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Address for correspondence and reprints: Dr. Hope Northrup, Division of Medical Genetics, Department of Pediatrics, The University of Texas Medical School at Houston, 6431 Fannin Street, Houston, TX 77030. E-mail: Hope.Northrup@uth.tmc.edu

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Reply to Volcik et al.

To the Editor:

Volcik et al. (2001 [in this issue]) provide supporting evidence that methylenetetrahydrofolate reductase (MTHFR) 677 and 1298 alleles have crossed over, as we have demonstrated in fetal tissue and in antenatal subjects (Isotalo et al. 2000). Their observations also support the findings of Hanson et al. (2001), who demonstrated, in a study of adults, a genotype frequency of 0.2% for both MTHFR 677CT/1298CC and MTHFR 677TT/1298AC. The only MTHFR crossover combination that we observed in an antenatal control group was 677TT/1298AC (Isotalo et. al 2000). We hypothesized that the allelic combinations 677TT/1298CC and 677CT/1298CC are potentially deleterious or lethal in utero; however, the existence of 677CT/1298CC in both adults and children with spina bifida (SB) casts some doubt on our hypothesis.

A major consideration not addressed by Volcik et al. (2001 [in this issue]), concerning their study group, is that their study focused on children with SB and on their parents. Children with SB have survived a fetal defect—one that is known to cause stillbirth and miscarriage. Without medical intervention, postgestational mortality in infants with SB is high. Therefore, the MTHFR genotype combinations and frequencies observed in the nonviable group that we studied may overlap with those in groups with SB.

Additionally, development of SB, as well as of other neural-tube defects, can be reduced by folate sufficiency and therefore is affected by diet and, possibly, by other defects within the folate-delivery and metabolic pathways. Folate status has been shown to affect the contribution of the MTHFR 677 genotype to SB (Christensen et al. 1999). Nutritional-status differences between the study groups may influence the survival of specific genotypes. The contribution that the mother makes to SB or to fetal demise may be, in part, genetic—as was possibly the case in the U.S. 677TT/1298AC representation—and most certainly is in part due to maternal folate sufficiency. The distribution of 677TT/1298AC combined genotypes was well represented in all children with SB and in Hispanic parents but not in U.S. parents. Notably, the only groups with a strong representation of 677CT/1298CC, relative to the 677TT/1298AC genotype, were the U.S. and Canadian mothers of children with SB. This is in contrast to the lack of 677CT/1298CC in our Canadian antenatal control group. Of 148 control subjects, Volcik et al. found 2 individuals with the 677CT/1298CC genotype.

Volcik et al.'s Canadian study group consisted of affected families with SB and did not contain controls; therefore, we find it difficult, in relation to our control group, to draw conclusions concerning their findings of the 677CT/1298CC combinations. Our Canadian group was predominantly of European (Celtic) descent, although some Canadians of other derivations were included. It is interesting to note that Weisberg et al. (1998) also studied a Canadian population of children with SB and their mothers and did not identify any individuals with the 677CT/1298CC or 677TT/1298CC genotypes.

We still hypothesize that combined common polymorphisms of MTHFR play a role in fetal demise and in the development of neural-tube defects. Maternal MTHFR is in the position to affect the quantity and form of folate delivered to the fetus, whereas fetal MTHFR may subsequently affect the utilization and distribution of the supplied folate. The most important determinant for the development of neural-tube defects, however, is likely the initial folate sufficiency of the mother. It is unfortunate that Volcik et al. did not examine patterns between the parental—in particular, the maternal—MTHFR genotypes and the genotypes of the children with SB that they studied. Perhaps there are specific maternal/fetal combinations of MTHFR that have a relationship with either fetal demise or the development of SB.

JAMES G. DONNELLY[1] AND PHILLIP A. ISOTALO[2]
[1]*Department of Pathology, New York University School of Medicine, New York; and* [2]*Department of Pathology, Mayo Clinic, Rochester, MN*

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Address for correspondence and reprints: Dr. J. G. Donnelly, Department of Clinical Pathology, 4E1, Bellevue Hospital Center, 462 1st Avenue, New York, NY, 10016. E-mail: james.donnelly@med.nyu.edu

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