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ORIGINAL ARTICLE

Candidate genes for temporal lobe epilepsy: a replication study

Annick Salzmann · Nader Perroud · Arielle Crespel
Carmen Lambercy · Alain Malafosse

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Abstract The objective of this study is to replicate previously published results regarding the involvement of several susceptibility genes in temporal lobe epilepsy (TLE): *interleukin 1β* (*IL-1β*), *interleukin 1α* (*IL-1α*), *interleukin 1RA* (*IL-1RA*), *apolipoprotein E* (*ApoE*) and *prodynorphin* (*PDYN*). We used a case-control approach comparing several polymorphisms within these candidate genes between unrelated TLE patients and matched controls. We were thus able to confirm the role of *ApoE*, *IL-1α* and *IL-1RA* genes in TLE disease, but failed to confirm the involvement of *IL-1β* and *PDYN*. This failure should be interpreted with caution, as this may be due to the small size of our study groups and the resultant lack of statistical power.

Keywords Temporal lobe epilepsy · Prodynorphin · Apolipoprotein E · Interleukin 1 · Genetics · Association

A. Salzmann · C. Lambercy · A. Malafosse (✉)
Division of Medical Genetics
University Hospitals of Geneva
Geneva, Switzerland
e-mail: alain.malafosse@hcuge.ch

A. Crespel
Epilepsy Laboratory
University Hospital of Montpellier
Montpellier, France

N. Perroud · A. Malafosse
Department of Psychiatry
University Hospitals of Geneva
Geneva, Switzerland

Introduction

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy [1] and this disorder is considered to be polygenic and complex. Various susceptibility genes and environmental factors are believed to be involved in the aetiology of TLE and concordance between genotype and phenotype is relatively weak. To understand the genetic background of complex diseases, association studies have been proposed as a method of choice [2]. However, this approach remains controversial and, in order to avoid false-positive association, replication of the first case-control study in independent groups of patients is recommended [3]. Recently a number of groups, including our own, have reported non-replications between several putative susceptibility genes and TLE [1, 4].

Since several other studies have reported an association between common variants in specific genes and TLE, our aim, in the present study, is to replicate them: *apolipoprotein E* (*ApoE*) [5], *interleukin 1α* (*IL-1α*), *interleukin 1β* (*IL-1β*), *interleukin 1RA* (*IL-1RA*) [6] and *prodynorphin* (*PDYN*) [7].

Methods

Subjects

Our study group consisted of 109 unrelated patients with a diagnosis of non-lesional TLE. They were admitted under partial epilepsy criteria in the epilepsy unit of the university hospital of Montpellier (France). These patients suffered from a severe form of epilepsy with poor control of their seizures. Poor control is defined as a failure to respond to two or three single drugs or a com-

bination of them. Diagnosis was based on patient history, clinical examination, interictal and ictal EEG analysis carried out with monitoring video-EEG, and MR evaluation. Demographic and clinical characteristics of our cohort of TLE patients have been reported in detail in a previous study [4].

The healthy control group was recruited from blood donors at the hospital in Geneva. To minimise morbidity among subjects in this group, only blood donors older than 35 years and without personal and/or family history of epilepsy and seizure were included. Patients and controls were European Caucasian for at least two generations. Written informed consent was obtained from all participants. The Research Ethics Board of the Department of Clinical Neurosciences of Geneva reviewed and approved this study.

Molecular methods

DNA was extracted from peripheral blood leukocytes by use of the Nucleon BACC 2 kit (Amersham). Genotyping reactions were carried out as described in the different studies [6, 8, 9].

Statistical analysis

For our statistical analysis, in addition to the total cohort of patients, we divided the TLE group into subgroups, according to the existence or not of familial risk and hippocampal sclerosis. This was done in order to facilitate comparison between our data and that from analogous published work. In order to perform case-control genetic comparisons, differences in genotype and allele frequencies between all TLE, TLE subgroups and healthy controls were analysed by using the Chi-square test: 3 by 2 tables for *PDYN*, *IL-1α* and *IL-1β*; 4 by 2 tables for *IL-1RA*. As age at onset displayed a non-parametric curve, the Mann–Whitney *U*-test was used in place of the *t*-test for the comparison of age at onset and the presence or absence of the *ApoE* ε4 allele. We used the statistical package SPSS V.11.0.

