

Association study between interleukin 1 β gene and epileptic disorders: a HuGe review and meta-analysis

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Previous studies have examined the association of a single nucleotide polymorphism at the promoter region of interleukin 1B (IL-1 β -511T) with temporal lobe epilepsy and febrile seizures susceptibility, but those studies have been inconclusive. Published studies up to March 2007 of temporal lobe epilepsy, febrile seizures and the IL-1 β -511T single nucleotide polymorphism were identified by searches of Medline and Embase databases. Meta-analysis of temporal lobe epilepsy and febrile seizures case-control data were performed to assess the association of IL-1 β -511T with temporal lobe epilepsy, temporal lobe epilepsy with hippocampal sclerosis, febrile seizures, and other epileptic disorders. Pooled odds ratios (OR) were estimated by means of a genetic-model-free approach. The quality of the included studies was assessed by a score. The results show a modest association (OR, 1.48; 95% confidence interval, 1.09–2.00; $P = 0.01$) between the IL-1 β -511T polymorphism and temporal lobe epilepsy with hippocampal sclerosis. **Genet Med 2008;10(2):83–88.**

Key Words: temporal lobe epilepsy, hippocampal sclerosis, interleukin 1B, IL-1 β , meta-analysis

The interleukin (IL)-1 family accounts for three genes: IL-1 α , IL-1 β (proinflammatory cytokines), and their inhibitor, the IL-1 RA (IL-1 β receptor antagonist). All three genes are located in the long arm of chromosome 2. Clinical studies show that IL-1 is a significant mediator of inflammatory diseases in vivo, as exemplified by patient responses to IL-1 inhibitors.^{1,2} Three biallelic polymorphisms in IL-1 β have been most frequently evaluated for their association with diverse conditions (reviewed in Refs. 3–5) besides epilepsy; all three result from C-to-T transitions at positions –511, –31, or +3954 from the transcriptional start site.⁴ The IL-1 β -511 (rs16944) single nucleotide polymorphism (SNP) leads to an increased expression of the encoded protein as a result of enhanced gene transcription.⁶ However, this activity seems to be dependent on the haplotype context of the promoter region of

IL-1 β . Chen et al.⁷ demonstrated that the IL-1 β -511T allele strongly enhanced the transcription of the IL-1 β gene in the context of the IL-1 β -31C allele. Conversely, the enhancement is significantly lower in the context of the IL-1 β -31T allele.⁷ These findings highlight the importance of understanding the haplotype structure of populations used for genetic studies. Nevertheless, this overexpression of IL-1 β might contribute to the development of febrile seizures (FS) and eventually to subsequent hippocampal neuronal damage.

Associations and objectives

IL-1 β -511T SNP has been associated with temporal lobe epilepsy (TLE)⁸ and FS⁹ susceptibility. However, these findings have not been replicated by others^{10,11} raising controversy about a role for this genetic variant in the susceptibility to develop these conditions. Conversely, the other two IL-1 β promoter polymorphisms have not been associated with TLE^{12,13} or FS.¹⁴ Persistent difficulties in obtaining robust and replicable results in genetic association studies are almost certainly because genetic effects are small, requiring studies with many thousands of subjects to detect any effects.¹⁵ However, there are other issues that might explain these difficulties, such as sampling, publication, and time-lag biases.¹⁶ Case-control studies are the most widely used for characterizing genetic associations with common diseases, although this approach is prone to finding gene variants associated spuriously with disease.¹⁷ This difficulty can be addressed, at least in part, by doing a systematic review of the literature and performing a meta-analysis.

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We therefore performed a systematic review of the association between IL-1 β -511 SNP and TLE or FS with the following objectives: first to estimate allele frequencies, second to estimate if there is an effect of this polymorphism on TLE and FS susceptibility, and if so, to determine its magnitude and third, to assess for methodological bias that could account for the differences in the reported studies.

