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ORIGINAL ARTICLE

Meta-analysis of associations of genetic polymorphisms with cerebral vasospasm and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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Abstract

Introduction Cerebral vasospasm (CV) and delayed cerebral ischemia (DCI) are among the most hazardous complications of aneurysmal subarachnoid hemorrhage (aSAH). Genetic factors are thought to play a significant role in the development of both complications.

Aim To perform a comprehensive meta-analysis of studies that study the association between different genetic polymorphisms and development of DCI and/or CV.

Methods We searched MEDLINE and Science Direct databases on May 29, 2021, using iterations of the keywords "subarachnoid hemorrhage", "vasospasm", "delayed cerebral ischemia", and "gene". After duplicates were removed, the two reviewers screened the titles of the articles and abstracts independently. A random-effect model was used to calculate the relative risk with 95% CI; a fixed-effect model was additionally explored.

Results We pooled data from 16 articles that reported an association between eNOS, apolipoprotein E4 (ApoE4), haptoglobin (Hp), or ryanodine-1 (RYR-1) and CV, DCI, or both. Presence of Hp 2–2 was associated both with CV (RR 2.10, 95% CI 1.33–3.31, $p=0.0014$) and DCI (RR 1.57, 95%CI 1.06–2.34, $p=0.026$). ApoE4 allele had a borderline association with CV (RR 1.48, 95%CI 0.99–2.21, $p=0.054$).

Conclusion Our meta-analysis supports the association between the presence of the Hp2-2 allele and the occurrence of CV and DCI after aSAH. Further studies investigating this association are needed to reinforce this finding.

Keywords Subarachnoid hemorrhage · Aneurysm · Genetics · Polymorphism · Allele · Meta-analysis · Complication

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of hemorrhagic stroke that results from the bleeding from the ruptured berry aneurysms. Depending on the clinical settings, mortality rate can reach 20–30%, and the survivors are at risk of functional impairment. Cerebral vasospasm (CV), delayed cerebral ischemia (DCI), and hydrocephalus are the most hazardous aSAH complications that predict poor outcome [21, 23].

DCI is one of the major contributors to disability in individuals with aSAH who survive the initial event. DCI is generally defined as "any neurologic deterioration that persists for more than 1 h and cannot be explained by any other neurologic or systemic condition, such as fever, seizures, hydrocephalus, sepsis, hypoxemia, sedation, and other metabolic causes" [34], though definitions may vary across studies. Pathogenesis of DCI is not completely clear, but available evidence shows that it is multifactorial and involves microvascular thrombosis, cortical spreading depolarizations, and CV. Although not all individuals who develop CV also develop DCI, CV is easily monitored and is still regarded as one of the markers for DCI.

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DCI is a clinical diagnosis, but a considerable amount of research has been performed to identify its biomarkers and predictors. Since a variety of enzyme systems and proteins are thought to be involved in the pathogenesis of DCI and CV, genetic background could account for variability in a number of patients who develop these complications, and particular polymorphisms could serve as predictors of their development. The search for biomarkers of hydrocephalus, another predictor of poor outcome, is unreasonable as it is directly dependent on the aSAH localization and volume, and thus is unlikely to be influenced by genetic background.

A recent systematic review that investigated different laboratory biomarkers to detect DCI, including, genetic polymorphisms and featured them in six following genes as predictive ones: haptoglobin, catecholamine-o-methyltransferase (COMT), angiotensin-converting enzyme, plasminogen activator-1, HMGB1, and EET [14]. The last comprehensive quantitative review dates back to the 2015 paper by Rosalind Lai and Du, who performed a meta-analysis on studies assessing the association between DCI, radiographic vasospasm, and different polymorphisms [28]. Although there have been single genes meta-analyses performed, there have been no collective meta-analyses since then.

Our aim was to perform an updated meta-analysis on association of different genetic polymorphisms with DCI and CV.

Methods

Search strategy

We searched MEDLINE and Science Direct databases on May 29, 2021, using iterations of the keywords "subarachnoid hemorrhage", "vasospasm", "delayed cerebral ischemia", and "gene" (see Online Resource 1 for the full search query). For the MEDLINE search, we did not limit the study type; for the Science Direct search, we set the article type as "Research articles" and "Conference abstracts". We additionally reviewed reference lists of the relevant retrieved meta-analyses and systematic reviews to identify any eligible papers.

Inclusion and exclusion criteria

We selected studies that met the following criteria: included patients with aneurysmal subarachnoid hemorrhage older than 18 years; investigated the association of genetic polymorphism with CV, DCI, or both as an outcome; reported relative risk with 95% CI or number of patients who got and did not get the outcome of interest.

We intended to translate articles written in languages other than the authors are fluent in if after an initial screening phase such an article appeared eligible. We intended to contact the authors of the conference abstracts that seemed to be eligible after the initial screening phase and ask for the required data if it was not reported or partially reported in the full-text articles.

Study selection, data extraction, and assessment of study quality

After duplicates were removed, the two reviewers (AI and YS) screened the titles of the articles and abstracts independently and transferred potentially eligible items to a separate spreadsheet. After the initial screening, the same authors reviewed selected items conjointly one more time and resolved any cases of inclusion nonconformity by consensus.

