Received: 10 March 2022 | Revised: 4 May 2022 | Accepted: 8 May 2022

DOI: 10.1002/rth2.12739

rpth research & practice in thrombosis & haemostasis

FORUM

A call to action: MTHFR polymorphisms should not be a part of inherited thrombophilia testing

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Handling Editor: Dr Mary Cushman

Abstract

Testing for polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene is still a standard part of thrombophilia testing in many laboratories. However, it is clear that these polymorphisms are not risk factors for arterial or venous thrombosis and therefore should not be part of thrombophilia testing. Eliminating MTHFR from thrombophilia testing will reduce patient concerns and health care costs.

KEYWORDS
guidelines, homocysteine, MTHFR, testing, thrombophilia

Essentials

- Thrombophilia testing commonly includes assays for polymorphisms in methylenetetrahydrofolate reductase (MTHFR) gene
- There is no evidence these polymorphisms are risk factors for venous or arterial thrombosis
- This testing increases health care costs and patient anxiety
- Thrombosis experts need to advocate for elimination of this testing

Who should be tested for inherited thrombophilia continues to be controversial, but there is general agreement that if such testing is performed, the assays included should at a minimum be associated with an increased risk of venous thromboembolism (VTE; eg, factor V Leiden, prothrombin G20210A gene mutation, antithrombin, and protein C/S deficiencies). We are concerned that MTHFR gene polymorphisms continue to be ordered for thrombophilia workup despite years of data demonstrating no associated increased risk of thrombosis. This is particularly prevalent in "thrombophilia panels," which are often ordered by non–thrombosis experts and risk potential misinterpretation. This misinformation creates stress and confusion in nonspecialist clinicians and especially patients.

The MTHFR story began in the 1990s when the search for novel cardiovascular risk factors fell on homocysteine. It was then well known that children born with the inherited metabolic defect homocystinuria, often due to mutations in the cystathionine beta synthetase gene, had severe and premature vascular disease as well as increased risk for VTE. It was a reasonable hypothesis that

The WTD Steering Committee members are listed in Appendix.

perhaps milder elevations would predispose to adult vascular disease. Indeed, a variety of small observational studies did find a correlation between homocysteine levels and vascular disease. MTHFR joins the story as a key enzyme in the folate metabolic pathway. In 1988, a "thermolabile" variant that was a slightly less effective enzyme was reported.[1] In 1995, the polymorphism responsible for this, a C>T transition at nucleotide 677, was discovered.[2] Soon thereafter, another polymorphism with decreased activity, A1298C transition, was described.[3] Population studies showed that these polymorphisms are very common, with a single variant present in 60% to 70% of the population. In fact, 10% were found to have either a homozygous polymorphism or were compound heterozygotes.[4] Studies quickly appeared showing people who had this polymorphism had higher homocysteine levels. Subsequent studies suggested a relationship between the presence of these polymorphisms and thromboembolism.[5] Soon, performing MTHRF mutation assays became enshrined in thrombophilia testing along with the robust "classic tests" such as antithrombin activity and genetic testing for factor V Leiden and others that have been definitively associated with an increased risk of VTE. It indeed was a compelling story—a common polymorphism leading to higher levels of homocysteine leading to thrombosis.

However, rigorously conducted large randomized clinical trials soon disproved this hypothesis, finding no change in recurrent thrombotic rates in those with MTHFR polymorphisms randomized to B vitamin supplementation or placebo.[6-8] Furthermore, in countries such as the United States, which mandated folate supplementation of grain products in 1996 to reduce neural tube defects, subclinical folate deficiency is uncommon.[9,10] Given that an MTHFR polymorphism increases serum homocysteine in low folate states, this renders these genetic markers as even less relevant. Indeed, in countries where folate supplementation is routine, MTFHR mutations do not significantly raise homocysteine levels.[11] Studies that control for confounders cast doubt on the relationship between the presence of MTHFR mutations or homocysteine and vascular disease.[11,12] In fact, high levels of homocysteine may be a marker of other vascular risk factors, such as renal disease, and are not independently causative.[13] Indeed, an elegant mouse study showed that high levels of homocysteine were antithrombotic in mice.[14] Finally, multiple large clinical trials of folate supplementation to reduce vascular disease were resoundingly negative.[8,12,15] Given this convincing data, it is clear that MTHFR polymorphisms do not meet the criteria to be called an inherited thrombophilia and therefore should not be included in thrombophilia panels.

Multiple guidelines from professional societies, such as the American College of Medical Genetics,[5] American College of Obstetricians and Gynecologists,[16] British Society of Haematology,[17] Society for Maternal-Fetal Medicine,[18] and the Choosing Wisely initiative of the American Board of Internal Medicine,[19] all agree that MTHFR testing should not be performed for the evaluation of thrombosis. While some laboratories have removed this test from thrombophilia panels, many still include MTHFR polymorphisms in their standard thrombophilia panel.

MTHFR polymorphisms are not an inherited thrombophilia. Therefore, they should not be included as part of a thrombophilia workup or in any thrombophilia laboratory test panels. Furthermore, patients who carry these polymorphisms should be reassured that this common finding does not place them at increased thrombotic risk and they do not, in fact, carry a thrombophilia. It is time for thrombosis experts to partner with their laboratories and remove MTHFR polymorphism testing from existing thrombophilia panels, as is supported by multiple professional societies and leading institutions. Doing so will prevent unnecessary anxiety for patients and reduce health care spending.[20]

APPENDIX

1 | THE WTD STEERING COMMITTEE

Prof. Cihan Ay, MD; Stefano Barco, MD, PhD; Lana Castellucci, MD, FRCPC, MSc; Gabriela Cesarman-Maus, MD, PhD; Erich Vinicius De Paula, MD, PhD; Mert Dumantepe, MD; Maria Cecilia Guillermo Esposito, MD; Federica Fedele, Lai Heng Lee, MBBS, MMed, FRCP (Edin), FAMS; Claire McLintock, MD; Eriko Morishita, MD; Charles Marc Samama, MD, PhD, FCCP; Helen Okoye, MBBS, FMCPath, FWACP; Todd Robertson.

RELATIONSHIP DISCLOSURE

GDB: consulting for Pfizer, Bristol-Myers Squibb, Janssen, Acelis Connected Health; research funding (to institution) from Boston Scientific; and Board of Directors for Anticoagulation Forum. JMC: scientific ad boards and consulting: Abbott, Anthos, Alnylam, Bristol Myers Squibb, Takeda, and Werfen; and research funding to the Institution CSL Behring. The remaining authors declare no conflicts of interest. TGD and JMC: wrote the manuscript and all authors contributed to revisions/editing of this manuscript.

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How to cite this article: Deloughery TG, Hunt BJ, Barnes GD, Connors JM. A call to action: MTHFR polymorphisms should not be a part of inherited thrombophilia testing. *Res Pract Thromb Haemost*. 2022;6:e12739. doi:10.1002/rth2.12739