

# Genetic Contributions to Acquired Epilepsies

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## Abstract

Whether genetic factors contribute to acquired epilepsies has long been controversial. Supporters observe that, among individuals exposed to seemingly the same brain insult, only a minority develops unprovoked seizures. Yet, only in relatively recent years have studies started to build a case for genetic contributions. Here, we appraise this emerging evidence, by providing a critical review of studies published in the field.

## Keywords

genetics, family history, acquired epilepsy, post-traumatic epilepsy, poststroke epilepsy

## Introduction

Epilepsy due to an acquired brain insult, such as a traumatic brain injury, stroke, tumor or central nervous system (CNS) infection (collectively termed “acquired epilepsy”), accounts for approximately one-third of all epilepsies.<sup>1</sup> Importantly, only a subset of individuals who sustain a brain insult develop epilepsy, for example, 2% to 5% of those sustaining head trauma, 2% to 4% of those having a stroke, and 5% to 10% of those who have a CNS infection.<sup>2,3</sup> The risk of acquired epilepsy depends on the characteristics of the brain insult, for example, type, severity, size, and location as well as factors related to the individual, for example, age, sex, and genetic factors.<sup>3</sup> In this setting, genetic factors do not affect the epilepsy risk directly, but they operate by increasing susceptibility to the consequences of the acquired brain insult.

A genetically determined vulnerability to acquired epilepsy has long been postulated and debated. Initial evidence stemmed from the clinical observation that among people who seemingly had the same brain insult, some develop unprovoked recurrent seizures and others do not.<sup>4</sup> However, data supporting such vulnerability have remained largely elusive until recent times. Only in the past decade or so have studies started to shed some light on the genetic contributions to specific forms of acquired epilepsy. Here, we review this recent body of work, which largely relates to 3 types of acquired epilepsy: post-traumatic epilepsy, poststroke epilepsy, and temporal lobe epilepsy with hippocampal sclerosis.

## Post-Traumatic Epilepsy

Traumatic brain injury is an important cause of acquired epilepsy, accounting for 15% of cases and for about 30% of





acquired epilepsies in those aged 15 to 34 years.<sup>5</sup> The risk of developing unprovoked seizures after head trauma is directly related to the severity of the injury.<sup>6</sup> Other risk factors include penetrating injuries, biparietal or multiple brain contusions, intracranial hemorrhage, frontal or temporal location of the lesion, age >65 years at the time of injury, and a past history of depression.<sup>6</sup> Remarkably, there is ample variability in brain responses to similar injuries: Most patients will not develop seizures, some will experience one or few seizures, and others will have frequent seizures and drug-resistant epilepsy.<sup>7</sup> Such a wide range of variability has been attributed to “constitutional” or genetic factors influencing the cerebral response to injury.<sup>7</sup>

Early studies attempted to characterize genetic contributions to post-traumatic epilepsy by including a family history of seizures or epilepsy in risk factor analyses, yielding conflicting results.<sup>8</sup> These studies were hampered by methodological limitations, such as selection bias, small sample size, short follow-up after head trauma, ambiguous definitions of head trauma or epilepsy, and reliance on patient reporting to collect information about family history.<sup>8</sup> These shortcomings were addressed by Christensen et al,<sup>9</sup> who conducted a population-based study of >1.6 million people born in Denmark (1977-2002) to assess the risk of epilepsy up to  $\geq 10$  years after traumatic brain injury. They found that the risk of epilepsy following any type of head trauma was 2.3-fold higher among individuals who had a family history of epilepsy (defined as having a parent or sibling who had been in outpatient care or hospitalized with a diagnosis of epilepsy, ascertained using International Classification of Diseases codes) compared to those without such a family history (adjusted relative risk [95% CI]: 5.73 [4.58-7.16] vs 2.47 [2.31-2.65]). Importantly, a family history of epilepsy conferred a substantially increased risk of epilepsy even following mild head trauma (adjusted relative risk [95% CI]: 5.75 [4.56-7.27]), albeit lower than for severe head trauma (10.09 [4.20-24.26]).

