

# Thrombosis and Haemostasis

## Exploring the Two-Way Link Between Migraines and Venous Thromboembolism: A Bidirectional Two-Sample Mendelian Randomization Study

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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**Background:** The objective of this study is to utilize Mendelian Randomization to scrutinize the mutual causality between migraine and Venous Thromboembolism (VTE) thereby addressing the heterogeneity and inconsistency that were observed in prior observational studies concerning the potential interrelation of the two conditions.

**Methods:** Employing a bidirectional Mendelian Randomization approach, the study explored the link between migraine and VTE, incorporating participants of European descent from a large-scale meta-analysis. An inverse-variance weighted (IVW) regression model, with random-effects, leveraging Single-Nucleotide Polymorphisms (SNPs) as instrumental variables was utilized to endorse the mutual causality between migraine and VTE. SNP heterogeneity was evaluated using Cochran's Q-test and to account for multiple testing, correction was implemented using the intercept of the MR-Egger method, and a leave-one-out analysis.

**Results:** The IVW model unveiled a statistically considerable causal link between migraine and the development of VTE (odds ratio [OR] = 96.155, 95% confidence interval [CI]: 4.342-2129.458,  $P = 0.004$ ), implying that migraine poses a strong-risk factor for VTE development. Conversely, both IVW and simple model outcomes indicated that VTE poses as a weaker-risk factor for migraine (IVW OR = 1.002, 95% CI: 1.000-1.004,  $P = 0.016$ ). The MR-Egger regression analysis denoted absence of evidence for genetic pleiotropy among the SNPs while the durability of our Mendelian Randomization results was vouched by the leave-one-out sensitivity analysis.

**Conclusion:** The findings of this Mendelian Randomization assessment provide substantiation for a reciprocal causative association between migraine and VTE within the European population.

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Exploring the Two-Way Link Between Migraines and Venous Thromboembolism: A Bidirectional Two-Sample Mendelian Randomization Study

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**Keyword:**

Mendelian randomization, migraine, venous thromboembolism, bidirectional, causality

**1. Introduction**

Venous Thromboembolism (VTE) encompasses both Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) <sup>1</sup>, ranking third globally as a prevalent vascular disorder associated with mortality<sup>2</sup>. This increases the mortality risk for patients and compounds the financial burden on healthcare services. Hence, the ongoing evaluation and assessment of VTE risk in clinical settings are crucial.

Migraine, characterized by recurrent episodes of severe unilateral headaches accompanied by pulsating sensations and autonomic symptoms, affects approximately one billion individuals worldwide.<sup>3</sup> Several research studies indicate an increase in VTE incidence among migraine

sufferers.<sup>4-8</sup> Hence, there is a significant need for further investigation to elucidate the causal relationship between VTE and migraines.

Mendelian randomization is a methodology that utilizes genetic variants as instrumental variables (IVs) to explore the causal association between a modifiable exposure and a disease outcome.<sup>9</sup> By leveraging the random allocation and fixed nature of an individual's alleles at conception, this approach helps alleviate concerns regarding reverse causality and environmental confounders commonly encountered in traditional epidemiological methods.

In order to mitigate confounding factors and ensure robust outcomes, this investigation adopts a pioneering approach by utilizing Mendelian Randomization to explore the genetic-level causal correlation between migraine and VTE. To the best of our knowledge, no previous study has employed this method to examine the association between these two pathological conditions, thereby lending an innovative and cutting-edge aspect to this research.