As we compared genotypic and allelic distributions of various polymorphic markers between healthy and diseased subjects, a Bonferroni correction should be applied to correct for multiple testing. Adjustments for multiple comparisons are recommended to avoid excessively easy rejection of the null hypothesis. However, reducing the type I error increases the type II error and therefore increases the frequency of incorrect statements of no relationship between two factors. This could thus lead to missing an association in data that is not the result of chance [10]. The rejection of the null hypothesis should be considered by taking into account both the evidence from the data and the relevance of other explanations. Moreover, our argument is based on previous findings and should be seen as a confirmation of research in the field of TLE. In this present study, choosing not to penalise ourselves by missing possibly important findings, we decided not to correct our results for multiple testing.

Ethnicity was recorded using a self-reporting questionnaire including perceived nationality, mother tongue and ethnicity of the subject together with all four grandparents. To reduce the possibility of stratification bias, we used an average F_{ST} between pairs of ethnic populations between 0.0009 and 0.0048 (table 5.5.1 in ref. [11]).

Power calculation

Statistical power to detect associations was estimated using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/purcell/gpc/). For age at onset we aimed to detect genetic effects explaining at least 2% of variance in the trait under an additive genetic model for a polymorphism with a minor allele frequency of 0.12. Power for detecting such effect was calculated for the nominal significance level α=0.05. For discrete traits, power for each study was calculated separately using an additive model with genetic relative risk of 2 and an α level=0.05.

Results

Throughout our study, genotypic distributions in both patients and controls were in Hardy–Weinberg equilibrium.

Apolipoprotein E

Five studies have been published on *ApoE* and TLE age at onset [1, 5, 12–14]. In one of them, a positive association was found between early age at onset of the disease and the presence of *ApoE* ε4 allele (ε4$^+$: 5±5 years vs. ε4$^-$: 14.9±10 years; p=0.005) [5]; however, the four other studies were unable to replicate this positive association. Our results confirmed a significant association between an early age at onset of epilepsy and the presence of allele ε4 (ε4$^+$: 10.54±6.36 years vs. ε4$^-$: 16.51±9.90 years; p=0.003) (Table 1). The study had 99% power to detect a gene effect, explaining 2% of the variance in the trait (Table 1).

Table 1 *ApoE* allele and genotype distributions and association between *ε4* allele and age at onset

	Controls	Patients	*p*	Age at onset of seizures		*p* (Mann–Whitney *U*-test)	Power
	n (%)	n (%)		Presence of ε4 allele	Absence of ε4 allele		
Genotype	227	109	NS*				
ε2–2	0 (0.0)	0 (0.0)					
ε2–3	25 (11.0)	9 (8.3)					
ε2–4	5 (2.2)	1 (0.9)		n=26	n=80		
ε3–3	151 (66.5)	72 (66.1)		Age: 10.54±6.36	Age: 16.51±9.90	***p*=0.003**	0.99
ε3–4	43 (18.9)	27 (24.8)					
ε4–4	3 (1.3)	0 (0.0)					
Allele	454	218	NS*				
ε2	30 (6.6)	10 (4.6)					
ε3	370 (81.5)	180 (82.6)					
ε4	54 (11.9)	28 (12.8)					

*NS, non-significant

Interleukin 1α

Based on pathophysiological hypotheses, several association studies have been carried out between interleukin-related genes and TLE. Two were performed with *IL-1α* and both showed no association [6, 15].

We partitioned our cohort of patients, like Kanemoto's group, based on the existence or non-existence of a hippocampal sclerosis (TLE-HS$^+$) [6], and like Ozkara's team, based on the absence of antecedent of febrile convulsion (TLE-FC$^-$) [15]. We found a significant positive genotypic association between the whole TLE sample and the promoter *IL-1α*–889 SNP, but this was observed in TLE-HS$^+$ patients (Table 2). However, as shown in Table 2, we did not have enough power to detect any significant association between TLE-HS$^-$ and controls (power=43%). Given the high frequency of the 1 allele in this sample (80.4%), an association could be suspected and further study with higher number of individuals is warranted. Interestingly, we also found a positive association between *IL-1α*–889 SNP and TLE-FC$^-$ (Table 2), but no statistical difference between TLE-HS$^+$-FC$^-$ vs. controls (data not shown).

