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Review

Gene Polymorphisms Increasing the Risk of Intracranial Aneurysms: Interleukin-1β-511C>T (Part I)

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Abstract. *Introduction:* Intracranial aneurysms (IAs) are devastating cerebrovascular diseases with multifactorial etiology. The role of inflammation is indisputable, and interleukins are pivotal in supporting local inflammatory pathways and endothelial dysfunction at the aneurysm wall. In the light of insufficient evidence reported in the literature, this meta-analysis was aimed to investigate the genetic linkage between IL-1β (rs16944) -511C>T polymorphisms and IAs susceptibility. *Methods:* A comprehensive online literature review was completed using the PubMed/Medline and Web of Science databases in accordance with the PRISMA guidelines. "Interleukin-1β," "IL-1β," "polymorphism," "intracranial aneurysm," and "subarachnoid hemorrhage" were the main keywords. Only human case-control studies, published from 2005 to 2021, written in English or translated, were screened. In the statistical analysis, we applied the fixed- and random-effect models, according to the level of heterogeneity, to assess the odds ratios (ORs) and 95% confidence intervals (CIs). RevMan 5.0 software was used for the statistics. *Results:* Only 4 studies were eligible, with a total of 2070 patients, 1050 of which were assigned to the study group. Combined results showed a statistically significant association between the risk of IAs and -511CC (OR=0.79, 95% CI [0.65-0.95], p=0.01), and CT (OR=0.69, 95% CI [0.58-0.82], p<0.0001; OR=0.71, 95% CI [0.55-0.93], p=0.01) allele variations, both in the fixed- and random- models. No correlation was identified for the -511TT genotype (p=0.42; p=0.78). All the texts showed a low level of publication bias. *Conclusion:* The present meta-analysis proved a potential role of IL-1β -511CC/CT genotypes in the pathogenesis of IAs. Additional studies are imperative to explain the underlying neuroimmune mechanisms, also allowing tailoring the potential inflammatory-target therapies for IAs. (www.actabiomedica.it)

Key words: Allele Variations; Gene Polymorphisms; IL-1β; Inflammatory Cytokines; Interleukin-1β; Intracranial Aneurysm; Subarachnoid Hemorrhage.

Introduction

Proinflammatory cytokines, as interleukins (ILs), control the adaptive immune response and upregulate inflammatory reactions. Recent advances in immunogenetics strongly support the liability of ILs in the pathogenesis of neuro-oncological and neurovascular diseases including intracranial aneurysms (IAs) (1-10). IAs are focal vessels enlargements featured by histological changes and vascular remodeling of the arterial wall (11-13). Recruit-

ing of macrophages, T lymphocytes, and platelets, infiltration of proteases and ILs through vessels wall, lead to endothelial dysfunction and arterial weakening (14-17). Thinning of vascular layers increases IAs growth, resulting in rupture and subarachnoid hemorrhage (SAH) (18-22). The interleukin-1β (IL-1β), a pleiotropic cytokine, promotes lymphocytes activation, boosts the immune cascade, and regulates inflammatory pathways (23-25). The genetic cluster, which encodes for the IL-1 family, was mapped on chromosome 2. C>T polymorphisms of the IL-1β gene, at the -511promoter region (rs16944), affect the over-expression of IL-1β and, consequently, promote inflammatory pathways (25-27).

The increased immune response and the high serum concentration of IL-1β may influence the IAs' natural history, worsening morbidity and mortality of SAH (28, 29).

Our meta-analysis intends to explore the genetic linkage between -511C>T polymorphic variations of IL-1β genotype and IAs susceptibility in different population samples. Future perspectives and novel immunotherapeutic targets are also discussed.

Methods

Literature selection process

The PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (https://www.webofscience.com) online databases were used for the literature review, which was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations. The keywords were "interleukin-1β," "IL-1β," "interleukin-1β polymorphism," "IL-1β polymorphism," "interleukin-1β genotype," "IL-1β genotype", combined with "intracranial aneurysm," "brain aneurysm," and "subarachnoid hemorrhage." The inclusion criteria were set as follows: articles written in English or translated, reference period ranging between 2005 and 2021, case-control human studies, genome-wide linkage analysis for IL-1β -511C>T (rs16944) polymorphisms, availability data on allele frequencies (CC/CT/TT).

