The Glycine N-Methyltransferase (GNMT) 1289 C→T Variant Influences Plasma Total Homocysteine Concentrations in Young Women after Restricting Folate Intake

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ABSTRACT Glycine N-methyltransferase (GNMT) is a key regulatory protein in folate metabolism, methionine availability, and transmethylation reactions. Perturbations in GNMT may lead to aberrations in homocysteine metabolism, a marker of numerous pathologies. The primary objective of this study was to examine the influence of the GNMT 1289 C→T alone, and in combination with the methylenetetrahydrofolate reductase (MTHFR) 677 C→T variant, on plasma total homocysteine concentrations in healthy young women (n = 114). Plasma total homocysteine was measured at baseline (wk 0) and after 2 wk of controlled folate restriction (135 µg/d as dietary folate equivalents). Plasma homocysteine concentrations did not differ among the GNMT C1289T genotypes at baseline. However, after folate restriction, women with the GNMT 1289 TT genotype (n = 16) had higher (P = 0.019) homocysteine concentrations than women with the CT (n = 51) or CC (n = 47) genotype. The influence of the GNMT 1289 C→T variant on homocysteine was dependent on the MTHFR C677T genotype. In subjects with the MTHFR 677 CC genotype, homocysteine was greater (P ≤ 0.05) for GNMT 1289 TT subjects relative to 1289 CT or CC subjects. However, in subjects with the MTHFR 677 TT genotype, plasma homocysteine concentrations did not differ among the GNMT C1289T genotypes. Overall, these data suggest that the GNMT 1289 C→T polymorphism influences plasma homocysteine and is responsive to folate intake. J. Nutr. 135: 2780–2785, 2005.

KEY WORDS: ● glycine N-methyltransferase ● methylenetetrahydrofolate reductase ● methionine synthase reductase ● homocysteine ● folate ● women

Glycine N-methyltransferase (GNMT)3 is a tetrameric protein (1), which is abundant in liver (2,3) and integrally linked to folate and methyl group metabolism (4–7). Glycine N-methyltransferase (GNMT) is a key regulatory protein in folate metabolism, methionine availability (8–11), and transmethylation reactions (6,10,12,13). GNMT catalyzes the S-adenosylmethionine (SAM)-dependent methylation of glycine to generate S-adenosylhomocysteine (SAH) and a biologically inert compound, sarcosine (13). GNMT influences transmethylation reactions by regulating both hepatic SAM concentrations (6,14,15) and the SAM:SAH ratio (6,10,12), a key variable in transmethylation potential (16,17).

Regulation of SAM and the SAM:SAH ratio by GNMT is dependent upon 3 allosteric relations. First, SAM inhibits methylenetetrahydrofolate reductase (MTHFR), which catalyzes the formation of 5-methyl-tetrahydrofolic acid (THF) from 5,10-methenyl-THF (18,19). Second, 5-methyl-THF, the product of MTHFR-catalyzed reactions and primary methyl donor for homocysteine remethylation, inhibits GNMT (14,20). Third, unlike most methyltransferases, GNMT possesses a high Ki value for SAH and is only weakly inhibited by SAH (21,22). Hence, when SAM is high, MTHFR is inhibited and 5-methyl-THF formation is reduced allowing for a more active GNMT to reduce excess SAM levels. In contrast, low SAM leads to an increase in 5-methyl-THF production, which inhibits GNMT and spares methyl-groups for transmethylation reactions (i.e., DNA methylation). The high concentrations of GNMT in the liver (1–3% of cytosolic protein), the production of an inert nontoxic compound, the high Ki value for SAM (22), and its relative resistance to inhibition by SAH are characteristics that make GNMT an ideal regulator of the SAM:SAH ratio (13,22).