Interleukin 1RA

IL-1RA is the second interleukin-related gene studied by Kanemoto et al. [6]. Once again they failed to show any association.

We observed significant differences in the allelic and genotypic frequencies between patients and controls, but here this concerns TLE-HS$^-$ (Table 3).

Interleukin 1β

In this case, Kanemoto et al. [6] and Ozkara et al. [15] did not find an association between *IL-1β*–3953 and TLE. We were also unable to find any significant statistical difference (Table 4).

In contrast, Kanemoto et al. found a statistically higher frequency of the *IL-1β*–511 2-2 genotype in TLE-HS$^+$ subjects compared to control subjects [6], and confirmed this result using a larger study group [16]. However this association was not observed in five other ethnically variable populations [1, 15, 17–19] or in our cohort of patients (Table 5).

In addition, we analysed the two *IL-1β* SNP haplotypes for the two subgroups of TLE (data not shown) and again we found no significant association. However, and as previously stated, negative results involving the TLE-HS$^-$ group should be kept with caution as power to detect an association is limited.

Prodynorphin

Stogmann et al. reported that *PDYN* promoter L allele confers an increased risk for TLE in patients with a family history of seizures (OR=2.25 (CI 1.41–3.62); *p*=0.0006) [7]. This result remained unconfirmed in three independent Caucasian populations [1, 20, 21].

In the present study, we find a non-significant trend of excess of the L allele in those patients with a family history of epilepsy (OR=1.60 (CI 0.82–3.31); *p*=0.163) (Table 6).

Table 2 *IL-1α*–889 allele and genotype distributions

	Controls	TLE	TLE-HS^{+a}	TLE-HS^{-b}	TLE FC^{-c}	p_u[d]							
	n (%)	n (%)	n (%)	n (%)	n (%)	TLE-HS^{+a} vs. controls	Power	TLE-HS^{-b} vs. controls	Power	TLE vs. controls	Power	TLE-FC^{-c} vs. controls	Power
Allele	470	218	172	46	108	0.059	0.89	0.066	0.43	**0.018**	0.95	0.079	0.74
1	316 (67.2)	166 (76.1)	129 (75.0)	37 (80.4)	82.0 (75.9)								
2	154 (32.8)	52 (23.9)	43 (25.0)	9 (19.6)	26.0 (24.1)								
Genotype	235	109	86	23	54	**0.027**		0.104		**0.0078**		**0.022**	
1-1	99 (42.1)	65 (59.6)	50 (58.1)	15 (65.2)	33 (61.1)								
1-2	118 (50.2)	36 (33.1)	29 (33.7)	7 (30.4)	16 (29.6)								
2-2	8 (7.7)	8 (7.3)	7 (8.1)	1 (4.4)	5 (9.3)								

[a]*TLE-HS*$^+$, TLE with hippocampal sclerosis; [b]*TLE-HS*$^-$, TLE without hippocampal sclerosis; [c]*TLE-FC*$^-$, TLE without antecedents of febrile convulsion; [d]p_u, *p* uncorrected

Table 3 *IL-1RA* allele and genotype distributions

	Controls	TLE-HS^{+a}	TLE-HS^{-b}	p_u[c]					
	n (%)	n (%)	n (%)	TLE-HS^{+a} vs. controls	Power	TLE-HS^{-b} vs. controls	Power	TLE-HS^{-b} vs. TLE-HS^{+a}	Power
Genotype	242	86	23	0.768	0.95	**0.001**	0.51	**0.036**	0.64
1-1	128 (52.9)	43 (50.0)	5 (21.7)						
1-2	90 (37.2)	36 (41.9)	13 (56.5)						
1-4	5 (2.1)	1 (1.2)	0 (0.0)						
1-5	0 (0.0)	0 (0.0)	1 (4.3)						
2-2	16 (6.6)	6 (7.0)	4 (17.4)						
2-4	3 (1.2)	0 (0.0)	0 (0.0)						
Allele	484	172	46	0.525		**<0.0001**		**0.022**	
1	351 (72.5)	123 (71.5)	24 (52.2)						
2	125 (25.8)	48 (27.9)	21 (45.7)						
4	8 (1.7)	1 (1.4)	0 (0.0)						
5	0 (0.0)	0 (0.0)	1 (2.2)						

