PLOS | ONE

RESEARCH ARTICLE

Prevalence and Geographical Variation of Prothrombin G20210A Mutation in Patients with Cerebral Vein Thrombosis: A Systematic Review and Meta-Analysis

Joaquín V. Gonzalez[1], Andrés G. Barboza[2,3], Fernando J. Vazquez[4,5], Esteban Gándara[6,7,8]*

1 Hospital Universitario, Universidad Nacional de Cuyo, Mendoza, Argentina, **2** Division of neurology and neuro-intensive care, Hospital Central de Mendoza, Mendoza, Argentina, **3** Facultad de Ciencias Médicas, Universidad del Aconcagua, Mendoza, Argentina, **4** Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **5** Internal Medicine Research Unit, Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **6** Thrombosis Program, Division of Hematology-Department of Medicine, University of Ottawa-Ottawa Hospital, Ottawa, Canada, **7** Ottawa Hospital Research Institute, Ottawa, Canada, **8** School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa-Ottawa Hospital, Ottawa, Canada

* gandara.esteban@gmail.com

OPEN ACCESS

Citation: Gonzalez JV, Barboza AG, Vazquez FJ, Gándara E (2016) Prevalence and Geographical Variation of Prothrombin G20210A Mutation in Patients with Cerebral Vein Thrombosis: A Systematic Review and Meta-Analysis. PLoS ONE 11 (3): e0151607. doi:10.1371/journal.pone.0151607

Editor: Pablo Garcia de Frutos, IIBB-CSIC-IDIBAPS, SPAIN

Received: December 1, 2015

Accepted: March 1, 2016

Published: March 31, 2016

Data Availability Statement: All relevant data are within the paper.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Objectives

To compare the prevalence of prothrombin G20210A in patients with objectively confirmed cerebral vein or cortical vein thrombosis against healthy controls, and evaluate geographical variations.

Design

Systematic review and meta-analysis of case control studies.

Methods

We conducted a systematic review of electronic databases including MEDLINE and EMBASE. The main outcome was the prevalence of prothrombin G20210A in patients with objectively confirmed cerebral vein or cortical vein thrombosis; we also analyzed individual country variations in the prevalence. The random-effects model OR was used as the primary outcome measure.

Results

In total 19 studies evaluated 868 cases of cerebral venous thrombosis and 3981 controls. Prothrombin G20210A was found in 103/868 of the patients with cerebral venous thrombosis and 105/3999 of the healthy controls [random effects pooled OR 5.838, 95% CI 3.96 to 8.58; $I^2$17.9%]. The prevalence of prothrombin G20210A was significantly elevated in Italian

studies (OR 9.69), in Brazilian studies (OR 7.02), and in German studies (OR 3.77), but not in Iranian studies (OR 0.98).

Conclusion

Prothrombin G20210A is significantly associated with cerebral venous thrombosis when compared to healthy controls, although this association is highly dependent on the country of origin.

Introduction

Cerebral venous thrombosis is rare thrombotic condition commonly associated with the presence of thrombophilia[1]. Prothrombin G20210A is one of the most common thrombophilias associated with venous thrombosis, including cerebral venous thrombosis[2]. In patients with deep vein thrombosis or pulmonary embolism the prevalence of prothrombin G20210A is highly dependent on the country of origin or ethnicity [3–7] but this variation has not been evaluated in patients with cerebral venous thrombosis. To address this issue, we examined the prevalence and geographical variation of carriers of the prothrombin G20210A in patients with cerebral vein or cortical vein thrombosis.

Methods

We conducted a systematic review of electronic databases including MEDLINE and EMBASE to assess the prevalence of Prothrombin G20210A in patients with cerebral vein thrombosis (S1 Text). The timeframe of the search was from Jan 1995 to February 2015 and was designed with the support of a librarian from the Ottawa Hospital Health Services. The search was supplemented by hand-search of relevant articles, abstract books from international meetings and published reviews.

Study Selection

Case control studies were included if they reported the prevalence of prothrombin G20210A in patients with objectively confirmed cerebral vein or cortical vein thrombosis. All potentially relevant articles were reviewed in full length to ensure that they satisfied the inclusion criteria: 1) enrolment of non-paediatric patients with cerebral vein or cortical vein thrombosis; 2) the study reported the diagnostic test used to confirm the diagnosis (including digital subtraction angiography, MRI, CT angiography or autopsy); 3) Prothrombin G20210A genotyping was available for all participants; 4) the numbers of cases and controls with and without prothrombin G20210A were provided in the article. Studies were excluded if their subjects did not receive objective testing for the prothrombin G20210A mutation, included a paediatric population or included patients in which the diagnostic methods was not reported or patient with self-reported cerebral venous thrombosis.

Data Extraction and Quality Assessment

Two reviewers (J.G. and E.G.) independently assessed the eligibility of all articles identified in the initial search strategy and used the Newcastle–Ottawa Quality Assessment Scale for Observational Studies to assess the methodological quality of the selected studies. A third reviewer adjudicated all discrepancies if needed (A.B.)

Outcome Measure

The primary outcome measure was the odds ratio (OR) for the prevalence of prothrombin G20210A patients with cerebral vein or cortical vein thrombosis as compared with healthy controls. We also aimed to analyze the prevalence of prothrombin G20210A mutation across different countries, if two or more studies were available.