The same two authors extracted data from the included studies using a predefined extraction form that included the title, authors, publication date, country, participant inclusion criteria, number of study participants, the average age of participants, investigated gene, polymorphism, the outcome of interest (CV or DCI), the mode of CV detection (if applicable), the number of participants who had the outcome, and the number of participants who did not have the outcome.

Two researchers assessed each of the included studies independently with the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies, which considers the following methodological items: research question statement, study population, participation rate, inclusion and exclusion criteria, sample size justification, timing of measurement of exposure of interest, timeframe, levels of exposure, exposure measures, outcome measures, blinding of assessors to the exposure, rate of loss to follow-up, adjustment for co-founders.

In case of discrepancies in the assessment, the items were re-evaluated. If the article seemed to use the required information but did not report it (e.g., mentioned that the result of the analysis did not reach statistical significance and did not include the exact data), we contacted the corresponding author and asked for the missing information. If no response followed, we assigned an article with a "not reported" statement and excluded it from the final analysis.

Data analysis

Meta-analysis was performed for polymorphisms that were investigated in more than one study and for which the required data we reported in a paper or given by the authors on a query. Separate analyses were performed for the association between each of the included polymorphisms and CV and DCI. Heterogeneity across the studies was assessed with the Cochrane Q statistic test and quantified with I2 and $\tau 2$. A random-effect model was used to calculate the relative risk with 95% CI. Publication bias was intended to be

assessed with funnel plot, Harbord's test, and Peters' test as appropriate as per limitations of these methods. All the statistical analysis was performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Identification and description of studies

The search identified 754 abstracts (345 from MEDLINE and 404 from Science Direct); removal of duplicates yielded 688 unique abstracts, 33 of which met the criteria for full-text review. Hand search of the reference lists identified 5 additional articles. Text review of the resulting 38 articles, which investigated polymorphisms a total of 25 genes, excluded 9 articles, which did not meet criteria (e.g., investigated traumatic SAH) or lacked data that we consequently could not get from the authors of the articles upon request. We also omitted 13 articles that were the only ones reporting on a particular polymorphism and thus not suitable for inclusion. We pooled data from 16 articles that reported an association between eNOS, apolipoprotein E4 (ApoE4), haptoglobin (Hp), or ryanodine-1 (RYR1) and CV, DCI, or both (see Fig. 1 and Table 1 for more information about the inclusion decision flow and the content of the included articles, respectively).

Cerebral vasospasm

A total of ten studies representing six polymorphisms in four genes (ApoE4, eNOS T786C, eNOS G894, eNOS intron VNTR, Hp2-2, and RYR1 C6178G) were included in the meta-analysis for CV. Presence of Hp2-2 allele was associated with CV (RR 2.10, 95% CI 1.33–3.31, $p = 0.0014$), and ApoE4 allele had a borderline association with CV (RR