## **2. Materials and Methods**

### **2.1 Research methodology**

A rigorous bidirectional two-sample Mendelian Randomization examination was implemented to probe the causal link between migraine and VTE risk, subsequent to a meticulous screening mechanism. For achieving credible estimations of Mendelian Randomization causality, efficacious genetic variances serving as IVs must meet three central postulates: (I) Relevance Assumption, asserting that variations must demonstrate intimate association with the exposure element; (II) Independence/Exchangeability Assumption, demanding no correlations be exhibited with any measured, unmeasured, or inconspicuous confounding elements germane to the researched correlation of interest; and (III) Exclusion Restriction Assumption, maintaining that the variation affects the outcome exclusively through the exposure, devoid of alternative routes.<sup>10,11</sup> A Single Nucleotide Polymorphism

(SNP) refers to a genomic variant where a single nucleotide undergoes alteration at a specific locus within the DNA sequence. SNPs were employed as IVs in this study for estimating causal effects. The study's design is graphically portrayed in Figure 1, emphasizing the three fundamental postulates of Mendelian Randomization. These postulates are of the utmost importance in affirming the validity of the Mendelian Randomization examination and ensuring the reliability of the resultant causal inferences.<sup>12</sup>

## 2.2 Data Sources

Our SNPs are obtained from large-scale Genome-Wide Association Studies (GWAS) public databases. The exposure variable for this study was obtained from the largest migraine GWAS meta-analysis conducted by the IEU Open GWAS project, which can be accessed at <https://gwas.mrcieu.ac.uk/datasets>.<sup>13,14</sup> The outcome variable was derived from the largest VTE GWAS conducted by FinnGen, available at <https://www.finngen.fi><sup>15</sup>. A comprehensive overview of the data sources used in our study can be found in Table 1.

The variances in genetic variations and exposure distributions across diverse ethnicities could potentially result in spurious correlations between genetic variants and exposures.<sup>16</sup> Consequently, the migraine and VTE GWAS for this study were sourced from a homogeneous European populace to circumvent such inaccurate associations. It is crucial to highlight that the data harvested from public databases were current up to March 31, 2023. Given the public nature of all data utilized in our study, there was no necessity for further ethical approval.

## 2.3 Filtering criteria of IVs

To select appropriate SNPs as IVs, we followed standard assumptions of Mendelian Randomization. Firstly, we performed a screening process using the migraine GWAS summary data, applying a significance threshold of  $P < 5 \times 10^{-8}$  (Assumption I). To ensure the independence of SNPs and mitigate the effects of linkage disequilibrium, we set the

linkage disequilibrium coefficient ( $r^2$ ) to 0.001 and restricted the width of the linkage disequilibrium region to 10,000 kb. PhenoScanner (<http://www.phenoscanter.medschl.cam.ac.uk/>) serves as a versatile tool, enabling users to explore genetic variants, genes, and traits linked to a wide spectrum of phenotypes.<sup>17,18</sup> Utilizing PhenoScanner v2, we ruled out SNPs linked with potential confounding constituents and outcomes, thereby addressing Assumptions II and III. Subsequently, we extracted the relevant SNPs from the VTE GWAS summary data, ensuring a minimum  $r^2 > 0.8$  and replacing missing SNPs with highly linked SNPs. We excluded SNPs without replacement sites and palindromic SNPs and combined the information from both datasets. Finally, we excluded SNPs directly associated with VTE at a significance level of  $P < 5 \times 10^{-8}$  and prioritized IVs with an F-statistic [ $F\text{-statistic} = (\beta/SE)^2$ ]  $> 10$  to minimize weak instrument bias.<sup>19</sup>

#### **2.4 Statistical analysis**

For our analysis, we employed the inverse-variance weighted (IVW) random-effects regression model to assess the causal relationship between migraine and VTE, utilizing SNPs as IVs. This approach allowed us to directly calculate the causal effect using summary data, eliminating the need for individual-level data. To assess SNP heterogeneity, we conducted Cochran's Q test and, in the presence of heterogeneity, relied on the results of the IVW model. To examine the presence of pleiotropy, we utilized the MR-Egger method and conducted Leave-one-out analysis. All statistical analyses were performed using the TwoSampleMR package in R 4.2.2 software, with a significance level set at  $\alpha = 0.05$ .