Diseases

TLE is the most common cause of partial epilepsies in the adult population.¹⁸ Although it was first recognized by Hughlings Jackson in 1888,¹⁹ the name was only established after the temporal lobectomy performed by Penfield in 1954.²⁰ Hippocampal sclerosis (HS) is the main pathologic substrate responsible for seizures. Even though it has been recognized for decades, the syndrome of TLE with HS has been recently defined.²¹ Traditionally, TLE has been considered to be an acquired disorder. However, the observations of familial monogenic forms,^{22,23} the frequent presence of positive familial antecedents for epileptic events,²⁴ and the identification of common variants in different genes²⁵ as risk factors highlight an evolving key role of genetics in TLE.

FS accounts for the most common human convulsive event.²⁶ They affect approximately 2–5% of all children in North America and Europe.²⁷ They are not thought of as a true epileptic disease but rather as a special syndrome characterized by its provoking factor (fever) and a typical age range of 6 months to 6 years. Although they are considered as a benign seizure disorder, up to 7% of affected children develop unprovoked seizures (epilepsy) later during life.²⁷ Twin and family studies point to an important genetic component in the etiology of FS.^{28,29}

Based on a series of 100 patients who had surgery for intractable TLE, Falconer et al.³⁰ observed that a significant proportion of those with HS had antecedents of prolonged FS in early childhood (30% in the HS group compared with 6% in the group without HS). However, prospective studies failed to confirm this relationship.³¹

Because it is well known that a rapid rise of fever or high body temperatures during an infectious disease can trigger seizures in individuals who are prone to FS,³¹ genes encoding proteins involved in the regulation of inflammatory processes and fever are plausible candidate genes in the elucidation of the molecular mechanisms of FS and TLE. Inflammation may also be involved in secondary epileptogenesis in TLE.³² This is supported by some studies that have demonstrated the presence of chronic inflammation in the hippocampus.³³

METHODS

Search strategy

The MEDLINE and EMBASE databases were searched with no language restrictions from their inception to March 30, 2007. The search strategy was ([interleukin 1 β OR IL-1 β OR interleukin 1] AND [temporal lobe epilepsy OR epilepsy OR seizures OR febrile seizures] AND [polymorph\$ OR muta-

tion\$ OR variant\$ OR genotype\$]). All references cited in these studies and published reviews were reviewed to identify additional works not indexed by the databases selected. When there were multiple publications from the same study group, the most complete and recent results were used.

Inclusion criteria

Eligible studies had to meet all the following criteria: (a) published in a peer-reviewed journal and independent studies using original data; (b) provided sufficient data to calculate the odds ratio (OR) with confidence interval (CI) and *P* value; (c) investigated the IL-1 β -511T polymorphism; (d) described the genotyping method or provided reference to it; (e) included patients with a diagnosis of an epileptic syndrome; (f) used healthy individuals as controls. Authors were contacted in cases in which there were queries regarding their studies.

Data extraction

Two investigators (M.K. and D.G.M.) independently extracted the following data from each publication: author; country of origin; selection and characteristics of cases and controls; demographic information; racial descent of the study population; numbers of eligible and genotyped cases and controls; and numbers of cases and controls for each IL-1 β -511 genotype. Disagreements were resolved by consensus.

Quality score assessment

Methodologic quality was independently assessed by two reviewers (M.K. and D.G.M.), according to a set of predefined criteria (Supplementary Table 1), based on the scale of Thakkinstian et al.³⁴ Disagreements were resolved by consensus. Scores ranged from 0 (lowest) to 10 (highest).

Statistical analyses

Data analyses were performed as follows. First, the pooled prevalence of the putative risk allele in controls was estimated by the inverse variance method (Appendix of Ref. 35). A Q test for heterogeneity was done for each ethnic group and the total control cohort. Under the null hypothesis of no difference in effect across studies, the Q statistic is χ^2 -distributed with degrees of freedom (df) equal to the number of studies minus 1.

Second, for the controls in each study, Hardy-Weinberg equilibrium (HWE) was assessed using the exact test.

Third, a Q test for heterogeneity was performed separately for three odds ratios (ORs), that is, T/T versus C/C (OR1), C/T versus C/C (OR2), and T/T versus C/T (OR3). If there was heterogeneity on at least one of these odds ratios, we estimated the overall gene effect by use of logistic regression with the random-effects model as described by Bagos and Nikolopoulos³⁶; otherwise, logistic regression with the fixed-effect model as described by Thakkinstian et al.³⁷ was used to estimate the overall gene effect.

