Impact of Genetic polymorphisms on the risk of epilepsy amongst patients with acute brain injury: a systematic review

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Abstract

Background and objectives: Stroke and traumatic brain injury (TBI) accounts for 70% of secondary epilepsy in old age. The genetic architecture of late seizure or epilepsy secondary to TBI or stroke are poorly understood. We, therefore, undertook a systematic review to test the association of single nucleotide polymorphisms (SNPs) with the risk of posttraumatic epilepsy (PTE) or post-stroke epilepsy (PSE).

Methods: We followed methods from our prespecified protocol on PROSPERO to identify indexed articles for this systematic review. We collated the association statistics from the articles to assess the association of SNPs with the risk of epilepsy amongst TBI or stroke patients. We assessed the study quality using the Quality of Genetic Association (Q-Genie) tool. We report Odds Ratio (OR) and Hazard Ratio (HR) with a 95% confidence interval (CI), including combined OR where a meta-analysis was possible.

Results: The literature search yielded 420 articles, of which 16 were included in our systematic review. Q-Genie-based assessment of the literature found that 58% of the included studies were of poor quality. We examined published data on 127 SNPs from 32 genes identified in PTE and PSE patients. Twelve studies reported that 718 TBI patients (21%) suffered from PTE. Four studies reported PSE in 1192 stroke patients (50%). Eleven SNPs were associated with a significantly increased risk of PTE. Three SNPs, *TRMP6* rs2274924, *ALDH2* rs671, and *CD40* -1C/T, were significantly associated with an increased risk of PSE, while two SNPs, *AT1R* rs12721273 and rs55707609, were significantly associated with reduced risk. Only two studies tested the association of

APOE ε4 with PTE; no other studies validated previously reported genetic association data. Hence, the limited data precluded meta-analysis of all but one SNP, i.e., the *APOE* ε4 allele. The meta-analysis for the association of the *APOE* ε4 allele with PTE was statistically non-significant (OR 1.8, CI 0.6-5.6).

Discussion: The current evidence on the association of genetic polymorphisms in epilepsy secondary to TBI or stroke is of low quality and lacks validation. A collaborative effort to pool genetic data linked to epileptogenesis in stroke and TBI patients is warranted.

Keywords: Gene polymorphism; Epilepsy; Acquired Brain Insult; Stroke; Traumatic Brain Injury.

Systematic review registration: PROSPERO CRD42022325617.

Glossary:

TBI= Traumatic Brain Injury; PTE= Posttraumatic epilepsy; PSE= Post-stroke epilepsy; SNPs= Single Nucleotide Polymorphisms; OR= Odds Ratio; HR= Hazard Ratio; CI= Confidence Interval; IPSERC= International Post Stroke Epilepsy Research Consortium.

Introduction

In 2015, more than three million adults in the United States suffered from epilepsy.[1] Its high incidence in the adult population[2,3] is mainly attributed to the development of epilepsy secondary to brain insults, such as traumatic brain injury (TBI) and stroke. Among the adult population, 25% percent of new-onset epilepsies are diagnosed in the old age group, which also includes a group of patients with a prior history of seizures at a young age who survive to old age.[4,5] Cerebrovascular disease and cerebral trauma account for about 16-38% and 20% of new-onset seizures amongst the elderly.[6–9] The mechanisms of posttraumatic epilepsy (PTE) and post-stroke epilepsy (PSE) are poorly understood. Genetic factors are responsible for approximately 30% of epilepsy syndromes and are known to increase the susceptibility to develop epilepsy after acquired brain insults.[10] The association of genetic factors with epilepsy in adult individuals suffering from TBI or stroke has been investigated by multiple groups.[11] Most of these studies investigated PTE or PSE in small samples, and the validity of these studies remains undetermined. Because acute brain injury due to stroke and TBI account for a large proportion of secondary epilepsy in the adult population, we decided to undertake a systematic review to determine the association of single nucleotide polymorphisms (SNPs) with the risk of epilepsy in these two patient populations.

Methods

Literature search

A comprehensive literature search was conducted from inception until 5th July 2022 in the following databases: PubMed, Embase, PsycINFO, Web of Science, and Google Scholar.

The key terms used to perform the literature search included: “epilepsy,” “seizure,” “epileptogenesis,” “convulsions,” “acquired brain insult,” “post-stroke epilepsy,” “stroke,” “ischemic stroke or IS,” “infarct,” “cerebral ischemia,” “hemorrhagic stroke,” “intracerebral hemorrhage or ICH,” “traumatic brain injury,” "posttraumatic epilepsy, "genetic,” “gene,” and “single nucleotide polymorphism or SNP.” For a detailed search strategy, see the eAppendix.

