

Prevalence of MTHFR C677T and A1298C Mutations and Thrombophilia in Puerto Rico

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Objectives

To determine the prevalence of MTHFR mutations in the Puerto Rican population and their relationship with thrombophilia. To determine if there are other risk factors that can worsen the risks for arterial and venous thromboembolisms in that population.

Background

The methylenetetrahydrofolate reductase (MTHFR) is coded by the gene with the symbol MTHFR on chromosome 1 location p36.3 in humans and there are DNA sequence variants (genetic polymorphisms) associated with this gene, although the two most common ones are C677T and A1298C. Deficiencies in production or function of this enzyme have been associated with increased risk of myocardial infarctions, stroke, venous thrombosis, several types of cancer, congenital defects, inflammatory bowel disease, and several neuropsychiatric conditions. It has been found at high frequencies in Europeans and American Caucasian population. In particular, the C677T polymorphism shows a wide regional and ethnic variation. Homozygosity (TT) among Whites is 6-14%. In African populations and in Blacks living outside of Africa such as in Brazil and in the United States, the frequency falls to less than 2% for the TT variant. The prevalence rises in Mediterranean and Hispanic population. For example, among Hispanics in prevalence ranges as high as 21%. The A1298C mutation, on the other hand, does not show as much population variance; its prevalence is more uniform within the currently studied groups. One study demonstrated that the high frequency of the C677T/C677T and C677T/A1298C genotypes that are found in Hispanics may contribute to a wide spectrum of anomalies, especially in population subject to poor nutrition and low folate intake.

Study Proposed

Cross-sectional Retrospective Review Study of medical records of patients with MTHFR within Puerto Rico with the collaboration of physicians that have identified those cases either as outpatient or inpatient.