### **3. Results**

In the present investigation, we capitalized on a bidirectional two-sample Mendelian Randomization analysis in individuals of European descent to scrutinize the potential causative correlation between migraines and VTE risk. Our investigation implies a potential

bidirectional pathogenic relationship between migraines and the risk of VTE, as supported by the specific analysis results detailed in Table 2.

### 3.1 Mendelian Randomization Analysis

During the IV screening process, it was identified that SNP r10908505 was associated with Body Mass Index (BMI) in VTE. Considering the established association between BMI and VTE<sup>1,15</sup>, this violated Assumption III and the SNP was subsequently excluded. The VTE dataset ultimately consisted of 11 SNPs, with individual SNP F-statistics ranging from 29.76 to 96.77 (all > 10), indicating a minimal potential for causal associations to be confounded by weak instrumental variable bias (Table S1). The IVW model revealed that migraine was a statistically significant risk factor for the onset of VTE [odds ratio (OR) = 96.155, 95% confidence interval (CI): 4.3422-129.458,  $P = 0.004$ ] (Table 2, Fig 2A). The scatter plot (Fig 2B) and funnel plot (Fig 2C) of migraine demonstrated a symmetrical distribution of all included SNPs, suggesting a limited possibility of bias affecting the causal association. The Cochran's Q test, conducted on the MR-Egger regression and the IVW method, yielded statistics of 5.610 and 5.973 ( $P > 0.05$ ), indicating the absence of heterogeneity among the SNPs (Table S2). These findings suggest a positive correlation between the strength of association between the IVs and migraine, satisfying the assumptions of instrumental variable analysis. The MR-Egger regression analysis showed no statistically significant difference from zero for the intercept term ( $P = 0.5617$ ), indicating the absence of genetic pleiotropy among the SNPs (Table S3). Additionally, the leave-one-out analysis revealed that the inclusion or exclusion of individual SNPs did not substantially impact the estimated causal effects, demonstrating the robustness of the Mendelian Randomization results obtained in our investigation (Fig 2D).

### 3.2 Reverse Mendelian Randomization Analysis

Upon screening for IVs in migraine patients, SNP rs6060308 was excluded due to its association with education<sup>20,21</sup> and violation of Assumption III. The final migraine dataset comprised 13 SNPs, with individual SNP F-statistics ranging from 30.60 to 354.34, all surpassing the threshold of 10 (Table S4). Both the IVW and simple models supported VTE as a risk factor for migraine. The IVW analysis yielded an OR of 1.002 (95% CI: 1.000-1.004,  $P = 0.016$ ), while the simple model yielded an OR of 1.003 (95% CI: 1.000-1.006,  $P = 0.047$ ) (Table 2, Fig 3A). The scatter plot (Fig 3B) and funnel plot (Fig 3C) exhibited symmetrical distributions across all included SNPs, indicating minimal potential for biases affecting the causal association. Heterogeneity among SNPs was observed through the Cochran Q test of the IVW method and MR-Egger regression, with Q statistics of 18.697 and 20.377, respectively, both with  $P < 0.05$  (Table S2). Therefore, careful consideration is necessary for the results obtained from the random-effects IVW method. MR-Egger regression analysis revealed a non-significant difference between the intercept term and zero ( $P = 0.3655$ ), suggesting the absence of genetic pleiotropy among the SNPs (Table S3). Additionally, the leave-one-out analysis demonstrated that the inclusion or exclusion of individual SNPs had no substantial impact on the estimated causal effect (Fig 3D).

#### 4. Discussion

VTE constitutes a grave health hazard to patients, necessitating rigorous clinical surveillance. Distinct from common VTE risk factors such as cancer<sup>22</sup>, diabetes<sup>23</sup>, lupus<sup>24</sup>, and APS<sup>25</sup>, migraines remain absent from prevalent VTE guidelines or advisories. The Mendelian Randomization findings from our research provide first-of-its-kind evidence of a causal nexus between migraines and VTE in individuals of European descent, signaling that migraines potentially predispose individuals to VTE (IVW OR = 96.155, 95% CI: 4.342-2129.458), while VTE presents a weak risk factor for migraines (IVW OR = 1.002, 95% CI:



1.000-1.004). Given the robustness of the IVW analysis, the Mendelian Randomization analysis is considered reliable.