Data Synthesis and Analysis

The meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (S1 and S2 Tables presents the meta-analysis of genetic association studies checklist). The random-effects model OR was used as the outcome measure, along with the corresponding 95% confidence intervals (CIs). The I^2 statistic was used to quantify heterogeneity among the pooled estimates across studies. An I^2 value less than 25% was considered low-level heterogeneity, 25% to 50% as moderate-level, and greater than 50% as high-level. Homozygote and heterozygote carriers of prothrombin G20210A were analyzed as one group due to the rarity of homozygote carriers. A funnel plot and test for bias using the Harbord and Egger test[8]. We also added a L'Abbé plot which is useful for exploring heterogeneity and identifying outlying trials in a meta-analysis[9]. The statistical analysis and graphs were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2013) and the bias analysis was performed with STATS direct (StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2013).

Results

As shown in fig 1 our initial electronic search identified 238 relevant abstracts (after removal of duplicates). One hundred and ninety five were considered non-relevant to the search and excluded. Of the 43 that were selected for full text review 21[10–30]were included in this review, 19[10–12,14,16–25,27–31]of which were used for the primary analysis (in Table 1 we present the studies characteristics and in Table 2 their quality assessment); 22 were excluded for the reasons described in Fig 1. Two studies were excluded from the primary analysis as they did not report the method used for the diagnosis of cerebral venous thrombosis[13,26]. Five of the studies were conducted in Italy[17,21,27,29,31], three in Brazil[18,25,28], three in Germany [10,20,24], two in Iran[16,23], one in France[19], one in India[32],one in Netherlands[30]one in Switzerland[11], one in Tunisia[14] and one in the United Kingdom[12].

In total the 19 studies evaluated 868 cases of cerebral venous thrombosis and 3999 controls (see Table 3 for a more comprehensive review of the number of patients included in each study individual OR and bias assessment). Prothrombin G20210A was found in 103/868 of the patients with cerebral venous thrombosis and 105/3999 of the controls [random effects pooled OR 5.838, 95% CI 3.96 to 8.58; $I^2$17.9%] (Fig 2) with low evidence of bias (Figs 3 and 4). As shown in Table 3 the addition of the two relevant studies not reporting the diagnostic methods used did not modify the random effects pooled OR[13,26].

As shown in Table 4, in Italian studies [17,21,27,29,31] prothrombin G20210A was found in 51/232 of patients with cerebral venous thrombosis and in 34/927 of the controls (random effects pooled OR 9.69, 95% 5.51 to 17.05; I^2 0%). In Brazilian studies[18,25,28] prothrombin G20210A was found in 14/82 of patients with cerebral venous thrombosis and in 14/576 of the controls (random effects pooled OR 7.02, 95% CI 2.79 to 17.63; I^2 21.8%). In the three German [10,20,24] studies prothrombin G20210A was found in 28/255 of patients with cerebral venous thrombosis and in 49/1563 of the controls (random effects pooled OR 3.77, 95% CI 2.22 to 6.26; I^2 0%). In the two Iranian studies[16,23] there was no difference in the prevalence

