Cancer and Clinical Oncology; Vol. 5, No. 2; 2016
ISSN 1927-4858 E-ISSN 1927-4866
Published by Canadian Center of Science and Education

Non-Association of Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms with Homocysteine Levels, Venous or Arterial Thromboses in 1,141 North-Central Appalachian Patients

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Received: March 27, 2016 Accepted: April 14, 2016 Online Published: August 22, 2016

doi:10.5539/cco.v5n2p21 URL: http://dx.doi.org/10.5539/cco.v5n2p21

Abstract

Objectives: MTHFR polymorphism testing has been used by clinicians for thrombophilia risk assessment. We questioned the utility of such testing.

Methods: 1,141 patients age 18 and above had MTHFR testing for both C677T and A1298C polymorphisms, 2006 through 2012. Available plasma homocysteine levels were obtained and ICD-9 billing codes were grouped to identify venous or arterial clots in these patients.

Results: 901 women and 240 men were tested; median age in women was 33 years (range 18-86); median age in men was 47 years (range 18-83). County of residence mapping confirmed that this MTHFR tested population was from north-central Appalachia. Only 144 (13%) of the 1,141 patients had no polymorphism at either the C677T or the A1298C locus; only 4 patients (0.4%) had 3 or more polymorphisms; 993 patients (87%) had either one or two polymorphisms.

We found polymorphism frequency pattern similar in both sexes. Although men had higher homocysteine levels, MTHFR polymorphisms did not associate with homocysteine levels in either sex. In 901 women tested, the ICD-9 coded incidence of arterial clots was 20%, and of venous clots was 21%; in 240 men tested, the incidence of arterial clots was 48% and of venous clots was 40%. MTHFR polymorphisms did not associate with arterial or venous clots in either sex.

Based on CPT billing codes, a minimal cost estimate was $137,000 for performing these 1,141 MTHFR tests.

Conclusions: MTHFR testing was costly and did not add useful information during thrombophilia evaluation in this patient population.

Keywords: Appalachia, embolism, homocysteine, MTHFR, polymorphism, thrombosis

Abbreviations

CPT: current procedural terminology of the American Medical Association

Hcy: homocysteine levels in micromoles per liter

ICD-9: international classification of diseases version 9

MTHFR: methylenetetrahydrofolate reductase

WVUH: West Virginia University Hospital

1. Introduction

Associating MTHFR polymorphisms with thrombosis or embolism has been controversial, and there is a growing consensus that MTHFR genetic testing should not be done for thrombophilia evaluation [USPSTF 2009, Leewood 2012; Hickey *et al*., 2013].

When we noted that ~90% of patients referred to our benign hematology clinic at West Virginia University Hospital (WVUH) had MTHFR polymorphisms [Gadiyaram *et al*., 2009], we decided to study all patients tested for both MTHFR C677T and A1298C polymorphisms at WVUH from 2006 through 2012, comparing the test results with homocysteine levels and ICD-9 codes identifying venous or arterial clots in the same tested patients.

2. Methods

During this Institutional Review Board approved study, the WVUH clinical laboratory information system (Sunquest, Tucson, AZ) identified all adult patients, age 18 and above, who had MTHFR testing during the years 2006 through 2012. In this case-based study, each individual patient had one episode of MTHFR testing and all patients were tested for both C677T and A1298C polymorphisms. Testing for MTHFR mutations was performed by direct mutation analysis using PCR amplification, signal generation, and release by cleavage of sequence-specific alleles (Invader MTHFR 677, Invader MTHFR 1298, Invader Plus Chemistry, Hologic, Madison, WI). The clinical laboratory system also searched for the highest plasma homocysteine level obtained in these same patients.

Patient County of residence at time of testing was identified and mapped. The hospital patient information system (EPIC, Madison, WI) was screened using multiple ICD-9 billing codes (listed in the Appendix) to identify venous or arterial clots occurring in these MTHFR tested patients. ICD-9 codes for many types of arterial clots were considered in aggregate as "arterial" and those for venous clots and emboli were considered in aggregate as "venous" (see Appendix). Individual patients were scored as having arterial clots, venous clots, or any clot.

Results were tabulated and analyzed using JMP V11 (SAS Inst. Inc., Cary, NC). Basic frequencies and percentages were calculated for demographics and other variables. Cross tabulations, correlations and t-tests were planned, if potential associations between variables were noted.

3. Results

The county of residence of the WVUH patient population having both MTHFR C677T and A1298C testing is shown in Figure 1. These patients clearly resided in the north central Appalachian region.