Our Mendelian Randomization analysis discloses a potential causal association between individuals suffering from migraines and VTE incidence, with a risk rate 96.155 times higher in comparison to non-migraine sufferers. Previous observational endeavors investigating VTE risk amidst migraine patients have been scant and have yielded discordant outcomes, complicating the provision of clinical directives.<sup>26,27</sup> In a longitudinal inquiry with a 19-year follow-up, Adelborg et al. discerned a heightened VTE risk in individuals afflicted with migraines.<sup>4</sup> Peng et al.'s prospective clinical study unveiled a more than double VTE risk increase in migraine patients during a 4-year follow-up.<sup>5</sup> Schwaiger et al.'s cohort study, incorporating 574 patients aged 55-94, observed a significant escalation in VTE risk among elderly individuals with migraines.<sup>6</sup> Bushnell et al. uncovered a tripled VTE risk during pregnancy in migraine-affected women.<sup>28</sup> Though these studies validate a potential correlation between migraines and VTE, their persuasiveness is restricted due to other prominent VTE risk factors (such as advanced age and pregnancy) and contradicting findings in existing observational studies. For instance, Folsom et al. observed no significant correlation between migraines and VTE risk in elderly individuals, contradicting Schwaiger's conclusion.<sup>7</sup> However, he clarified that the cohort incorporated in his study didn't undergo rigorous neurological migraine diagnosis, possibly leading to confounding biases and generating findings that contradict other scholarly endeavors.<sup>7</sup> These contradictions originate from observational studies examining associations rather than causal relationships, invariably involving a confluence of various confounding factors. Mendelian Randomization, leveraging SNPs as IV's to ascertain the causal link between migraines and VTE risk, can eliminate other confounding elements resulting in more reliable outcomes. Based on this finding, monitoring VTE risk among migraine patients in clinical practice is recommended.

The reverse Mendelian Randomization analysis reveals that compared to non-VTE patients, those with VTE among individuals of European ancestry exhibit a marginally heightened susceptibility to migraines, with a relative risk of 1.02 (as per the IVW method). This discovery concurs with the existing void in research on migraines among VTE patients. Thus, even with slightly increased risks of migraines in VTE patients, we do not advocate for heightened concern regarding the emergence of migraines among this patient group.

Our endeavor seeks to offer a preliminary examination of the potential mechanisms underlying the interplay between migraines and VTE. The incidence of VTE habitually involves Virchow's triad, encompassing endothelial damage, venous stasis, and hypercoagulability.<sup>29</sup> On the genetic association front, the SNPs rs9349379 and rs11172113, acting as IVs for migraines, display relevance to the mechanisms underpinning VTE. Prior research earmarks the gene corresponding to rs9349379, *PHACTR1* (Table S1), as a catalyst for the upregulation of *EDN1*.<sup>30</sup> Elevated *EDN1* expression is associated with increased VTE susceptibility<sup>31</sup>, and *EDN1* inhibition can diminish VTE incidence<sup>32</sup>, potentially through Endothelin 1-mediated vascular endothelial inflammation leading to thrombus formation<sup>33</sup>. The SNP rs11172113 corresponds to the gene *LRP1* (Table S1).<sup>34</sup> *LRP1* can facilitate the upregulation of *FVIII*, culminating in an increase in plasma coagulation factor VIII<sup>35</sup>, thereby leading to heightened blood coagulability and an associated elevated VTE risk<sup>36</sup>. While various studies propose divergent mechanisms, they collectively signal that migraines can instigate a hypercoagulable state, thereby promoting the onset of VTE. The SNPs serving as IVs for VTE did not unveil any association with the onset of migraines. This corroborates our Mendelian Randomization analysis outcomes, indicating that VTE is merely a weak risk factor for migraines.