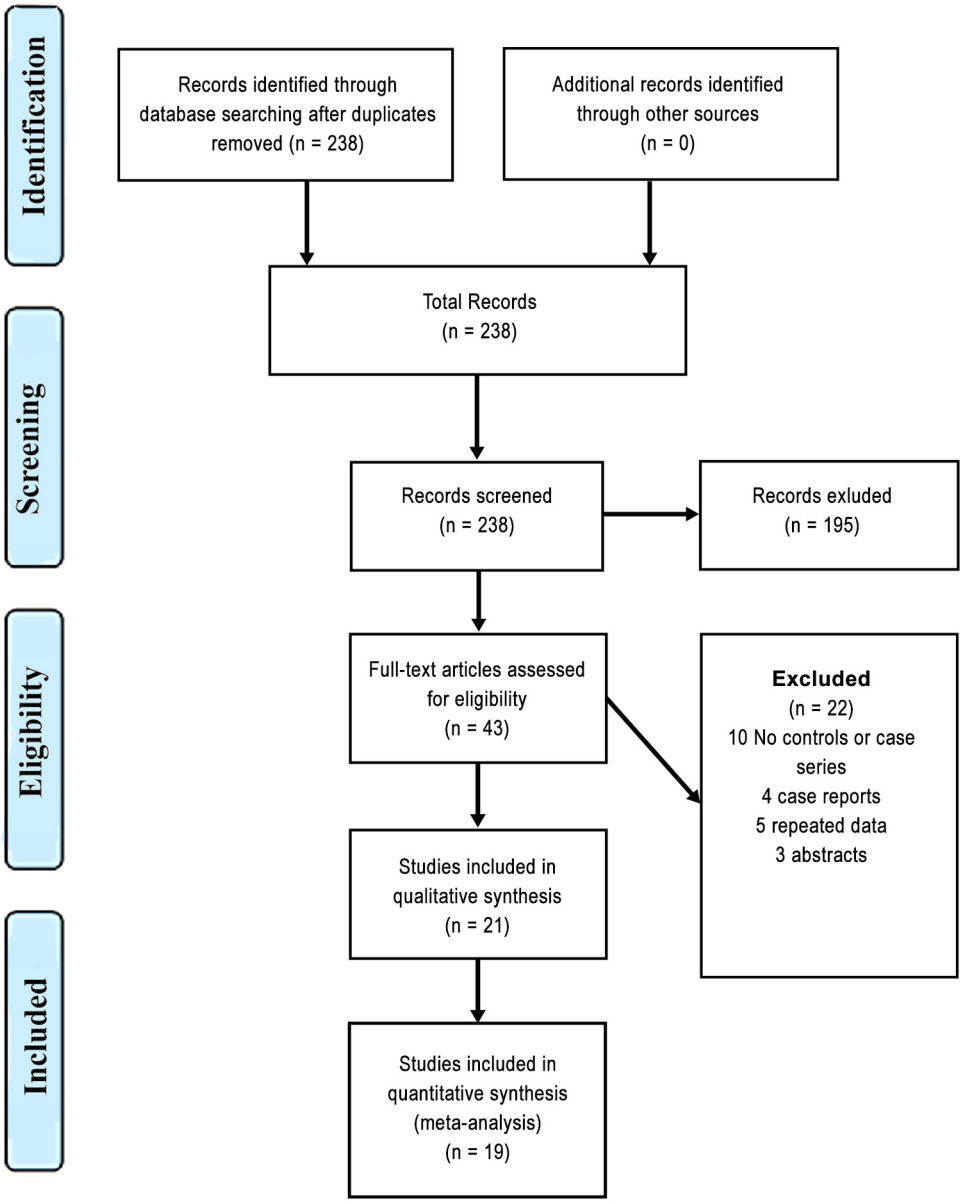

Fig 1. Flow diagram.

doi:10.1371/journal.pone.0151607.g001

prothrombin G20210A between patients with cerebral venous thrombosis and controls (random effects pooled OR 0.98, 95% CI 0.18 to 5.39; I^2 0%).

Discussion

Our systematic review confirmed a significant association of prothrombin G20210A with cerebral venous thrombosis but this association is highly dependent to the country of origin. Individual country meta-analysis suggested significant association between prothrombin G20210A and cerebral venous thrombosis in studies conducted in Italy[17,21,27,31], Brazil[18,25,28] and Germany[10,20,24]. Consistently with prior literature[3] suggesting a low prevalence of the condition in those from Asian or African descent, none of the studies included from India

Table 1. Characteristics of the studies included.

Study	Year	Country	Diagnostic method	N CVT	N Controls	Matched?	Hardy-Weinberg equilibrium assessed?	% pregnancy CVT	% OCP CVT	% Female with CVT
Ashjazadeh[16]	2012	Iran	MRI and MRV	57	50	Yes, age/gender/ ethnicity	No	7	47	66
Ben Salem-Berrabah[14]	2012	Tunisia	CT scan, MRI/ MRV or autopsy	26	197	No	Yes, in equilibrium	.	.	80
Bombeli[11]	2002	Switzerland	CT scan, MRI/ MRV or autopsy	51	120	No	No	.	3.2	76.5
Boncoraglio [17]	2004	Italy	Angiography, CT or MRI	26	100	No, healthy hospital workers	No	.	42	73
Colaizo[29]	2007	Italy	Digital angiography, CT or MRI	45	286	sex, age and social status	Yes	NA	NA	69%
Gadelha[18]	2005	Brazil	Angiography or MRI	21	217	Age/racial background, no history of thrombosis or genetic relationship	No	.	85%	84
Hillier[12]	1998	UK	Digital angiography, CT, autopsy or MRI	15	300	No	No	.	38	70
Koopman[30]	2009	Netherlands	Digital angiography, CT, surgery or MRI	19	19	Age and Sex	No	20%	60%	79%
Le Cam-Duchez[19]	2005	France	Angiography or MRI	26	84	Age and sex	No	9	44	69
Lichy[20]	2005	Germany	MRI and/or angiography	77	203	No	No	11.30%	43%	78%
Madonna[21]	2000	Italy	MRI and/or angiography	10	254	Sex and age	No	.	33	60%
Martinelli [31]	2003	Italy	MRI, CT and/or angiography	121	242	Sex, age, geographic origin, and level of education	No	NA	96%	74%
Nagaraja[32]	2007	India	MRI/MRV	96	103	Age	No	100	0	100
Rahimi[23]	2010	Iran	MRI	24	100	Age/ gender; Kurdish descent	No	.	.	70%
Reuner[10]	1998	Germany	MRI and/or angiography	45	354	No	No	10	85	75%
Ringelstein[24]	2012	Germany	MRI and/or angiography	136	1054	No, but same ethnicity	Not done for prothrombin gene	.	NR	34
Rodrigues[25]	2004	Brazil	MRI and/or angiography	42	134	No	No	20	60	67
Ventura[27]	2004	Italy	MRI, CT and/or angiography	30	40	Age/gender	No		9	53
Voetsch[28]	2000	Brazil	MRI, CT and/or angiography	14	225	Age/gender	No	.	.	71
Excluded from main analysis										
Tufano[26]	2014	Italy	Not reported	56	184	Age/gender same ethnicity		NR	53.7	73%
Margaglione [13]	2001	Italy	Not reported	28	1304	No		.	.	.

CVT: Cerebral venous thrombosis; OCP: Oral contraception; CT: computerized axial tomography; MRI/MRV: Magnetic resonance imaging (MRI) or magnetic resonance venography; Angiography: digital subtraction angiography

doi:10.1371/journal.pone.0151607.t001

Table 2. Quality assessment.

Study	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Ashjazadeh [16]	*	*	*	*		*	*	*
Ben Salem-Berrabah[14]	*	*				*	*	*
Bombeli[11]	*	*	*	*		*	*	*
Boncoraglio [17]	*	*				*	*	*
Colaizo[29]	*	*	*	*		*	*	*
Gadelha[18]	*	*	*	*		*	*	*
Hillier[12]	*	*	*	*		*	*	*
Koopman [30]	*	*				*	*	*
Le Cam-Duchez[19]	*	*	*	*		*	*	*
Lichy[20]	*	*	*	*		*	*	*
Madonna[21]	*	*	*	*		*	*	*
Martinelli [31]	*	*	*			*	*	*
Nagaraja[32]	*	*	*	*		*	*	*
Rahimi[23]	*	*				*	*	*
Reuner[10]	*	*	*	*		*	*	*
Ringelstein [24]	*	*	*	*		*	*	*
Rodrigues [25]	*	*	*	*		*	*	*
Ventura[27]	*		*			*	*	*
Voetsch[28]	*	*	*	*		*	*	*

doi:10.1371/journal.pone.0151607.t002

[33], Iran[16,23] or Tunisia[14]reported an association between prothrombin G20210A and cerebral venous thrombosis. For the first time, and to the best of our knowledge, information about the geographical variations of prothrombin G20210A with cerebral venous thrombosis has been presented.