Studies involving animals, those lacking a control group, editorials, letters to editors, reviews, and case reports were excluded. Eligible articles were filtered based on the best match and relevance. The quality level of the articles was estimated through the Newcastle-Ottawa quality assessment scale (NOS). A NOS score greater than 6 documented a high-quality study.

Statistical analysis

The Mantel-Haenszel method for fixed effects was applied to estimate the pooled odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity of the study sample was calculated by Cochrane's Q test, whereas p^q <0.05 and I^2 >50% were considered significant. In the case of high-level heterogeneity, the Der Simonian-Laird method was used for the random effects model. Z-test for overall effect was always completed and the ORs and CIs of each endpoint were built in as Forest plots. The *p*-value was set at < 0.05. Begg's rank correlation and Egger's regression asymmetry methods were used to assess the risks of publication bias. The relative funnel plots were reported. RevMan 5.0 software (Cochrane Informatics & Knowledge Management Department) was used for the meta-analysis.

Results

Literature Volume

The search retrieved a total of 58 articles. After removing duplicates, screening, and application of the exclusion criteria, 9 studies were found initially eligible. Then implementation of the inclusion criteria allowed to select 4 studies. Figure 1 shows the PRISMA flow chart on the study (Figure 1).

All studies tested allelic frequencies of the IL-1β gene -511C>T (rs16944) polymorphisms. 3 articles were prospective observational and the other retrospective. NOS score was 6 in 2 studies and 7 in the remaining. The studies were conducted in Italy, China, India, and Poland.

Demographics and Genetic Data

1050 IAs belonged to the study groups, whereas the control groups consisted of 1020 healthy subjects,

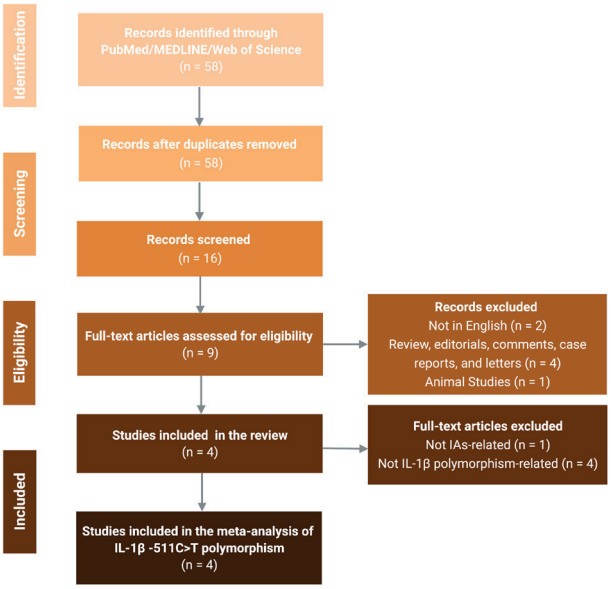


Figure 1. PRISMA flow diagram on the meta-analysis selection process

for a total of 2070 recruited patients. The average patients' age was 55 and 56.8 years for the IAs groups and control groups, respectively. Males were 40.5% and 34.6% in the study and control groups, respectively. Patients' demographics and genetic records were summarized in Table 1.

Quantitative Synthesis and Heterogeneity Analysis

Cochrane's Q test revealed a high level of heterogeneity (I2=77%, I2=53%, I2=79%) for all the tests. Accordingly, both fixed- and random-effect model was applied in the entire dataset. Concerning the -511CC polymorphism, the results were as follows: OR=0.79, 95% CI [0.65-0.95], p=0.01, and OR=0.79, 95% CI [0.53-1.18], p=0.25, for the fixed- and random-effect model, respectively (Figure 2).

Both fixed and random model analysis on the -511CT polymorphism unveiled high statistical significance: OR=0.69, 95% CI [0.58-0.82], p<0.0001; and OR=0.71, 95% CI [0.55-0.93], p=0.01 (Figure 3).

Results of the -511TT genotype examination were as follows: OR=0.91, 95% CI [0.72-1.15], p=0.42; OR=1.08, 95% CI [0.62-1.88], p=0.78, for the fixed- and random-effect models, respectively (Figure 4).