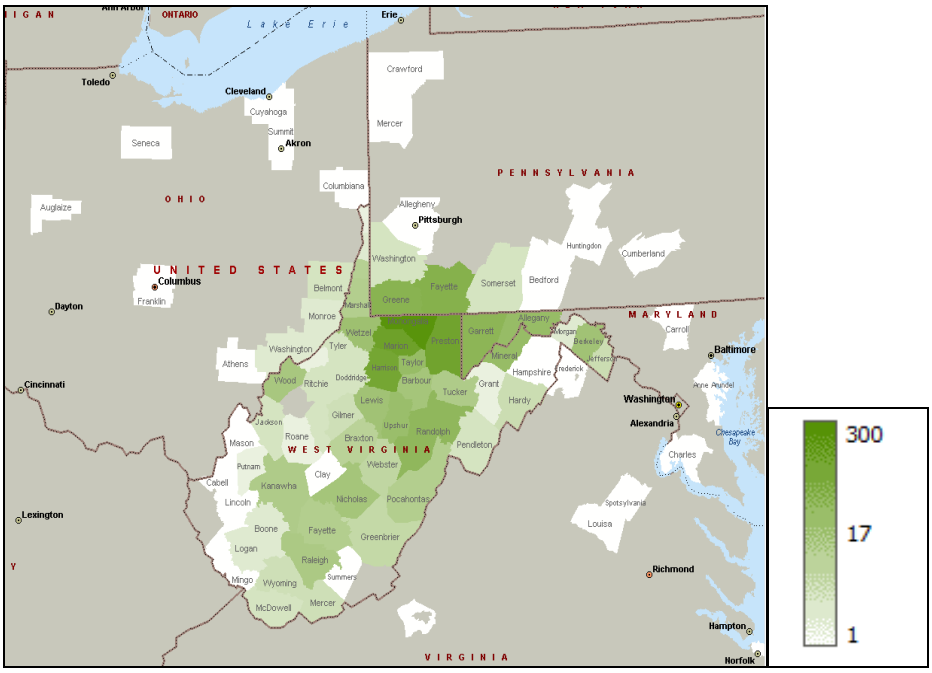

Figure 1. County of residence for MTHFR-tested patients at West Virginia University Hospital, 2006-2012

As shown in Table 1, there were 901 women and 240 men tested for MTHFR polymorphisms at both C677 and A1298 alleles. The median age in women was 33 years (range 18-86), while the median age in men was 47 years (range 18-83). Only 144 patients (13%) had no MTHFR polymorphism, and only 4 patients (0.4%) had 3 or more MTHFR polymorphisms, so the majority -- 993 patients (87%) -- had 1 or 2 MTHFR polymorphisms. There was no evident difference in polymorphism frequency between men and women at either the C677 or A1298 alleles.

Table 1. MTHFR Polymorphism Test Results in 1,141 Women and Men at West Virginia University Hospital, 2006-2012

		Women # (%)	Men # (%)	Total # (%)
C677	A1298	111 (12%)	33 (14%)	144 (13%)
C677T	A1298	224 (25%)	51 (21%)	275 (24%)
C677TT	A1298	103 (11%)	25 (10%)	128 (11%)
C677	A1298C	179 (20%)	53 (22%)	232 (20%)
C677T	A1298C	192 (21%)	54 (23%)	246 (22%)
C677TT	A1298C	1 (<1%)	1 (<1%)	2 (<1%)
C677	A1298CC	91 (10%)	22 (9%)	113 (10%)
C677T	A1298CC	0	1 (<1%)	1 (<1%)
C677TT	A1298CC	1 (<1%)	0	1 (<1%)
	Total Number	901 (79%)	240 (21%)	1,141 (100%)
	Age, median (range)	33 yr (18-86)	47 yr (18-83)	

As shown in Table 2, ICD-9 coded arterial or venous clots were compared to MTHFR polymorphisms in females, in males, and in both sexes (ICD-9 codes used to assign arterial or venous clots in these patients are listed in an appendix). Also, plasma homocysteine levels were tested and available in 610 patients and these levels were compared to MTHFR polymorphisms.

Men had slightly higher median homocysteine levels than woman for all polymorphism patterns. However, when MTHFR polymorphism frequency was compared to homocysteine levels in men alone, in women alone, and in both groups combined, in no case did the median homocysteine level appear to differ according to MTHFR C677 or A1298 polymorphism pattern.

In the 901 women, a 20% incidence of arterial clots and 21% incidence of venous clots was compared to each specific MTHFR polymorphism pattern (for example, of 111 women with no polymorphism at either C677 or A1298, 25% had arterial and 25% had venous clots). There was no association of either arterial or venous clots in women with any MTHFR polymorphism pattern.