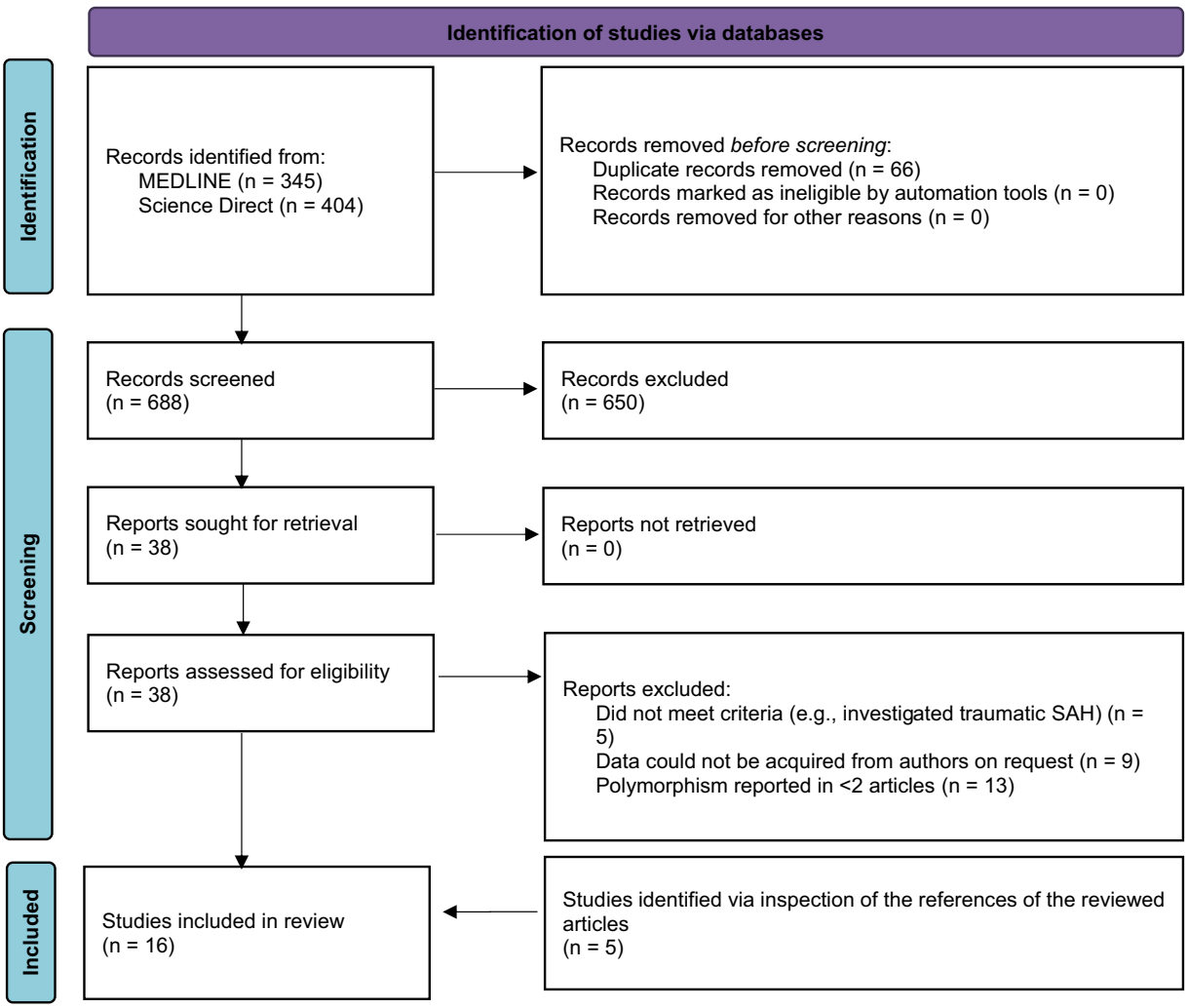

Fig. 1 PRISMA 2020 flow diagram for study inclusion

Table 1 Characteristics of included studies

Study	Year of publication	Country	Inclusion criteria	*N* of participants (women/men)	Average age	Gene	Outcome*
Ateia et al. [2]	2020	Egypt	Aneurysmal SAH, age 30–65, no preexisting neurological deficit, systemic diseases	50 (29/21)	–	Hp	DCI
Hendrix et al. [9]	2017	USA	Ruptured intracranial aneurysm, ≥ 19 years, no associated genetic disease/syndrome that could account for the presence of an intracranial aneurysm or systemic diseases (e.g., congestive heart failure, cirrhosis, etc.) that could affect the renin-angiotensin system, alive after 4 days	149 (114/35)	54.9 ± 12.5	RYR1	DCI, CV (radiological + ultrasound)
Hendrix et al. [10]	2017	USA	Ruptured intracranial aneurysm, ≥ 19 years, no associated genetic disease/syndrome that could account for the presence of an intracranial aneurysm or systemic diseases (e.g., congestive heart failure, cirrhosis, etc.) that could affect the renin-angiotensin system, alive after 4 days	149 (114/35)	54.9 ± 12.5	eNOS	DCI
Murthy et al. [22]	2016	USA	Ruptured intracranial aneurysm, ≥ 18 years, presentation within 24 h	133 (95/38)	53 ± 13.9	Hp	DCI
Csajbok et al. [4]	2016	Sweden	Ruptured intracranial aneurysm, presentation within 2 days, residents of Sweden	148 (108/40)	56 (20.0; 81.0)	APOE	CV (radiological + ultrasound)
Leclerc et al. [19]	2015	USA	> 18 years, ruptured intracranial aneurysm	74 (54/20)	54.7 ± 15.5	Hp	DCI, CV (radiological)
Ohnishi et al. [25]	2013	Japan	Ruptured intracranial aneurysm	95 (53/42)	62.2 ± 13.9	Hp	DCI, CV (radiological)
Rueffert et al. [29]	2011	Germany	Ruptured intracranial aneurysm	46 (34/12)	48.5 ± 12.6	RYR1	CV (radiological + ultrasound)
Wu et al. [36]	2011	China	Ruptured intracranial aneurysm, no head injury, no brain herniation, survived beyond 3 days after aSAH	185 (101/84)	54.89	APOE	CV (ultrasound)
Juvela S, Siironen J, Lappalainen J [16]	2009	Finland	Ruptured intracranial aneurysm	105 (52/53)	48.1 ± 11.3	APOE	DCI

Table 1 (continued)

Study	Year of publication	Country	Inclusion criteria	*N* of participants (women/men)	Average age	Gene	Outcome*
Ko et al. [18]	2008	USA	Ruptured intracranial aneurysm, could undergo at least one angio within the vasospasm period	347 (246/101)	54.7 ± 13	eNOS	CV (radiological)
Starke et al. [32]	2008	USA	Ruptured intracranial aneurysm, presented within 2 days of SAH	77 (49/28)	54.2 ± 11.4	eNOS	DCI, CV (radiological)
Song et al. [30]	2006	South Korea	Ruptured intracranial aneurysm, no cerebral infarction or myocardial ischemia	133 (78/55)	53.7 ± 11.3	eNOS	DCI
Khurana et al. [17]	2004	USA	Ruptured intracranial aneurysm	NR	NR	eNOS	DCI, CV (radiological + ultrasound)
Niskakangas et al. [24]	2001	Finland	Ruptured intracranial aneurysm	108 (65/43)	51.5 (19–79)	APOE	DCI
Dunn et al. [5]	2001	UK	Ruptured intracranial aneurysm	96 (58/38)	48.7	APOE	DCI

*Methods of CV confirmation are indicated in the brackets for studies in which CV was among the investigated variables/outcomes methods

1.48, 95%CI 0.99–2.21, $p = 0.054$); Fig. 2). Heterogeneity analysis showed a significant heterogeneity for meta-analysis of all polymorphisms besides Hp2-2 (Fig. 2).