Table 1. Overview of the studies about IL-1β gene polymorphisms and IAs

Author, Year	Study type	Country	Timeframe	N° of patients		Age		Gender		Genotype				NOS
				IAs Group	Control Group	IAs Group (average y-o)	Control Group (average y-o)	IAs Group [N° of male (%)]	Control Group [N° of male (%)]	Polymorphism	Allele	IAs Group (N° of patients)	Control Group (N° of patients)	
Slowik et al, 2006 (44)	POS	Poland	2003-2005	231	231	49.9	50.4	99 (42)	99 (42)	IL-1β -511C>T	CC	100	111	7
											CT	99	106	
											TT	32	14	
Fontanella et al, 2010 (45)	POS	Italy	2003-2007	215	155	55	53.7	74 (34)	50 (32)	IL-1β -511C>T	CC	94	64	7
											CT	88	68	
											TT	33	23	
Sathyan et al, 2015 (46)	ROS	India	2014	220	250	41.2	NA	123 (56)	NA	IL-1β -511C>T	CC	79	90	6
											CT	82	116	
											TT	33	37	
Xu et al, 2021 (47)	POS	China	2016-2020	384	384	57.1	66.5	117 (30)	117 (30)	IL-1β -511C>T	CC	44	88	6
											CT	128	187	
											TT	76	109	

C: Cytosine; IAs: Intracranial Aneurysms; N: Number; NA: Not Available; NOS: Newcastle-Ottawa quality assessment Scale; POS: Prospective Observational Study; ROS: Retrospective Observational Study; T: Thymidine; y-o: years old.