Similarly, in the 240 men, a 48% incidence of arterial clots and 40% incidence of venous clots was compared to each specific MTHFR polymorphism pattern and there was no association of either arterial or venous clots in men with any MTHFR polymorphism pattern.

Finally, in the entire patient population of 1,141, the 26% incidence of arterial and 25% incidence of venous clots identified by ICD-9 billing codes had no association of with any particular MTHFR polymorphism pattern (Table 2).

Table 2. MTHFR Polymorphisms vs Homocysteine (Hcy) Levels and ICD-9 Designated Arterial or Venous Clots in 1,141 Women, Men, and All Patients at West Virginia University Hospital, 2006 - 2012

Women		#	median Hcy micromole/L (range)		Art. Clot # (%)		Vein Clot # (%)	Any Clot # (%)
C677	A1298	111	8	4-15.1	28 (25%)		28 (25%)	42 (38%)
C677T	A1298	224	9	3.9-36.2	35 (16%)		34 (15%)	60 (27%)
C677TT	A1298	103	8.1	4-42.2	25 (24%)		22 (21%)	38 (37%)
C677	A1298C	179	8.7	3.9-22	33 (18%)		42 (23%)	63 (35%)
C677T	A1298C	192	8.5	3.0-44	40 (21%)		44 (23%)	69 (36%)
C677TT	A1298C	1	--	--	--		--	--
C677	A1298CC	91	7.9	4.0-18.8	20 (22%)		17 (19%)	31 (34%)
C677T	A1298CC	0	--	--	--		--	--
C677TT	A1298CC	0	--	--	--		--	--
	Total #	901			181 (20%)		187 (21%)	303 (34%)
Men		#	median Hcy micromole/L (range)		Art. Clot	# (%)	Vein Clot # (%)	Any Clot # (%)
C677	A1298	33	10.2	3.5-35	17 (52%)		9 (27%)	24 (73%)
C677T	A1298	51	9.7	4.5-21.1	25 (49%)		24 (47%)	38 (75%)
C677TT	A1298	25	13.6	9.9-63	7 (28%)		9 (36%)	15 (60%)
C677	A1298C	53	10	3.7-19.5	24 (45%)		24 (45%)	41 (77%)
C677T	A1298C	54	10.7	6-22.6	27 (50%)		25 (46%)	41 (76%)
C677TT	A1298C	1	--	--	1 (<1%)		--	1 (<1%)
C677	A1298CC	22	10.5	3.7-22	12 (55%)		6 (27%)	16 (73%)
C677T	A1298CC	1	--	--	1 (<1%)		--	1 (<1%)
C677TT	A1298CC	0	--	--	--		--	--
	Total #	240			114 (48%)		97 (40%)	177 (74%)
All Patients		#	median Hcy micromole/L (range)		Art. Clot	# (%)	Vein Clot # (%)	Any Clot # (%)
C677	A1298	144	9	3.5-35	45 (31%)		37 (26%)	66 (46%)
C677T	A1298	275	9	3.9-36.2	60 (22%)		58 (21%)	98 (36%)
C677TT	A1298	128	9	4.0-63	32 (25%)		31 (24%)	53 (41%)
C677	A1298C	232	9.5	3.7-22	57 (25%)		66 (28%)	104 (45%)
C677T	A1298C	246	9	3.0-44	67 (27%)		69 (28%)	110 (45%)
C677TT	A1298C	2	--	--	1 (<1%)		--	1 (<1%)
C677	A1298CC	113	8.3	3.7-22	32 (28%)		23 (20%)	47 (42%)1
C677T	A1298CC	1	--	--	1 (<1%)		--	1 (<1%)
C677TT	A1298CC	0	--	--	--		--	--
	Total #	1,141			295 (26%)		284 (25%)	480 (42%)

4. Discussion

MTHFR (5, 10-methylenetetrahydrofolate reductase), an enzyme involved in homocysteine metabolism, converts folate, a cofactor for homocysteine conversion, into its major circulating form 5-methyltetrahydrofolate. Polymorphisms in the gene encoding MTHFR have been thought to influence blood levels of homocysteine, which has been considered a risk factor for venous or arterial thromboses, venous thromboembolism, myocardial infarction, and stroke. [Jacques *et al*., 1996; Selhub *et al*., 1996]