Delayed cerebral ischemia

A total of ten studies representing three polymorphisms in three genes (ApoE4, eNOS T786C, and Hp2-2) were included in the meta-analysis for DCI. Among analyzed polymorphisms, only Hp2-2 had an association with DCI (RR 1.57, 95%CI 1.06–2.34, $p = 0.026$; see Fig. 3). Heterogeneity was low (Fig. 3).

Discussion

Our study represents a synthesis of the current knowledge about the association of individual polymorphisms in different genes and CV and DCI after aSAH. Rosalind Lai and Du performed a similar meta-analysis in 2015 [28], but considering a foreseeable increase in the number of studies on genetic correlates of the subarachnoid hemorrhage outcomes over the past six years, our meta-analysis expands the findings of the previous one. Presence of the Hp2-2 allele was associated with DCI and CV in our analysis; in addition, the presence of ApoE4 allele had a borderline association with CV.

In our study, we identified studies reporting associations of 28 different genes with CV and DCI, of which 4 genes for CV (ApoE4, eNOS, Hp, and RYR1) and 3 genes for DCI (ApoE4, eNOS, and Hp) were reported in more than 2 studies and could, therefore, be included into meta-analysis. The majority of the reported genes were related to the function of different blood vessel wall components (e.g., eNOS, RYR1, cystathionine β-synthase), coagulation (e.g., plasminogen activator inhibitor-1, prothrombin), or cerebral metabolic and antioxidant systems (e.g., APOE4, epoxide hydrolase).

ApoE4

ApoE is one of the regulators of lipoprotein uptake and lipid metabolism in body tissues, including the brain. It is encoded by the *APOE* gene that has three alleles, ε2, ε3, and ε4, located on chromosome 19p13. ApoE polymorphisms are suggested to be implicated in a range of cerebral processes. For instance, besides its undoubtful influence on the risk of Alzheimer's disease, the presence of ApoE4 promotes a more robust brain inflammation in traumatic brain injury, brain ischemia, and hemorrhage and reduces dendritic sprouting [27]. Although the exact pathophysiological pathway through which ApoE could influence the course of aSAH is unknown, it is suggested that it stimulates neuronal autophagy and thus promotes survival of viable neurons [15, 20]. ApoE4 seems to be less efficient in this regard than ApoE3 and causes a higher rate of apoptosis after aSAH [15].

We included several studies that investigated the association of the presence of the ApoE4 allele with CV and DCI. For DCI, Dunn et al. reported a trend for a protective effect of ApoE4, which did not reach a statistical significance [5].