Fourth, if the main effect of the genotype was statistically significant, further comparisons of OR1, OR2, and OR3 were

explored. These pairwise differences were used to indicate the most appropriate genetic model as follows.

- Recessive model: if $OR1 = OR3 \neq 1$ and $OR2 = 1$.
- Dominant model: if $OR1 = OR2 \neq 1$ and $OR3 = 1$.
- Overdominant model: if $OR2 = 1/OR3 \neq 1$ and $OR1 = 1$.
- Codominant model: if $OR1 > OR2 > 1$ and $OR1 > OR3 > 1$
- (or $OR1 < OR2 < 1$, and $OR1 < OR3 < 1$).

Finally, using the most appropriate genetic model to collapse the three genotypes into two groups, the pooled estimate of risk was obtained using the fixed effect inverse variance method.

Publication bias was assessed using Egger’s and Begg-Matsumdar tests. Statistical analysis was done with Stata, version 9 (Stata Corporation, College Station, TX). $P < 0.05$ was considered statistically significant, except for heterogeneity, Egger’s and Begg’s tests, in which a level of 0.10 was used.

RESULTS

Study inclusion and characteristics

The combined search yielded 42 references. After overlapping references and those that did not meet inclusion criteria were discarded, 14 references were retained. These references were then filtered to ensure conformity to inclusion criteria. In two overlapping reports^{8,12} from Kanemoto et al., we retained the one⁸ with the largest and more recent sample size. Healthy controls included in the studies of Virta et al.⁹ and Peltola et al.³⁸ were the same, thus they were counted once. Finally, 13

references met our criteria for inclusion (Table 1). Four of them analyzed the association with TLE,^{10,13,39,40} four did it with FS,^{9,14,41,42} two included patients with temporal and extratemporal partial epilepsy,^{8,38} one reference included FS and TLE patients,⁴³ one study included patients with TLE, extratemporal partial epilepsy and generalized epilepsy,⁴⁴ and a further study included patients with FS and patients with epilepsy not typified.¹¹ Therefore, the studies compared a total of 1866 epilepsy cases and 1930 controls. Within the population of epileptic patients, there were a total of 610 TLE cases and 560 FS cases. The studies differed in the type of FS included. Four studies included simple and complex FS,^{9,14,41,42} whereas two did not identify the type of FS included.^{11,43} There were also differences in the analysis of TLE cases, in which four studies included only TLE with HS cases.^{10,13,40,44} The quality of studies ranged from 0 to 8, out of a possible score of 10. Five studies were conducted in Asia,^{8,11,14,39,42} seven in Europe,^{9,13,38,40,41,43,44} and one in the USA.¹⁰ Results of HWE analysis for controls were reported in four studies.^{10,14,40,44} Our calculation of HWE for the rest of included studies showed that one report deviated from HWE.⁴¹ In all studies, investigators used the same DNA genotyping method.

Pooled prevalence of IL-1β-511T in control populations

The thirteen included studies estimated the T-allele frequency. Eight of them were performed in Caucasians and five in Asians. There was heterogeneity across the studies ($P = 0.002$) when data from Caucasians and Asians were analyzed together. However, there was not marked heterogeneity across the studies in Asians ($P = 0.97$) nor across the studies in Cau-

Table 1
Genotype frequencies in epileptic disorders cases and controls from the 13 studies included in the analysis of IL-1β-511 polymorphism