Our search included only human subject studies, patients aged ≥18 years suffering from stroke and TBI who developed seizure/epilepsy.

There were no restrictions based on the date or language of publication, gender, and ethnicity.

Outcomes

The primary outcome was the association between genetic SNPs and the risk of developing PTE and PSE.

The secondary outcome was the impact of ethnic variations on the existing associations between SNPs and the risk of developing PTE and PSE.

Inclusion and exclusion criteria

We conducted our systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2020 guidelines[12] (checklist provided in the supplemental material).

We included observational case-control and cohort studies that included patients aged≥18 years suffering from PTE or PSE, reported genetic data on polymorphisms, and

published the data in indexed journals. The investigators used variable definitions for PTE and PSE (Table 1). Considering the lack of uniformity and reporting regarding definitions of PTE and PSE, we accepted the study definitions as reported.

We excluded studies that did not report genetic polymorphism data associated with PTE or PSE, if the publications were duplicates, if the reports were irrelevant systematic or narrative reviews, conference proceedings, dissertations, preprints, and unpublished or ongoing studies.

We pre-registered the protocol of this systematic review on PROSPERO (registration CRD42022325617).[13]

Data extraction

Two authors (S.M. and E.E.) independently extracted the following data from the included studies: Surname of the first author, year of publication, country, ethnicity, the sample size of the study, gene polymorphisms, genotype, and allele frequencies, the mean or median age of cases and controls, male/female numbers, genotyping method, follow-up duration, and the definition of epilepsy.

Risk of bias (quality) assessment

The methodological quality of the included studies was assessed independently by two review authors (S.M. and E.E.) using the quality of genetic association studies (Q-Genie) tool.[14] Using this 11-point scale, we assessed the following for every screened article: scientific rationale(s) of the study research objectives; identification of comparison groups; both technical and non-technical categorization of the genetic variant that was

assessed in the study; outcome classification; investigation of sources of bias; suitability of sample size; a detailed account of statistical analysis; test of genetic research' assumptions; and result interpretation. These individual items are scored from 1 (poor) to 7 (excellent). Per Q-Genie, the studies with a control group with a score of ≤35 indicate poor quality, >35 and ≤45 indicate moderate quality, and >45 indicates high quality. Studies without a control group with a score of ≤32 indicate poor quality, >32 and ≤40 indicate moderate quality, and >40 indicate high quality.

Any conflicts or disagreements were resolved by consulting with the corresponding author (N.K.M.).

Statistical analysis

The association between genetic SNPs and PTE or PSE was determined using odds ratio (OR) or hazard ratio (HR) and 95% Confidence interval (CI). For genetic polymorphisms, a random effect meta-analysis was conducted if genotype data from two or more studies could be pooled. Forest plots representing the association of individual genetic SNPs with PTE and PSE were created using R version 4.2.0. (http://www.R-project.org/).

Data availability

The full dataset and statistical codes will be available on reasonable request from any qualified investigator.

Results

Our search yielded 420 articles, of which 70 full-text articles were assessed. Finally, 16 articles met our inclusion criteria and were included in this systematic review. The study flow diagram is represented in Figure 1.

The included studies investigated 127 SNPs from 32 genes in patients who suffered from PTE or PSE (list of SNPs in eTable 1). All the SNPs reported in the supplementary table were genotyped by the studies. No significant association was found for these SNPs in the univariable analysis, and thus they were not analyzed any further.

Twelve studies[15–26] examined the association between genetic polymorphisms and PTE, while four studies[27–30] investigated the association between genetic polymorphisms and PSE. In addition, there were five case-control,[21,27–30] two prospective cohorts,[16,23] and nine retrospective cohort studies.[15,17–20,22,24–26] Five studies were conducted in China,[16,27–30] while the remaining 11 were conducted in the United States of America (USA).[15,17–26] The publication years ranged from 2003 to 2020. The summarized characteristics of the included studies are given in Table 1.

Risk of Bias (Quality) Assessment

Amongst the studies that investigated genetic polymorphism in PTE, three were of poor quality,[16,23,26] five were of moderate quality,[15,17,19,24,25] and four were of good quality.[18,20–22] All the studies that investigated genetic polymorphisms in PSE were of poor quality (N=4).[27–30] The average scores of poor quality studies for the individual items, including non-technical classification of the exposure, other sources of bias, sample size and power, and testing of assumptions and inferences for genetic analysis, were 2.5, 3.2, 2.6,

and 3.1 out of 7, respectively. It indicates that the studies did not use a blinded assessor to conduct genotyping; they did not report other potential sources of bias; their sample size was small; no *apriori* power calculation was done; and they did not test for other assumptions for genetic analysis, such as haplotype analysis. The quality assessment for each study is given in the eTable 2.