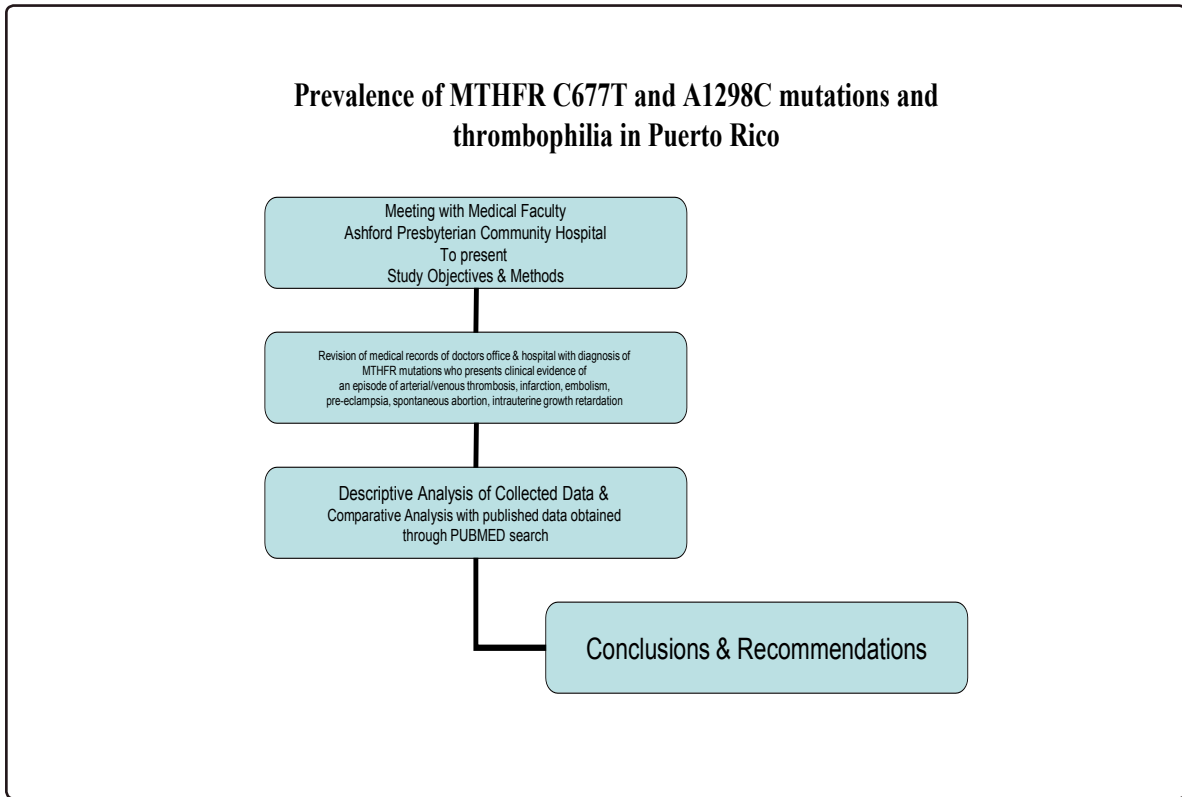
Method and Results

A revision of 2914 active medical records from patients in an ambulatory solo-practice of community-based mixed hematology and medical oncology physician was done. 179 patients have been identified with hypercoagulable states (thrombophilia) for a prevalence of 6.14%. A random cross-sectional selection of 10% of the 179 patients was done for total of 18 cases. MTHFR mutations were identified in 7 out of 18 cases for a prevalence of 39.89% of which 4 (57.14%) were homozygous for 2 copies of C677T, 2 (28.57%) homozygous for 2 copies of A1298C, and 1 (14.29%) heterozygous for 1 copy of C677T and 1 copy of A1298C. Most of them are women. Their age have a range from 17 to 48 with a mean of 39. All cases of MTHFR mutations had normal serum homocysteine levels. The thrombotic events recorded in them were recurrent miscarriage syndrome (3/7), deep venous thrombosis (3/7), and transient ischemic attack (1/7). Only two cases had MTHFR mutation as the only hypercoagulable state and five cases had other co-existence conditions such as anti-thrombin III deficiency, protein C and S deficiencies, Lupus Anticoagulant, and factor V Leiden mutation.