First author, year of publication	Country	Ethnic group	Epileptic syndrome	n	Controls, genotypes (n)				Allele T frequency ^b	Cases, genotypes (n)				Quality score
					CC	CT	TT	T carriers ^a		CC	CT	TT	T carriers	
Heils, 2000 ⁴⁰	Germany	C	TLEHS, TLE	219	57	60	16	76	0.35	33	42	11	53	8
Buono, 2001 ¹⁰	USA	C	TLEHS	180	44	68	7	75	0.34	31	24	6	30	5
Virta, 2002 ⁹	Finland	C	FS	435	146	182	72	254	0.41	7	18	10	28	6
Peltola, 2001 ³⁸	Finland	C	FE	448	146	182	72	254	0.41	5	31	12	43	5
Tilgen, 2002 ⁴³	Germany	C	FS, TLE	268	52	59	15	74	0.35	63	60	19	79	1
Chou, 2003 ¹¹	Taiwan	A	FS, ENT	181	24	37	22	59	0.49	36	43	19	62	0
Jin, 2003 ³⁹	China	A	TLEHS, TLE	227	26	62	27	89	0.50	28	56	28	84	7
Kanemoto, 2003 ⁸	Japan	A	TLEHS, TLE, FE	382	44	82	37	119	0.48	56	97	66	163	7
Kira, 2005 ¹⁴	Japan	A	FS	387	53	75	30	105	0.43	66	107	56	163	7
Haspolat, 2005 ⁴¹	Turkey	C	FS	225	63	50	39	89	0.42	23	37	13	50	4
Cavalleri, 2005 ⁴⁴	UK	C	TLEHS, TLE, FE, IGE	1053	161	162	41	203	0.34	309	306	74	380	4
Matsuo, 2006 ⁴²	Japan	A	FS	45	5	8	5	13	0.50	13	8	6	14	0
Ozkara, 2006 ¹³	Turkey	C	TLEHS	146	41	41	17	58	0,38	16	21	10	31	3

The studies are presented in decreasing order based on the date of publication. Abbreviations: TLEHS, temporal lobe epilepsy with hippocampal sclerosis. TLE, temporal lobe epilepsy. FS, febrile seizures. FE, Focal epilepsy. ENT, epilepsy Not Tipified. IGE, Idiopathic Generalized epilepsy. C, Caucasians. A, Asians.

^aT carriers: CT and TT genotypes.

^bAllele T Frequency in Controls Populations.

casians ($P = 0.25$). Pooled allele T frequencies were 0.40 (95% CI, 0.37–0.43) in all populations, 0.37 (95% CI, 0.36–0.38) in Caucasians and 0.47 (95% CI, 0.465–0.475) in Asians ($P < 0.001$ for the difference in proportions).

IL-1 β -511T polymorphism and epileptic disorders risk

Heterogeneity was checked for OR1 (T/T vs. C/C), OR2 (C/T vs. C/C), and OR3 (T/T vs. C/T). Results indicated heterogeneity for OR2 and OR3 but not for OR1 (for OR1: $\chi^2_{11} = 16.39$ $P = 0.127$; for OR2: $\chi^2_{11} = 25.14$ $P = 0.009$; for OR3: $\chi^2_{11} = 25.14$ $P = 0.009$). Hence, these 12 studies were pooled by use of logistic regression with the random-effects model as described by Bago and Nikolopoulos.³⁶ The overall gene effect was not significant, with the estimated OR1 and OR2, being 1.159 (95% CI, 0.949–1.415) and 1.049 (95% CI, 0.903–1.219), respectively. There was no evidence of publication bias ($P > 0.5$ for Begg and Egger tests).

IL-1 β -511T polymorphism and febrile seizures risk

Heterogeneity was checked for OR1 (T/T vs. C/C), OR2 (C/T vs. C/C), and OR3 (T/T vs. C/T). Results indicated no heterogeneity for the three OR (for OR1: $\chi^2_5 = 6.64$ $P = 0.249$; for OR2: $\chi^2_5 = 8.85$ $P = 0.115$; for OR3: $\chi^2_5 = 6.38$ $P = 0.271$). Therefore, logistic regression with the fixed-effect model as described by Thakkinstian et al.³⁷ was used to assess the overall gene effect. The overall gene effect was not significant (likelihood ratio [LR] = 1.25, $P = 0.53$), with the estimated OR1, OR2 and OR3 being 1.16 (95% CI, 0.841–1.614), 1.14 (95% CI, 0.876–1.482) and 1.02 (95% CI, 0.747–1.397), respectively. There was no evidence of publication bias ($P > 0.85$ for Begg and Egger tests).

