Genes Associated With Adult Cerebral Venous Thrombosis

Thomas Marjot, BSc; Sunaina Yadav, MS; Nazeeka Hasan, MRes; Paul Bentley, MRCP; Pankaj Sharma, PhD, MD, FRCP

Background and Purpose—Quantitative predictions of the risk of cerebral venous thrombosis (CVT) conferred by certain genotypes have yet to be reliably established. We conducted a comprehensive meta-analysis of all candidate genes studied to assess their genetic contribution to the etiology of CVT. We compared our findings against equivalent analyses for pediatric CVT and adult ischemic stroke.

Methods—Databases were searched to August 2010 for all genes investigated in adult CVT, and odds ratios (ORs) for each gene-disease association were calculated. A mendelian randomization strategy was also undertaken to determine whether a causal relation to one gene could be ascertained.

Results—We identified 26 case-control studies investigating 6 polymorphisms in 6 genes and included 1183 CVT cases and 5189 controls. Statistically significant associations with CVT were found for factor V Leiden/G1691A (OR = 2.40; 95% CI, 1.75 to 3.30; \( P < 0.00001 \)) and prothrombin/G20210A (OR = 5.48; 95% CI, 3.88 to 7.74; \( P < 0.00001 \)). After iterative analysis controlling for interstudy heterogeneity, methylene tetrahydrofolate reductase/C677T was also found to be significantly associated (OR = 2.30; 95% CI, 1.20 to 4.42; \( P = 0.02 \)). Variants in the remaining 3 genes (Janus kinase-2, plasminogen activator inhibitor-1, and protein Z) were not significantly associated. Pooled ORs for CVT risk in adults for factor V Leiden and prothrombin were significantly greater when compared against childhood CVT and adult arterial ischemic stroke. A causal relation with methylene tetrahydrofolate reductase may exist.

Conclusions—CVT has a genetic basis. Genes involved in the clotting cascade provide a greater level of thrombosis risk in the cerebral venous circulation compared with its arterial circulation, and a greater level of risk exists for adults compared with children. (Stroke. 2011;42:00-00.)

Key Words: cerebral venous thrombosis ■ meta-analysis ■ thrombophilia ■ polymorphism ■ genetics

Cerebral venous thrombosis (CVT) is a rare form of cerebrovascular disease that accounts for <1% of all strokes, with an associated mortality consistently ~10% to 13%. Numerous etiologic risk factors have been reported for adult CVT, including spontaneous intracranial hypotension, thalidomide use in multiple myeloma, inflammatory bowel disease, high altitude, tamoxifen, erythropoietin, phytoestrogens, the oral contraceptive pill, and pregnancy. The proportion of cases with no identified risk factors is reported to be 15%, with inherited thrombophilias constituting ~22% of CVT cases.

Case-control studies that have included a candidate gene-based approach have attempted to clarify the extent of a genetic etiology for CVT. However, results from such association studies have been conflicting, primarily because they lack sufficient power. Pooling all available data can overcome many of these deficiencies and has proved successful for a number of vascular disorders.

Our aim was to fully evaluate the strength of association of CVT with all previously studied gene variants and to compare and contrast our findings with recently published data from CVT in children and ischemic stroke in adults.

Methods

Data Sources
To identify all published case-control studies evaluating any candidate gene and CVT in humans, electronic searches of MEDLINE, EMBASE, and GOOGLE SCHOLAR were conducted. All published manuscripts until and including August 1, 2010, as well as letters, any previous meta-analyses, and abstracts, were included. All foreign language literature was included and translated when necessary. The references of all identified publications were manually reviewed for additional studies, and the MEDLINE “relevant articles” function was used to ensure comprehensive use of this database. Furthermore, some investigators were contacted for additional unpublished material.

Study Selection

Study selection was performed independently by 2 reviewers, and disagreements were resolved by consensus and by the opinion of a third reviewer when necessary. Inclusion criteria included the following: (1) case-control studies wherein CVT was analyzed as a
dichotomous trait; (2) studies in populations of European descent; (3) CVT objectively confirmed via angiography, magnetic resonance imaging, or computed tomography brain imaging; and (4) reported genotype frequency for both cases and controls. Studies were excluded when cases of CVT had a background of antiphospholipid syndrome or myeloproliferative disorders.