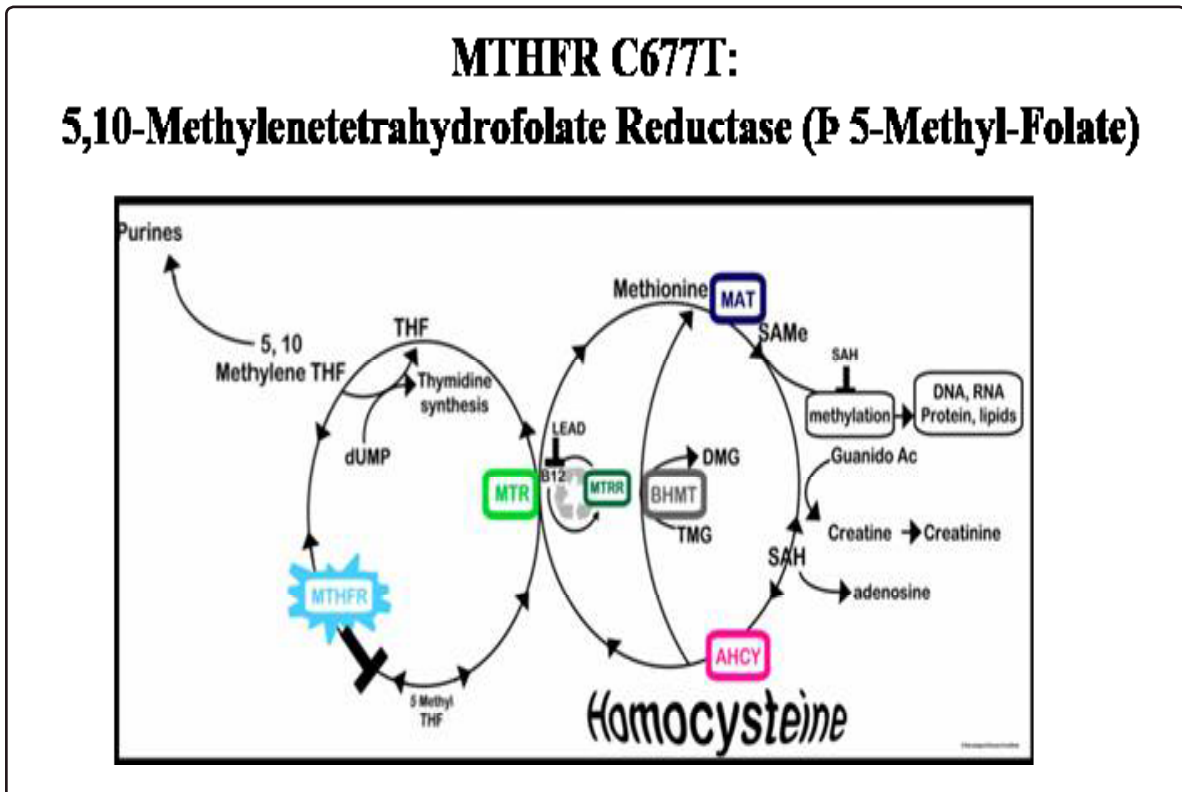
Discussion

Our study sample was small but this is the first puertorrican data published and it is concordant with the published data that states the MTHFR C677C among Hispanics may be higher than in other reported groups. The only discrepancy is that in our group all had normal serum homocysteine levels. It's important what few studies said; the different genotypes between arterial and venous thrombosis and their prevalence may have a crossover and can vary. So, a complete and larger study is needed to distinguish the real difference or crossover between the genotypes, the serum homocysteine level, the personal thromboembolic event, and their family history.

PPT 1



PPT 2



PPT 3

Table 1: Published expert consensus recommendations available evaluating the utilization of MTHFR C677T testing for thrombosis and inherited thrombophilia

Professional Organization	Year	Type of Clinical Consensus	Recommendations for stand-alone MTHFR C677T testing?	Reflex testing in presence of elevated serum homocysteine (>13 umol/L)?
ACMG	2001	Working Group Consensus Statement	No	No
ACOG	2001	Practice Bulletin Guideline	No	No
CAP	2002	Expert Consensus Recommendation	No	No
AHA	205	Expert Recommendation	No	Yes-optional
ACCP	2008	Clinical Guideline	No	No
BHSC	2010	Clinical Guideline	No	No

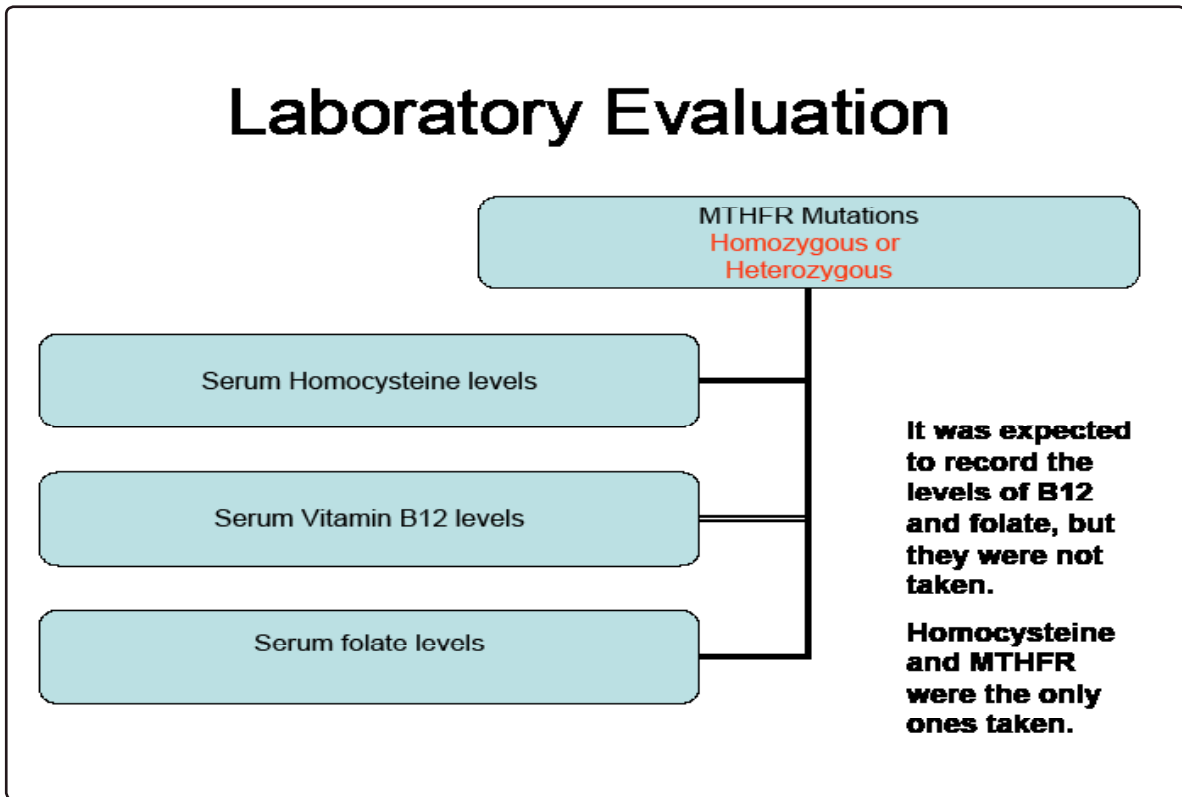
ACMG: American College of Medical Genetics; ACOG: American College of Obstetrics and Gynecology; CAP: College of American Pathologist; AHA: American Heart Association; ACCP: American College of Chest Surgeons; BHSC: British Hematology Standards Committee; MTHFR: Methylene TetraHydroFolate Reductase