MTHFR polymorphism C677T results in a C→T substitution at nucleotide 677, causing thermolability of the enzyme at 37^{o}C. Homozygotes (C677TT) have more than 50% reduction in enzyme activity, but the effect on homocysteine levels depends on folate intake. Homocysteine levels are about 25% higher in homozygous carriers only when plasma folate concentration is low. [Frosst *et al*.,1995] MTHFR polymorphism A1298C results in an A→C substitution at nucleotide 1298, causing the activity of the enzyme to be decreased, but not to the same extent as the C677T polymorphism. [Weisberg *et al*., 1998]

In 2005, Den Heijer performed a large meta-analysis, including 8,364 cases and 12,468 controls, and found a small increase in risk for MTHFR 677TT carriers (odds ratio, 1.20; 95% CI, 1.08-1.32) which increased in association with homocysteine levels. [Den Heijer *et al*., 1995]

In 2007, Bezemer performed a population based case control study with 9,231 participants, but found no association between MTHFR polymorphism and risk of venous thrombosis. [Bezemer *et al*., 2007]

Recently, secondary prevention trials have looked at the effect of lowering homocysteine levels with vitamin B supplementation, but have found that, despite decreased homocysteine levels in the vitamin treatment groups, none of these trials prevented recurrent venous thrombosis or recurrent cardiovascular disease. [Den Heijer *et al*., 2005; Bonaa *et al*., 2006; Lonn *et al*., 2006; Ray *et al*., 2007; Toole *et al*., 2004] However, many healthcare providers have continued to order MTHFR polymorphism testing as part of thrombophilia evaluations.

When we noted a 92% prevalence of MTHFR polymorphisms in 90 patients presenting to our benign hematology clinic for coagulopathy evaluation [Gadiyaram *et al*., 2009], we decided to study our entire MTHFR test population from 2006 through 2012.

Although a high MTHFR polymorphism prevalence (87%) at WVUH was re-confirmed, we found no association between any MTHFR polymorphism and ICD-9 documented clots, nor did we find an association between MTHFR polymorphisms and homocysteine levels. Thus, routine MTHFR testing did not demonstrably contribute to thrombophilia risk assessment in our patient population. We think that MTHFR testing should no longer be routinely ordered for that purpose.

There are several limitations to our data. This was a single center retrospective study representing laboratory testing at one northern Appalachian University Hospital & Clinic population [Figure 1]. The study has no available concurrent "control" group (i.e. healthy people MTHFR tested for no reason except to serve as controls). In our region, we are not aware of any appropriate control or patient population available for comparison with our data.

Since MTHFR polymorphism prevalence is known to vary worldwide, we looked at our MTHFR polymorphism prevalence versus that reported by Gueant-Rodriguez [Gueant-Rodriguez *et al*., 2006] and noted that our patient population appeared "European" more than "West African" or "Mexican", which agrees with West Virginia's 2011 population demographic, having only 1.3% Hispanic and 3.5% African American ethnicity (http://quickfacts.census.gov).

Although Moll and Varga [Moll & Varga, 2015] stated that 7-to-12% of North Americans have an MTHFR-A1298C polymorphism, 52% of our 1,141 patients had such a polymorphism (Table 1). The reason for, and significance of, this higher prevalence is unknown.

In this retrospective review, we found that patient selection for MTHFR testing at our center was heavily skewed, since almost 80% of the MTHFR-tested patients were women from hospital or clinic sources, and only 20% were men. Also, the MTHFR tested women were significantly younger than the men. One hypothesis for this skew is that there may be higher incidence of "pre-event" thrombophilia testing concern for young or pregnant women with history of fetal loss or high risk pregnancy, while males may more often be selected for testing after presenting "post-event" with clinically apparent clots.

The data on venous & arterial clots in these patients was extracted using ICD-9 billing codes, and we do not know the ICD-9 coding error rate at WVUH. The ICD-9 documented clots could precede or follow MTHFR testing and were not necessarily concurrent. We chose to aggregate the ICD-9 codes as "arterial" or "venous"

(see appendix) since a much larger patient population than ours would likely be needed to investigate the significance of individual clot subtypes.

Use of anti-coagulant medications by individual patients during the study period was unknown. Also, other coagulation testing in these 1,141 patients was performed with variable frequency. For example, the factor V polymorphism was tested in 967 patients and 69 (7%) were abnormal; the factor II polymorphism was tested in 958 patients and 46 (5%) were abnormal; anti-cardiolipin IgG was tested in 884 patients and 28 (3%) were abnormal; anti-cardiolipin IgM was tested in 887 patients and 81 (9%) were abnormal. Plasma homocysteine levels were tested in 610 (53%) patients (results in Table 2).