**Data Extraction**

Two reviewers independently completed the data extraction. For each selected study, information was extracted pertaining to the year of study, study design, and methodology of CVT diagnosis. Baseline characteristics for cases and controls were documented, including the number of subjects studied, mean age, variation in age, sex, ancestry, and proportion of additional risk factors, including oral contraceptive use, pregnancy, malignancy, and other acquired prothrombotic conditions. We extracted genotype data for cases and controls, including the proportion of homozygous and heterozygous genotypes (minor and major alleles).

**Data Analysis**

Data were analyzed by Review Manager version 5.0. For each gene variant, a pooled odds ratio (OR) and 95% CI were calculated by using a Mantel-Haenszel statistical method with a random-effects analysis model. This analysis allowed the strength of the genetic association to be determined, and a pooled OR for each polymorphism was considered statistically significant when \( P < 0.05 \). For each meta-analysis, an I\(^2\) test for heterogeneity was performed, with significance set at \( P < 0.05 \). When heterogeneity was significant, an iterative analysis was completed to identify the source of interstudy variation. For any significant and positive associations, a population-attributable risk (PAR) was calculated to estimate the number of CVT cases arising in the population as a consequence of the observed polymorphism. PAR was estimated according to the following equation, by using a fixed-effects model and with the prevalence of exposure estimated according to the gene variant frequency in control subjects:

\[
\text{PAR} = 100 \times \frac{\left[ \text{prevalence} \times (\text{OR} - 1) \right]}{\left[ \text{prevalence} \times (\text{OR} - 1) + 1 \right]}
\]

OR comparisons were also made with previous meta-analyses that investigated single-nucleotide polymorphisms (SNPs) in arterial ischemic stroke and CVT in pediatric populations. Publication bias was tested by using funnel plots and Egger regression asymmetry tests (2 tailed) by Comprehensive Meta-Analysis version 2 software.

**Results**

Our initial search strategy identified 1825 potentially relevant studies, including 209 duplicates that were removed, leaving 1616 studies. An additional 1590 were excluded according to our predefined inclusion and exclusion criteria, leaving a final total of 26 studies that addressed 6 polymorphisms in 6 different genes studied in 1183 CVT cases and 5189 controls (Figure and Table in the online-only Data Supplement, http://stroke.ahajournals.org).

**Factor V Leiden/G1691A**

The factor V Leiden mutation was the most investigated polymorphism (Figure 1), with 19 studies investigating a total of 4787 subjects (767 cases, 4020 controls) (online-only references 1–20). The prevalence of the homozygous G1691A polymorphism was low (3 of 767 CVT patients, 5 of 4020 controls). A random-effects model for the heterozygous gene variant revealed a pooled OR of 2.40 (95% CI, 1.75 to 3.30; \( P < 0.00001 \)). There was no evidence of interstudy heterogeneity \( (P_{\text{HET}} = 0.72, I^2 = 0) \). The Egger regression intercept probability value (2 tailed) was 0.312, suggesting a low probability of publication bias. This finding was supported by the symmetrical funnel plot of the precision of the OR in relation to its standard deviation. The PAR for adult CVT was determined to be 6.8%.

**Prothrombin/G20210A**

The prothrombin SNP G20210A (Figure 2) was investigated in a total of 15 studies in 4336 subjects (767 cases, 3690 controls; only-only references 1,2,4–6,9–11,13,14,16,17,21–23). The heterozygous gene variant revealed a pooled OR of 2.40 (95% CI, 1.75 to 3.30; \( P < 0.00001 \)). There was no evidence of interstudy heterogeneity \( (P_{\text{HET}} = 0.72, I^2 = 0) \). The Egger regression intercept probability value (2 tailed) was 0.312, suggesting a low probability of publication bias. This finding was supported by the symmetrical funnel plot of
the precision of the OR in relation to its standard deviation. The PAR conferred by this variant was 14.2%.

