Anti-LGI1 Encephalitis is Associated with Unique HLA Subtypes

Running head: HLA Subtypes in Anti-LGI1 Encephalitis

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ABSTRACT

Objective: Autoimmune encephalitis, represented by anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, has increasing clinical significance based on recent discoveries of neuronal autoantibodies. However, its immunopathogenesis is not fully understood. Here, we investigated whether autoimmune encephalitis is associated with the human leukocyte antigen (HLA) subtypes.

Methods: We compared the HLA genotypes of 11 anti-LGI1 and 17 anti-NMDAR encephalitis patients to the control groups, which consisted of 210 epilepsy patients and 485 healthy Koreans.

Results: Anti-LGI1 encephalitis was associated with the DRB1*07:01–DQB1*02:02 haplotype (10 patients, 91%) in HLA class II genes, as well as with B*44:03 (8 patients, 73%) and C*07:06 (7 patients, 64%) in the HLA class I region. The prevalence of these alleles in anti-LGI1 encephalitis was significantly higher than that in the epilepsy controls or healthy controls. By contrast, anti-NMDAR encephalitis was not associated with HLA genotypes. Additional analysis using HLA–peptide binding prediction algorithms and computational docking underpinned the close relationship.

Interpretation: This finding suggests that most anti-LGI1 encephalitis develops in a population with specific HLA subtypes, providing insight into a novel disease mechanism.

INTRODUCTION

The number of patients who are diagnosed with autoimmune encephalitis continues to increase subsequent to the recent discovery of antibodies against neuronal synaptic proteins.[1,2] The clinical significance and spectrum of autoimmune encephalitis is also rapidly expanding after the initial discovery of the two most prevalent types of autoimmune encephalitis, namely anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.[3-5] Treatments use conventional or novel immune modulators including steroids, immunoglobulin, cyclophosphamide, rituximab, and tocilizumab, and these are especially effective against anti-synaptic antigen antibodies.[6-9] Nevertheless, many patients with autoimmune encephalitis still suffer from long-term neurological deficits.

Recent discoveries provided the immune pathogenesis of anti-LGI1 and anti-NMDAR encephalitis. In anti-LGI1 encephalitis, the antibody neutralizes LGI1–ADAM22 interaction and reduces synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.[10] In anti-NMDAR encephalitis, the antibody–antigen interaction decreases the synaptic receptor by receptor internalization.[3] Ovarian teratoma and sometimes herpes simplex virus-1 trigger the anti-NMDAR antibodies.[6,11,12] However, our understanding of the initial immune priming is still limited especially with regard to anti-LGI1 encephalitis.

Among the possible sources of pathogenesis in anti-LGI1 or anti-NMDAR encephalitis, genetic susceptibility has not been evaluated previously. Of the genes that predispose to systemic or neurological autoimmune diseases, human leukocyte antigen (HLA) is the most relevant and important group.[13] HLA genes correspond to the major histocompatibility complex in humans and encode antigen-presenting proteins on the surface of the cells that are directly involved in immune responses. Genetic associations between HLA and a variety of autoimmune diseases have been reported including ankylosing

spondylitis, Behcet's disease, rheumatoid arthritis, and type I diabetes.[14-17] Neurological disorders such as narcolepsy with cataplexy or MuSK antibody-positive myasthenia gravis also have correlations with HLA.[18-20] Autoimmune encephalopathy with the IgLON5 autoantibody, characterized by parasomnia and tauopathy, is also associated with specific HLA genotypes.[21] However, the relationship between HLA genotypes and anti-LGI1 or anti-NMDAR encephalitis in adult patients has not been studied. Therefore, we here investigated HLA subtypes associated with the diseases, and discuss the implications of unique HLA subtypes in the immunopathogenesis.