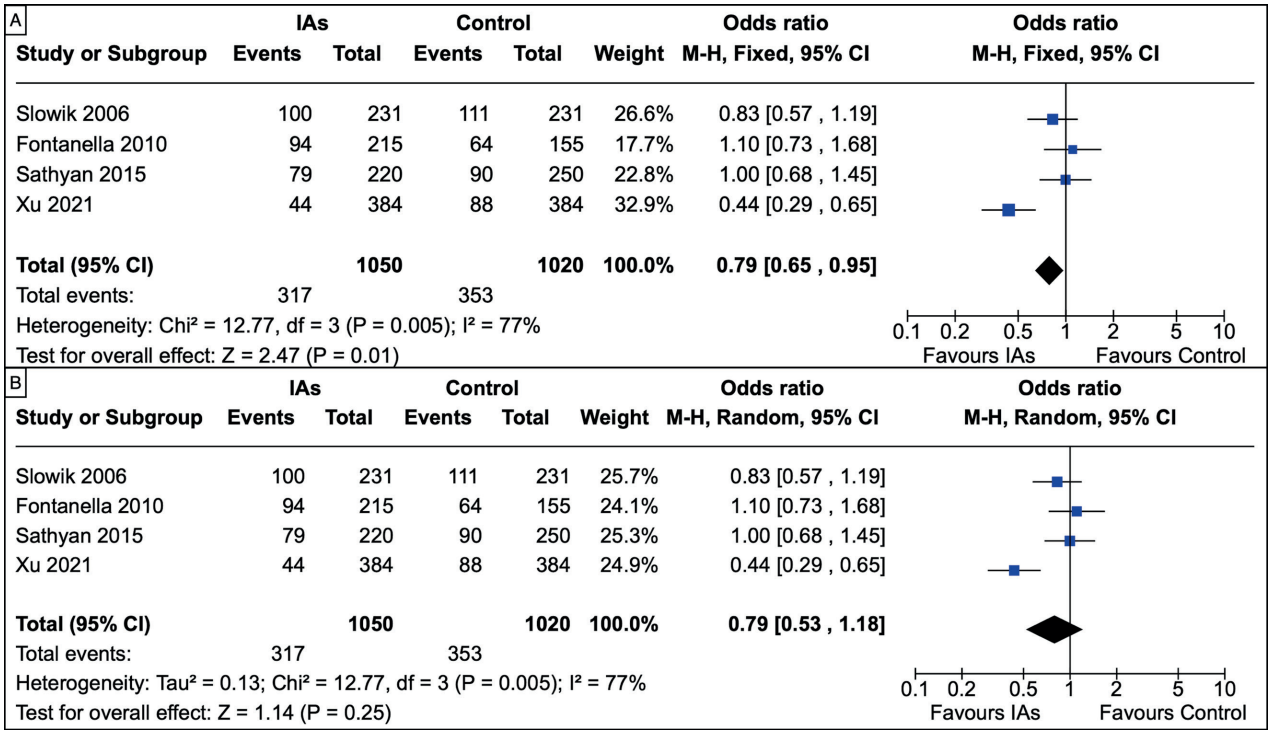


Figure 2. Forest plot for -511CC polymorphism

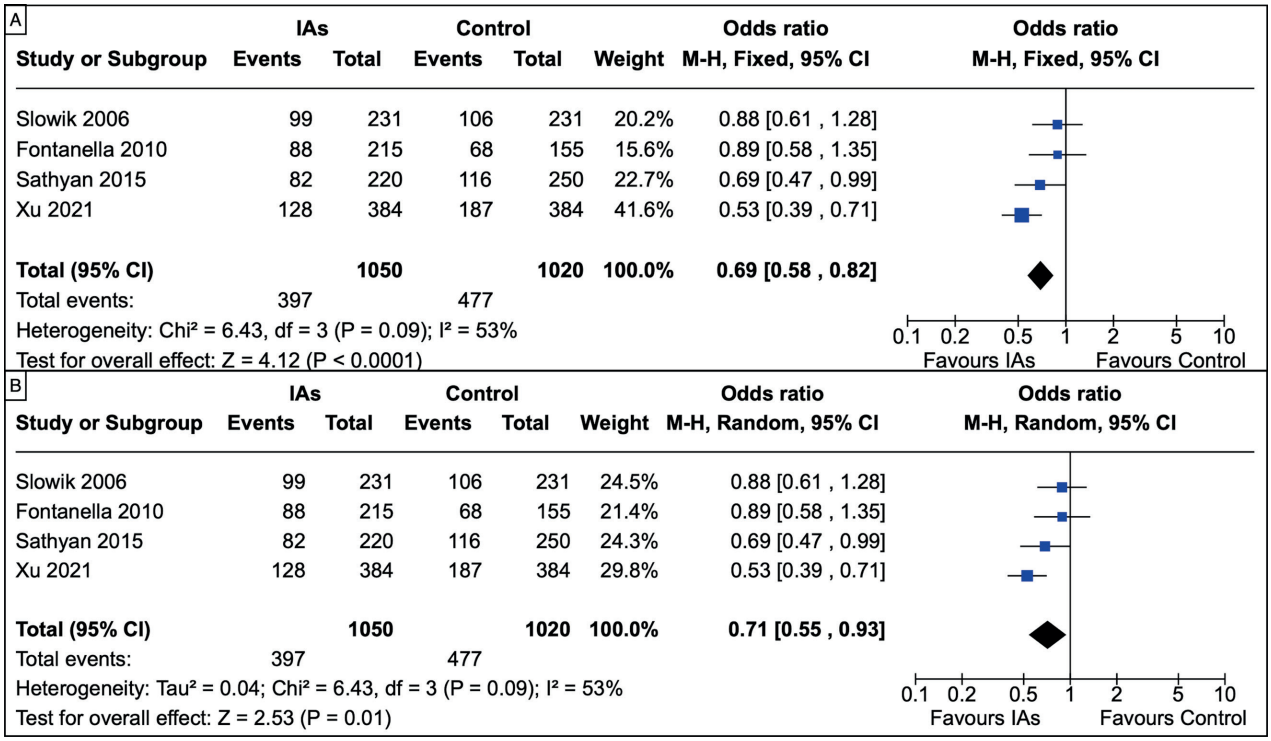


Figure 3. Forest plot for -511CT polymorphism

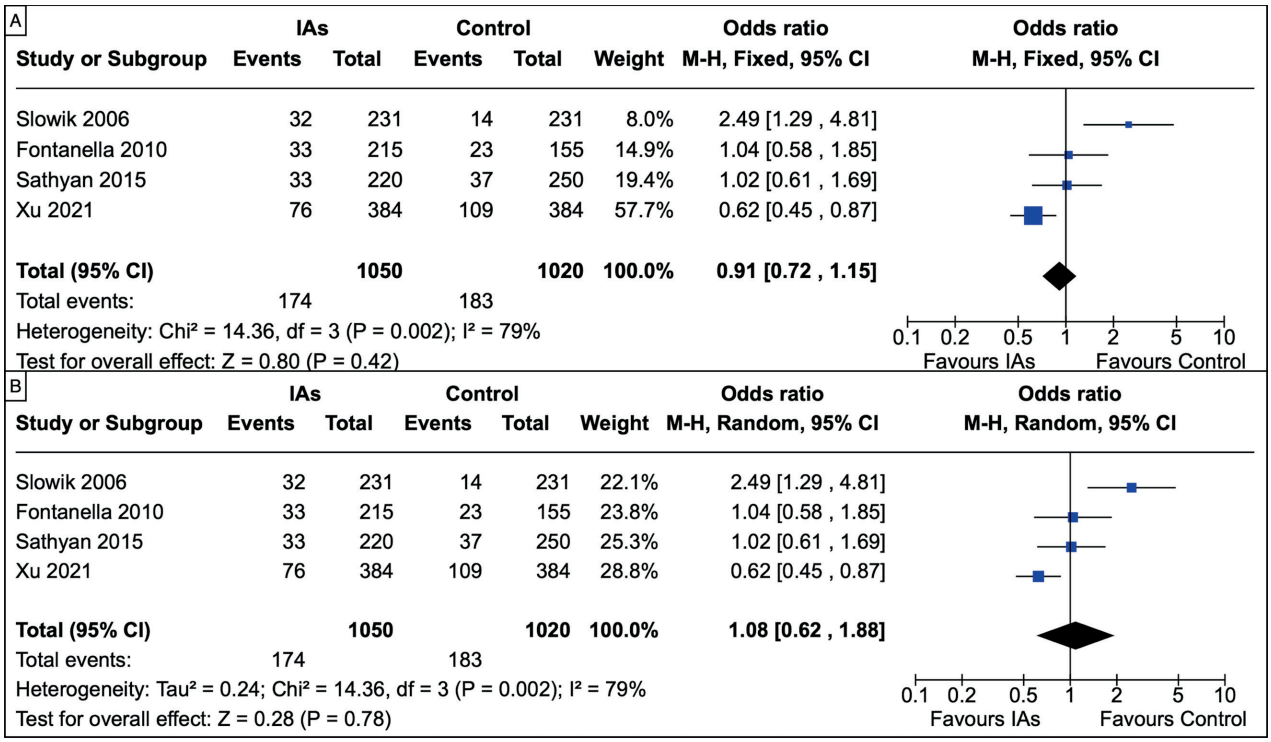


Figure 4. Forest plot for -511TT polymorphism

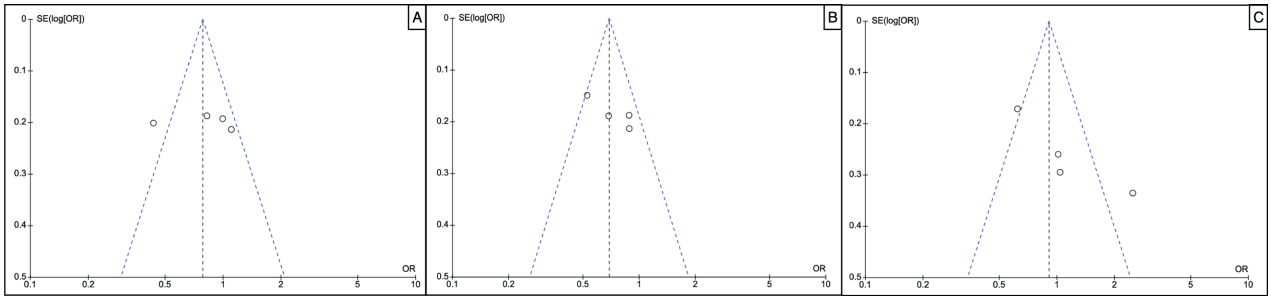
Publication Bias

Low risks of bias were detected by Begg's rank and Egger's methods for the -511CC/CT/TT genotypes evaluation (Figure 5).

Discussion

The present study was aimed to prove the associations between IL-1β -511C>T genotype variations and the risk of IAs.

-511C>T polymorphisms stimulate the aberrant production of IL-1β and the systemic increment of immune and inflammatory processes (25-27). The abnormal expression of IL-1β was demonstrated to interfere with the pathogenesis and prognosis of several neurological disorders, as multiple sclerosis, Parkinson's and Alzheimer's disease, and high-grade brain tumors (27, 30-41). The rise of IL-1β in serum concentration and cerebrospinal fluid of SAH-patients explains its role in the genesis and rupture of IAs (42, 43). Furthermore, the local interleukin increase triggers the endothelial dysfunction at the aneurysm wall by upregulating the



(A) -511CC, (B) -511CT, and (C) -511TT polymorphisms

Figure 5. Funnel plot for -511 CC/CT/TT polymorphisms

synthesis of proteases, leukocytes' adhesion molecules, and nitric oxide (NO) (17).