Genetic polymorphisms and posttraumatic epilepsy

Our systematic review identified 12 studies that included 718 patients with PTE and 2688 controls. Although these candidate gene studies investigated 120 SNPs from 28 genes, they provided genotype data on only 18 SNPs from 13 genes. After pooling the data from two studies,[23,24] we identified that *APOE* ε4 allele was not significantly associated with the risk of PTE (OR 1.8; CI 0.6-5.6) (Figure 2). Two other studies[25,26] assessed the *APOE* ε4 allele in PTE; however, they could not be pooled since they did not provide data on the ε4 allele. Both those studies did not find a significant association between the *APOE* ε4 allele and the risk of PTE ($p>0.05$). [25,26]

In four studies,[18–20,22] adjusted cox proportional hazard analysis identified six genetic polymorphisms, including *SLC1A3* rs4869682 (HR 2.1; CI 1.2-3.6), *SLC1A1* rs10974620 (HR 3.4; CI 1.3-9.3) and rs7858819 (HR 3.4; CI 1.1-10.5), *ADK* rs11001109 (HR 4.5; CI 1.3-15.8), *NT5E* rs9444348 (HR 3.0; CI 1.2-7.3), and *IL-β* rs1143634 (HR 2.8; CI 1.4-5.9) that were significantly associated with the risk of PTE (Figure 3a). In the remaining four studies,[15–17,21] adjusted logistic regression analysis identified five genetic polymorphisms, including *GAD1* rs3828275 (OR 5.6; CI 1.2-25.9) and rs3791878 (OR 4.9; CI 1.2-19.3), *UGT1A6* (19T>G/541A>G/552A>C) (OR 2.4; CI 1.1-5.1), *A1AR* rs3766553 and

rs10920573 that were significantly associated with the risk of PTE. In addition, the *A1AR* rs3766553 gene polymorphism was significantly associated with early (OR 5.4; CI 1.1-27.4) and delayed-onset PTE (OR 4.6; CI 1.4-15.5). In contrast, *A1AR* rs10920573 (OR 3.6; CI 1.2-10.7) gene polymorphism was exclusively associated with only late PTE (Figure 3b). The various covariates adjusted in the multivariable analysis in different studies are presented in Table 1.

Except for one study from China,[16] all other studies were conducted in the USA. Four studies from the USA included Caucasian patients.[15,17,19,25] Whereas six studies included white[18,20,22] and mixed ethnicity patients,[21,23,24] one study[26] did not mention the patients' ethnicity. Even though these studies reported race and ethnicity, they did not report SNP data specific to the patient's race or ethnicity. We, therefore, could not assess the impact of ethnic variations on the studied genetic SNPs.

Genetic polymorphisms and post-stroke epilepsy

Our systematic review identified four studies[27–30] that included 1192 patients with PSE and 1270 patients without PSE. These studies reported seven SNPs from four genes. In individual studies, *TRPM6* rs2274924 (OR 1.4; CI 1.1-1.7), *ALDH2* rs671 (OR 1.7; CI 1.3-2.3), and *CD40* -1C/T (OR 1.6; CI 1.3-2.0) were significantly associated with the risk of PSE. The *AT1R* rs12721273 (OR 0.6; CI 0.8-0.8) and rs55707609 (OR 0.8; CI 0.6-1.0) gene polymorphisms were associated with a lower risk of PSE (Figure 4). We could not assess the impact of ethnic variations on genetic SNPs and the risk of PSE, as all four studies were conducted in the Chinese population. We also could not perform a subgroup

analysis by stroke subtypes as the studies did not classify stroke into ischemic or hemorrhagic.

Discussion

Our systematic review identified 16 articles that investigated the association of SNPs with PTE and PSE. These included 127 SNPs from 32 genes. Eleven SNPs were associated with the increased risk of PTE, three SNPs with an increased risk of PSE, and two SNPs with a lower risk of PSE. Only two studies could be pooled for a meta-analysis in which we tested the association of *APOE* ε4 with PTE. The meta-analysis, however, failed to show a statistically significant association between *APOE* ε4 with PTE.

The genetic mechanisms of epilepsy in stroke or TBI patients are understudied. Despite significant advances in human genetics over the last decade, our systematic review found only 16 studies that tested genetic association with PTE or PSE. These studies had a small sample size of 106 to 962 patients. In addition, these studies used disparate methodologies, and except for the studies that investigated *APOE* ε4, none of the other studies were validated in follow-up studies. Only one SNP (rs3749034) from *GAD1* gene overlapped between two studies;[17,26], however, it was not significantly associated with the risk of PTE. A significant challenge in conducting genetic association studies and follow-up validation is that only a small proportion of individuals with TBI or stroke who develop epilepsy (4-19%).[31,32] Hence, a follow-up validation study can be challenging.