Variation in a number of genes has been suggested to raise the risk of post-traumatic epilepsy, including *IL-1 $\beta$*  (encoding the pro-inflammatory cytokine interleukin-1 $\beta$ ),<sup>10</sup> *MTHFR* (encoding the enzyme methylenetetrahydrofolate reductase),<sup>11</sup> *SLC1A3* (encoding the neuronal excitatory amino acid transporter 1),<sup>12</sup> *GADI* (encoding the glutamic acid decarboxylase-67 responsible for  $\gamma$ -aminobutyric acid synthesis from glutamate),<sup>13</sup> and genes implicated in adenosine homeostasis (*ADK*, *NT5E*, and *AIAR*; Table 1).<sup>14,15</sup> However, these findings were obtained from small studies which examined selected single-nucleotide polymorphisms (SNPs) within 1 to 3 genes, using a hypothesis-driven candidate gene approach. Critically, no gene association study in post-traumatic epilepsy has included a replication cohort. Thus, these results should be viewed as preliminary, requiring validation in larger patient cohorts. The epilepsy genetics literature comprises many examples of genes claimed to be associated with epilepsy, which do not withstand replication.<sup>16</sup> This might also be the case for the suggested increased risk of post-traumatic epilepsy conferred by the *APOE*  $\epsilon 4$  allele,<sup>17</sup> which was not replicated in 4 other studies (Table 1).<sup>18-21</sup>

## Poststroke Epilepsy

Stroke is the leading cause of acquired epilepsy, accounting for almost one-third of acquired epilepsies.<sup>5</sup> Its relevance is even greater in the elderly (age >65 years), where it accounts for 2 of 3 new cases of acquired epilepsy.<sup>5</sup> Stroke characteristics, namely stroke severity, cerebral hemorrhage, and cortical involvement, are the key risk factors for poststroke epilepsy.<sup>23</sup> Other suggested risk factors include early seizures, occurring within 7 days of stroke and younger age at stroke.<sup>23</sup>

A family history of epilepsy also increases the risk of post-stroke epilepsy,<sup>24,25</sup> although to a lesser degree than stroke characteristics. In a recent Swedish, register-based, cohort study of 86 550 adults with stroke, the survival-adjusted risk of late poststroke seizures (ie, seizures occurring more than 7 days after stroke, corresponding in most cases to poststroke epilepsy) was higher among patients who had  $\geq 1$  first degree relative with epilepsy compared to those without: 6.8% (95% CI: 6.2-7.4) versus 5.9% (95% CI: 5.7-6.1) at 2 years and 9.5% (95% CI: 8.7-10.3) versus 8.2% (95% CI: 8.0-8.4) at 5 years.<sup>25</sup> In an analysis adjusting for age, sex, stroke type and number of relatives, the hazard ratio for late poststroke seizures in patients with  $\geq 1$  first degree-relative with epilepsy was 1.18 (95% CI: 1.09-1.28). These findings were retained after adjusting for stroke severity and other potential confounders. In particular, the authors excluded that the increased risk of late poststroke seizures conferred by a family history of epilepsy was attributable to a familial predisposition to stroke.

Four studies have explored susceptibility genes for post-stroke epilepsy (Table 2).<sup>26-29</sup> Variation in 3 genes was found to increase the risk of poststroke epilepsy, that is, *ALDH2* (encoding the enzyme mitochondrial aldehyde dehydrogenase 2), *CD40* (encoding the costimulatory receptor CD40), and *TRPM6* (encoding the transient receptor potential melastatin type 6 magnesium-permeable channel).<sup>27-29</sup> Each genetic variation was associated with altered serum concentrations of a specific molecule, which were postulated to mediate its effects (Table 2). However, these studies had several major limitations potentially compromising the validity of their findings, including small sample sizes; lack of characterization of the stroke subtype(s) in the study populations; failure to detail the follow-up after stroke and if there were any differences in length of follow-up between patients who developed unprovoked seizures and those who did not; ambiguous definitions of poststroke epilepsy; and failure to adjust analyses for potential confounders. Furthermore, each of these studies examined a specific SNP only (typically without adequately justifying the selection) and did not include a replication cohort. Thus, replication of their results is sorely needed.

## Temporal Lobe Epilepsy With Hippocampal Sclerosis

Hippocampal sclerosis is the most common histopathological substrate in drug-resistant temporal lobe epilepsy,<sup>30</sup> and its resection or destruction often results in seizure freedom.<sup>31</sup> The