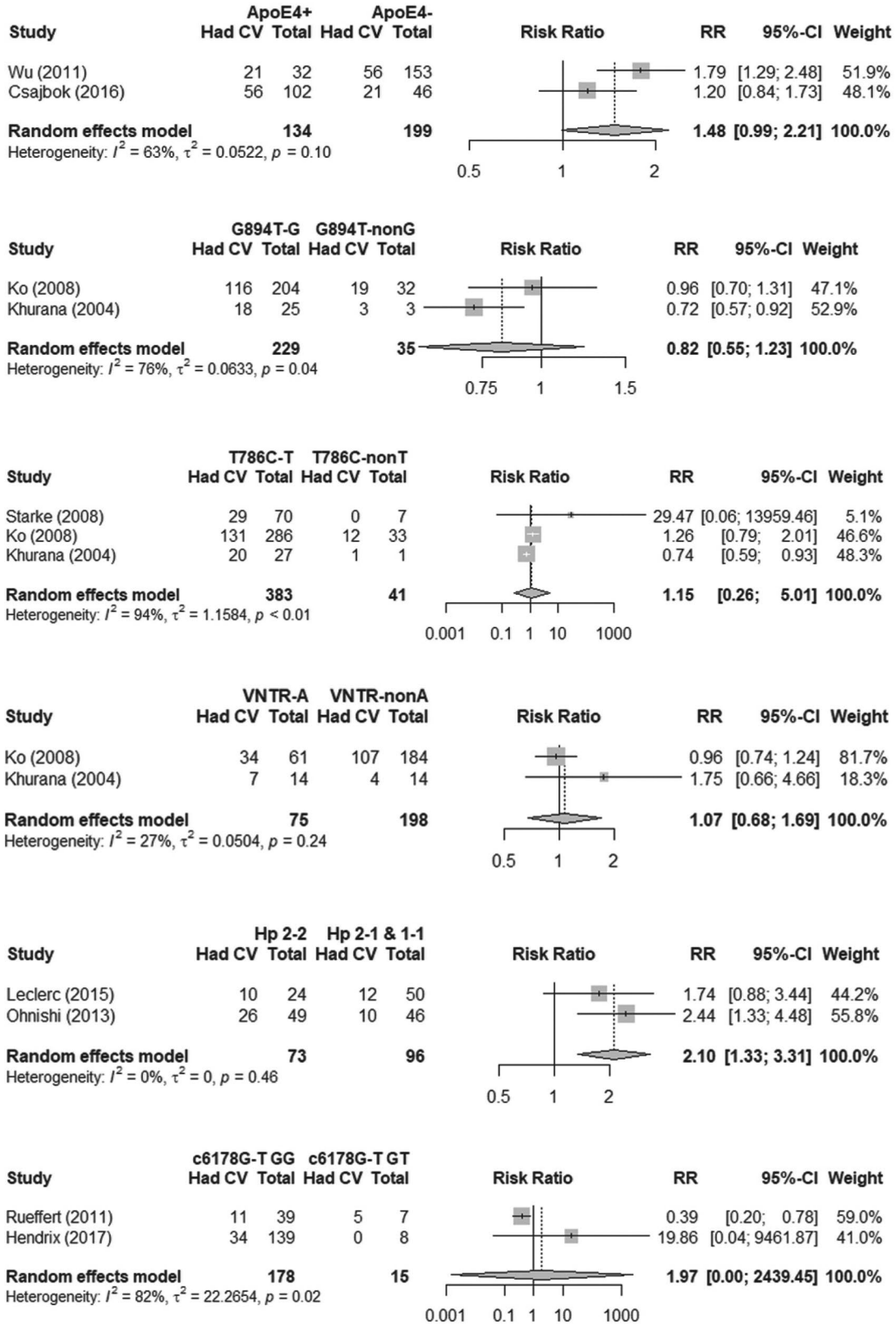

Fig. 2 Random effects model analysis of association of ApoE4, eNOS, Hp, and RYR1 polymorphisms with CV

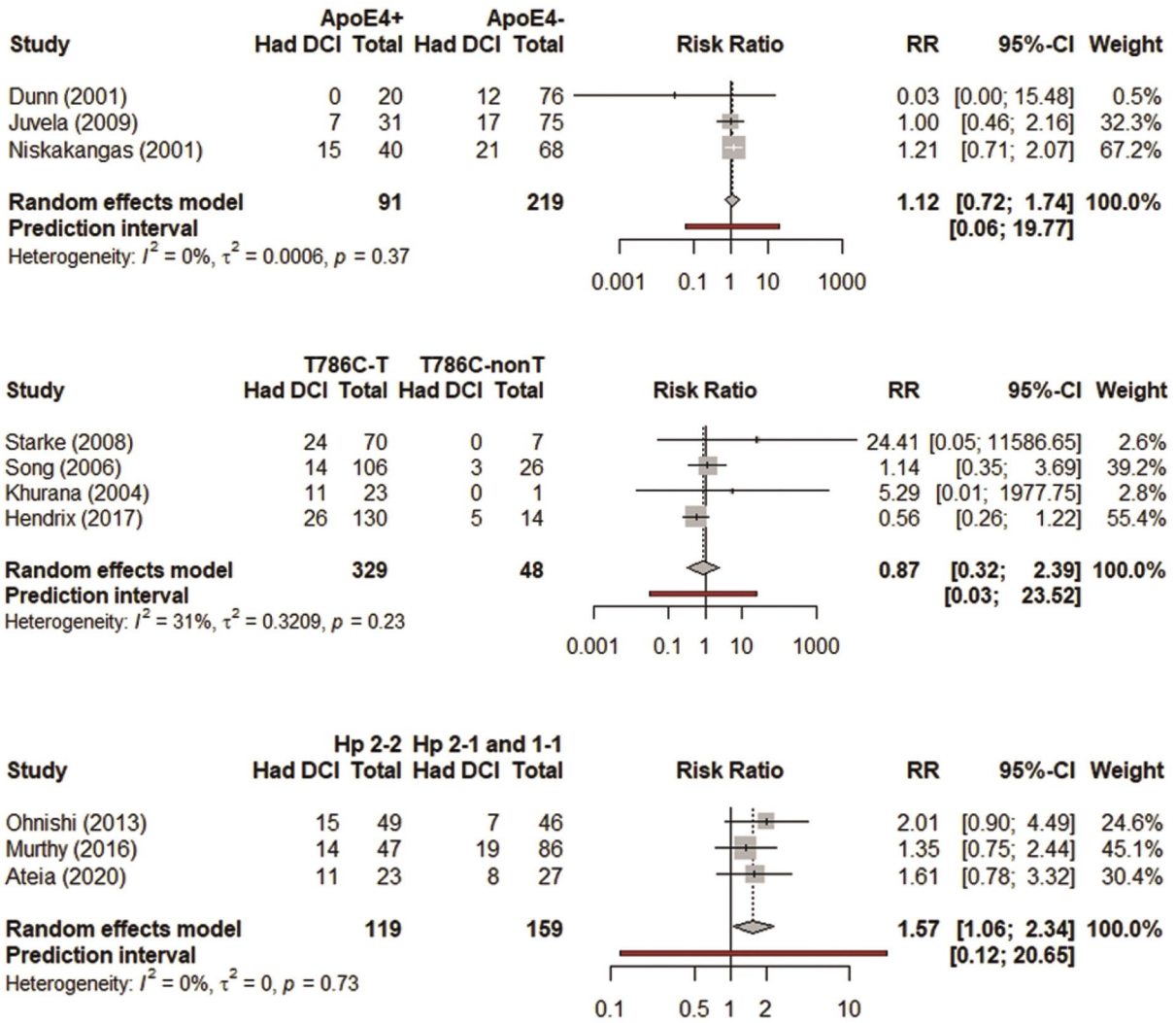

Fig. 3 Random effects model analysis of association of ApoE4, eNOS T786C, and Hp polymorphisms with DCI

Niskakangas et al. and Juvela et al. reported no association between the presence of ApoE4 and DCI [16, 24]. Two studies that investigated interlink between CV and ApoE4 showed conflicting results: Wu et al. found that ApoE4 was encountered more frequently in patients who had CV, while Csajbok et al. reported no association between ApoE4 and CV [4, 36].