### **Strengths and limitations**

This study possesses several notable strengths. Firstly, it fulfills all three assumptions of Mendelian Randomization, minimizing the influence of confounding factors and addressing the limitations inherent in observational studies, thus yielding more robust findings. We carefully excluded two SNPs (rs10908505 and rs6060308) that could potentially impact the results. In addition, we employed PhenoScanner v2 to comprehensively probe confounding variables related to VTE, as described earlier, and factors associated with migraines, such as acute migraine medication overuse, obesity, depression, stress, and alcohol, leading to the subsequent exclusion of relevant SNPs. This ensured that the selected SNPs specifically captured the causal effects and eliminated potential confounding effects from polygenic associations with disease susceptibility. Secondly, the study sample was restricted to individuals of European descent, minimizing the potential bias introduced by population heterogeneity and enhancing the internal validity of the findings. Thirdly, the use of strongly correlated SNPs ( $F \gg 10$ ) in both Migraine  $\rightarrow$  VTE and VTE  $\rightarrow$  Migraine analyses enhances the validity of the IVs. Finally, this study pioneers the hypothesis of a plausible causal association between VTE and an elevated susceptibility to migraines, offering novel insights into their potential relationship.

Nonetheless, it is essential to acknowledge the presence of several limitations in this study that warrant consideration. Firstly, the study participants were predominantly of European ancestry, which, although it avoids the influence of ethnicity on the results, limits the generalizability of the findings to other ethnic groups. Secondly, our study solely establishes the causal relationship between migraine and VTE risk without elucidating the underlying mechanisms. Thirdly, we only selected SNPs that met the stringent genome-wide significance level ( $P < 5 \times 10^{-8}$ ), potentially excluding truly relevant variations that did not reach this threshold. Lastly, as our Mendelian Randomization analysis relies on publicly available summary statistics data, the lack of detailed clinical information hinders subgroup analysis.

## 5. Conclusion

In essence, the bidirectional Mendelian Randomization analysis, conducted within the European populace, indicates the presence of a relatively strong causal correlation between migraines and VTE, while the causative relationship between VTE and migraines appears exceedingly faint. These deductions imply the need for rigorous monitoring of VTE in individuals of European descent suffering from migraines, thus requiring synergistic effort between general physicians and neurologists. Nevertheless, VTE patients should refrain from undue worries concerning the incidence of migraines. Further, we stress the importance of harnessing information gleaned from a wide array of observational studies and controlled experiments to strengthen the credibility of drawn causal inferences. This is pivotal in establishing a mutual corroboration with the results obtained through Mendelian Randomization analysis. Hence, the exigency for additional stringent observational studies and comprehensive laboratory research prevails to corroborate the conclusions made in this study.

## 6. conflict of interest disclosure

None declared.

## Summary Table

### What is known about this topic?

- Previous research has not definitively established whether migraine is a risk factor for VTE, and observational studies have contradictory findings.
- Previous studies do not provide evidence for the prevention of VTE occurrence in patients with migraines.

### What does this paper add?

- Migraine has been identified as a strong-risk factor for VTE.
- VTE has been identified as a weak-risk factor for migraine.
- For the first time, genetic evidence has been presented to emphasize the importance of preventing VTE occurrence in individuals with migraines.

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### Figure captions

**Visual Summary:** This study utilized Mendelian Randomization to investigate the bidirectional causal relationship between migraine and VTE. Our results suggest that migraine is a significant risk factor for VTE, as shown by a solid black arrow, whereas VTE appears to be a minor risk factor for migraine, indicated by a faded gray arrow.