IL-1 β -511T polymorphism and temporal lobe epilepsy risk

Heterogeneity was checked for OR1 (T/T vs. C/C), OR2 (C/T vs. C/C), and OR3 (T/T vs. C/T). Results indicated no heterogeneity for the three OR (for OR1: $\chi^2_6 = 3.36$ $P = 0.762$; for OR2: $\chi^2_6 = 6.29$ $P = 0.392$; for OR3: $\chi^2_6 = 2.71$ $P = 0.844$). Therefore, logistic regression with the fixed-effect model as described by Thakkinstian et al.³⁷ was used to assess the overall gene effect. The overall gene effect was not significant (LR = 2.69, $P = 0.26$), with the estimated OR1, OR2, and OR3 being 1.16 (95% CI, 0.861–1.576), 0.92 (95% CI, 0.733–1.149) and 1.27 (95% CI, 0.952–1.691), respectively. There was no evidence of publication bias ($P > 0.6$ for Begg and Egger tests).

IL-1 β -511T polymorphism and temporal lobe epilepsy with hippocampal sclerosis risk

Heterogeneity was checked for OR1 (T/T vs. C/C), OR2 (C/T vs. C/C), and OR3 (T/T vs. C/T). Results indicated no heterogeneity for the three OR (for OR1: $\chi^2_5 = 4.83$ $P = 0.437$; for OR2: $\chi^2_5 = 5.18$ $P = 0.394$; for OR3: $\chi^2_5 = 6.39$ $P = 0.27$). Therefore, logistic regression with the fixed-effect model as described by Thakkinstian et al.³⁷ was used to assess the overall gene effect. The LR test indicated that the overall gene effect was significant (LR = 6.72, $P = 0.03$), with the estimated OR1, OR2, and OR3 being 1.41 (95% CI, 1.01–1.96), 0.92 (95% CI, 0.72–1.19) and 1.52 (95% CI, 1.11–2.08), respectively. These estimates suggest a recessive effect of the T allele for this phenotype. Therefore, T/T was compared with C/T and C/C genotypes combined. Figure 1 presents the fixed-effect pooled OR for this comparison. Overall, a significant increase in TLEHS risk for T allele homozygotes was observed. There was no evidence of publication bias ($P > 0.5$ for Begg and Egger tests).

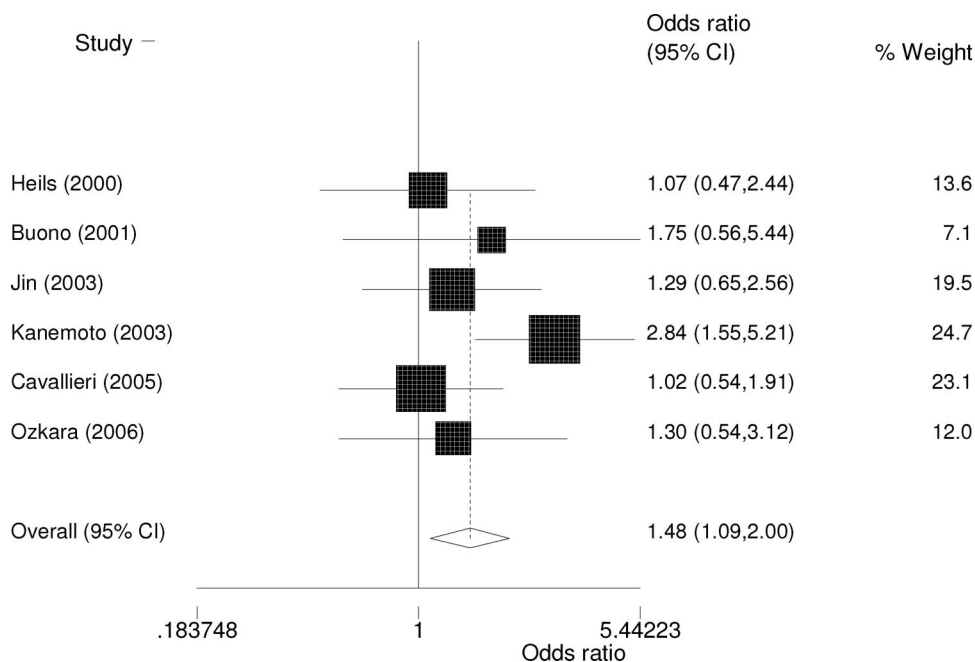


Fig. 1. Forest plots of OR with 95% CIs of temporal lobe epilepsy with hippocampal sclerosis associated with the IL-1 β -511T polymorphism. The OR (black squares), with the size of the square inversely proportional to its variance, and 95% CIs (horizontal lines). Pooled results (unshaded black diamond). The studies are ordered by publication year.