**Table 1.** Gene association studies in post-traumatic epilepsy.

| Study                             | Country | Population (age)   | Ethnicity | Follow up post-TBI | PTE definition   | Genotypes examined                            | Genotypes associated with PTE risk and serum markers of disease states                         | Replication cohort included in the study? |
|-----------------------------------|---------|--|-----------|--------------------|--|---|--|---|
| Friedman et al <sup>18</sup>      | Israel  | 69 patients with “blunt” TBI admitted to rehabilitation hospital or seen at outpatient rehabilitation clinic (age range: 18-73 years).   | NA        | 6-8 months         | NA   | APOE  | None   | No  |
| Diaz-Arrastia et al <sup>17</sup> | USA     | 106 patients admitted to a level I trauma center with moderate-to-severe TBI <sup>a</sup> (mean age $\pm$ SD: 38.8 $\pm$ 19.4 years).  | Mixed     | 6 months           | Seizures occurring >7 days post-TBI.   | APOE  | APOE $\epsilon$ 4 allele associated with increased risk of PTE (RR = 2.41, 95% CI: 1.15-5.07). | No  |
| Anderson et al <sup>19</sup>      | USA     | 51 patients with TBI <sup>b</sup> who had participated in a double-blind placebo-controlled trial assessing the use of valproate for prophylaxis of post-traumatic seizures (age $\geq$ 14 years). | Mixed     | 2 years            | PTE not formally defined. However, “late seizures” referred to those occurring >7 days post-TBI.   | APOE  | None   | No  |
| Miller et al <sup>20</sup>        | USA     | 322 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 18-75 years).   | Caucasian | 6 months-18 years  | PTE not formally defined. However, “late seizures” referred to those occurring between 1 week and 6 months post-TBI, and “delayed-onset late seizures” referred to those occurring >6 months post-TBI. | APOE  | None   | No  |
| Raymont et al <sup>21</sup>       | USA     | 199 Vietnam war veterans with “mostly penetrating” TBI (mean age $\pm$ SD: subjects without PTE, 58.8 $\pm$ 3.5 years; subjects without PTE, 57.8 $\pm$ 2.3 years) and 55 uninjured veterans.      | NA        | 30-35 years        | Occurrence of any seizure post-TBI.  | APOE $\epsilon$ 4, GAD, COMT, GRIN, BDNF, DBH | None after adjustment for multiple comparisons.  | No  |

(continued)

4 **Table 1.** (continued)

| Study                      | Country | Population (age)   | Ethnicity | Follow up post-TBI | PTE definition   | Genotypes examined             | Genotypes associated with PTE risk and serum markers of disease states   | Replication cohort included in the study? |
|----------------------------|---------|--|-----------|--------------------|--|--------------------------------|--|---|
| Wagner et al <sup>14</sup> | USA     | 187 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 18-75 years).   | Caucasian | 6 months-6 years   | PTE not formally defined. However, "late seizures" referred to those occurring between 1 week and 6 months post-TBI, and "delayed-onset late seizures" referred to those occurring >6 months post-TBI. | A1AR (5 SNPs)                  | SNP rs3766553: GG genotype associated with higher risk of late seizures than AG genotype (adjusted OR = 3.02, 95% CI: 1.11-8.25) and with higher risk of delayed-onset late seizures than AG genotype (adjusted OR = 4.62, 95% CI: 1.38-15.52).<br>SNP rs10920573: CT genotype associated with higher risk of late seizures than CC genotype (adjusted OR = 3.55, 95% CI: 1.18-10.64). | No  |
| Scher et al <sup>11</sup>  | USA     | 800 epilepsy cases (mean age $\pm$ SD: 32.0 $\pm$ 8.5 years) vs 800 age-, sex-, and race-matched controls selected randomly from a cohort of military personnel on active duty in 2003-2007 who had archived serum samples at US Department of Defense Serum Repository. Of epilepsy cases, 118 classified as PTE. | Mixed     | NA                 | Patients with $\geq$ 1 medical encounter consistent with a TBI occurring any time before or proximate to (no more than 30 days after) the first documented encounter for epilepsy.                     | MTHFR (C677 T and A1298C)      | C677 T: Among patients $\geq$ 2 medical encounters for epilepsy, TT genotype associated with higher risk of PTE than CC genotype (adjusted OR = 2.55, 95% CI: 1.12-5.80).  | No  |
| Darrah et al <sup>13</sup> | USA     | 257 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 16-75 years).   | Caucasian | 6 months-8 years   | PTE not formally defined. However, seizures occurring $\geq$ 1 week post-TBI classified into those occurring 1 week-6 months post-TBI and those occurring >6 months post-TBI.                          | GAD1 (6 SNPs) and GAD2 (1 SNP) | SNP rs3791878 (GAD1): GG homozygotes associated with higher risk of developing seizures 1 week-6 months post-TBI than T-carriers (adjusted OR = 4.89, 95% CI: 1.24-19.25).   | No  |

(continued)