SUBJECTS AND METHODS

Subjects

We prospectively enrolled consecutive patients with anti-LGI1 or anti-NMDAR encephalitis who visited or were admitted to the neurology department of Seoul National University Hospital between June 2015 and December 2015. We diagnosed patients based on clinical suspicion and antibody testing with the following procedures.[22] First, we defined possible autoimmune encephalitis patients as those who presented with a subacute onset of the typical symptoms including memory impairment, altered mental status, and abnormal behavior.[2] Alternative causes of subacute encephalitis such as infection were excluded. Next, we screened the presence of brain-reactive autoantibodies by immunostaining the rat brain with the patients' serum and CSF as previously described.[23] Thereafter, synaptic autoantibodies including anti-NMDAR, LGI1, contactin-associated protein-like 2 (CASPR2), AMPA1, AMPA2, and γ-aminobutyric-acid type B (GABA-B) receptor were tested using a cell-based immunocytochemistry kit (Euroimmun AG, Lübeck, Germany). Classic paraneoplastic autoantibodies including anti-Hu, Yo, Ri, Ma2, CV2/CRMP5, and amphiphysin were tested using an immunoblotting kit (Euroimmun). We reviewed the demographics and clinical information of the enrolled patients and the results of the diagnostic tests. The study was approved by the Institutional Review Board of the Seoul National University Hospital. Written informed consent to participate was obtained from the patients or their representatives.

HLA Genotyping

We extracted genomic DNA from the peripheral blood of every anti-LGI1 or anti-NMDAR patient and performed HLA genotyping as described previously.[24] Briefly, the genotypes of the HLA-A, B, C, DRB1, and DQB1 genes of each subject were determined at the four-digit

allele level using direct DNA sequence analysis following established protocols (Biowithus, Seoul, Korea). Additionally, C*07:01 and C*07:06 were discriminated by sequencing exon 5 and 6. HLA-A, B, and C belong to HLA class I, while HLA-DRB1 and DQB1 belong to HLA class II. In this study, we established two control groups in the following manner. The HLA genotyping data of the collected Korean epilepsy patients who visited the Seoul National University Hospital to investigate the adverse effects of anti-epileptic drugs, some reported separately,[24,25] were compared for the epilepsy control group. The genotyping method of the epilepsy controls was exactly the same with that used in the present study. The previously reported HLA frequencies in the Korean population were used for the healthy control group values,[26-28] which genotyped by sequence-specific oligonucleotide probes. All subjects with anti-LGI1 or anti-NMDAR encephalitis and the two control groups were originated from the general Korean population.

Statistical Analyses

Fisher's exact test was used to compare the frequencies of the HLA alleles or haplotypes between the autoimmune encephalitis patients and the control groups. An HLA haplotype is a series of HLA alleles by chromosome. The frequency of an allele or a haplotype in this study indicates a carrier frequency, unless specified otherwise. The degrees of association between the HLA data and diseases were expressed as the odds ratio (OR) and 95% confidence interval (CI). For allelic and haplotype comparisons, we used Bonferroni's method for correction for multiple comparisons. The *p* values determined by Fisher's exact test were corrected by multiplying the values times the total number of the detected alleles for each locus: 24 for the HLA-A, 44 for the HLA-B, 22 for the HLA-C, 33 for the HLA-DRB1, and 15 for the HLA-DQB1 alleles. Only the corrected *p* values under 0.05 (two-tailed) were considered statistically significant. In control groups, the presence of the Hardy-Weinberg

equilibrium was determined and haplotypes were estimated using Arlequin software version 3.5.2.2.[29] The linkage disequilibrium value (LD) between two alleles, for example, A with allele frequency P_A and B with allele frequency P_B, was calculated with the expression $LD = P_{AB} - P_A \times P_B$, where P_{AB} is the estimated haplotype frequency of A–B. The relative linkage disequilibrium (RLD) was defined as the ratio of the LD to the possible maximum of LD when $LD > 0$.[30] Thus, RLD values in control groups were calculated with the formula $RLD = LD/\min\{P_A \times (1 - P_B), (1 - P_A) \times P_B\}$, where 'min{}' function indicates a minimum value in the bracket. The statistical analyses were conducted using the SPSS software version 21.0 (SPSS, Chicago, IL, U.S.A.).