DISCUSSION

Main findings

Overall, we demonstrate a modest association between the IL-1 β -511T polymorphism and TLE with HS. We observed a nonsignificant increased risk to develop FS and TLE (irrespective of the presence of HS) in IL-1 β -511T allele carriers. Furthermore, the pooled prevalence of the IL-1 β -511T allele, based on the analysis of 13 epidemiologic studies from diverse populations, differed between Caucasian and Asian populations. There was no evidence of publication bias, and we found low between-study heterogeneity. Control populations from all studies but one were in “Hardy Weinberg equilibrium.”

Kanemoto et al.¹² and Virta et al.⁹ were the first to report an association between the IL-1 β -511T polymorphism and TLEHS and FS, respectively. However, these findings were not replicated by others raising controversy about the real role of this genetic variant in the susceptibility to develop these diseases. Indeed, this apparent contradiction is very often found in the field of genetics of complex disorders. Discrepant findings may be due to multiple causes such as differences in the populations analyzed, difficulties with the phenotype definition, or designs with low power to detect genetics effects that necessarily are small.⁴⁵ The effect of common alleles is of a small magnitude; thus studies with many hundreds of subjects are required to detect them. This difficulty could be solved, at least in part, by doing a systematic review of the literature and thereby performing a meta-analysis.

Limitations

The data set analyzed is of a relatively small magnitude; thus, sensitivity analysis could not be done limiting the robustness of our findings. The quality of the studies is heterogeneous, with many studies receiving low quality scores as judged by the criteria in Appendix Table 1. This concern is of particular importance for the reports that assessed the association with FS. Not all investigators provided appropriate descriptions of the criteria for the identification and selection of cases, a few of them did so for controls, and only one study mentioned that genotyping was performed under blinded conditions.³⁹ Furthermore, because variables not completely analyzed such as age, ethnicity, and gender could bias results, future studies and meta-analyses with a greater number of cases and designs of better quality are needed to provide a better estimate of the effect of this polymorphism in the development of these disorders.

Biological mechanism

IL-1 β -511T seems to be a functional SNP⁶ and IL-1 β is increasingly recognized as a cytokine with a significant role in different epileptogenic mechanisms.^{46,47} Accordingly, carriers of the IL-1 β -511T allele are higher producers of IL-1 β ⁶ than carriers of the IL-1 β -511C allele. Furthermore, IL-1 β , among other pro-inflammatory cytokines, seems to influence the electrophysiology of neurons.⁴⁸ For example, in the kainate-induced animal epilepsy model, the application of IL-1 β prolonged hippocampal seizures by enhancing glutamatergic

neurotransmission.⁴⁹ Moreover, IL-1 β has been shown to contribute to an enhanced neuronal hyperexcitability and a decreased seizure threshold.⁵⁰ Furthermore, FS are often triggered by a rapid rise in body temperature^{50,51}; therefore, endogenous pyrogens, like IL-1, plausibly could contribute to the development of FS.

Concluding remarks

To date, there is insufficient evidence to identify absolutely any gene variant as a putative risk factor for the development of epilepsy. Our findings indicate that IL-1 β gene variants might be associated with TLEHS development. However, more evidence is needed from epidemiologic studies to provide a better characterization of the role of this gene and its common variant in the genetic susceptibility to develop TLEHS and other epileptic disorders. Therefore, we cannot recommend systematic analysis of the IL-1 β genotype in the routine management of patients with epilepsy, but this developing understanding of the IL-1 β gene in epilepsy will have potential research implications.

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