**Methylene Tetrahydrofolate Reductase/C677T**
The homozygous methylene tetrahydrofolate reductase (MTHFR)/C677T polymorphism (Figure 3) was investigated in a total of 7 studies in 1556 subjects (233 CVT cases, 1323 controls; online-only references 3,5,7,10,16,17,24), providing a pooled OR of 1.83 (95% CI, 0.88 to 3.80; $P_{HET} = 0.09$). There was evidence of interstudy heterogeneity ($I^2 = 68\%$), and after an iterative analysis, 1 study was found to be responsible for this heterogeneity. Removal of this study eliminated interstudy heterogeneity ($I^2 = 39\%$) and generated a revised OR of 2.30 (95% CI, 1.20 to 4.42; $P = 0.02$). The Egger regression intercept probability value (2 tailed) was 0.237, suggesting a low probability of publication bias. This concept was supported by the symmetrical funnel plot of precision of the OR in relation to its standard deviation. After controlling for heterogeneity, the PAR was 17.9%.

**Plasminogen Activator Inhibitor-1**
The plasminogen activator inhibitor-1 4G/5G polymorphism was investigated in 2 studies in a total of 434 subjects (134 CVT cases, 300 controls; online-only references 8 and 9). A pooled OR of 0.93 (95% CI, 0.53 to 1.61; $P = 0.80$) was generated.

**Protein Z/G79A**
The heterozygous polymorphism in protein Z/G79A was investigated in 2 studies with 434 subjects (131 CVT cases, 303 controls; online-only references 6 and 14). A pooled OR of 1.34 (95% CI, 0.43 to 4.20; $P = 0.61$) was generated.

**Janus Kinase-2/V617F**
The Janus kinase-2/V617F polymorphism was investigated in 3 studies including 533 subjects (96 CVT cases; 437 controls; online-only references 4,25,26). However the polymorphism, in either the homozygous or heterozygous state, was completely absent in all individuals studied. With only the wild-type genotype being expressed, an OR for risk was not estimable.

**Comparison of Adults With Neonates and Children**
Kenet et al. performed a meta-analysis on the impact of thrombophilia on first childhood stroke, including CVT (Figure 4). Using a fixed-effects model, Kenet et al generated a pooled OR of risk from the factor V Leiden gene variant of 2.74 (95% CI, 1.73 to 4.34) and for the prothrombin G20210A polymorphism, an OR of 1.95 (95% CI, 0.93 to 4.07). Figure 5 compares the similarity of pooled ORs of genes studied in CVT in both adults and children.

<table>
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<th>CVT Cases</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<td>Weight</td>
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<td>1.52 [0.34, 7.56]</td>
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<td>2.04 [0.51, 8.18]</td>
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<td>45</td>
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<td>14.5%</td>
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<td>40</td>
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<td>9.43 [2.97, 30.71]</td>
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<td>100.0%</td>
<td>1.52 [0.34, 7.56]</td>
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</tbody>
</table>
Comparison With Arterial Ischemic Stroke

Figure 5 compares 4 gene polymorphisms studied herein in CVT as well as previously reported in >18,000 arterial stroke cases and >36,000 controls. The 2 variants of factor V Leiden and prothrombin had positive associations with both arterial ischemic stroke and CVT, although ORs were comparably smaller in the arterial stroke group. For MTHFR, the arterial ischemic stroke 95% CI existed entirely within the CIs for CVT. Plasminogen activator inhibitor-1 showed a statistically significant protective association with arterial stroke compared with a nonstatistically significant protective OR in the case of CVT; again, the 95% CI for arterial ischemic stroke existed entirely within the CVT CIs.

Comparison of Genetic Effects With Biochemical Markers of Risk: Mendelian Randomization

We sought to establish whether the putative biochemical intermediaries of gene variants are associated with equivalent quantitative levels of risk. The homocysteine pathway (and MTHFR/C677T) was determined to be the most investigated. However, we found insufficient literature defining the OR for a unit change in a biochemical intermediate in the development of CVT. We therefore used studies that linked biochemical intermediates with deep vein thrombosis (DVT) as a surrogate for CVT. There is sufficient evidence to infer a link between peripheral venous thromboembolism and CVT. A single study had previously interrogated homocysteine levels in DVT. The data from that article, when scaled logarithmically with the OR for a +2.26 μmol/L homocysteine change conferred by MTHFR/C677T, generated an expected OR of 1.6 (95% CI, 1.1 to 2.1). A meta-analysis of the OR found in our current study for MTHFR/C677T in CVT (after controlling for heterogeneity) and in DVT generated a pooled observed OR of 1.40 (95% CI, 0.63 to 3.13). The CIs for the expected OR fall entirely within the CI for the observed OR, suggesting a causal relation between MTHFR and CVT.