Similar to deep vein thrombosis and pulmonary embolism the question that remains unanswered is the value of screening for prothrombin G20210A with cerebral venous thrombosis in order to predict who is at high risk of recurrent venous thromboembolism? Our results would suggest that given it high prevalence in countries such as Italy or Brazil, it would be reasonable to screen for this condition, especially in those with unprovoked events[34]. On the other hand, evidence suggests that the rate of recurrent venous thromboembolism associated with prothrombin G20210A gene mutation is low in those with deep vein thrombosis or pulmonary embolism[35,36]. Two our knowledge only two studies, conducted in Italy, have reported the rate of recurrent venous thromboembolism in patients with prothrombin G20210A and cerebral venous thrombosis who discontinue anticoagulation[26,37], none of them showed an increased risk for recurrent venous thromboembolism in carriers of prothrombin G20210A diagnosed with cerebral venous thrombosis.

Table 3. Meta-analysis and individual study data.

Study	Carriers of PTGM^/CVT* cases	Carriers of PTGM^/Healthy controls	Odds ratio	95% CI
Ashjazadeh	2/57	2/50	0.87	0.11 to 6.43
Ben Salem-Berrabah	0/26	5/197	0.66	0.035 to 12.28
Bombeli	2/28	2/80	3.00	0.40 to 22.38
Boncoraglio	3/26	3/100	4.21	0.79 to 22.26
Colaizo	8/45	9/286	6.65	2.41 to 18.31
Gadelha	5/31	2/217	20.67	3.81 to 111.99
Hillier	0/15	4/300	2.12	0.10 to 41.26
Koopman	1/19	0/19	3.16	0.12 to 82.64
Le Cam-Duchez	7/26	3/84	9.94	2.35 to 42.063
Lichy	8/77	5/202	4.56	1.44 to 14.43
Madona	5/10	16/259	15.18	3.98to 57.93
Martinelli	26/121	5/242	12.97	4.83 to 34.78
Nagaraja	0/96	0/103	-	
Rahimi	0/24	1/100	1.35	0.053 to 34.25
Reuner	4/45	8/354	4.22	1.21 to 14.62
Ringelstein	14/136	33/1007	3.38	1.76 to 6.50
Rodrigues	7/42	1/134	26.60	3.167 to 223.42
Ventura	9/30	1/40	16.71	1.98 to 141.07
Voetsch	2/14	5/225	7.33	1.28 to 41.77
Total (random effects)	**103/868**	**105/3999**	**5.83**	**3.96 to 8.58**
I^2 (inconsistency)			17.9%	**0.00 to 53.41**
Bias indicators. Harbold-Egger: bias = -0.30 (92.5% CI = -2.05 to 1.46) P = 0.74				
Analysis with excluded studies	**Carriers of PTGM^/CVT* cases**	**Carriers of PTGM^/Healthy controls**	**Odds ratio**	**95% CI**
Margaglione	6/28	56/1301	6.06	2.36 to 15.54
Tufano	16/55	10/183	7.09	2.99 to 16.82
Total (random effects)	125/951	171/5483	5.93	4.32 to 8.13
I^2 (inconsistency)			8.09%%	**0.00 to 43.53**
Bias indicators. Harbold-Egger: bias = -0.21 (92.5% CI = -1.83to 1.41) P = 0.80				

^PTGM: prothrombin G20210A;

*CVT: cerebral vein thrombosis

doi:10.1371/journal.pone.0151607.t003

Other systematic reviews have addressed the prevalence of prothrombin G20210A in patients diagnosed with cerebral venous thrombosis[2,38]. Our results confirms prior findings in other systematic reviews[2,38] suggesting a significant association between prothrombin G20210A diagnosed with cerebral venous thrombosis and provide. Also for the first time information about geographical variations associated with the prevalence of prothrombin G20210A in patients with cerebral vein thrombosis is presented. As previously suggested in patients with deep vein thrombosis or pulmonary embolism[3–7], we found that the prevalence of