Homocysteine is a by-product and potential marker of transmethylation reactions (23). Elevations in homocysteine are associated with increased risk for cognitive disorders (24), cardiovascular disease (25), neural tube and other birth defects (26), and pregnancy complications (26). Several functional polymorphisms in key one-carbon metabolizing genes, including MTHFR 677 C→T, MTHFR 1298 A→C, methionine synthase 2756A→G, methionine synthase reductase (MTRR) 66A→G, and cystathionine β-synthase 844ins68, either alone

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2 To whom correspondence should be addressed.
3 Abbreviations used: DFE, dietary folate equivalents; GNMT, glycine-N-methyltransferase; MTHFR, methylenetetrahydrofolate reductase; MTRR, methionine synthase reductase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; THF, tetrahydrofolic acid; Hcy, total homocysteine.

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or in combination, influence plasma homocysteine and/or disease risk (27). However, many of these variants are diet responsive and should be studied within the context of the nutritional status of the host.

Homocysteine metabolism may also be influenced by GNMT. In murine models, GNMT induction is associated with decreased plasma tHcy concentrations (10,13,28). However, more data are required to ascertain whether an inverse relation exists between GNMT and homocysteine. Further, it is unclear whether the changes in plasma tHcy are a direct consequence of changes in GNMT activity. Factors that modulate GNMT may also influence other homocysteine metabolizing enzymes including cystathionine β-synthase and betaine-homocysteine S-methyltransferase (28).

A recent study examining the role of GNMT in liver cancer progression in humans (29) identified 3 single nucleotide polymorphisms in the human GNMT gene. Of these polymorphisms, a 1289 C→T polymorphism was associated with cancer risk. To date, the implications of the GNMT 1289 C→T polymorphism upon GNMT activity and homocysteine metabolism have not been examined.

The purpose of this study was to examine the influence of the GNMT 1289 C→T polymorphism alone and in combination with the MTHFR 677 C→T polymorphism on plasma total homocysteine and serum folate concentrations in young women before and after a 2-wk period of folate restriction. In addition, the influences of the MTRR 66A→G and MTHFR 1298 A→C variants alone and in combination with the MTHFR 1277 C→T variant on the response variables were assessed.

SUBJECTS AND METHODS

Subjects

The subjects were recruited from Cal Poly Pomona University and surrounding areas in Southern California between 1999 and 2003. All subjects were healthy women (n=114) with no history of vascular, gastrointestinal, renal, or hepatic disease; normal blood glucose and lipid concentrations, normal blood chemistry; 18–46 y old; non-smoker; not taking drugs known to interfere with folate metabolism; not a current user (within the past 3 mo) of supplemental vitamins and/or minerals; not pregnant or planning a pregnancy; not lactating; and possessed the appropriate MTHFR 677 C→T genotype. The screening and experimental procedures for the previously conducted trials were reviewed and approved by the Institution Review Board of Cal Poly Pomona University, and informed consent was obtained from each participant.

Experimental design

We pooled data obtained from 114 young women who participated in 1 of 2 controlled folate feeding protocols conducted between 1999 and 2003 by our research group (30–32). Both protocols consisted of a folate restriction phase that provided 135 μg DFE/d and lasted a minimum of 2 wk. Both protocols also included measurements of plasma tHcy and serum folate at baseline (wk 0) and after 2 wk of folate restriction (wk 2). In addition, both protocols assessed the MTHFR 677 C→T genotype.

The present study is an extension of our previous work. In addition to the MTHFR 677 C→T genotype, the MTHFR 1298 C→T, MTRR 66A→G, and GNMT 1289 C→T genetic polymorphisms were assayed. The influence of these genetic polymorphisms alone and in combination with the MTHFR 677 C→T on plasma tHcy and serum folate were examined at baseline (wk 0) and after folate restriction with 135 μg DFE/d (wk 2).