Discussion

Our work shows that genetic mechanisms appear to have an important role in the development CVT. Of the 6 genes and their 6 respective polymorphisms, 2 (factor V Leiden/G1691A and prothrombin/G20210A) appear to have a significant association with the risk of CVT in adult populations,
whereas MTHFR/C677T also appears to be associated with adult CVT after iterative analysis for heterogeneity. The remaining polymorphisms in the 3 other genes, plasminogen activator inhibitor-1, protein Z, and Janus kinase-2, failed to support any statistically significant association.

Factor V and prothrombin had PARs of 6.6% and 14.4%, respectively. These estimates imply that together, these 2 common variants alone may contribute to between 204 and 463 of the 1500 cases of CVT occurring per year in the United States alone. Comparisons of genes identified and their pooled ORs were made between cerebral venous stroke and cerebral ischemic stroke to determine what, if any, similarities between these 2 presumed pathologically related conditions could be made. Broadly, our results seem to indicate that a greater genetic liability seems to exist for venous compared with arterial thrombosis. Our work echoes similar comparative findings in children.13

The evidence for the impact of age in genetically influenced conditions still remains inconclusive. Many have suggested that the genetic liability of multifactorial conditions may be more pronounced in youth, when exposure to environmental risk factors is limited. However, several studies suggest that specific gene variants, factor V Leiden, for example, still confer an important risk in elderly individuals.19,20 Our comparative analysis suggests an incongruity between the ORs for children and for adults where such data exist. Our results do not suggest that genetic liability is greater in neonatal and pediatric cases; in fact, for prothrombin, the converse was observed. Environmental insults early in life, such as obstetric complications or neonatal sepsis, may have a more significant effect on cerebral venous blood flow. CVT in the early stages of life seems to be a more environmentally determined condition than a genetic one, which seems to play a greater role in adulthood. Whether our work will allow individuals to ascertain their risk of CVT during high-risk exposures, for example, in pregnancy, is as yet undetermined.

The current study is the first to apply mendelian randomization analysis to venous thrombotic conditions. For MTHFR, a degree of concordance between the observed risk and that predicted from the associated biochemical changes was found. This concordance helps to validate any gene–venous thrombosis–positive associations and suggests that the risk imparted by each genotype variant is the direct consequence of each gene’s understood biochemical actions. However, this result should be interpreted with caution, as it was necessary to use biochemical data from DVT, and an assumption, albeit reasonable, has been made that it and CVT share similar pathologic mechanisms.

Our work needs to be placed in the context of genome-wide association (GWA) models. The viability of that model has been made possible because of advances in gene-chip technology, which now allow a million SNPs to be screened simultaneously. Several GWA studies have now been published for a variety of clinical disorders, including vascular diseases.21–24 Recently, findings from a GWA investigation in venous thromboembolism, including DVT and pulmonary embolism, have confirmed the contribution of factor V Leiden and ABO blood group loci to disease risk.25 Furthermore, a GWA study managed to replicate the mild effects of 2 novel SNPs recently suspected to be associated with venous thromboembolism. This should trigger further gene association studies in CVT, especially with regard to ABO loci, for which a candidate-gene investigation has yet to be conducted. However, despite the large number of SNPs used, the resolution to cover the whole human genome is only moderate, and many of these GWA studies are only able to detect common gene variants and remain underpowered to detect the low-relative-risk genes in conditions with a multifactorial etiology. Therefore, there still exists an important role for the candidate-gene approach based on a mechanistic understanding of the condition under evaluation.