[a]*TLE-HS*$^+$, TLE with hippocampal sclerosis; [b]*TLE-HS*$^-$, TLE without hippocampal sclerosis; [c]p_u, *p* uncorrected

Table 4 *IL-1β*+3953 allele and genotype distributions

	Controls	TLE-HS+[a]	TLE-HS–[b]	p_u[c]			
	n (%)	n (%)	n (%)	TLE-HS+[a] vs. controls	Power	TLE-HS–[b] vs. controls	Power
Genotype	234	86	23	NS[d]	0.97	NS[d]	0.60
1-1	118 (50.4)	45 (52.3)	14 (60.9)				
1-2	101 (43.2)	34 (39.5)	8 (34.8)				
2-2	15 (6.4)	7 (8.2)	1 (4.3)				

[a]*TLE-HS*+, TLE with hippocampal sclerosis; [b]*TLE-HS*–, TLE without hippocampal sclerosis; [c]p_u, *p* uncorrected; [d]*NS*, non-significant

Table 5 *IL-1β*–511 allele and genotype distributions

	Controls	TLE-HS+[a]	TLE-HS–[b]	p_u[c]			
	n (%)	n (%)	n (%)	TLE-HS+[a] vs. controls	Power	TLE-HS–[b] vs. controls	Power
Genotype	227	86	23	NS[d]	0.98	NS[d]	0.51
1-1	99 (43.6)	35 (40.7)	12 (52.2)				
1-2	108 (47.6)	45 (52.3)	9 (39.1)				
2-2	20 (8.8)	6 (7.0)	2 (8.7)				

[a]*TLE-HS*+, TLE with hippocampal sclerosis; [b]*TLE-HS*–, TLE without hippocampal sclerosis; [c]p_u, *p* uncorrected; [d]*NS*, non-significant

Table 6 *PDYN* allele and genotype distributions

	Controls	Familial-risk TLE	OR (95% CI)	p_u[a]	Power	Nonfamilial-risk TLE	OR (95% CI)	p_u[a]	Power
	n (%)	n (%)				n (%)			
Allele	412	42		0.163	0.68	166		NS[b]	0.98
L	106 (25.7)	15 (35.7)	1.60 (0.82–3.31)			50 (30.1)	1.24 (0.84–1.85)		
H	306 (74.3)	27 (64.3)	0.62 (0.32–1.21)			116 (69.9)	0.80 (0.54–1.20)		
Genotype	206	21	0.32			83		NS[b]	
LL	14 (6.8)	2 (9.5)	1.44 (0.30–6.83)			7 (8.4)	1.26 (0.49–3.25)		
LH	78 (37.9)	11 (52.4)	1.81 (0.73–4.45)			36 (43.4)	1.26 (0.75–2.11)		
HH	114 (55.3)	8 (38.1)	0.50 (0.20–1.25)			40 (48.2)	0.75 (0.45–1.25)		

[a]p_u, *p* uncorrected; [b]*NS*, non-significant

Discussion

In this present paper, we attempt to replicate published association studies between TLE, and subtypes of this disease, and several candidate genes.

Some evidence has implicated ApoE in the hippocampal response to injury. Indeed, astrocytes reply to neuronal damage by synthesising and releasing ApoE. Three major isoforms of ApoE have been identified, ε2, ε3 and ε4 [8]. The *ApoE* ε4 allele has often been associated with neurological diseases and/or their early-age onset in carriers: Alzheimer's disease [22], amyotrophic lateral sclerosis [23] and Parkinson's disease [24]. Although three other TLE association studies were unable to find such effect [1, 13, 14] and the present sample size is small, we have enough power to detect a statistically significant result between an early age at onset of TLE and the presence of the ε4 allele. Moreover, the present study is the second one that reports an early age at onset in ε4 TLE carriers. These results suggest that TLE is one of the multiple neurological diseases for which ApoE has a general role in

neuronal degeneration or regeneration, rather than a specific role in their aetiopathogenesis.

IL-1 shows two structurally distinct forms, IL-1α and IL-1β, that act on the IL-1 receptor. Interleukin 1 receptor antagonist protein (IL-1RA) acts on the same receptor and inhibits IL-1α and IL-1β binding. IL-1α and IL-1β are involved in various immune responses, inflammatory processes, apoptosis and haematopoiesis. They are produced by monocytes and macrophages. Moreover, IL-1α and IL-1β are also synthesised by glial and neuronal cells [25]. Their implication in the central nervous system was demonstrated by the presence of high-density IL-1 receptors in molecular and granular layers of dentate gyrus [26], suggesting a physiological role for IL-1 in the hippocampus.