Our meta-analysis showed no association of ApoE4 with either CV or DCI in a random-effect model. Although there was a significant association of ApoE4 with CV on the fixed-effect model, high heterogeneity renders this result unreliable. Interestingly, existing meta-analyses show the association of different ApoE alleles with the occurrence of aSAH. For instance, Zhao and colleagues showed that ApoE4 is mildly associated with a slightly increased risk of aSAH in Asians, but not in any other populations [37]; the presence of ε2 allele, either homozygotic or heterozygotic, was shown to be associated with aSAH in individuals of Asian descent, while only homozygotic ε2/ε2 genotype was associated with the higher risk in Caucasian population in meta-analysis by Arati et al. [1]; and Hu and colleagues demonstrated a 1.23-fold increase in odds of aSAH in ε4 carriers in all ethnicities and 3.38-fold in odds of aSAH in Caucasian carriers of ε2/ε2 [13]. Therefore, although the polymorphisms in the APOE gene seem to play a role in the emergence of aSAH, they do not appear to impact the risk of CV or DCI after aSAH.

eNOS

The eNOS gene is located on chromosome 7q35 and codes for endothelial nitric oxide synthase (eNOS), an enzyme that generates inorganic nitric oxide (NO) from L-arginine. NO is a potent vasodilator, which is suggested to play a role in cerebral autoregulation via acting on the smooth muscle

cells of small-diameter cerebral arteries [8]. Recent human data from a translational study also suggest that cerebral NO concentration significantly increases during the first 7 days after SAH, which correlated with the markers of mitochondrial damage as measured by the in vivo cerebral microdialysis during neuromonitoring in seven patients with severe aSAH [11]. Therefore, the polymorphisms in the gene of the enzyme that produces it might be implicated in the development of ischemic complications after aSAH.

There are several polymorphisms investigated for association with different cardiogenic and vascular conditions, including coronary artery disease, atrial fibrillation, and carotid atherosclerosis. For instance, T786C polymorphism is associated with increased risk of coronary artery disease and myocardial infarction [33, 38], and VNTR polymorphisms predispose individuals to ischemic stroke and ischemic osteonecrosis of the femur head [31, 35].

Several studies that investigated the association between eNOS polymorphisms and CV and DCI after aSAH were eligible for our meta-analysis. Studies evaluating eNOS T786C polymorphism were available for both CV and DCI; eNOS G894T and 27 VNTR polymorphisms were additionally available for CV. Association of G894T and 27 VNTR with CV was investigated by Khurana et al. [17] and Ko et al. [18], and both groups reported there was no significant association of either of the polymorphisms with CV.

For the association between T786C polymorphism DCI, a study by Hendrix et al. [9, 10] showed a possible reduction in the risk with T homozygosity or heterozygosity compared to T noncarriers, which did not reach statistical significance; it contrasts with four other included studies [17, 30, 32], which showed an increase in the risk.

In our meta-analysis, we found no significant associations between polymorphisms in eNOS and the development of CV or DCI.

Of note, while endothelial NOS has been largely investigated in association with aSAH, other NOS isoforms—neuronal and inducible—have gained little attention in clinical research so far. Neuronal NOS (nNOS), which is mainly expressed in the brain and skeletal muscles, could be of particular interest for further investigations, because it seems to be one of the main drivers of NO production in the nervous tissue [6]. The potential role of nNOS involvement in the development of post-aSAH ischemic complications is supported by findings from the bench studies. For instance, Pluta and his group, which investigated the dynamics of NOS expression in the cerebral vessels in the primate model of aSAH, discovered two phases of NOS-related changes in the development of DCI [26]. During the first phase, which lasts up to a week, hemoglobin products destroy neurons expressing nNOS localized to the adventitia of the cerebral vessels; during the second phase, eNOS is inhibited by asymmetric dimethylarginine, a product of protein turnover released during the protein decay, prolonging the vasospasm [26]. Considering this hypothesis, nNOS polymorphisms could be associated with CV, while eNOS polymorphisms could be associated with DCI, which should be a matter for further clinical research.

Hp

Hp gene is located on chromosome 16p13 and encodes haptoglobin, an acute-phase reactant produced by the liver. Haptoglobin (Hp) acts as a scavenger protein for cell-free hemoglobin, which otherwise exhibits tissue toxicity [12]. Cell-free hemoglobin induces the formation of free radicals and interacts with NO enhancing its inactivation and can lead to vasoconstriction. Therefore, the presence of free, unbound hemoglobin is thought to be one of the major drivers of delayed ischemic complications after aSAH [12]. This hypothesis is also supported by the fact that administration of Hp in aSAH may have therapeutic implications: for instance, injection of Hp into CSF prevented CV in a sheep model of aSAH [12].

Humans have two Hp alleles, 1 and 2, a combination of which yields three possible genotypes (Hp1-1, Hp1-2, and Hp2-2). A product of Hp2-2, which is a cyclic polymer in contrast to linear polymers produced by Hp1-1 and Hp1-2 genotypes, is reported to have a lesser scavenging potency [3]. Hp2-2 genotype has been associated with an increased risk of numerous complications after aSAH, including ischemic events.