As with any meta-analysis, there are a number of limitations worth consideration. First, the studies selected for this analysis failed to fully control for age, and it may be that this factor was an influential determinant. Furthermore, a proportion of studies failed to ensure that controls were matched for age and sex. Second, investigations included studies containing pregnant women and those using the oral contraceptive pill or receiving hormone replacement therapy. These factors have all been shown to be prothrombotic. However, insufficient data exist for us to be able to perform subgroup analyses as to how these preexisting states likely influenced the observed genetic results. Third, populations of European ancestry only were studied. Despite recognized differences in the prevalence of polymorphisms between races,26–28 the biologic effect of a certain genotype has been assumed to be consistent across ethnicities.29 Meta-analysis of genetic polymorphisms in ischemic stroke has shown similarities between ORs for those of European and non-European descent.30 Such research has yet to be applied to venous-derived stroke, and further investigation is needed to understand the relation among race, genetics, and CVT before combining data from subjects of differing ancestral descent. Of course, we have data relating only to patients who survived a CVT event, and it is possible that survival bias may have influenced our result. However, because mortality rates associated with CVT are comparatively low, we do not anticipate this to have greatly altered our results, but of course, this possibility does need to be considered when interpreting our findings. Finally, publication bias is an important methodological feature that impacts on all meta-analyses to some extent. We attempted to minimize such bias by including foreign language studies, manually searching for abstracts and letters, and contacting authors for potentially unpublished information. Despite these efforts and the scrutiny of results with funnel plotting and Egger regression testing, the impact of publication bias can never fully be excluded.

The current study marks the most extensive meta-analysis of hemostatic genes implicated in CVT to date. Genetic variants involved in the clotting cascade serve as important risk factors in venous stroke in adults, and we provide robust comparisons of thrombotic risk between CVT in children and arterial stroke in adults. Furthermore, a causal relation between MTHFR and the broad category of venous thrombotic conditions is suggested.
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Disclosures
T.M. and P.S. are currently leading and coordinating the Biorepository to Establish the Aetiology of Sionvenous Thrombosis (BEAST) study, an international collaboration to undertake a genome wide study to dissect out the genes involved in CVT.

References
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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/02/28/STROKEAHA.110.602672.DC1

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SUPPLEMENTAL MATERIAL

430 EMBASE  395 MEDLINE  1000 Google Scholar

1825 manuscripts identified

1616

116

55 potentially relevant studies

26 studies

209 duplicates

1500 non case-control

61 with incomplete genotype data or single studies or met exclusion criteria

29 of non-European descent

Supplemental fig. 1

Flow chart illustrating number of studies included in the meta-analysis
## Supplemental Table 1

### The Genetics of Cerebral Venous Thrombosis

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<tr>
<th>Gene (Number of studies)</th>
<th>Polymorphism</th>
<th>Genetic model</th>
<th>Total cases</th>
<th>Total controls</th>
<th>Allele frequency ratio (cases)</th>
<th>Allele frequency ratio (controls)</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P-value</th>
<th>PAR</th>
<th>Inter-study heterogeneity</th>
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<tr>
<td>Factor V (19)</td>
<td>G1691A</td>
<td>Dominant</td>
<td>736</td>
<td>4020</td>
<td>0.116:0.884 (G/A)</td>
<td>0.052:0.948 (G/A)</td>
<td>2.40</td>
<td>1.75 – 3.30</td>
<td>P &lt; 0.00001</td>
<td>6.8%</td>
<td>P = 0.72; P 0%</td>
</tr>
<tr>
<td>Prothrombin (15)</td>
<td>G20210A</td>
<td>Dominant</td>
<td>646</td>
<td>3609</td>
<td>0.14:0.86 (G/A)</td>
<td>0.038:0.962 (G/A)</td>
<td>5.37</td>
<td>3.73 – 7.53</td>
<td>P &lt; 0.00001</td>
<td>14.4%</td>
<td>P = 0.67; P 0%</td>
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<td>MTHFR (7)</td>
<td>C677T</td>
<td>Recessive</td>
<td>233</td>
<td>1323</td>
<td>0.236:0.764 (C/T)</td>
<td>0.182:0.818 (C/T)</td>
<td>2.30</td>
<td>1.20 – 4.42</td>
<td>P = 0.02</td>
<td>17.9%</td>
<td>P = 0.14; I² 39%</td>
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<td>PAI-1 (2)</td>
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<td>Recessive</td>
<td>134</td>
<td>300</td>
<td>0.702:0.296 (4G/5G)</td>
<td>0.71:0.29 (4G/5G)</td>
<td>0.93</td>
<td>0.53 – 1.61</td>
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<td>32%</td>
<td>P = 0.22; I² 32%</td>
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<tr>
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<td>Recessive</td>
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<td>110</td>
<td>0.4:0.6 (G/A)</td>
<td>0.363:0.637 (G/A)</td>
<td>1.34</td>
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<td>Not estimable</td>
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*In absence of iterative analysis OR is 1.83 (95% CI, 0.88–3.80, p=0.09).*
SUPPLEMENTAL METHODS