In contrast to Kanemoto et al. [6], we found a positive association between TLE and *IL-1α*–889, which is a variation in the 5' regulatory region. This result is in agreement with the work of Peltola et al. These authors also found a significantly higher frequency for *IL-1α* allele 1 in patients with localisation-related epilepsy, such as TLE, lobe temporal epilepsy, parieto-occipital epilepsy and multifocal epilepsy [27]. Despite higher frequencies of *IL-1α* allele 1 and genotype 1-1 in all the sub-groups compared to the controls, only some of them reach significance (the whole TLE population and the TLE-HS$^+$ and TLE-FC$^-$ sub-groups). This is probably due to a lack of statistical power and larger groups of patients will be needed to confirm this association and determine whether it is subgroup specific. It is noteworthy that the *IL-1α*–889 polymorphism is functional: 2-2 homozygotes showed an increased transcriptional activity compared to 1-1 homozygotes and heterozygotes [28]. This suggests that vulnerability to TLE may be related to deregulation of the immune system, a hypothesis further supported by the finding that three immune-related proteins are down- or up-regulated – specifically the complement factor 3, C3 – in brain of TLE patients [29]. Interestingly, the promoter region of C3 was found to be very responsive to IL-1 [30].

Discrepancies have been reported in the association studies between various epileptic syndromes and the *IL-1RA* VNTR, which is described as a putative protein-binding site and may influence gene expression [31]. For the first time, in contrast to the research of Kanemoto et al. [6] and despite weak statistical power, we observed quite a strong positive association between this variant and TLE: when compared to controls, TLE-HS$^-$ patients displayed lower frequencies of allele 1 and genotype 1-1, and higher frequencies of allele 2 and genotype 1-2 and 2-2. Tsai et al. reported an association between the same polymorphism and FS, but in the opposite sense: the *IL-1RA* allele 1 was significantly more frequent in FS children than in controls [32]. Due to the small sample size, we were unable to test the associations between *IL-1RA* VNTR and the TLE-HS$^-$-FC$^+$ and TLE-HS$^-$-FC$^-$ sub-groups. Before proposing pathophysiological hypotheses for these different associations, replication using larger study groups is required.

Similarly, conflicting results were also reported for *IL-1β*–511 SNP, which is an AP-2 binding site [33]. The positive association with *IL-1β*–511 SNP observed in a Japanese population [6] may be restricted to this ethnic population. However *IL-1β*–511 allele 2 was significantly more present in Caucasian patients with localisation-related epilepsy, such as TLE, lobe temporal epilepsy, parieto-occipital epilepsy and multifocal epilepsy [27]. Finally, the *IL-1β*–511 SNP was associated with FS only in Finnish [34] and German cohorts of patients [35]. Very recently, Kauffman et al. assessed a meta-analysis by pooling together all published studies up to March 2007, regardless of the cohorts' ethnicity. They found a modest association between *IL-1β*–511 allele 2 and TLE-HS$^+$ [36]. It is noteworthy that our results also showed no significant association for the *1L-1β*+3953 SNP, in accordance with previously published studies [6, 15]. In contrast, the present negative results for TLE-HS$^-$ and these two SNP must be interpreted with caution due to the weak power of association detection.

Finally, this present study, as well as some previous related studies [1, 20, 21], were unable to replicate the initial association between *PDYN* and TLE with a family history for seizures [7]. However, a recently stratified analysis, which pools four previous studies [1, 7, 20, 21], showed a significant association [37]. Our non-observance of this association is possibly due to a lack of statistical power. Moreover, a study reported an association between 32 autosomal dominant lateral temporal epilepsy index cases and *PDYN* [38].

Conclusion

The present study adds further data to the search for susceptibility genes involved in TLE. Despite failure to replicate most of the previously reported positive associations, the publishing of our results is important for future meta-analyses. Similarly, the positive association we report for the first time with *IL-1α* and *IL-1RA* requires further analysis for confirmation of this result.

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Conflict of Interest statement The Authors certify that there is no actual or potential conflict of interest in relation to this article

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