Our meta-analysis showed an increased risk of DCI in people with Hp2-2 genotype and a borderline association of Hp2-2 with CV. This contrasts to some other studies: for example, a relatively recent individual patient data analysis, which included 939 patients with aSAH, found no association with any primary or secondary outcome, including CV and DCI [7]. Notably, this analysis included six unpublished studies, which suggests a possible publishing bias leading to excluding studies that found no association between Hp genotypes and aSAH outcomes. Nevertheless, considering existing research data and physiology of haptoglobin, further investigations on the role of the protein in development of ischemic events after subarachnoid hemorrhage have a rationale both for a possible prediction and for management of these events.

Limitations of the study

Although we could identify studies that investigated polymorphisms in a total of 25 genes, only studies on 4 genes were in a sufficient number to be included in a meta-analysis. Our literature search involved only two databases, which, despite the size and comprehensiveness of the databases, could result in the omission of studies, especially published

in languages other than English. In addition, we could not get unreported data from the authors of the articles upon request. Some subanalyses only included two studies—which is a minimal amount required to conduct a meta-analysis—resulting in a high risk of type II error. We also acknowledge that bias might exist towards publishing statistically significant data, while we did not attempt to obtain unpublished data unless there was a clue in an article pointing to the possible existence of such relevant data; therefore, our analysis might exclude unreported data with negative results.

Conclusions

In conclusion, our meta-analysis supports the association between the presence of the Hp2-2 allele and the occurrence of CV and DCI after aSAH. Further studies investigating this association are needed to reinforce this finding. A number of studies on the role of some genetic polymorphism and allele candidates could not be included in the analysis, and further evidence from additional research is needed to investigate their role in CV and DCI.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-021-01829-5.

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Declarations

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

Ethics approval Ethical approval was waived by the local Ethics Committee in view of the nature of the study.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

1. Arati S, Sibin MK, Bhat DI, Narasingarao KVL, Chetan GK (2016) Polymorphisms of apolipoprotein E and aneurysmal subarachnoid haemorrhage: a meta-analysis. Meta Gene 9:151–158
2. Ateia AM, Elbassiouny A, El-Nabi SH, Fahmy NA, Ibrahim MH, El-Garawani I, Geba KM, Khalaf M (2020) Predictive value of haptoglobin genotype as a risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 199:106296
3. Bulters D, Gaastra B, Zolnourian A et al (2018) Haemoglobin scavenging in intracranial bleeding: biology and clinical implications. Nat Rev Neurol 14(7):416–432
4. Csajbok LZ, Nylén K, Öst M, Blennow K, Zetterberg H, Nellgård P, Nellgård B (2016) Apolipoprotein E polymorphism in aneurysmal subarachnoid haemorrhage in West Sweden. Acta Neurol Scand 133(6):466–474
5. Dunn LT, Stewart E, Murray GD, Nicoll JA, Teasdale GM (2001) The influence of apolipoprotein E genotype on outcome after spontaneous subarachnoid hemorrhage: a preliminary study. Neurosurgery 48(5):1006–1010
6. Förstermann U, Sessa WC (2012) Nitric oxide synthases: regulation and function. Eur Heart J 33(7):829–837
7. Gaastra B, Ren D, Alexander S et al (2019) Haptoglobin genotype and aneurysmal subarachnoid hemorrhage: Individual patient data analysis. Neurology 92(18):e2150–e2164
8. Guo Z-N, Shao A, Tong L-S, Sun W, Liu J, Yang Y (2016) The role of nitric oxide and sympathetic control in cerebral autoregulation in the setting of subarachnoid hemorrhage and traumatic brain injury. Mol Neurobiol 53(6):3606–3615
9. Hendrix P, Foreman PM, Harrigan MR et al (2017) Ryanodine receptor 1 polymorphism is not associated with aneurysmal subarachnoid hemorrhage or its clinical sequelae. World Neurosurg 100:190–194
10. Hendrix P, Foreman PM, Harrigan MR et al (2017) Endothelial nitric oxide synthase polymorphism is associated with delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. World Neurosurg 101:514–519
11. Hosmann A, Milivojev N, Dumitrescu S, Reinprecht A, Weidinger A, Kozlov AV (2021) Cerebral nitric oxide and mitochondrial function in patients suffering aneurysmal subarachnoid hemorrhage-a translational approach. Acta Neurochir 163(1):139–149
12. Hugelshofer M, Buzzi RM, Schaer CA et al (2019) Haptoglobin administration into the subarachnoid space prevents hemoglobin-induced cerebral vasospasm. J Clin Invest 129(12):5219–5235
13. Hu X, Xie Z, Zan X, Ma L, Li H, You C, Jiang Y (2018) Role of apolipoprotein E genotypes in aneurysmal subarachnoid hemorrhage: susceptibility, complications, and prognosis. World Neurosurg 118:e666–e676
14. Jabbarli R, Rauschenbach L, Dinger TF, Darkwah Oppong M, Rodemerk J, Pierscianek D, Dammann P, Junker A, Sure U, Wrede KH (2020) In the wall lies the truth: a systematic review of diagnostic markers in intracranial aneurysms. Brain Pathol 30(3):437–445
15. Jiang L, Zhong J, Dou X, Cheng C, Huang Z, Sun X (2015) Effects of ApoE on intracellular calcium levels and apoptosis of neurons after mechanical injury. Neuroscience 301:375–383
16. Juvela S, Siironen J, Lappalainen J (2009) Apolipoprotein E genotype and outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg 110(5):989–995
17. Khurana VG, Sohni YR, Mangrum WI, McClelland RL, O'Kane DJ, Meyer FB, Meissner I (2004) Section on cerebrovascular surgery: Galbraith Award: Endothelial nitric oxide synthase (eNOS) and heme oxygenase-1 (HO-1) gene polymorphisms predict susceptibility to aneurysmal subarachnoid hemorrhage (SAH) and post-SAH cerebral vasospasm. Clin Neurosurg 51:343–350
18. Ko NU, Rajendran P, Kim H et al (2008) Endothelial nitric oxide synthase polymorphism (-786T->C) and increased risk of angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 39(4):1103–1108
19. Leclerc JL, Blackburn S, Neal D, Mendez NV, Wharton JA, Waters MF, Doré S (2015) Haptoglobin phenotype predicts the development of focal and global cerebral vasospasm and may influence outcomes after aneurysmal subarachnoid hemorrhage. Proc Natl Acad Sci USA 112(4):1155–1160