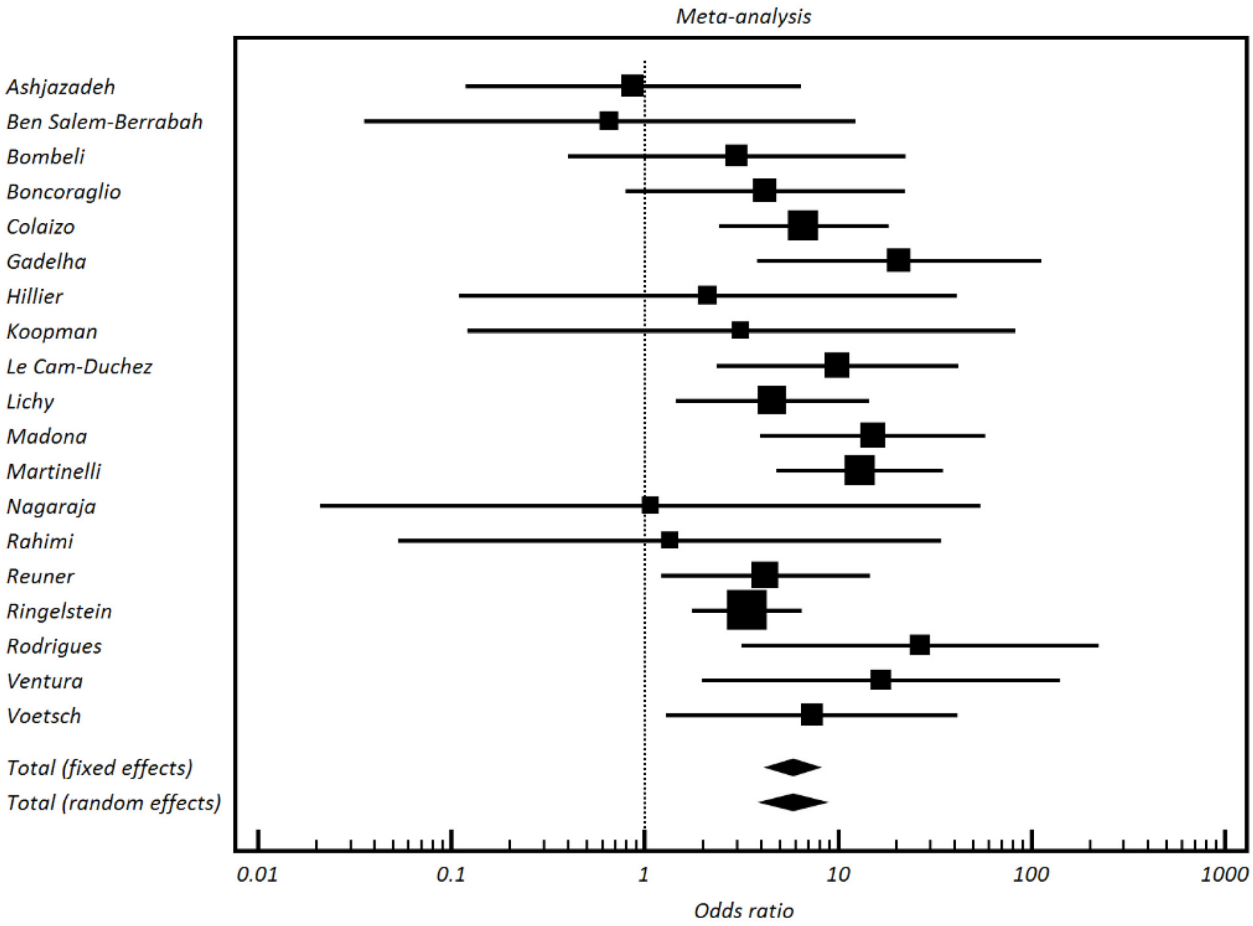

Fig 2. Forest plot prevalence of prothrombin G20210A.

doi:10.1371/journal.pone.0151607.g002

prothrombin gene mutation was higher in southern European countries, and no association in Asian countries.

Our systematic review has limitations. First, we did could not evaluate the prevalence of prothrombin gene mutation in patients with unprovoked cerebral venous thrombosis. Second, not all the studies used matching and, as such, potentially introduced bias. Third, homozygous prothrombin G20210A could not be assessed owing to the small number of patients affected. Fourth, our individual country analysis did not take into different genetic populations who might live in a country[39]. Fifth, we did not adjust for important risk factors (such as provoked cerebral vein thrombosis vs. unprovoked; female vs. male) which could introduce some bias. Finally, most of the studies included did not reported on the Hardy-Weinberg equilibrium and given that only two of the studies reported on it we did not conducted a sensitivity analysis[40,41].

In conclusion, our systematic review confirmed a significant association of prothrombin G20210A with cerebral venous thrombosis but suggest that this association is highly dependent to the country of origin. More studies should evaluate the role of prothrombin G20210A as a predictor of recurrent venous thromboembolism in patients with cerebral venous thrombosis, especially in those countries where its prevalence high prevalence.