Data about the potential causative role of IL-1β genotypes in the formation and progression of IAs are contradictory and scant, accounting only for 4 case-control studies. In 2006, Slowik and colleagues reported a case-control study on 231 SAH patients. They genotyped the IL-1β polymorphisms finding a link between the -511TT allele variation and the risk of IAs (44). In 2010, a prospective study involving 215 consecutive patients affected by IAs was performed on the Italian population, whose results did not support any genetic association between IL-1β and aneurysmal SAH (45). Sathyan et al. conducted genetic tests for cytokine genes in the population of south India concerning the IL-1β rs16944 polymorphisms, confirming no genetic liability (46). Even a more recent study by Xu and colleagues, in 2021, failed to identify genetic associations between aneurysms and IL-1β in univariate and multivariate logistic regression analyses (47).

Contrary to what was reported by every single study, our meta-analysis highlighted a strong association between -511C>T polymorphisms and brain aneurysms. Despite the high level of heterogenicity, both fixed- and random-effects models proved significant genetic relationships between the -511CC ($p=0.01$) and 511CT ($p<0.0001$; $p=0.01$) polymorphisms. The present data can be interpreted as a starting point for future researches aimed to identify genetic aspects involved in the natural history of IAs, concurrently providing valuable insights for the management of SAH (19, 48).

Future Perspectives: Anti-Inflammatory Target Therapy

The overactivation of the inflammatory cascade is responsible for the IAs progression and the post-SAH complications also, including cerebral ischemia, cortical spreading depression, hydrocephalus, and vasospasm (28, 49-55).

In-depth knowledge of molecular pathways, underlying the inflammation-based aneurysmal development, is of dramatic importance to identify novel therapeutic targets (56). Blood products, interleukins, chemokines, and tumor necrosis factors bind respective ligands, expressed on endothelial cells, and upregulate leukocytes activation (57-59).

In this rationale, one among the earlier therapeutic approach was aimed at inhibiting the activation of lymphocytes and suppressing the immune response (60).

Since 1998, the ISUIA study (International Study of Unruptured Intracranial Aneurysms) investigated the role of acetylsalicylic acid (ASA) in preventing IAs rupture (61-63). ASA acts as an antiplatelet and anti-inflammatory agent. It blocks cyclooxygenase 2, inhibits the recruitment of macrophages, suppresses the metalloproteinases, and increases endothelium protection by NO (61, 64-68). Despite encouraging premises, the ASA was not finally approved as prophylactic for unruptured IAs. Statins have a pleiotropic effect in reducing the local immune response and increasing NO production (69-71). A combined treatment, ASA plus statins, has been tested on human and animal models and was potentially effective to reduce the risk of aneurysm rupture (72-74).

Lymphocytes' activity can also be modulated through the T-helper regulatory cells. Boosting the T-reg expression is a potentially valid approach in reducing inflammation and preserving endothelial integrity (75-79). M2 macrophages are involved in the tissue repairing processes and collagen production, counterbalancing the proinflammatory reaction of the microglia. Further advanced strategies were designed to promote the polarization of the microglial M2 and to heighten their neuroprotective effect (80-82).

Stem cell-based approaches have a rationale for IAs similarly to what known in neuro-oncology and regenerative medicine. In fact, mesenchymal stem cells may be theoretically administered to modulate the pro-inflammatory microenvironment and prevent the aneurysm rupture (83-88). Furthermore, emerging therapeutic frontiers are based on the neuro-immune communication strategies through the vagus nerve stimulation or tailoring of NO and acetylcholine receptors, to suppress the inflammatory microenvironment post-SAH (89, 90).

Limitations of the Study

The main limitations of this meta-analysis are the unavoidable selection bias, the limited number of patients involved, and the high population hetero-

geneity. Moreover, the acquired risk factors were not considered.

Conclusion

Genetic polymorphisms of proinflammatory cytokines increase the production of ILs, ultimately resulting in the upregulation of inflammatory processes at the IAs wall.

As opposed to what was reported by previous case-control studies, the present meta-analysis showed a direct association between the IL-1β -511CC/CT allele variations and the occurrence of IAs.

Further ethnicity-related data are necessary to clarify the genetic linkage between IL-1β and SAH, concurrently providing future directions for clinical research and novel therapeutic strategies.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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