PPT 4

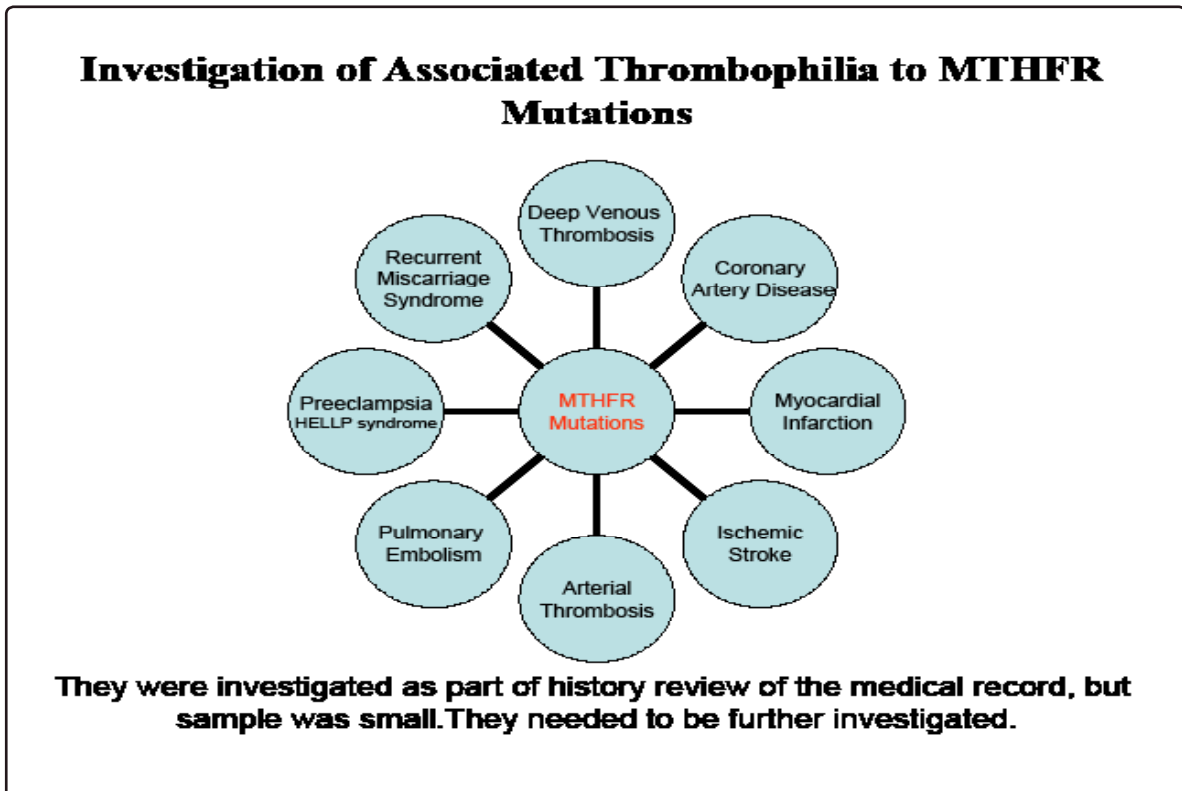
Table 2: Patients with MTHFR Mutations in Our Study