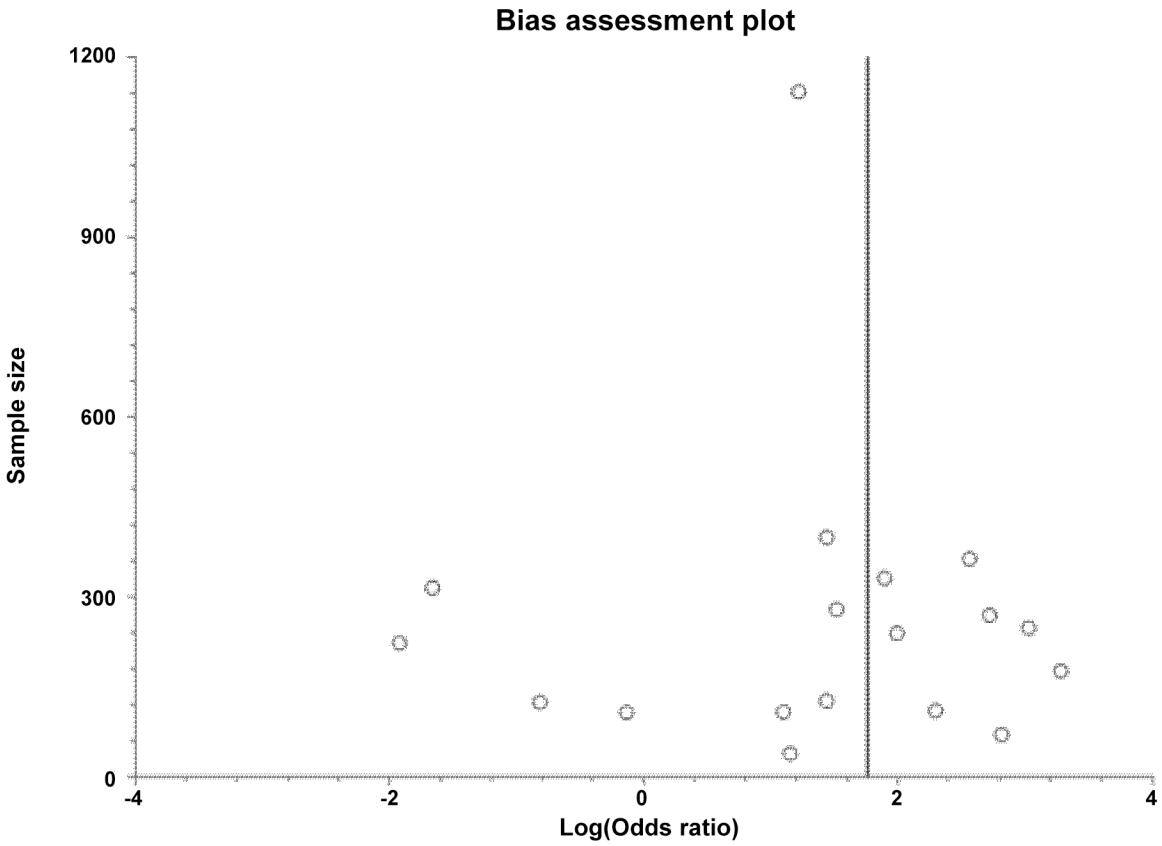

Fig 3. Bias assessment plot.

doi:10.1371/journal.pone.0151607.g003

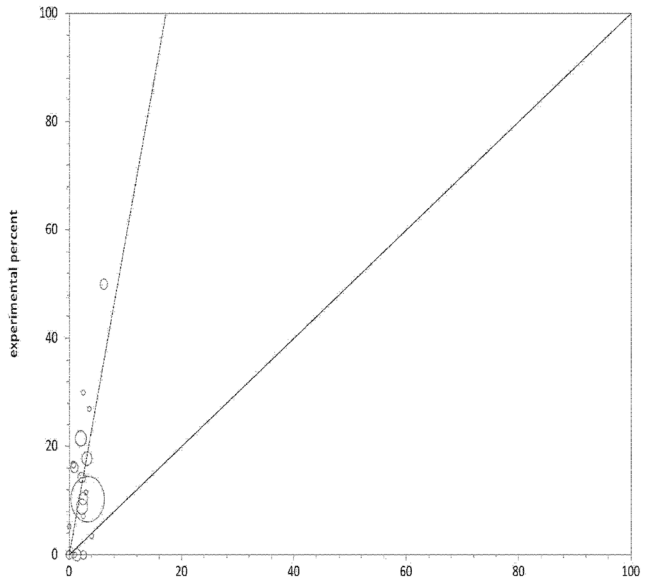

Fig 4. L'Abbé bias plot.

doi:10.1371/journal.pone.0151607.g004

Table 4. Individual country meta-analysis.

Study	Carriers of PTGM^/CVT* cases	Carriers of PTGM^/Healthy controls	Odds ratio	95% CI
Italy				
Boncoraglio	3/26	3/100	4.21	0.79 to 22.26
Colaizzo	8/45	9/286	6.65	2.41 to 18.31
Madona	5/10	16/259	15.18	3.98 to 57.93
Martinelli	26/121	5/242	12.97	4.83 to 34.78
Ventura	9/30	1/40	16.71	1.98 to 141.07
Total (random effects)	**51/232**	**34/927**	**9.69**	**5.51 to 17.05**
I^2 (inconsistency)			**0.00%**	**0.00 to 64.1**
Bias indicator. Horbold-Egger: bias = 1.8 (92.5% CI = -2.96to 6.63) P = 0.38				
Brazil				
Gadelha	5/26	5/217	10.0	2.70 to 37.72
Rodrigues	7/42	7/134	3.62	1.19 to 11.03
Voetsch	2/14	2/225	18.58	2.40 to 143.52
Total (random effects)	**14/82**	**14/576**	**7.02**	**2.79 to 17.63**
I^2 (inconsistency)			**22.82%**	**0.00 to 97.41**
Bias indicator. Horbold-Egger: bias = 1.37 (92.5% CI = -20.93 to 23.68) P = 0.69				
Germany	**Carriers of PTGM^/CVT* cases**	**Carriers of PTGM^/Healthy controls**		
Lichy	10/77	5/202	5.88	1.94 to 17.82
Reuner	4/45	8/354	4.22	1.21 to 14.62
Ringelstein	14/136	33/1007	3.38	1.76 to 6.50
Total (random effects)	**28/255**	**49/1563**	**3.77**	**2.22 to 6.26**
I^2 (inconsistency)			**0.00%**	**0.00 to 72.29**
Bias indicators. Horbold-Egger: bias = 0.93 (92.5% CI = -3.34 to 5.21) P = 0.31				
Iran	**Carriers of PTGM^/CVT* cases**	**Carriers of PTGM^/Healthy controls**		
Ashjazadeh	2/57	2/50	0.87	0.11 to 6.43
Rahimi	0/24	1/100	1.35	0.05 to 34.25
Total (random effects)	**2/81**	**3/150**	**0.98**	**0.18 to 5.39**
I^2 (inconsistency)			**0.00%**	**0.00 to 0.00**
Bias indicators not done due to low number of studies				

^PTGM: prothrombin G20210A;

*CVT: cerebral vein thrombosis

doi:10.1371/journal.pone.0151607.t004

Supporting Information

S1 Table. 2009 PRISMA checklist.
(DOC)

S2 Table. Meta-analysis of genetic association studies checklist.
(DOCX)

S1 Text. Literature search.
(PDF)

Acknowledgments

Ms. Risa Shorr for helping with the literature search.