**Table 1.** (continued)

| Study                        | Country | Population (age)   | Ethnicity | Follow up post-TBI | PTE definition                       | Genotypes examined                                | Genotypes associated with PTE risk and serum markers of disease states  | Replication cohort included in the study? |
|------------------------------|---------|--|-----------|--------------------|--------------------------------------|---|---|---|
| Diamond et al <sup>c10</sup> | USA     | 256 patients admitted to a level I trauma center with moderate-to-severe TBI <sup>e</sup> (age 18-70 years).                                       | Caucasian | 3 years            | Seizures occurring >7 days post-TBI. | <i>IL-1β</i> (5 SNPs)                             | SNP rs1143634: CT genotype associated with higher risk of PTE than homozygotes (adjusted HR = 2.84, 95% CI: 1.37-5.90).   | No  |
| Diamond et al <sup>c15</sup> | USA     | 162 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 18-70 years).   | White     | 3 years            | Seizures occurring >7 days post-TBI. | ADK (9 SNPs), NT5E (3 SNPs), and SLC29A1 (2 SNPs) | SNP rs11001109 (ADK): AA homozygotes associated with higher risk of PTE than G-carriers (adjusted HR = 4.47, 95% CI: 1.27-15.77). SNP rs9444348 (NT5E): AG genotype associated with higher risk of PTE than homozygous individuals (adjusted HR = 2.95, 95% CI: 1.19-7.31). | No  |
| Ritter et al <sup>c22</sup>  | USA     | 253 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 18-75 years).   | White     | 3 years            | Seizures occurring >7 days post-TBI. | SLC1A1 (28 SNPs), and SLC1A6 (4 SNPs)             | None after adjustment for multiple comparisons.   | No  |
| Kumar et al <sup>c12</sup>   | USA     | 260 patients admitted to a level I trauma center with severe TBI <sup>d</sup> (age 18-75 years), 212 of whom included in the analysis of PTE risk. | White     | 3 years            | Seizures occurring >7 days post-TBI. | SLC1A2 (21 SNPs) and SLC1A3 (18 SNPs)             | SNP rs4869682 (SLC1A3): GG-homozygotes associated with higher risk of PTE than T-carriers (adjusted HR = 2.08, 95% CI: 1.20-3.62).  | No  |

Abbreviations: CT, computed tomography; GCS, Glasgow coma scale; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; NA, not available; OR, odds ratio; PTE, post-traumatic epilepsy; RR, relative risk; SNP, single nucleotide polymorphism; TBI, traumatic brain injury.

<sup>a</sup>Patients were enrolled if meeting one of the following criteria: cerebral contusion noted on CT scan; depressed skull fracture; penetrating brain injury; early posttraumatic seizure ( $\leq 7$  days of injury). Patients with preexisting epilepsy or neurologic conditions (eg, brain tumor, nontraumatic hemorrhage, or major cortical infarction) commonly associated with epilepsy were excluded.

<sup>b</sup>A qualifying injury had  $\geq 1$  of the following characteristics: immediate posttraumatic seizures; depressed skull fracture; penetrating brain injury; or CT evidence of a cortical contusion or subdural, epidural, or intracerebral hematoma.

<sup>c</sup>Studies from the same center.

<sup>d</sup>Admission GCS score  $\leq 8$ , positive brain CT findings and extraventricular drainage catheter placement for intracranial pressure. Exclusion criteria included penetrating head injury, prolonged cardiac or respiratory arrest before admission and a premorbid seizure history.

<sup>e</sup>Admission with GCS score  $\leq 12$  and positive brain CT findings. However, 6 patients with GCS  $>12$  included in the study based on CT findings. A history of premorbid seizures was an exclusion criterion.

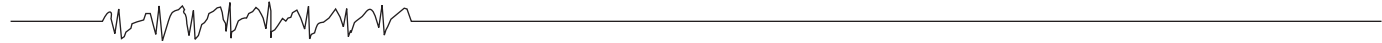
**Table 2.** Gene Association Studies in Poststroke Epilepsy.