Diet and supplements

The 5-d menu utilized during folate restriction provided ~135 μg DFE/d (30,32). Subjects consumed breakfast and dinner under the supervision of investigators at the Cal Poly Pomona Human Nutrition metabolic kitchen. Lunch and snacks as well as 14 breakfast or dinner meals of the subjects choosing were provided as "take-away" items and consumed off-site. The nutrient content (except folate) and energy provisions of the menus were analyzed with ESHA Food Processor Nutrient Data Base (version 7.81; ESHA Research). Dietary intakes of choline and betaine were estimated using recently published data (33,34). The menus provided an estimated 2000–2300 kcal (8375–9632 kJ/d) with 54–66% from carbohydrate, 10–14% from protein, and 21–30% from fat. For nutrients that were not provided in recommended amounts via the diet, supplements were administered to ensure that total intakes (menus plus supplements) were at least 85% of recommended amounts (30,32). The supplements included a multiminerals (LifeTime, Nutritional Specialties), given every day; a multivitamin (Trader Darwin's Stress Vitamin, Trader Joe's), cut into thirds and given every 4 d; vitamin K (KAL, Nutraeutical), given every other day; choline (TwinLab, Twin Laboratories), given every other day; and iron (TwinLab, Twin Laboratories) given as needed (based on weekly hematocrit measures).

Sample collection and blood processing

Baseline and weekly venous blood samples were collected from subjects who had fasted for 10 h into serum separator gel and clot activator tubes and EDTA tubes. Serum, plasma, and peripheral leukocytes were obtained for serum folate, plasma total homocysteine, and genotype analyses, respectively.

Analytical methods

Folate content of diet. The folate content of the diets was determined before starting the study and twice during the study. Each meal, including the beverage, was blended with 150 mL of cold 0.1 potassium phosphate buffer/L (pH 6.3) containing 57 mmol ascorbic acid/L, dispensed into 50-mL conical tubes and stored at ~2°C. Duplicates of the blended samples were thawed, homogenized, and subjected to trienzyme treatment (35) and double extraction (36). The total folate content of each meal was determined microbiologically (37).

Genotype determinations. DNA for genotyping was extracted from stored leukocytes (~80°C) using a commercially available kit (DNeasy Tissue Kit, Qiagen). MTHFR C677T variants were determined by the method of Frost et al. (38). MTHFR A1298C variants were determined using the primer pairs and restriction enzymes described by van der Put and Blom (39) and the PCR conditions described by Friedman and colleagues (40). MTRR A66G variants were determined using the primer pairs and restriction enzymes described by Jacques et al. (41) and the PCR conditions described by Olteanu and Banjeree (42).

A novel RFLP was developed in our laboratory for the determination of MTHFR C1298T variants. The primers for the PCR reaction were: 5'-TGGAGCCTGAGCAACCTGCGG-3' sense and 5'-TCTCCCGTGATGTTGTC-3' antisense and were obtained commercially (Invitrogen). Amplification was performed using initial denaturation at 95°C for 2 min followed by 30 cycles of 95°C for 30 s, 58°C for 15 s, and 72°C for 15 s with a final extension of 72°C for 5 min. PCR supermix (Invitrogen) was used as the PCR buffer. The 229 bp PCR product was digested with MvuI I (Invitrogen) producing a 15-, 98-, and 116-bp band for the CC genotype, a 131-, 116-, and 98-bp band for the TT genotype, and a 131-, 98-, and 15-bp band for the CT genotype. The digested products were size-fractionated on a 3.0% agarose gel (Invitrogen) and viewed under UV light.

Plasma tHcy. Plasma tHcy was measured in duplicate at baseline and after folate restriction by use of a modified HPLC method with fluorometric detection (43,44). The intra- and interassay CV based on the positive control (e.g., pooled plasma analyzed in duplicate with every assay conducted) were 5 and 7%, respectively.
Serum folate. Serum folate was measured in duplicate microbiologically using Lactobacillus casei (37) at baseline and weekly thereafter. The intra-and interassay CV for the positive control (e.g., pooled serum analyzed in triplicate with every assay conducted) were 10 and 12%, respectively.

Statistical analysis. All analyses were conducted with SPSS 11.0 (SPSS; Mac OS X version). All data summaries of plasma tHcy and serum folate are presented as means ± SD. The influence of individual genotypes for the 4 genes (GNMT C1289T, MTRR A66G, MTHFR A1298C, and MTHFR C677T) and genetic variants of 3 of these in combination with the MTHFR C677T genotypes were assessed using 1-way ANOVA. When this was significant, Tukey’s HSD procedure was used for mean separations. Differences were considered significant at \( P \leq 0.05 \).