Author Contributions

Conceived and designed the experiments: JG AB FV EG. Performed the experiments: JG AB FV EG. Analyzed the data: JG AB FV EG. Contributed reagents/materials/analysis tools: JG AB FV EG. Wrote the paper: JG AB FV EG.

References

1. Ferro JM, Canhão P, Stam J, Bousser M-G, Barinagarrementeria F, Investigators for the I. Prognosis of Cerebral Vein and Dural Sinus Thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004; 35: 664–670. PMID: 14976332
2. Lauw MN, Barco S, Coutinho JM, Middeldorp S. Cerebral Venous Thrombosis and Thrombophilia: A Systematic Review and Meta-Analysis. Semin Thromb Hemost. 15.10.2013 ed. 2013; 39: 913–927. doi: 10.1055/s-0033-1357504 PMID: 24129682
3. Rosendaal FR, Doggen CJM, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic Distribution of the 20210 G to A Prothrombin Variant. Thromb Haemost. Schattauer Publishers; 1998; 79: 706–708.
4. Tang L, Hu Y. Ethnic diversity in the genetics of venous thromboembolism. Thromb Haemost. Schattauer Publishers; 2015; 114: 901–909. doi: 10.1160/TH15-04-0330
5. Margaglione M, Grandone E. Population genetics of venous thromboembolism. A narrative review. Thromb Haemost. Schattauer Publishers; 2011; 105: 221–231. doi: 10.1160/TH10-08-0510
6. ZAKAI NA, McCLURE LA. Racial differences in venous thromboembolism. J Thromb Haemost. Blackwell Publishing Ltd; 2011; 9: 1877–1882. doi: 10.1111/j.1538-7836.2011.04443.x
7. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nat Rev Cardiol. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.; 2014; 11: 140–156.
8. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. 2011.
9. Egger M. Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd ed. Egger Matthias, Smith George Davey Altman DG, editor. BMJ Publishing Group; 2008. doi: 10.1002/9780470693926
10. Reuner KH, Ruf A, Grau A, Rickmann H, Stolz E, Jüttler E, et al. Prothrombin Gene G20210→A Transition Is a Risk Factor for Cerebral Venous Thrombosis. Stroke. 1998; 29: 1765–1769. doi: 10.1161/01.STR.29.9.1765 PMID: 9731592
11. Bombeli T, Basic A, Fehr J. Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems. Am J Hematol. Wiley Subscription Services, Inc., A Wiley Company; 2002; 70: 126–132. doi: 10.1002/ajh.10103
12. Hillier CE, Collins PW, Bowen DJ, Bowley S, Wiles CM. Inherited prothrombotic risk factors and cerebral venous thrombosis. QJM. 1998; 91: 677–680. PMID: 10024925
13. Margaglione M, Brancaccio V, Ciampa A, Papa ML, Grandone E, Di Minno G. Inherited thrombophilic risk factors in a large cohort of individuals referred to Italian thrombophilia centers: distinct roles in different clinical settings. Haematologica. 2001; 86: 634–639. PMID: 11418373
14. Ben Salem-Berrabah O, Fekih-Mrissa N, N'Siri B, Ben Hamida A, Benammar-Elgaaied A, Gritli N, et al. Thrombophilic polymorphisms—factor V Leiden G1691A, prothrombin G20210A and MTHFR C677T – in Tunisian patients with cerebral venous thrombosis. J Clin Neurosci. 2012; 19: 1326–1327. doi: 10.1016/j.jocn.2011.11.029 PMID: 22721898
15. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High Risk of Cerebral-Vein Thrombosis in Carriers of a Prothrombin-Gene Mutation and in Users of Oral Contraceptives. N Engl J Med. Massachusetts Medical Society; 1998; 338: 1793–1797. doi: 10.1056/NEJM199806183382502
16. Ashjazadeh N, Farjadian M, Shirin P. Factor V G1691A and prothrombin G20210A gene polymorphisms among Iranian patients with cerebral venous thrombosis. Neurol Asia. 2012; 17: 199–203.
17. Boncoraglio G, Carriero MR, Chiapparini L, Ciceri E, Ciusani E, Erbetta A, et al. Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis. Eur J Neurol. Blackwell Science Ltd; 2004; 11: 405–409. doi: 10.1111/j.1468-1331.2004.00802.x
18. Gadelha T, André C, Jucá AA V, Nucci M. Prothrombin 20210A and Oral Contraceptive Use as Risk Factors for Cerebral Venous Thrombosis. Cerebrovasc Dis. 2005; 19: 49–52. PMID: 15528884
19. Le Cam-Duchez V, Bagan-Triquenot A, Ménard J-F, Mihout B, Borg J-Y. Association of the protein C promoter CG haplotype and the factor II G20210A mutation is a risk factor for cerebral venous thrombosis. Blood Coagul Fibrinolysis. 2005; 16.