| Study                         | Country | Population (age)  | Ethnicity   | Follow-up after stroke | PSE definition  | Gene (SNP) examined | Genotype associated with PSE risk   | Genotype associated with PSE risk and serum levels of molecules involved in pathophysiological processes   | Replication cohort included in the study? |
|-------------------------------|---------|---|-------------|------------------------|---|---------------------|---|--|---|
| Balcerzyk et al <sup>26</sup> | Poland  | 80 patients with stroke <sup>a</sup> (age 6 months-18 years), 138 age- and sex-matched controls with no history of stroke/vascular diseases and 122 patients' parents. Of 80 patients, 74 included in the analysis of PSE risk. | NA          | NA                     | NA  | IL-6 (-174G/C)      | -174G/C: All patients with PSE (n = 13) were G-carriers and thus none were CC-homozygotes. In contrast, 25% (n = 15 of 61) of patients with stroke who did not develop epilepsy were CC-homozygotes. <sup>b</sup> | NA   | No  |
| Yang et al <sup>27</sup>      | China   | 225 patients with PSE <sup>a</sup> (mean age ± SD: 63.3 ± 7.6 years), 240 age- and sex-matched patients with ischemic stroke who did not develop epilepsy and 267 healthy controls.   | Han Chinese | NA                     | No formal definition. Patients with PSE "defined on their clinical symptoms and a positive EEG test." | ALDH2 (rs671)       | SNP rs671: Frequency of the A allele higher in patients with PSE than in patients with ischemic stroke who did not develop epilepsy (31.8% vs 21.3%; adjusted OR = 1.98, 95%: 1.36-2.87).                         | SNP rs671: In both patient groups, A-carriers had significantly higher serum concentrations of 4-hydroxy-2-nonenal (4-HNE) than GG-homozygotes. 4-HNE is regarded as a marker of oxidative stress. | No  |
| Zhang et al <sup>28</sup>     | China   | 389 patients with PSE <sup>a</sup> (mean age ± SD: 64.5 ± 9.9 years), 410 age- and sex-matched patients with ischemic stroke who did not develop epilepsy, and 160 healthy controls.  | Han Chinese | NA                     | No formal definition. Patients with PSE "defined by clinical symptoms and positive EEG performance."  | CD40 (-1C/T)        | -1C/T: Frequency of the T allele higher in patients with PSE than in patients with ischemic stroke who did not develop epilepsy (50.5% vs 38.5%; OR = 1.63, 95%: 1.33-1.99).                                      | -1C/T: In patients with PSE, T-carriers had significantly higher serum concentrations of soluble CD40 ligand (sCD40 L) than CC-homozygotes. sCD40 L is involved in inflammatory response.          | No  |
| Fu et al <sup>29</sup>        | China   | 378 patients with PSE <sup>a</sup> (mean age ± SD: 56.3 ± 10.4 years), 420 sex- and age-matched patients with stroke <sup>a</sup> who did not develop epilepsy.   | NA          | NA                     | No formal definition. Patients with PSE "defined on their clinical symptoms and a positive EEG test." | TRPM6 (rs2274924)   | SNP rs2274924: Frequency of the C allele higher in patients with PSE than in patients with ischemic stroke who did not develop epilepsy (37.1% vs 30.2%; OR = 1.36, 95%: 1.11-1.68).                              | SNP rs2274924: In patients with PSE, C-carriers had significantly lower serum concentrations of Mg <sup>2+</sup> than TT-homozygotes.  | No  |

Abbreviations: Mg<sup>2+</sup>, magnesium; NA, not available; OR, odds ratio; PSE, poststroke epilepsy; SNP, single nucleotide polymorphism; TBI, traumatic brain injury.

<sup>a</sup>Stroke type unknown.

<sup>b</sup>Comparison of genotypes between patients with PSE and stroke patients without epilepsy was performed using the chi-square test ( $\chi^2 = 0.41$ ,  $P = .045$ ). However, the  $\chi^2$  test is not appropriate due to the presence of 0 values (ie, none of the patients with PSE had a CC-genotype). If comparisons had been carried out using the Fisher exact test, no significant differences would have been detected ( $P = .058$ ).



pathogenesis of hippocampal sclerosis has long been debated and remains incompletely understood. Prolonged febrile seizures, including febrile status epilepticus, have been associated with acute hippocampal injury and subsequent development of hippocampal sclerosis and temporal lobe epilepsy.<sup>32</sup> In some children with prolonged febrile seizures, however, there are preexisting hippocampal abnormalities which may predispose to hippocampal damage.<sup>33</sup> The prospective FEBSTAT (Consequences of Prolonged Febrile Seizures in Childhood) study suggests that both mechanisms may be operative.<sup>32,33</sup>

Genetic factors are also implicated. Children with their first febrile seizure had a 3-fold higher risk of presenting with febrile status epilepticus than a simple febrile seizure if they had a first-degree family history of febrile seizures.<sup>34</sup> An increased prevalence of a family history of febrile and afebrile seizures has been observed in patients with temporal lobe epilepsy and hippocampal sclerosis.<sup>35</sup> Furthermore, a clinically heterogeneous form of familial mesial temporal lobe epilepsy, often characterized by antecedent febrile seizures, hippocampal sclerosis, and drug resistance, has been described.<sup>36,37</sup> In these families, most individuals with drug-resistant epilepsy and hippocampal sclerosis have favorable seizure outcomes after epilepsy surgery, similarly to sporadic patients.<sup>38</sup>