So far, only one systematic review[33] has investigated the association of genetic SNPs with PTE. It, however, included only four studies, did not apply methods to assess the quality, and identified only two significant SNPs from *IL-1β* and *A1AR* genes.[15,17,19,21] Our

systematic review is comprehensive, includes twelve studies on PTE;[15–26] and uses a quality assessment tool, Q-genie. Our review identified 120 SNPs from 28 genes among which 11 SNPs were significantly associated with PTE.

Identifying common pathways that result in epilepsy secondary to different types of brain injuries, like TBI or stroke, would be desirable. Unfortunately, the current state of the literature identified through our systematic search failed to identify any genetic SNP shared between PTE and PSE populations.

Genome-wide association studies (GWAS) have previously been conducted for other common epilepsies, which have informed their diverse biological mechanisms.[34–36] However, no GWAS has been conducted to test the genetic association with PTE or PSE.

Ours is the first systematic review investigating the association of genetic SNPs and the risk of PSE. There are very few studies that investigated the genetic markers of PSE. Only four studies[27–30] in our systematic review described the role of candidate gene SNPs in causing PSE. Unfortunately, all four studies in our systematic review had limitations e.g. poor quality scores on Q-Genie; and none explored the independent association of these genetic markers in a multivariable analysis. [27–30] An additional source of heterogeneity arose from the disparate definitions used to define PSE, and none used the updated International League Against Epilepsy definition.[37]

Interestingly, a few genetic SNPs identified in our systematic review have been implicated as a risk factor for other epilepsy subtypes. For example, *ADK* rs11001109 was found to be significantly associated with pharmacoresistant epilepsy (OR 1.7; CI 1.1-2.7) in a genetic association study of 194 adult patients.[38] *IL-1beta* rs1143634 was significantly associated with the risk of temporal lobe epilepsy in a study of 287 adult patients (OR 2.0;

CI 1.3-3.1).[39] The presence of C677T polymorphism of the *MTHFR* gene was associated with an increased risk of epilepsy.[40,41] A meta-analysis of nine studies including 2210 patients found a significant association of *APOE* ε4 with epilepsy (OR 1.3; CI 1.0-1.6).[42] Another meta-analysis showed that the presence of *APOE* ε4 carriers state was associated with the early onset of temporal lobe epilepsy.[43]

Currently, there is no data on the genetics of PSE from any other part of the world except China. Studies thus far have only utilized the hypothesis-driven candidate gene approach. There is a need to conduct genome-wide association studies; however, such studies require large sample sizes.

In summary, there is a critical need for a larger collaborative effort to recruit a diverse patient population and investigate the mechanisms by which genetic factors drive epileptogenesis after brain insults like TBI or stroke. The International Post Stroke Epilepsy Research Consortium (IPSERC)[44] is one such effort, convened to build a community of researchers with variable (and complimentary) expertise across the globe to conduct adequately powered studies to understand and prevent PSE. Similar efforts in other patients with cerebral pathologies and risk of epilepsy are warranted.

Contributors

NKM conceptualized the idea of the review, helped design the methodology, and supervised each step of execution of the review. SM and EE contributed to the literature search, data extraction and conducted the quality assessment. SM conducted the statistical analysis. SM prepared the initial manuscript draft. NKM, TQ, JD, DL, SM, GF,

YZ, CY, VKS, JF, and PK critically reviewed the initial draft. All authors contributed to, reviewed, and approved the final draft of the paper.

Disclosure

S. Misra, E. Eldem, N.K. Mishra report no disclosures relevant to the manuscript. NKM and PK are the co-convenors of the IPSERC. NKM is a member of the editorial board of *Neurology*. VKS is current recipient of Senior Clinician Scientist Award from National Medical Research Council, Singapore