**Abbreviations:** VTE, venous thromboembolism; SNP, single nucleotide polymorphisms

**Figure 1:** Illustrates the research methodology for the bidirectional Mendelian randomization analysis concerning migraine and VTE. Assumption I: Relevance Assumption; Assumption II: Independence/Exchangeability Assumption; Assumption III: Exclusion Restriction Assumption

**Figure 2:** Explores the correlation between migraine risk and VTE, validating the presence of heterogeneity and pleiotropy. (A) The forest plot displays individual IVs, with each point flanked by lines that depict the 95% confidence interval. The effect of SNPs on the exposure (migraine) is shown along the x-axis, whereas their impact on the outcome (VTE) is presented on the y-axis. A fitted line reflects the Mendelian Randomization analysis results. (B) A scatter plot visualizes each IV, with the SNP effects on both exposure and outcome similar to that of the forest plot. Again, a fitted line represents the Mendelian Randomization results. (C) The funnel plot positions the coefficient  $\beta_{IV}$  from the instrumental variable regression on the x-axis to demonstrate the association's strength, while the inverse of its standard error ( $1/SE_{IV}^{\dagger}$ ) on the y-axis indicates the precision of this estimate. (D) A leave-one-

out sensitivity analysis is shown on the x-axis, charting the estimated effects from the Mendelian Randomization analysis. With each SNP associated with migraine successively excluded, the analysis recalculates the Mendelian Randomization effect estimates, culminating with the “all” category that encompasses all considered SNPs. **Abbreviations:** VTE, venous thromboembolism; IV, instrumental variable; SNP, single nucleotide polymorphisms; SE, standard error †SE is the standard error of  $\beta$ .

**Figure 3:** Presents the relationship between VTE risk and migraine, also verifying heterogeneity and pleiotropy through similar graphic representations as detailed for Figure 2, but with the exposure and outcome reversed — SNPs effect on VTE and outcome on migraine.

**Table 1: Description of GWAS used for each phenotype**

Variable	Sample size	ID	Population	Database	Year
Migraine	337159	ukb-a-87	European	IEU Open GWAS project	2017
VTE	218792	finn-b-I9_VTE	European	FinnGen	2021

*Abbreviations:* GWAS, genome-wide association studies; VTE, venous thromboembolism

*NOTE:* Basic information of GWAS for migraine and VTE is displayed in this table.

**Table 2: Mendelian Randomization regression causal association results**

Exposures	SNPs (n.)	Methods	$\beta$	SE	OR (95%CI)	P
Migraine	11	<b>IVW</b>	4.566	1.580	96.155(4.342~2129.458)	0.004
VTE	12	<b>IVW</b>	0.002	0.001	1.002(1.000~1.004);	0.016
		Simple mode	0.003	0.001	1.003(1.000~1.006)	0.047

A b b r e W T E t, i o r e n : o u s t h r o m b o e m b o l i s m ;

polymorphisms; SE, standard error; OR, odds ratio; CI: confidence interval

NOTE: This table displays the causal relationship between Migraine leading to VTE and VTE leading to Migraine.

**Table S1: The instrumental variables utilized for the genetic prediction of VTE**

SNP	Chromosome	Position	Corresponding Gene	EA/OA	MAF	$\beta^{\dagger}$	SE	F
rs10218452	1	3075597	<i>PRDM16</i>	G/C	0.2297	0.0047	0.0005	54.27597569
rs12532479	7	40427634	<i>SUGCT</i>	C/T	0.1054	0.0043	0.0007	51.03629124
rs12134493	1	115677946	<i>NGF</i>	A/G	0.1189	0.0042	0.0006	32.80165289
rs9486715	6	97059769	<i>FHL5</i>	C/G	0.3205	0.0036	0.0004	354.342976
rs12344007	9	84642933	<i>LOC105376107</i>	C/G	0.1177	0.0035	0.0006	155.6758158
rs34499708	9	119241165	<i>ASTN</i>	A/G	0.2312	0.0033	0.0005	44.08193879