20. Lichy C, Dong-Si T, Reuner K, Genius J, Rickmann H, Hampe T, et al. Risk of cerebral venous thrombosis and novel gene polymorphisms of the coagulation and fibrinolytic systems. J Neurol. Steinkopff-Verlag; 2006; 253: 316–320. doi: 10.1007/s00415-005-0988-4
21. Madonna P, De Stefano V, Coppola A, Albisinni R, Cerbone AM. G20210A PRTH Gene Mutation and Other Thrombophilic Polymorphisms in Patients With Cerebral Vein Thrombosis. Stroke. 2000; 31: 1785–1790. doi: 10.1161/01.STR.31.7.1785-c
22. Nagaraja D, Noone ML, Bharatkumar VP, Christopher R. Homocysteine, folate and vitamin B12 in puerperal cerebral venous thrombosis. J Neurol Sci 43–47), 2008Date Publ 15 Sep 2008. 2008; 43–47.
23. Rahimi Z, Mozafari H, Bigvand Amir Hossein Amiri, Doulabi Reza Mohammad, Vaisi-Raygani A, Afshari D, et al. Cerebral Venous and Sinus Thrombosis and Thrombophilic Mutations in Western Iran: Association With Factor V Leiden. Clin Appl Thromb. 2010; 16: 430–434.
24. Ringelstein M, Jung A, Berger K, Stoll M, Madlener K, Klötzsch C, et al. Promotor polymorphisms of plasminogen activator inhibitor-1 and other thrombophilic genotypes in cerebral venous thrombosis: a case-control study in adults. J Neurol. Springer-Verlag; 2012; 259: 2287–2292. doi: 10.1007/s00415-012-6477-7
25. Rodrigues CA, Rocha LKA, Morelli VM, Franco RF, Lourenço DM. Prothrombin G20210A mutation, and not factor V Leiden mutation, is a risk factor for cerebral venous thrombosis in Brazilian patients. J Thromb Haemost. Blackwell Science Inc; 2004; 2: 1211–1212. doi: 10.1111/j.1538-7836.2004.00785.x
26. Tufano A, Guida A, Coppola A, Nardo A, Di Capua M, Quintavalle G, et al. Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. Blood Transfus. Edizioni SIMTI—SIMTI Servizi Srl; 2014; 12: s337–s342. doi: 10.2450/2013.0196-12
27. Ventura P, Cobelli M, Marietta M, Panini R, Rosa MC, Salvioli G. Hyperhomocysteinemia and Other Newly Recognized Inherited Coagulation Disorders (Factor V Leiden and Prothrombin Gene Mutation) in Patients with Idiopathic Cerebral Vein Thrombosis. Cerebrovasc Dis. 2004; 17: 153–159.
28. Voetsch B, Damasceno BP, Camargo ECS, Massaro A, Bacheschi LA, Scaff M, et al. Inherited Thrombophilia as a Risk Factor for the Development of Ischemic Stroke in Young Adults. Thromb Haemost. Schattauer Publishers; 2000; 83: 229–233.
29. Colaizzo D, Amitrano L, Iannaccone L, Vergura P, Cappucci F, Grandone E, et al. Gain-of-function gene mutations and venous thromboembolism: distinct roles in different clinical settings. J Med Genet. 2007; 44: 412–416. PMID: 17307838
30. Koopman K, Uyttenboogaart M, Hendriks HGD, Luijckx G-J, Cramwinckel IR, Vroomen PC, et al. Thromboelastography in patients with cerebral venous thrombosis. Thromb Res. 2009; 124: 185–188. doi: 10.1016/j.thromres.2008.12.032 PMID: 19187954
31. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood. 2003; 102: 1363–1366. PMID: 12714502
32. Dindagur N, Kruthika-Vinod TP, Christopher R. Thrombophilic gene polymorphisms in puerperal cerebral veno-sinus thrombosis. J Neurol Sci. 2006; 249: 25–30. doi: 10.1016/j.jns.2006.05.061 PMID: 16839569
33. Nagaraja D, Kruthika-Vinod TP, Christopher R. The prothrombin gene G20210A variant and puerperal cerebral venous and sinus thrombosis in South Indian women. J Clin Neurosci. 2007; 14: 635–638. doi: 10.1016/j.jocn.2006.05.001 PMID: 17433691
34. Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and Management of Cerebral Venous Thrombosis: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2011; 42: 1158–1192. doi: 10.1161/STR.0b013e31820a8364 PMID: 21293023
35. Segal JB Necochea AJ,et al B DJ. Predictive value of factor v leiden and prothrombin g20210a in adults with venous thromboembolism and in family members of those with a mutation: A systematic review. JAMA J Am Med Assoc. 2009; 301: 2472–2485.
36. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Can Med Assoc J. 2008; 179: 417–426.
37. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Long-Term Evaluation of the Risk of Recurrence After Cerebral Sinus-Venous Thrombosis. Circ. 2010; 121: 2740–2746.
38. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood. 2006; 107: 2766–2773. PMID: 16397131
39. Arruda VR, Annichino-Bizzacchi JM, Goncalves MS, Costa FF. Prevalence of the prothrombin gene variant (nt20210A) in venous thrombosis and arterial disease. ThrombHaemost. Hematology-Hemotherapy Center, State University of Campinas, Campinas-SP, Brazil. vrarruda@hotmail.com; 1997; 78: 1430–1433.

40. Attia J, Thakkinstian A, D'Este C. Meta-analyses of molecular association studies: Methodologic lessons for genetic epidemiology. J Clin Epidemiol. 2003; 56: 297–303. doi: 10.1016/S0895-4356(03)00011-8 PMID: 12767405

41. Salanti G, Sanderson S, Higgins JPT. Obstacles and opportunities in meta-analysis of genetic association studies. Genet Med. The American College of Medical Genetics; 2005; 7: 13–20.