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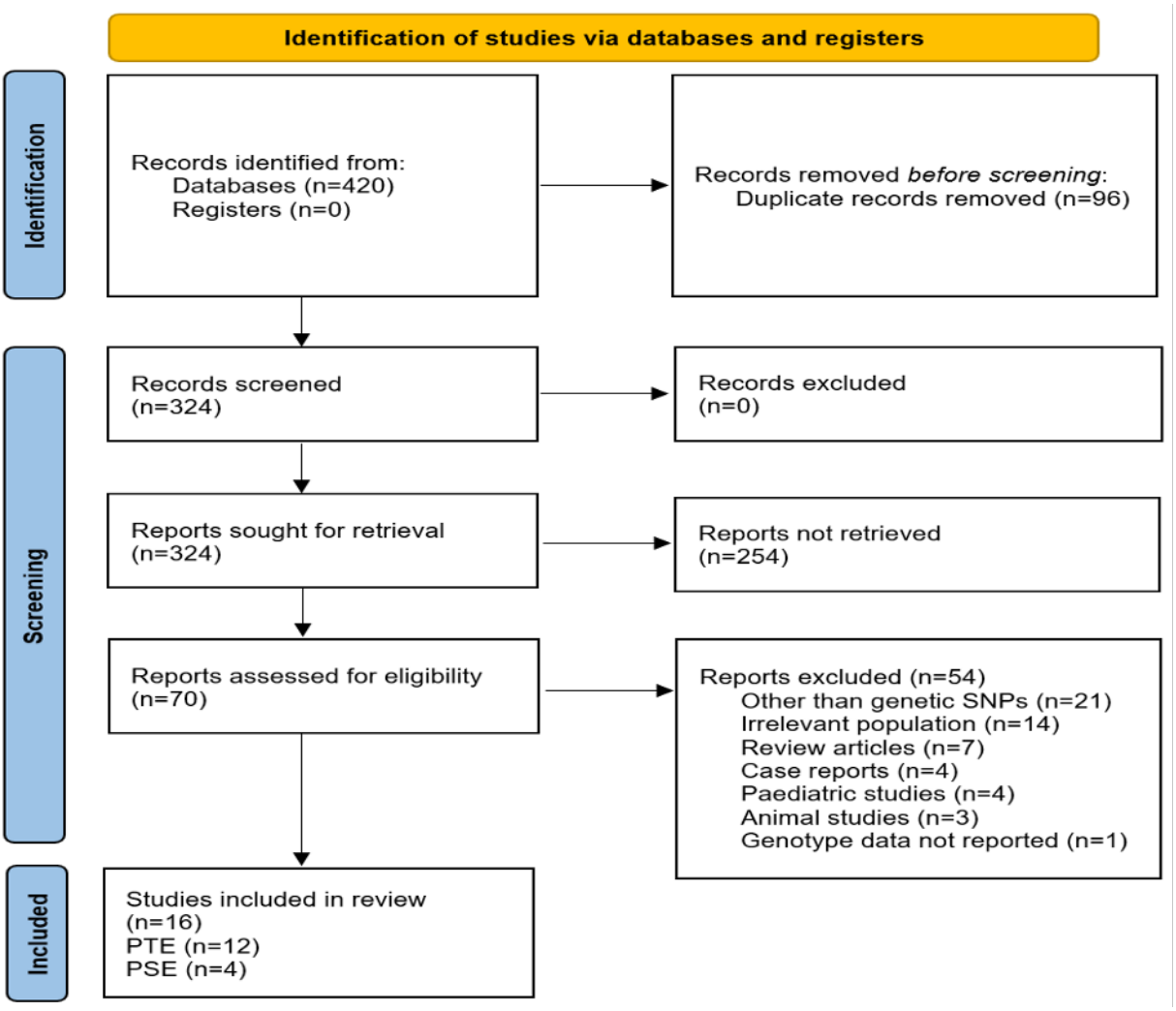

Figure 1: PRISMA flow diagram for the systematic review

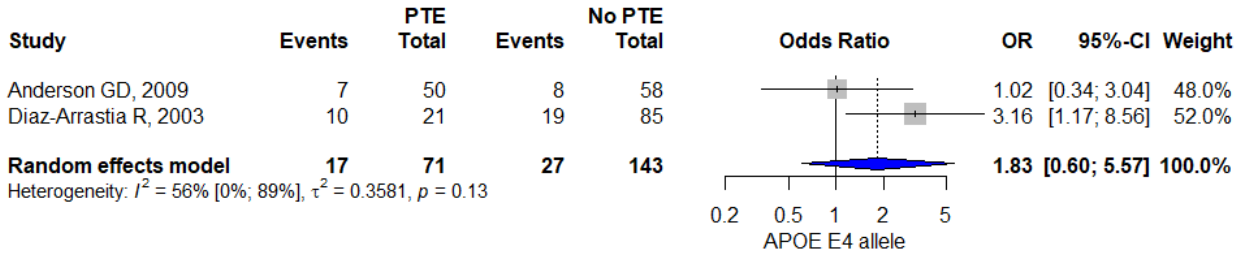

Figure 2: The association of the *APOE* ε4 allele with the risk of posttraumatic epilepsy