20. Li X, Peng J, Pang J et al (2018) Apolipoprotein E-mimetic peptide COG1410 promotes autophagy by phosphorylating GSK-3β in early brain injury following experimental subarachnoid hemorrhage. Front Neurosci 12:127
21. Muehlschlegel S (2018) Subarachnoid hemorrhage. Continuum 24(6):1623–1657
22. Murthy SB, Caplan J, Levy AP, Pradilla G, Moradiya Y, Schneider EB, Shalom H, Ziai WC, Tamargo RJ, Nyquist PA (2016) Haptoglobin 2–2 genotype is associated with cerebral salt wasting syndrome in aneurysmal subarachnoid hemorrhage. Neurosurgery 78(1):71–76
23. Neifert SN, Martini ML, Hardigan T, Ladner TR, MacDonald RL, Oermann EK (2020) Trends in incidence and mortality by hospital teaching status and location in aneurysmal subarachnoid hemorrhage. World Neurosurg 142:e253–e259
24. Niskakangas T, Ohman J, Niemelä M, Ilveskoski E, Kunnas TA, Karhunen PJ (2001) Association of apolipoprotein E polymorphism with outcome after aneurysmal subarachnoid hemorrhage: a preliminary study. Stroke 32(5):1181–1184
25. Ohnishi H, Iihara K, Kaku Y, Yamauchi K, Fukuda K, Nishimura K, Nakai M, Satow T, Nakajima N, Ikegawa M (2013) Haptoglobin phenotype predicts cerebral vasospasm and clinical deterioration after aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 22(4):520–526
26. Pluta RM (2008) Dysfunction of nitric oxide synthases as a cause and therapeutic target in delayed cerebral vasospasm after SAH. Acta Neurochir Suppl 104:139–147
27. Rebeck GW (2017) The role of APOE on lipid homeostasis and inflammation in normal brains. J Lipid Res 58(8):1493–1499
28. Rosalind Lai PM, Du R (2015) Role of genetic polymorphisms in predicting delayed cerebral ischemia and radiographic vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis. World Neurosurg 84(4):933–941
29. Rueffert H, Gumplinger A, Renner C, Dengl M, Reske A, Kaisers UX, Meixensberger J (2011) Search for genetic variants in the ryanodine receptor 1 gene in patients with symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Neurocrit Care 15(3):410–415
30. Song M-K, Kim M-K, Kim T-S, Joo S-P, Park M-S, Kim B-C, Cho K-H (2006) Endothelial nitric oxide gene T-786C polymorphism and subarachnoid hemorrhage in Korean population. J Korean Med Sci 21(5):922–926
31. Song GG, Lee YH (2017) Association of eNOS polymorphisms with susceptibility to osteonecrosis of the femur head: a meta-analysis. Z Rheumatol 76(3):267–273
32. Starke RM, Kim GH, Komotar RJ et al (2008) Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab 28(6):1204–1211
33. Tangurek B, Ozer N, Sayar N, Terzi S, Yilmaz H, Dayi SU, Ciloglu F, Aksu H, Asilturk R, Cagil A (2006) The relationship between endothelial nitric oxide synthase gene polymorphism (T-786 C) and coronary artery disease in the Turkish population. Heart Vessels 21(5):285–290
34. Vergouwen MDI, Vermeulen M, van Gijn J et al (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke 41(10):2391–2395
35. Wei LK, Au A, Menon S et al (2017) Polymorphisms of MTHFR, eNOS, ACE, AGT, ApoE, PON1, PDE4D, and ischemic stroke: meta-analysis. J Stroke Cerebrovasc Dis 26(11):2482–2493
36. Wu H-T, Zhang X-D, Su H, Jiang Y, Zhou S, Sun X-C (2011) Association of apolipoprotein E polymorphisms with cerebral vasospasm after spontaneous subarachnoid hemorrhage. Acta Neurochir Suppl 110(Pt 1):141–144
37. Zhao D, Zhang Z, Wu G-B et al (2016) Apolipoprotein E gene polymorphism and the risk of subarachnoid hemorrhage: a meta-analysis of case-control studies. Acta Neurochir 158(8):1515–1522
38. Zigra A-M, Rallidis LS, Anastasiou G, Merkouri E, Gialeraki A (2013) eNOS gene variants and the risk of premature myocardial infarction. Dis Markers 34(6):431–436