RESULTS

Subject characteristics and baseline measures

The final study group was comprised of 114 women with a median age of 22 y (range, 18–46 y) and a median BMI of 24.0 kg/m² (range, 17.6–36.6 kg/m²). The racial/ethnic composition was 57 Mexican Americans, 21 Caucasians, 21 African Americans, 14 Asians, and 1 Arabian. At baseline, the plasma tHcy concentration was 12.2 nmol/L (range, 3.7–25.8 nmol/L). The serum folate concentration was 29.9 nmol/L (range, 10.9–45.0 nmol/L).

Frequencies cannot be used to assess the prevalence of these TT/CC genotype. Because this was a nonrandom sample, these CT/CC genotype and none of the subjects had the TT/MTRR 66 GG. One subject had the MTHFR 677/CC for the MTHFR A1298C; and 46% AA, 42% AG, and 25% TT for MTHFR C677T; 56% AA, 36% AC and 8% AA, 36% AC and 8% AC.

Influence of individual genotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>n</th>
<th>Plasma tHcy</th>
<th>Serum folate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Folate restriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \mu \text{mol/L} )</td>
<td></td>
</tr>
<tr>
<td>GNMT C1289</td>
<td>47</td>
<td>5.4 ± 0.0</td>
<td>6.3 ± 1.2b</td>
</tr>
<tr>
<td>CC</td>
<td>51</td>
<td>5.6 ± 1.1</td>
<td>6.3 ± 1.1b</td>
</tr>
<tr>
<td>CT</td>
<td>16</td>
<td>5.7 ± 1.4</td>
<td>7.2 ± 1.5a</td>
</tr>
<tr>
<td>TT</td>
<td>73</td>
<td>5.4 ± 1.0</td>
<td>6.1 ± 1.2b</td>
</tr>
<tr>
<td>MTHFR C677</td>
<td>66</td>
<td>5.9 ± 0.9</td>
<td>7.0 ± 1.0a</td>
</tr>
<tr>
<td>AA</td>
<td>29</td>
<td>5.9 ± 1.3</td>
<td>7.0 ± 1.1a</td>
</tr>
<tr>
<td>AC</td>
<td>63</td>
<td>5.7 ± 1.1</td>
<td>6.7 ± 1.3a</td>
</tr>
<tr>
<td>GG</td>
<td>41</td>
<td>5.4 ± 1.0</td>
<td>6.1 ± 0.9a</td>
</tr>
<tr>
<td>MTRR A66</td>
<td>9</td>
<td>5.5 ± 0.9</td>
<td>6.1 ± 1.0ab</td>
</tr>
<tr>
<td>AA</td>
<td>52</td>
<td>5.5 ± 1.1</td>
<td>6.2 ± 1.2</td>
</tr>
<tr>
<td>AG</td>
<td>48</td>
<td>5.6 ± 1.1</td>
<td>6.6 ± 1.3</td>
</tr>
<tr>
<td>GG</td>
<td>14</td>
<td>5.7 ± 1.1</td>
<td>6.6 ± 1.0</td>
</tr>
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</table>

\( ^1 \) Values are means ± SD. Means in a column with superscripts without a common letter differ, \( P \leq 0.05 \).
and CC/CC genotypes. In addition, plasma tHcy was greater (P ≤ 0.05) for the CC/TT genotype than for the CC/CC genotype (Table 2).

**MTHFR A1298C/MTHFR C677T.** At baseline, plasma tHcy and serum folate concentrations did not differ among the various allele combinations (data not shown). After folate restriction with 135 μg DFE/d, plasma tHcy was higher for the AA/TT genotype relative to the AC/CC genotype. Additionally, serum folate was lower (P ≤ 0.05) for the AA/TT genotype than for the AC/CC genotype.

**MTRR A66G/MTHFR C677T.** At baseline, plasma tHcy and serum folate concentrations did not differ among the various allele combinations (data not shown). After folate restriction with 135 μg DFE/d, plasma tHcy was higher (P ≤ 0.05) for the AG/TT genotype compared with the AA/CC genotype (Table 2). Also, serum folate was lower (P ≤ 0.05) for the AA/TT genotype than for the GG/CC genotype (Table 2).

