzyme activity that was labile to heat (6). Subsequently Kang et al (7) found a high frequency of thermolabile MTHFR in patients with coronary artery disease. However, because MTHFR thermolability was not consistently associated with elevated homocysteine concentrations in his patients and because the studies of thermolability required relatively large amounts of fresh white blood cells, few confirmatory studies were originally conducted. All this changed with the cloning of the MTHFR gene and the discovery that a common polymorphism in this gene, a C-to-T substitution at nucleotide 677 (677C→T), resulting in the substitution of alanine for valine, was the cause of the thermolabile enzyme activity in both the general population and in patients with severe MTHFR deficiency (8–10). This led to a simple polymerase chain reaction–based test for the thermolabile allele and to many studies to determine the role of this polymorphism in explaining both hyperhomocysteinemia and the protective role of folic acid against neural tube defects and possibly vascular disease.

The study by James et al (11) in this issue of the Journal has expanded the territory of research into folate metabolism and birth defects to the area of Down syndrome. Although maternal age is the major risk factor for trisomy 21, most children with Down syndrome are born to mothers aged < 30 y. It would be of great medical importance to identify younger mothers at increased risk for Down syndrome. The cause of trisomy 21 is usually maternal nondisjunction. DNA hypomethylation has been associated with abnormal chromosome segregation, and methyl deficiency can result in DNA hypomethylation. This knowledge led James et al to examine folate metabolism and the 677C→T polymorphism of the MTHFR gene in the mothers of children with Down syndrome. They found a higher frequency of both the C/T and T/T genotypes in the mothers of children with Down syndrome than in the control mothers. Although the absolute number of mothers with the T/T genotype was twice as high in the mothers of children with Down syndrome than in the control mothers, the sample size was small and the difference was not significant. When the frequencies of mothers with at least one T allele were compared, the odds ratio for mothers of children with Down syndrome was 2.6 (P < 0.03). Interestingly, although both total plasma homocysteine concentrations and ratios of plasma homocysteine to methionine were higher in the mothers of children with Down syndrome than in the control mothers, the increase was not dependent on MTHFR genotype. Similarly, although sensitivity to the antifolate methotrexate was increased in lymphocytes from mothers of children with Down syndrome, again this was unrelated to MTHFR genotype. Finally, mothers of children with Down syndrome, regardless of MTHFR genotype, had low dietary intakes of folic acid from food, although 28% of mothers of children with Down syndrome with a T allele reported taking a vitamin supplement containing 400 μg folic acid at the time of conception.

This study suggests that factors involving both genotype and nutrition may underlie susceptibility to nondisjunction and therefore trisomy 21. Genetic-environmental interactions will continue to be unmasked as an increasing number of genes involved in homocysteine and folate metabolism are cloned. Prime candidate genes for future study in this regard are both

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methionine synthase and methionine synthase reductase, for which polymorphisms have been found. Homocysteine metabolism has been studied in patients with Down syndrome because CBS is located on chromosome 21; homocysteine concentrations in Down syndrome are low because of the 3 copies of CBS. The work by James et al has opened up a totally new approach to homocysteine metabolism in Down syndrome, one that will certainly be pursued further by them and other groups to confirm and expand these exciting preliminary findings.

REFERENCES