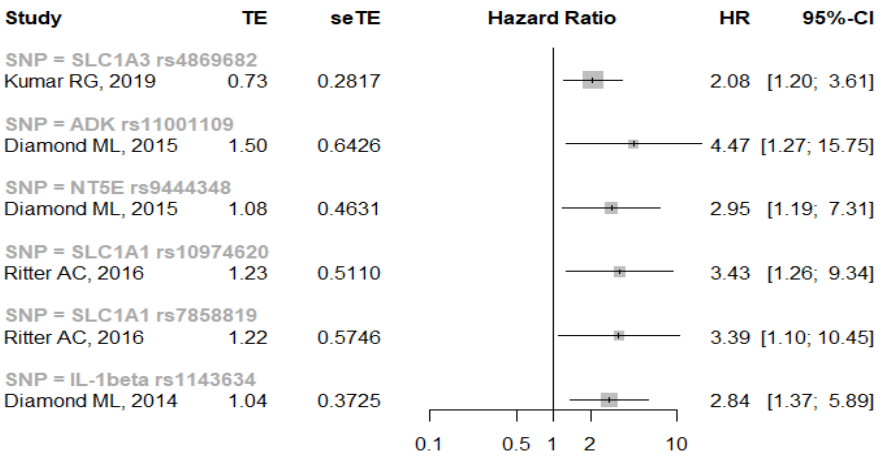

Figure 3a

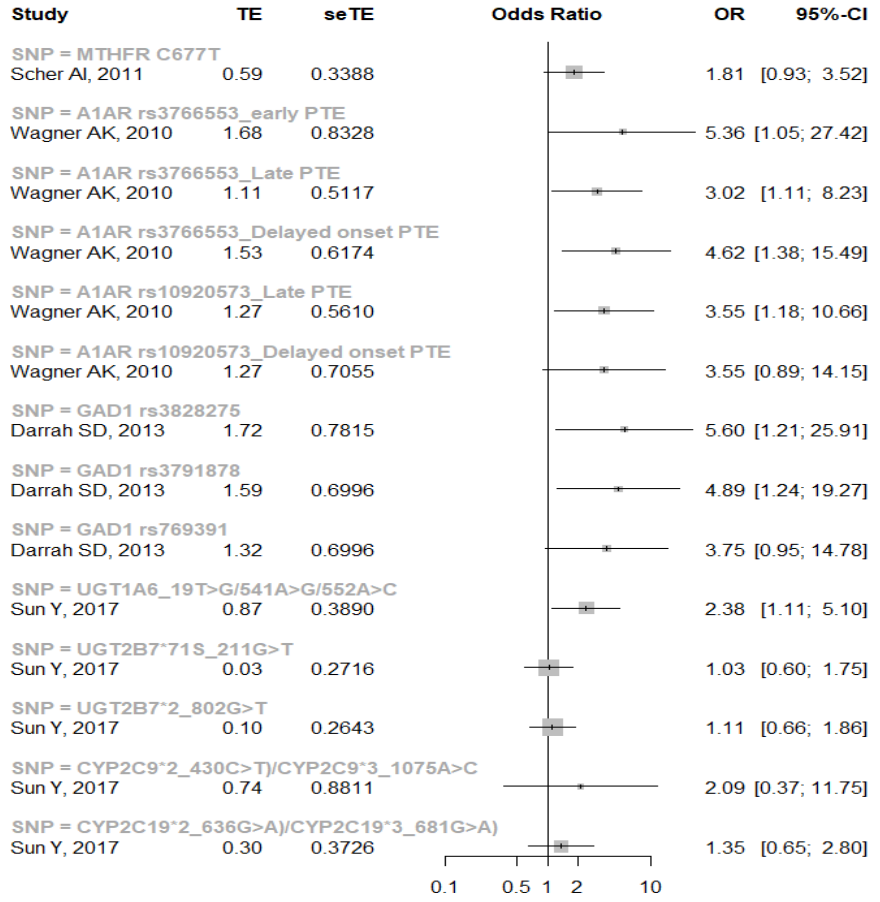

Figure 3b

Figure 3: Adjusted (a) cox proportional hazard and (b) logistic regression analyses for the association between genetic SNPs and the risk of posttraumatic epilepsy.