Number	Sex	Age	Hyper-coagulable state	Thrombotic event(s)	Co-Morbid Condition(s)
1	F	17	MTHFR homo 2 copies C677T	Transient Ischemic Attack	Oral Contraceptive Pills
2	F	33	MTHFR, 2 copies A1298C & Prot S def	Recurrent Miscarriage Syndrome	None
3	F	26	MTHFR 2 copies C677T & Lupus Anticoagulant	Recurrent Miscarriage Syndrome	None
4	M	48	MTHFR homo 2 copies C677T	Deep Venous Thrombosis of leg	Left knee arthroscopic surgery
5	F	38	MTHFR 1 for C677T & A1298C plus ATII, Prot C&S def	Recurrent Miscarriage Syndrome and Angina Pectoris	None
6	F	42	MTHFR 2 copies C677T Factor V Leiden	CNS Venous Sinus Thrombosis	None
7	F	32	MTHFR 2 copies for A1298C & ATIII def	Internal Jugular Vein Thrombosis	None

PPT 5



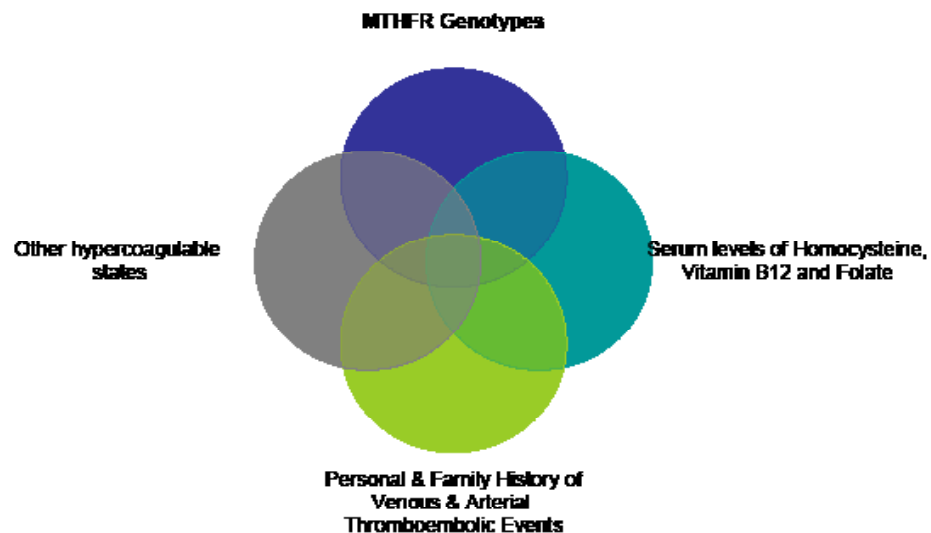
PPT 6



PPT 7

Recommendations

We Need to Study the Relationship & Crossover of the Following in Puerto Rico



Conclusions

The prevalence of the MTHFR mutation was 40% approximately with 57% for the C677T mutation.

It is more frequent in women and they present more with venous thrombosis such as recurrent miscarriage syndrome and deep venous thrombosis.

70% of the cases of the MTHFR mutations co-exist with another ones such as Factor V Leiden mutation, Lupus Anticoagulant, and Deficiencies of Anti-Thrombin III and/or Protein C & S.

References

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