A number of early studies investigated the role of common susceptibility variants in temporal lobe epilepsy with hippocampal sclerosis, suggesting an association with SNPs in the *IL-1 $\beta$*  and *PRNP* genes.<sup>39,40</sup> However, these findings failed to be replicated in larger cohorts.<sup>16</sup> A subsequent 2-stage genome-wide association study (GWAS) including 1977 cases with mesial temporal lobe epilepsy and hippocampal sclerosis and 11 143 controls of European Ancestry provided suggestive evidence for common variation in the *SCN1A* gene (encoding the  $\alpha$ -subunit of the type 1 voltage-gated sodium channel) to increase susceptibility to mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures.<sup>41</sup> Recently, the International League Against Epilepsy (ILAE) Consortium on Complex Epilepsies published its second meta-analysis of GWASs involving 15 212 cases with epilepsy and 29 677 controls, which identified 2 novel loci for focal epilepsy with hippocampal sclerosis: 3q25.31, implicating *C3orf33*, *SLC33A1* or *KCNAB1*, and 6q22.31, implicating the gap junction gene *GJAI*.<sup>42</sup>

A recent study examined the role of rare and de novo variants in mesial temporal lobe epilepsy with hippocampal sclerosis by applying whole-exome sequencing (WES) to 47 Han Chinese patients, including 23 patient–parent trios.<sup>43</sup> Compared to WES data from 692 Han Chinese controls, significant enrichment of rare variants was observed in *SEC24B*, a gene involved in vesicle trafficking and development. Gene-set association analysis showed variant enrichment in the fragile X mental retardation protein–related group of genes. Trio-based analysis detected 21 de novo variants, many of which have been implicated in neuropsychiatric disorders. Overall, these results should be interpreted with caution due to the study's small sample size, and their replication in larger cohorts is awaited.

## Other Acquired Epilepsies

Genetic influences have been investigated in other types of acquired epilepsy. Three independent groups recently described the association of anti-leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis with the human leukocyte allele (HLA)-II alleles *DRB1\*07:01* and *DQB1\*02:02*.<sup>44–46</sup> Two groups detected this association by applying selective HLA genotyping,<sup>44,45</sup> whereas the third group performed a GWAS.<sup>46</sup> Remarkably, these findings were obtained despite the inclusion of only a small number of patients with anti-LGI1 encephalitis in each study (19 Dutch, 11 Korean, and 54 German patients, respectively).<sup>44–46</sup> Each study also found other HLA alleles, that is, *DRB4*, *DQA1\*02:01*, *B\*44:03*, increased susceptibility to anti-LGI1 encephalitis, but replication is warranted.

Most recently, a small study explored genetic contributions to nodding syndrome, a rare disorder characterized by nodding head, epileptic seizures, stunted growth, and neurological deterioration, affecting children aged 5 to 16 years in Tanzania, Uganda, and Republic of South Sudan.<sup>47</sup> The disorder has been linked to an infection by the parasitic worm *Onchocerca volvulus*.<sup>47</sup> Benedek et al<sup>48</sup> analyzed 7 HLA loci in 48 cases with nodding syndrome versus 51 controls from South Sudan and suggested that 5 HLA alleles, that is, *B\*42:01*, *C\*17:01*, *DRB1\*03:02*, *DQB1\*04:02*, and *DQA1\*04:01*, might confer protection from the disorder. Due to the limited sample size, these findings should be viewed as preliminary, requiring replication in larger cohorts.

## Conclusions

Over the past decade or so, there has been progress in elucidating genetic contributions to acquired epilepsy. Two well-designed epidemiological studies have quantified the increased risk of developing unprovoked seizures after a traumatic brain injury<sup>9</sup> or stroke<sup>25</sup> in the setting of a family history of epilepsy. Many genetic variants have been suggested to increase susceptibility to certain forms of acquired epilepsy. However, most of these variants were identified in studies which were hampered by many limitations, including small sample size, unclear definitions, and the investigation of only selected genes. Therefore, replication of these findings is required.

Considering that disease susceptibility alleles have small effect sizes, large collaborative efforts are needed to assemble adequately sized cohorts to investigate genetic variants raising the risk of acquired epilepsy. Large collaborative frameworks are already a reality in epilepsy genetics research and are leading important discoveries.<sup>42,49</sup> The application of novel approaches, such as polygenic risk scores, will also advance the field.<sup>50</sup> Undoubtedly, genetic influences in acquired epilepsy are only starting to be unraveled. With the expanding opportunities to investigate disease susceptibility variants, further progress is expected in the upcoming years. This promises to unlock insights into the underlying mechanisms and enable



development of targeting medicine to prevent epilepsy following acquired brain injury.


### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

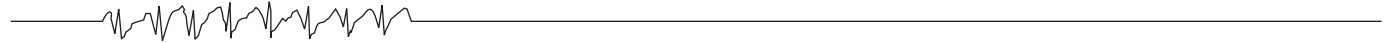
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### References

1. Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. *Lancet Neurol.* 2005;4(10):627-634.
2. Christensen J. The Epidemiology of posttraumatic epilepsy. *Semin Neurol.* 2015;35(3):218-222.
3. Herman ST. Epilepsy after brain insult: targeting epileptogenesis. *Neurology.* 2002;59(9 Suppl 5):S21-S26.
4. Shorvon SD. The causes of epilepsy: changing concepts of etiology of epilepsy over the past 150 years. *Epilepsia.* 2011;52(6):1033-1044.
5. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia.* 1993;34(3):453-468.
6. Pitkanen A, Immonen R. Epilepsy related to traumatic brain injury. *Neurotherapeutics.* 2014;11(2):286-296.
7. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia.* 2003;44(s10):11-17.
8. Yablon SA. Posttraumatic seizures. *Arch Phys Med Rehabil.* 1993;74(9):983-1001.
9. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet.* 2009;373(9669):1105-1110.
10. Diamond ML, Ritter AC, Failla MD, et al. IL-1beta associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. *Epilepsia.* 2014;55(7):1109-1119.
11. Scher AI, Wu H, Tsao JW, et al. MTHFR C677 T genotype as a risk factor for epilepsy including post-traumatic epilepsy in a representative military cohort. *J Neurotrauma.* 2011;28(9):1739-1745.
12. Kumar RG, Breslin KB, Ritter AC, Conley YP, Wagner AK. Variability with astroglial glutamate transport genetics is associated with increased risk for post-traumatic Seizures. *J Neurotrauma.* 2019;36(2):230-238.
13. Darrah SD, Miller MA, Ren D, et al. Genetic variability in glutamic acid decarboxylase genes: associations with post-traumatic seizures after severe TBI. *Epilepsy Res.* 2013;103(2-3):180-194.
14. Wagner AK, Miller MA, Scanlon J, Ren D, Kochanek PM, Conley YP. Adenosine A1 receptor gene variants associated with post-traumatic seizures after severe TBI. *Epilepsy Res.* 2010;90(3):259-272.
15. Diamond ML, Ritter AC, Jackson EK, et al. Genetic variation in the adenosine regulatory cycle is associated with posttraumatic epilepsy development. *Epilepsia.* 2015;56(8):1198-1206.
16. Cavalleri GL, Lynch JM, Depondt C, et al. Failure to replicate previously reported genetic associations with sporadic temporal lobe epilepsy: where to from here? *Brain.* 2005;128(Pt 8):1832-1840.
17. Diaz-Arrastia R, Gong Y, Fair S, et al. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. *Arch Neurol.* 2003;60(6):818-822.
18. Friedman G, Froom P, Sazbon L, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology.* 1999;52(2):244-248.
19. Anderson GD, Temkin NR, Dikmen SS, et al. Haptoglobin phenotype and apolipoprotein E polymorphism: relationship to post-traumatic seizures and neuropsychological functioning after traumatic brain injury. *Epilepsy Behav.* 2009;16(3):501-506.
20. Miller MA, Conley Y, Scanlon JM, et al. APOE genetic associations with seizure development after severe traumatic brain injury. *Brain Inj.* 2010;24(12):1468-1477.
21. Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, Grafman J. Correlates of posttraumatic epilepsy 35 years following combat brain injury. *Neurology.* 2010;75(3):224-229.
22. Ritter AC, Kammerer CM, Brooks MM, Conley YP, Wagner AK. Genetic variation in neuronal glutamate transport genes and associations with posttraumatic seizure. *Epilepsia.* 2016;57(6):984-993.
23. Ferlazzo E, Gasparini S, Beghi E, et al. Epilepsy in cerebrovascular diseases: review of experimental and clinical data with meta-analysis of risk factors. *Epilepsia.* 2016;57(8):1205-1214.
24. Leone MA, Tonini MC, Bogliun G, et al. Risk factors for a first epileptic seizure after stroke: a case control study. *J Neurol Sci.* 2009;277(1-2):138-142.
25. Eriksson H, Wirdefeldt K, Asberg S, Zelano J. Family history increases the risk of late seizures after stroke. *Neurology* 2019;93(21):e1964-e1970.
26. Balcerzyk A, Nowak M, Kopyta I, et al. Impact of the -174G/C interleukin-6 (IL-6) gene polymorphism on the risk of paediatric ischemic stroke, its symptoms and outcome. *Folia Neuropathol.* 2012;50(2):147-151.
27. Yang H, Song Z, Yang GP, et al. The ALDH2 rs671 polymorphism affects post-stroke epilepsy susceptibility and plasma 4-HNE levels. *PLoS One.* 2014;9(10):e109634.
28. Zhang B, Chen M, Yang H, Wu T, Song C, Guo R. Evidence for involvement of the CD40/CD40 L system in post-stroke epilepsy. *Neurosci Lett.* 2014;567:6-10.
29. Fu CY, Chen SJ, Cai NH, et al. Increased risk of post-stroke epilepsy in Chinese patients with a TRPM6 polymorphism. *Neurol Res* 2019;41(4):378-383.
30. Semah F, Picot MC, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology.* 1998;51(5):1256-1262.