In theory, a clinical selection process for ordering a homocysteine level (or any other test) could affect the likelihood of an abnormal result, skewing results in this subpopulation and affecting any association with MTHFR polymorphisms. Also, universal folate supplementation in United States food products since 1998 may have influenced homocysteine levels in our population. In any case, we found no association of MTHFR polymorphisms with homocysteine levels in the patients tested.

5. Conclusion

MTHFR testing for C677T and A1298C polymorphisms in our patient population did not demonstrably contribute to thrombophilia risk assessment at this northern Appalachian University medical center. Using current procedural terminology of the American Medical Association (CPT) laboratory codes to estimate test cost, the WVUH clinical laboratory billed approximately $120 to perform testing of both MTHFR alleles in each of 1,141 patients, for a CPT conservative cost estimate of $137,000. Our data support the growing consensus that MTHFR testing should not be routinely ordered for thrombophilia testing [USPSTF 2009; Leawood 2012; Hickey, Curry, Toriello 2013], and we intend to bring these data to the attention of the clinicians who order these tests.

Acknowledgements

Kim Evans & Nancy Vest, WVUH Decision Support Group, for ICD-9 coding assistance.

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Appendix: International classification of diseases version 9 (ICD-9) coagulation codes used, in aggregate, to identify thromboses in 1,141 MTHFR-tested patients at West Virginia University Hospital and Clinics

ICD-9 Codes for arterial clots and emboli

362.31	central retinal artery
410.01	anterolat ami init episd
410.02	ami anterolateral subseq
410.1	anter ami nec episd
410.11	anter ami nec init episd
410.12	ami anterior wall subseq
410.2	mi inferolateral, unspec
410.21	inferolat ami init episd
410.22	ami inferolateral subseq
410.31	inferopos ami init episd
410.32	ami inferopost subseq
410.4	ami inferior wall
410.41	infer ami nec init episd
410.42	ami inferior wall subseq
410.5	latrl ami nec episd
410.51	latrl ami nec init episd
410.52	ami lateral nec subseq
410.61	true post infarct, init
410.7	subendo infrc episd
410.71	subendo infrc init episd

410.72 subendo infarct subseq
410.8 ami nec episd
410.81 ami nec initial episd
410.82 ami nec subsequent episd
410.9 ami nos unspecified
410.91 ami unspecified site initial episode of care
410.92 ami nos subsequent episd
433 basilar art occl wo infarc
433.01 occlusion and stenosis of basilar artery with cerebral infarction
433.1 carotid art occ wo infarc
433.10 subclavian art
433.11 occlusion and stenosis of carotid artery with cerebral infarction
433.2 vertebral art occ wo infarct
433.21 occlusion and stenosis of vertebral artery with cerebral infarction
433.3 mult precerebral occ wo infarc
433.31 mult precerebral occ w infarc
433.8 other precerebral occ wo infarc
433.81 other precerebral occl w infarc
433.9 precerebral occl wo infarct
433.91 precerebral occl w infarct
434 cerebral thrombosis without mention of cerebral infarction
434.01 cerebral thrombosis with cerebral infarction
434.9 cerebral art occ wo infarc
434.91 unspecified cerebral artery occlusion with cerebral infarction
437.3 circle of willis
440.0 aorta occlusion
440.8 aorto-iliac arteries
444.22 femoral art
444.22 popliteal art
444.22 tibeal art
444.89 hepatic artery
447.4 celiac axis
557 ac vasc insuff intestine
557.0 mesenteric art, inferior
557.0 mesenteric art, superior
593.81 renal arteries

ICD-9 codes for venous clots and emboli

325 superior saggital sinus vein
326.35 central vein occlusion of retina
362.30 ophthalmic vein
415.11 iatrogenic pulmonary embolism and infarction

415.12 postoperative septic pulmonary embolism
415.13 saddle embol pulmon art
415.19 other pulmonary embolism and infarction
434.1 cerebral embolism without mention of cerebral infarction
434.11 cerebral embolism with cerebral infarction
434.41 popliteal vein
451.11 phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
452.00 portal vein
453.4 ac dvt/embl low ext nos
453.41 ac dvt/emb prox low ext
453.41 femoral vein
453.41 iliac vein
453.42 ac dvt/emb distl low ext
453.5 recurrent deep vein thrombosis of lower extremity
453.51 upper leg dvt (deep venous thromboembolism) chronic
453.52 lower leg dvt (deep venous thromboembolism) chronic
453.6 saphenous vein
453.81 brachial vein
453.85 subclavian vein
453.86 jugular vein
453.87 vena-cava

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