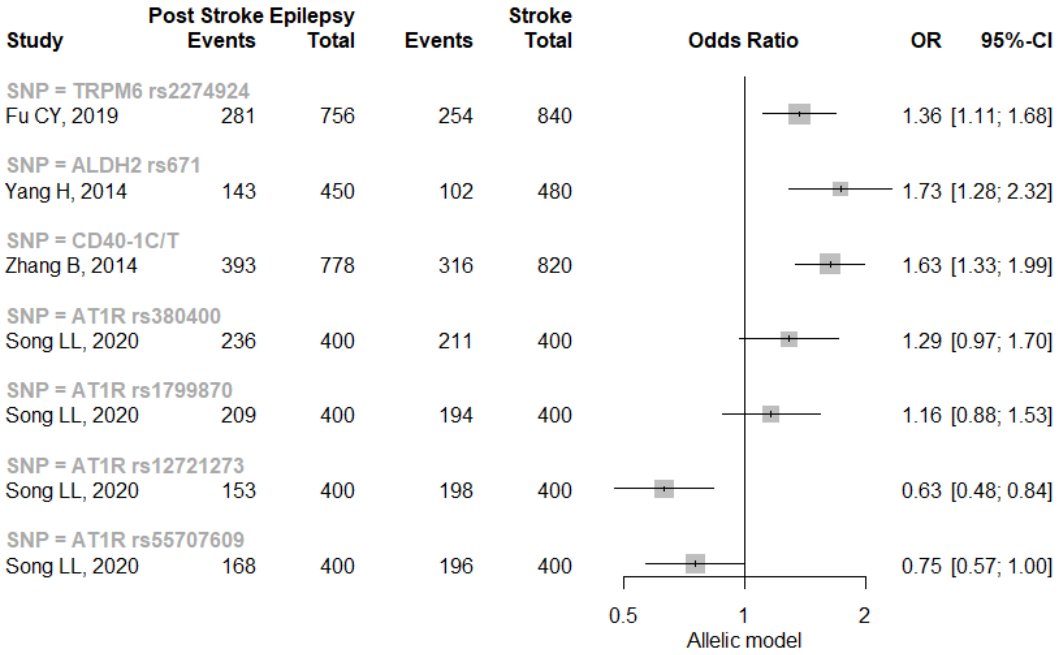

Figure 4: Association between genetic SNPs and risk of post-stroke epilepsy.

Table 1: Summarized characteristics of genetic studies on epilepsy post acquired brain insults included in this systematic review

S. No	Study Author, Year	Country (Ethnicity)	Acquired epilepsy	Study design	Sample size (Cases/ Controls)	Gene Polymorphisms	Genotyping methodology	Males (Cases/ Controls)	Mean age (Cases/ Controls)	Definition of PTE/ PSE	Adjusted for confounders	Follow up (in years)	Overall Quality
1	Song LL, 2020 [28]	China (Asian)	PSE.	Case-control	200/ 200	*ATIR* rs380400, rs1799870, rs12721273, rs55707609	PCR-Sequencing	-	59.45 ± 6.51/ 58.34 ± 5.12	Clinical symptoms and EEG abnormalities	None	NA	Poor
2	Fu CY, 2019 [27]	China (Asian)	PSE.	Case-control	378/ 420	*TRMP6* rs2274924	DNA Sequencing	224/248	56.28 ± 10.42/ 54.86 ± 11.22	Clinical symptoms and positive EEG.	None	NA	Poor
3	Yang H, 2014 [30]	China (Asian)	PSE.	Case-control	225/ 240	*ALDH2* rs671	PCR-RFLP	137/142	63.27 ± 7.56/ 61.15 ± 8.77	Clinical symptoms and positive EEG.	None	NA	Poor
4	Zhang B, 2014 [29]	China (Asian)	PSE.	Case-control	389/ 410	*CD40* (-1C/T)	PCR-RFLP	219/241	64.46 ± 9.87/ 62.32 ± 8.06	Clinical symptoms and positive EEG.	None	NA	Poor

5	Kumar RG, 2019 [22]	United States (White)	PTE.	Retrospective cohort	56/204	*SLC1A2* (21 SNPs), *SLC1A3* (18 SNPs)	iPLEX Gold SNP Assay	45/163	34.6 ± 2.74/35.2 ± 1.1 (SE.)	Not defined. Mentioned early PTS ≤7 days & late PTS> seven days	Age, GCS, depressed skull fracture, SDH	3	Good
6	Scher AI, 2011 [21]	United States (Mixed)	PTE.	Case-control	162/800	*MTHFR* (C677T), *MTHFR* (A1298C)	PCR-MS	-	-	Patients with at least one medical encounter consistent with TBI occurring before or proximate to (no more than 30 days after) the 1st documented medical encounter for epilepsy	Age, sex, race, DNA concentration	NA	Good

7	Sun Y, 2017 [16]	China (Asian)	PTE.	Prospective cohort	83/312	*UGT1A6*, *UGT2B7*, *CYP2C9*, and *CYP2C19*	PCR-RFLP	-	-	Detection of seizures on EEG monitoring. Convulsive seizures are defined as per clinical symptoms.	Valproic Acid doses	0.25	Poor
8	Diamond ML, 2014 [19]	United States (Caucasian)	PTE.	Retrospective cohort	42/214	*IL-1β* (5 SNPs)	TaqMan assays	32/177	32.5 ± 1.97/35.5 ± 1.04	Time to first seizure occurring beyond first-week post-injury.	Time to mortality, age, sex, GCS, SDH, ISS, depressed skull fracture	3	Moderate
9	Diamond ML, 2015 [20]	United States (White)	PTE.	Retrospective cohort	24/138	*ADK* (9 SNPs), *NT5E* (3 SNPs), and *SLC29A1* (2 SNPs)	i-PLEX Gold SNP Assay	17/113	31.3 ± 2.27/33.6 ± 1.23 (SE.)	At least one documented seizure after the first week post-injury	ISS, IHI, SDH	3	Good