Search terms:

Medline search strategy

1) *Exp intracranial Thrombosis/ (3557)
2) *Exp Sinus Thrombosis, intracranial/ (2359)
3) *Cerebral veins/ (2566)
4) Cerebral adj3 Ve$ adj3 Thrombosis (1485)
5) Cerebral adj3 sin$ adj3 Thrombosis (628)
6) Intracranial Thrombosis (1288)
7) CSVT (37)
8) CVT (592)
9) Cerebral vein$ (3058)
10) Cortical vein$ (412)
11) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (7242)
12) *Exp Polymorphism, genetic/ (144021)
13) *Exp Mutation/ (494657)
14) Thombophilia/ (3834)
15) Genotype/ (109800)
16) Prothrombotic (2805)
17) Thombophil$ (6069)
18) 12 OR 13 OR 14 OR 15 OR 16 OR 17 (669958)
19) 11 and 18 (405)
20) 11 and 18; Limits: Humans and publications since 1993 (364)

EMBASE search strategy

1) *Exp Cerebral Sinus Thrombosis/ (3109)
2) *Exp Brain vein/ (2070)
3) Cerebral adj3 Ve$ adj3 Thrombosis (1379)
4) Cerebral adj3 Sin$ adj3 Thrombosis (2245)
5) Sinus Thrombosis (3959)
6) CSVT (55)
7) CVT (878)
8) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 (715)
9) *Exp genetic polymorphism/ (244186)
10) mutation/ OR gene mutation/ OR mutant/ (317819)
11) Genotype OR Haplotype (163802)
12) Thrombophilia (5406)
13) Prothrombotic (3494)
14) Thrombophil$ (7209)
15) 9 OR 10 OR 11 OR 12 OR 13 OR 14 (623946)
16) 8 AND 15 (498)
17) 8 AND 15; Limits: Humans and publications since 1993 (441)

**SUPPLEMENTAL REFERENCES**


SEARCH TERMS

Medline search strategy

21) Exp intracranial Thrombosis/ (3557)
22) Exp Sinus Thrombosis, intracranial/ (2359)
23) Cerebral veins/ (2566)
24) Cerebral adj3 Ve$ adj3 Thrombosis (1485)
25) Cerebral adj3 sin$ adj3 Thrombosis (628)
26) Intracranial Thrombosis (1288)
27) CSVT (37)
28) CVT (592)
29) Cerebral vein$ (3058)
30) Cortical vein$ (412)
31) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (7242)
32) Exp Polymorphism, genetic/ (144021)
33) Exp Mutation/ (494657)
34) Thrombophilia/ (3834)
35) Genotype/ (109800)
36) Prothrombotic (2805)
37) Thrombophil$ (6069)
38) 12 OR 13 OR 14 OR 15 OR 16 OR 17 (669958)
39) 11 and 18 (405)
40) 11 and 18; Limits: Humans and publications since 1993 (364)

**EMBASE search strategy**

18) Exp Cerebral Sinus Thrombosis/ (3109)
19) Exp Brain vein/ (2070)
20) Cerebral adj3 Ve$ adj3 Thrombosis (1379)
21) Cerebral adj3 Sin$ adj3 Thrombosis (2245)
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29) Thrombophilia/ (5406)
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