The Glycine N-Methyltransferase (GNMT) 1289 C→T Variant Influences Plasma Total Homocysteine Concentrations in Young Women after Restricting Folate Intake1

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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). 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-tetrahydrofolate (THF) from 5,10-methylene-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 SAM (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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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, tetrahydrofolate; tHcy, total homocysteine.
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 A66A→G and MTHFR 1298 A→C variants alone and in combination with the MTHFR 677 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 selection 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 multimineral (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, Nutraceutical), 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. Plasma, serum, 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 ~20°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 (DNAeasy Tissue Kit, Qiagen). MTHFR C677T 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′-TGCACTTGAGACACCTGCGG-3′ sense and 5′-TCC- CCGTCCGGTGATCGTGC-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 Mwo I (Invitrogen) producing a 15-, 98-, and 116-bp band for the CC genotype, a 131-, 116-, and 98-bp band for the CT genotype, and a 131-, 98-, and 15-bp band for the CT genotype. The digested products (98,116,131 bp) 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 on the frequency of the genotypes (GNMT C1289T, MTHR 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 of the entire group was 5.6 ± 1.1 μmol/L and the serum folate concentration was 29.9 ± 12.2 nmol/L.

Frequency of variant genotypes

The frequency of the genotypes \(( n = 114)\) was 41% CC, 45% CT, and 14% TT for GNMT C1289T; 64% CC, 11% CT and 25% TT for MTHFR C677T; 56% AA, 36% AC and 8% CC for the MTHFR A1298C; and 46% AA, 42% AG, and 12% GG for the MTRR A66G. Additionally, 3.5% of the subjects were MTHFR 677 TT/GNMT 1289 TT or MTHFR 677 TT/AC/MTHFR C677T.

Influence of individual genotypes

**GNMT C1289T.** At baseline, plasma tHcy and serum folate concentrations did not differ among the genotypes (Table 1). After folate restriction with 135 μg DFE/d, plasma tHcy was higher \(( P = 0.019)\) for the TT genotype compared with the CC and CT genotypes (Table 1). Serum folate concentrations did not differ among the genotypes (Table 1).

**MTHFR C677T.** At baseline, plasma tHcy tended to be higher \(( P = 0.082)\) and serum folate lower \(( P = 0.082)\) for the TT genotype than for the CC genotype (Table 1). After folate restriction with 135 μg DFE/d, plasma tHcy was higher \(( P \leq 0.05)\) for the TT and CT genotypes compared with the CC genotype, whereas serum folate tended to be lower \(( P = 0.064)\) for the TT genotype than for the CC genotype (Table 1).

**MTHFR A1298C.** At baseline, plasma tHcy concentrations did not differ among the genotypes (Table 1). However, serum folate was lower \(( P \leq 0.01)\) for the AA genotype than for the AC genotype (Table 1). After folate restriction with 135 μg DFE/d group, plasma tHcy was greater \(( P \leq 0.05)\) for the AA genotype compared with the AC genotype (Table 1). In addition, serum folate concentrations were lower \(( P \leq 0.01)\) for the AA genotype than for the AC genotype.

**MTRR A66G.** At baseline, plasma tHcy and serum folate concentrations did not differ \(( P > 0.05)\) among the genotypes (Table 1). Following folate restriction with 135 μg DFE/d, serum folate tended to be higher \(( P = 0.061)\) for the GG genotype than for the AA genotype (Table 1).

Influence of the genetic variants in combination with the MTHFR C677T genotype

**GNMT C1289T/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 greater \(( P \leq 0.05)\) for the TT/CC genotype compared with the CT/CC

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The influence of individual genotypes on plasma tHcy and serum folate concentrations in young women at baseline (wk 0) and after folate restriction with 135 μg DFE/d for 2 wk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
<td><strong>n</strong></td>
<td><strong>Plasma tHcy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>μmol/L</td>
</tr>
<tr>
<td>GNMT^C1289T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>47</td>
<td>5.4 ± 0.9</td>
</tr>
<tr>
<td>CT</td>
<td>51</td>
<td>5.6 ± 1.1</td>
</tr>
<tr>
<td>TT</td>
<td>16</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>MTHR A66G</td>
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<td></td>
</tr>
<tr>
<td>CC</td>
<td>73</td>
<td>5.6 ± 1.0</td>
</tr>
<tr>
<td>CT</td>
<td>12</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>TT</td>
<td>29</td>
<td>5.9 ± 1.3</td>
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<tr>
<td>MTHFR C677T</td>
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<td></td>
</tr>
<tr>
<td>AA</td>
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<td>5.7 ± 1.1</td>
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<tr>
<td>AC</td>
<td>41</td>
<td>5.4 ± 1.0</td>
</tr>
<tr>
<td>GG</td>
<td>9</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>MTHFR A1298C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>52</td>
<td>5.5 ± 1.1</td>
</tr>
<tr>
<td>AG</td>
<td>48</td>
<td>5.6 ± 1.1</td>
</tr>
<tr>
<td>GG</td>
<td>14</td>
<td>5.7 ± 1.1</td>
</tr>
</tbody>
</table>

