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Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductasegene may be maternal risk factors for Down syndrome.

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Abstract

Background

Down syndrome, or trisomy 21, is a complex genetic disease resulting from the presence of 3 copies of chromosome 21. The origin of the extra chromosome is maternal in 95% of cases and is due to the failure of normal chromosomal segregation during meiosis. Although advanced maternal age is a major risk factor for trisomy 21, most children with Down syndrome are born to mothers <30 y of age.

Objective

On the basis of evidence that abnormal folate and methyl metabolism can lead to DNA hypomethylation andabnormal chromosomal segregation, we hypothesized that the C-to-T substitution at nucleotide 677 (677C-->T) mutation of themethylenetetrahydrofolate reductase (MTHFR) gene may be a risk factor for maternal meiotic nondisjunction and Down syndrome in young mothers.

Design

The frequency of the MTHFR 677C-->T mutation was evaluated in 57 mothers of children with Down syndrome and in 50 age-matched control mothers. Ratios of plasma homocysteine to methionine and lymphocyte methotrexate cytotoxicity were measured as indicators of functional folate status.

Results

A significant increase in plasma homocysteine concentrations and lymphocyte methotrexate cytotoxicity was observed in the mothers of children with Down syndrome, consistent with abnormal folate and methyl metabolism. Mothers with the 677C-->T mutation had a 2.6-fold higher risk of having a child with Down syndrome than did mothers without the T substitution (odds ratio: 2.6; 95% CI: 1.2, 5.8; $P < 0.03$).

Conclusion

The results of this initial study indicate that folate metabolism is abnormal in mothers of children with Down syndrome and that this may be explained, in part, by a mutation in the MTHFR gene.