rs3827986	20	19475014	<i>SLC24A3</i>	A/C	0.4535	0.0026	0.0005	163.200625
rs7104488	11	3259830	N/A	T/C	0.2545	0.0026	0.0004	244.9225
rs9349379	6	12903957	<i>PHACTR1</i>	G/C	0.4049	-0.0032	0.0004	31.23813842
rs10166942	2	234825093	<i>TRPM8</i>	C/A	0.1947	-0.0036	0.0005	38.88447137
rs11172113	12	57527283	<i>LRP1</i>	C/G	0.4132	-0.0041	0.0004	36.91806026

† SNPs are sorted in descending order of  $\beta$  values  $\times 10^{-8}$ . SE is the standard error of  $\beta$ .

Abbreviations: VTE, venous thromboembolism; SNP, single nucleotide polymorphism; MAF, Minor Allele Frequency; SE, standard error; N/A: Not available

NOTE: This table displays the basic information of SNPs related to VTE in migraine patients.

**Table S2: Mendelian Randomization heterogeneity analysis results**

Exposures	Methods	Statistic Q	P
<b>Migraine</b>	MR-Egger regression	5.610	0.778

	IVW	5.973	0.818
	MR-Egger regression	18.697	0.044
<b>VTE</b>	IVW	20.377	0.040

*Abbreviations:* VTE, venous thromboembolism

*NOTE:* The statistical results of the MR-Egger regression and IVE methods in bidirectional two-sample Mendelian Randomization

**Table S3: MR-Egger regression analysis of instrumental variables**

Exposures	Intercept	SE	P
Migraine	0.0183	0.0304	0.5617
VTE	0.0004	0.0004	0.3655

*Abbreviations:* VTE, venous thromboembolism; SE, standard error

*NOTE:* The results of the MR-Egger analysis of instrumental variables.

**VTE**

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**Table S4: The instrumental variables utilized for the genetic prediction of Migraine**

SNP	Chromosome	Position	Nearby Gene	EA/OA	MAF	$\beta^{\dagger}$	SE	F
rs117716477	12	104240958	<i>TTC41P</i>	A/T	0.0165	0.4855	0.0659	47.76704407
rs149244513	9	136059258	N/A	A/A	0.0303	0.2709	0.0473	92.90462924
rs495203	9	136145240	<i>ABO</i>	T/T	0.4355	0.2504	0.0160	96.76556535
rs2066865	4	155525276	<i>FGG</i>	A/C	0.3021	0.2171	0.0174	42.90600915
rs3756011	4	187206249	<i>F11</i>	A/T	0.4274	0.2044	0.0160	30.67249314
rs2885055	19	10729097	<i>SLC44A2</i>	A/T	0.1779	0.1381	0.0208	41.32309482
rs5896	11	46745003	<i>F2</i>	T/G	0.2217	0.1129	0.0202	46.80647176
rs628094	9	135877287	N/A	A/G	0.3175	0.1039	0.0171	29.75994807
rs9266721	6	31349819	<i>HLA-S</i>	A/C	0.3977	-0.0903	0.0163	38.98824179
rs62350309	4	187277666	<i>F11-AS1</i>	G/A	0.1031	-0.1640	0.0263	57.25988075
rs13377102	10	71213386	<i>TSPAN15</i>	A/A	0.1089	-0.1836	0.0257	65.84779698
	1	169467654	<i>F5</i>	A/T	0.0202	-1.1765	0.0625	47.76704407

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rs1894692

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† SNPs are sorted in descending order of  $\beta$  value.  
 $5 \times 10^{-8}$ . SE is the standard error of  $\beta$ .

*Abbreviations:* SNP, single nucleotide polymorphism; EA/OA: Effect allele/Other allele; MAF: Minor Allele Frequency; SE, standard error; N/A: Not available

*NOTE:* This table displays the basic information of SNPs related to migraine in VTE patients.