^ Values are means ± SD. Means in a column with superscripts without a common letter differ, \( P \leq 0.05 \).
the restriction period, folate intake was controlled and pro-
line and after a 2-wk period of folate restriction. Throughout
sessed the influence of the GNMT 1289 C
varying folate intakes may modify the influence of genetic
all segments of the U.S. population (45). Because high and/or
food supply, which has had a dramatic effect on folate status in
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 (Ta-
ble 2).

**DISCUSSION**

This study was conducted after folic 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 influence of the GNMT 1289 C→T, MTHFR 677
C→T, MTHFR 1298 A→C, and MTRR 66 A→G at base-
line and after a 2-wk period of folate restriction. Throughout
the restriction period, folate intake was controlled and pro-
vided 135 μg DFE/d.

For the GNMT 1289 C→T polymorphism, plasma tHcy
concentrations did not differ at baseline. However, after con-
trolled folate restriction, plasma tHcy concentration was
higher (P = 0.0019) in women with the GNMT 1289 TT
genotype than in women with the CC or CT genotype. The
influence of the GNMT C1289T polymorphism on plasma
tHcy was dependent on the MTHFR C677T genotype. In
subjects with the MTHFR 677 CC genotype, plasma tHcy was
greater (P = 0.002) for GNMT 1289 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 in subjects with the MTHFR 677 TT genotype.
Although our samples sizes are small, these initial data suggest
that the GNMT 1289 C→T and MTHFR 677 C→T polymor-
phisms operate via similar mechanisms to affect plasma
homocysteine.

GNMT is intricately linked to plasma homocysteine metab-
olism through its regulation of hepatic SAM concentrations
and the SAM:SAH ratio. Hypothetically, a less active GNMT
would lead to reductions in SAM and subsequently homocys-
teine production. However, a less active GNMT would also
lead to increases in SAM, inhibition of MTHFR and decreases
in 5-methyl-THF. Decreases in 5-methyl-THF, the predomi-
nant in vivo source of methyl groups for homocysteine re-
methylation to methionine, would subsequently contribute to
increases in plasma homocysteine concentrations. In the
present study, the higher (P ≤ 0.05) homocysteine concen-
trations in young women after 2 wk of folate restriction with
135 μg DFE/d, plasma tHcy was higher (P
0.05) for the CC/TT genotype than for the CC/CC
genotype (Table 2). Also, serum folate was lower (P ≤ 0.05)
for the AA/TT genotype than for the GG/CC genotype (Ta-
ble 2).

**TABLE 2**

<table>
<thead>
<tr>
<th>Plasma tHcy</th>
<th>Serum folate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTHFR</strong></td>
<td><strong>CC</strong></td>
</tr>
<tr>
<td><strong>GNMT</strong></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>5.8 ± 1.0 (31)c</td>
</tr>
<tr>
<td>CT</td>
<td>6.1 ± 1.0 (32)bc</td>
</tr>
<tr>
<td>TT</td>
<td>7.2 ± 1.6 (10)a</td>
</tr>
<tr>
<td><strong>MTHFR</strong></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>6.4 ± 1.5 (27)ab</td>
</tr>
<tr>
<td>AC</td>
<td>6.0 ± 0.0 (36)b</td>
</tr>
<tr>
<td>CC</td>
<td>6.1 ± 1.0 (9)ab</td>
</tr>
<tr>
<td><strong>MTRR</strong></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>5.9 ± 1.0 (38)b</td>
</tr>
<tr>
<td>AG</td>
<td>6.4 ± 1.4 (25)ab</td>
</tr>
<tr>
<td>GG</td>
<td>6.5 ± 0.8 (10)ab</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 0.03% 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/677 TT genotype and A1298C/CC genotype. The absence of the MTHFR 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 inactive coB(II)alamin to methylcoB(III)alamin, the required cofactor for methionine synthase (59). In a 5-methylTHF–dependent reaction, methionine synthase remethylates 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 (41,50,53,57–63). 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 TT/C polymorphism. The apparent influence of the MTHFR 677 TT genotype among women with the MTHFR 677 CC genotype (Table 2). Thus, the higher prevalence of 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. Guinotto 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 135 and 400 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 folate fortification of stable 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 folate 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