### DISCUSSION

This study was conducted after folate acid fortification of the food supply, which has had a dramatic effect on folate status in all segments of the U.S. population (45). Because high and/or varying folate intakes may modify the influence of genetic variants in genes involved in 1-carbon metabolism, we assessed the effect of folate restriction on plasma tHcy and serum folate concentrations in young women after 2 wk of folate restriction with 135 μg DFE/d.

The MTHFR 677 TT genotype was dependent on the MTHFR C677T genotype. In subjects with the MTHFR 677 CC genotype, plasma tHcy was greater (P = 0.002) for MTHFR 677 TT subjects relative to 1289 CT or 1289 CC subjects (Table 2). In contrast, plasma tHcy concentrations did not differ among the GNMT C1289T genotypes with MTHFR 677 TT genotype. Although our sample sizes are small, these initial data suggest that the GNMT 1289 T variant may be associated with lower homocysteine levels in women with higher folate status.

**TABLE 2**

<table>
<thead>
<tr>
<th>MTHFR&lt;sup&gt;677&lt;/sup&gt;</th>
<th>Plasma tHcy</th>
<th>Serum folate</th>
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<tbody>
<tr>
<td></td>
<td>μmol/L</td>
<td>nmol/L</td>
</tr>
<tr>
<td>GNMT&lt;sup&gt;1289&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>5.8 ± 1.0 (31)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24.5 ± 8.6 (31)</td>
</tr>
<tr>
<td>CT</td>
<td>6.1 ± 1.0 (32)&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>20.2 ± 8.8 (32)</td>
</tr>
<tr>
<td>TT</td>
<td>7.2 ± 1.6 (10)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.0 ± 10.4 (10)</td>
</tr>
<tr>
<td>MTHFR&lt;sup&gt;1298&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>6.4 ± 1.5 (27)&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>20.2 ± 7.9 (27)&lt;sup&gt;abc&lt;/sup&gt;</td>
</tr>
<tr>
<td>AC</td>
<td>6.0 ± 0.0 (36)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24.0 ± 10.0 (36)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CC</td>
<td>6.1 ± 1.0 (9)&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>21.5 ± 8.4 (9)&lt;sup&gt;abc&lt;/sup&gt;</td>
</tr>
<tr>
<td>MTRR&lt;sup&gt;666&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>5.9 ± 1.0 (30)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.8 ± 8.6 (30)&lt;sup&gt;abc&lt;/sup&gt;</td>
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<tr>
<td>AG</td>
<td>6.4 ± 1.4 (25)&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>22.7 ± 9.5 (25)&lt;sup&gt;abc&lt;/sup&gt;</td>
</tr>
<tr>
<td>GG</td>
<td>6.5 ± 0.8 (13)&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>26.7 ± 8.4 (13)&lt;sup&gt;abc&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1 Values are means ± SD (n). Means for the various gene-gene comparisons with superscripts without a common letter differ, P ≤ 0.05. Some of the post hoc comparisons were not significantly different because of the small and unequal sample sizes for some of the genotype combinations.

2 N/A, not available.
reduced enzyme activity in vitro (47,48); yet, it has no effect on catalytic function and thermostability (49). To date, most studies have not demonstrated an effect of the MTHFR 1298 CC genotype on homocysteine and/or serum folate concentrations (40,47,50–57). In the present study, plasma tHcy was higher (P ≤ 0.05) after folate restriction for the MTHFR 1298 AA genotype compared with the AC genotype and lower for serum folate at baseline (P ≤ 0.01) and after folate restriction. However, these data were highly influenced by the MTHFR 677 C→T polymorphism (Table 2). Of women with the MTHFR 1298 AA genotype, 50% possessed the MTHFR 677 TT genotype, whereas only 0.33% of the women with the MTHFR 1298 AC genotype possessed the MTHFR 677 TT genotype (Table 2). Thus, the higher prevalence of the MTHFR 677 TT genotype among women with the MTHFR 1298 AA genotype relative to the MTHFR 1298 AC genotype contributed to the higher plasma homocysteine and lower serum folate. As shown in this study and others (47,50,52,58), plasma tHcy or blood folate concentrations did not differ between the MTHFR A1298C/MTHFR 677CC genotypes. The absence of the MTHFR 677 TT/1298 CC genotype due to linkage disequilibrium between the MTHFR C677T and A1298C genotypes prevents a conclusive assessment of the combined influence of the MTHFR homozygous variants.