10	Ritter AC, 2016 [18]	United States (White)	PTE.	Retrospective cohort	49/204	*SLC1A1* (28 SNPs), *SLC1A6* (4 SNPs)	iPLEX Gold SNP Assay	38/163	34.94 ± 14.61/ 35.40 ± 15.71	Not defined	SDH, depressed skull fracture	3	Good
11	Wagner AK, 2010 [15]	United States (Caucasian)	PTE.	Retrospective cohort	33/125	*A1AR* (5 SNPs)	TaqMan assays	25/103	32.32 ± 2.69/ 33.68 ± 1.26	PTE is not defined. Late PTS- first seizure >7 days. Delayed onset PTS- first seizure >6 months post-TBI.	Age, sex, GCS, brain surgery	0.5-6	Moderate
12	Darrah SD, 2013 [17]	United States (Caucasian)	PTE.	Retrospective cohort	51/174	*GAD 1* (6 SNPs), *GAD 2* (1 SNP)	TaqMan assays and iPLEX Gold SNP assays	42/141	35.40 ± 3.48/ 34.2 ± 1.1	PTE is not defined. PTS- < 1 week after TBI, 1 week-6 months post-TBI, at least six months	Age, sex, GCS, SDH, brain surgery	0.5-8	Moderate

										post-TBI.			
13	Diaz-Arrastia R, 2003 [23]	United States (Mixed)	PTE.	Prospective cohort	21/ 85	*APOE* ε4 allele	PCR-RFLP	17/ 53	36.9 ± 13.8/ 39.4 ± 20.6	Late PTS>7 days	None	0.5	Poor
14	Anderson GD, 2009 [24]	United States (Mixed)	PTE.	Retrospective cohort	50/ 58	*APOE* ε4 allele	PCR-Two restriction enzymes	44/ 52	36 ± 17/ 40 ± 15	PTE is not defined. Early P.T.S. <7 days. Late PTS>7 days	Seizure type, TBI severity, education	2	Moderate
15	Miller MA, 2010 [25]	United States (Caucasian)	PTE.	Retrospective cohort	60/ 262	*APOE* ε4 allele	PCR-RFLP	46/ 170	32.59 ± 2.18/ 33.2 ± 0.98	PTE not defined. Late PTS- 1st seizure >7 days	None	0.5-18	Moderate
16	Raymont V, 2010 [26]	United States (Not mentioned)	PTE.	Retrospective cohort	87/ 112	*APOE* ε4 (3 SNPs), *GAD1* (3 SNPs), *GAD2* (5 SNPs), *COMT* (2 SNPs), *GRIN2A* (7 SNPs), *GRIN2B* (3	A.B.I. Assay, 5' – exonuclease allelic discrimination (Taqman) assay	-	57.8 ± 2.3/ 58.8 ± 3.5	Any seizure post-TBI.	None	30-35	Poor

						SNPs), *GRIN2C* (4 SNPs) *BDNF* (4 SNPs), DBH rs444							

Abbreviations: PSE- Post Stroke Epilepsy, PTE- Post Traumatic Epilepsy, PTS- Post Traumatic Seizure, NA- Not applicable, USA- United States of America, PCR- Polymerase Chain Reaction, RFLP- Restriction Fragment Length Polymorphism, DNA- Deoxyribonucleic Acid, MS- Mass Spectrometry, SNP- Single Nucleotide Polymorphism, GCS- Glasgow Coma Scale, SDH- Subdural Hematoma, ISS- Injury Severity Score, IHI- Isolated Head Injury, APOE- Apolipoprotein, AT1R- Angiotensin II type 1 receptor, TRPM- Melastatin-related transient receptor potential ion channel, ALDH2- Aldehyde dehydrogenase 2, CD- Cluster of Differentiation, SLC1A- Solute Carrier 1A, MTHFR- Methylenetetrahydrofolate reductase, UGT- UDP Glucuronosyltransferase Family, CYP- Cytochrome P, IL- Interleukin, ADK- adenosine kinase, NT5E- ecto-5'-nucleotidase, A1AR- adenosine A1 receptor, GAD- Glutamic acid decarboxylase.