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31. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. *Lancet Neurol.* 2014;13(11):1114-1126.
  32. Lewis DV, Shinnar S, Hesdorffer DC, et al. Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. *Ann Neurol.* 2014;75(2):178-185.
  33. McClelland AC, Gomes WA, Shinnar S, et al. Quantitative evaluation of medial temporal lobe morphology in children with febrile status epilepticus: results of the FEBSTAT study. *AJNR Am J Neuro Radiol.* 2016;37(12):2356-2362.
  34. Hesdorffer DC, Shinnar S, Lewis DV, et al. Risk factors for febrile status epilepticus: a case-control study. *J Ped.* 2013;163(4):1147-1151.e1.
  35. Briellmann RS, Torn-Broers Y, Jackson GD, Berkovic SF. Seizures in family members of patients with hippocampal sclerosis. *Neurology.* 2001;57(10):1800-1804.
  36. Cendes F, Lopes-Cendes I, Andermann E, Andermann F. Familial temporal lobe epilepsy: a clinically heterogeneous syndrome. *Neurology.* 1998;50(2):554-557.
  37. Kobayashi E, D'Agostino MD, Lopes-Cendes I, et al. Hippocampal atrophy and T2-weighted signal changes in familial mesial temporal lobe epilepsy. *Neurology.* 2003;60(3):405-409.
  38. Kobayashi E, D'Agostino MD, Lopes-Cendes I, et al. Outcome of surgical treatment in familial mesial temporal lobe epilepsy. *Epilepsia.* 2003;44(8):1080-1084.
  39. Kanemoto K, Kawasaki J, Yuasa S, et al. Increased frequency of interleukin-1beta-511 T allele in patients with temporal lobe epilepsy, hippocampal sclerosis, and prolonged febrile convulsion. *Epilepsia.* 2003;44(6):796-799.
  40. Walz R, Castro RM, Velasco TR, et al. Surgical outcome in mesial temporal sclerosis correlates with prion protein gene variant. *Neurology.* 2003;61(9):1204-1210.
  41. Kasperaviciute D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. *Brain.* 2013;136(Pt 10):3140-3150.
  42. International League Against Epilepsy Consortium on Complex E. Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat Comm.* 2018;9(1):5269.
  43. Wong JKL, Gui H, Kwok M, et al. Rare variants and de novo variants in mesial temporal lobe epilepsy with hippocampal sclerosis. *Neurol Genet.* 2018;4(3):e245.
  44. Van Sonderen A, Roelen DL, Stoop JA, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann Neurol.* 2017;81(2):193-198.
  45. Kim TJ, Lee ST, Moon J, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol.* 2017;81(2):183-192.
  46. Mueller SH, Farber A, Pruss H, et al. Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Ann Neurol.* 2018;83(4):863-869.
  47. Dowell SF, Sejvar JJ, Riek L, et al. Nodding syndrome. *Emerg Infect Dis.* 2013;19(9):1374-1384.
  48. Benedek G, Abed El Latif M, Miller K, et al. Protection or susceptibility to devastating childhood epilepsy: nodding syndrome associates with immunogenetic fingerprints in the HLA binding groove. *PLoS Negl Trop Dis.* 2020;14(7):e0008436.
  49. Epi25 Collaborative. Ultra-rare genetic variation in the epilepsies: a whole-exome sequencing study of 17,606 individuals. *Am J Hum Genet.* 2019;105(2):267-282.
  50. Perucca P, Bahlo M, Berkovic SF. The genetics of epilepsy. *Ann Rev Genomics Hum Genet.* 2020;21:205-230.



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**Title:**

Genetic Contributions to Acquired Epilepsies

**Date:**

2021-01

**Citation:**

Perucca, P. & Scheffer, I. E. (2021). Genetic Contributions to Acquired Epilepsies. EPILEPSY CURRENTS, 21 (1), pp.5-13. <https://doi.org/10.1177/1535759720954254>.

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