MTRR catalyzes the SAM-dependent reductive methyltransferase of inactivating cofactor C(2)/azlamin to methylcobalamin(3/4)amin, the required cofactor for methionine synthase (59). In a 5-methyl-

3

THF-dependent reaction, methionine synthase reconstitutes homocysteine to methionine. To date, the majority of studies reported that the MTRR 66 A→G variant has no influence on plasma tHcy and/or blood folate (41,50,53,57,59–63). In the present study, plasma tHcy and serum folate concentrations did not differ among women differing in the MTRR A66G genotype at baseline or after folate restriction. However, after folate restriction, the relation between the MTRR A→G variant and the measured variables was influenced by the MTHFR 677 C→T variant. This finding highlights the importance of considering the MTHFR C677T genotype when examining the influence of the MTRR A66G genotype on plasma tHcy.

Folate status modifies the influence of the MTHFR 677 C→T polymorphism on plasma tHcy. Guinotte et al. (30) observed lower (P ≤ 0.05) blood folate and higher (P ≤ 0.05) plasma tHcy concentrations in young women with the TT genotype compared with the CC genotype with folate intakes of 800 μg DFE/d. These differences disappeared with folate intakes of 800 μg DFE/d. Similarly, Ashfield-Watt et al. (64) reported higher (P ≤ 0.05) plasma tHcy in participants with the TT genotype relative to the CC genotype with folate intakes of ~282 and 660 but not 800 μg DFE/d. For the MTHFR 677 C→T polymorphism, it was shown that the folate protects the human MTHFR gene, both wild type and mutant, from thermal inactivation (65). Folate status/intake may also influence GNMT activity (66). In rodents, folate deficiency was associated with an increase in GNMT activity (66), which is consistent with data reporting an inhibitory effect of 5-methyl-THF on GNMT (14,20). Data from the present study suggest that the influence of the GNMT 1289 C→T polymorphism should be assessed in combination with data on folate status/intake and that this variant may be of greater importance in countries that have not implemented widespread folic acid fortification of staple food items.

Because the GNMT 1289 C→T variant appears to influence plasma homocysteine, it may be an important modulator of diseases/conditions associated with perturbations in homocysteine metabolism. In the present study, plasma tHcy was ~1 μmol/L higher in women with the GNMT 1289 TT genotype compared with women with the CC or CT genotypes. A similar difference in plasma tHcy was observed between women with the MTHFR 677 TT and CC genotypes. It is possible that larger differences in plasma tHcy concentrations between genotypes may occur in populations consuming less folate. In this regard, a meta-analysis including studies whose populations were not exposed to widespread folic acid fortification reported that persons with the MTHFR 677 TT genotype had plasma tHcy concentrations that were ~2.5 μmol/L greater than the CC genotype and that their risk of developing cardiovascular disease was ~16% higher (67). It is also possible that the influence of the GNMT 1289 C→T polymorphism on plasma tHcy may be different in men and in older populations.

In summary, the GNMT 1289 TT genotype influenced plasma tHcy concentrations after a 2-wk period of controlled folate restriction, an effect that was most evident in women with the MTHFR 677 CC genotype. The MTHFR 677 C→T polymorphism also influenced plasma tHcy and serum folate concentrations after restricted folate intake and contributed to the effects observed individually for the MTHFR 1298 A→C polymorphism. The apparent influence of the GNMT 1289 C→T variant on plasma tHcy concentrations is intriguing and should be reexamined in larger populations in combination with data on MTHFR C677T genotype and folate intake/status.

LITERATURE CITED