HLA Peptide Binding Prediction

We utilized NetMHC 4.0[31] for HLA class I peptide binding prediction, and ProPred[32] and NetMHCII 2.2[33] for HLA class II; these are among the most accurate tools for predicting major histocompatibility complex class I and II peptide binding.[34-36] ProPred and the two NetMHC servers use different algorithms with quantitative matrices and artificial neural networks, respectively. The LGI1 protein sequence obtained from UniProt (accession number O95970)[37] was submitted to each server. Fourteen HLA-A, 18 HLA-B, and 10 HLA-C alleles were collected from those overlapping between the total detected alleles in this study and those offered by the NetMHC server; these alleles were then analyzed for the HLA class I binding prediction. Following this, 14 HLA-DR alleles from the ProPred server, and 11 HLA-DR and 6 DQ alleles from the NetMHCII server were compared to determine the HLA class II binding prediction.

In silico Docking

We performed computational docking to describe the binding of DRB1*07:01 and the LGI1

segment predicted by the above method. Because the crystallographic structure of DRB1*07:01 has not been experimentally determined, the heterodimer structure including DRB1*07:01 was created by homology modeling with Swiss-Model[38] and UCSF Chimera[39] from the template structure of HLA-DRB1*01:01 (Protein Data Bank code 3PDO).[40] We predicted the tertiary structure of the LGI1 segment with the PEPstrMOD server.[41] AutoDock Tools 1.5.6rc3[42] was then used to add hydrogens, assign Gasteiger charges and specify rotatable bonds to the proteins. The docking of the LGI1 segment into DRB1*07:01 was performed with the AutoDock Vina software[43] with the docking grid encompassing the entire peptide-binding cleft and the option 'number of torsions' set to zero.[44]

RESULTS

HLA Genotyping of Autoimmune Encephalitis Patients

We performed the HLA genotyping of 11 patients with anti-LGI1 encephalitis and 17 with anti-NMDAR encephalitis. The clinical characteristics of the patients and distribution of HLA alleles are available in Table 1 and Supplementary Tables 1 and 2.

Unique HLA Subtypes in Anti-LGI1 Encephalitis

Most notably, we found that anti-LGI1 encephalitis was associated with unique HLA subtypes (Tables 2 and 3 and Supplementary Table 3). Ten of the 11 patients (91%) with anti-LGI1 encephalitis had the DRB1*07:01–DQB1*02:02 haplotype. However, the frequencies of the DRB1*07:01–DQB1*02:02 haplotype was 9% in the epilepsy controls and 12% in the healthy controls, indicating a significant association of the haplotype with anti-LGI1 encephalitis (OR = 106.7, 95% CI = 12.9–881.3, $p = 1.3\times10^{-8}$ vs the epilepsy controls; OR = 73.6, 95% CI = 9.3–585.7, $p = 7.6\times10^{-8}$ vs the healthy controls) (Fig 1A). When we analyzed each allele separately, both the DRB1*07:01 and DQB1*02:02 alleles were associated with anti-LGI1 encephalitis (Fig 1B, C). Of the HLA class I subtypes, the frequencies of the B*44:03 and C*07:06 alleles were higher in the anti-LGI1 encephalitis than in the epilepsy and healthy control groups. The B*44:03 allele was found in 8 of the 11 patients (OR = 21.7, 95% CI = 5.4–87.6, $p = 3.4\times10^{-4}$ vs the epilepsy controls; OR = 13.9, 95% CI = 3.6–53.6, $p = 2.8\times10^{-3}$ vs the healthy controls) with anti-LGI1 encephalitis, and C*07:06 was found in 7 of the patients (OR = 28.9, 95% CI = 7.4–112.5, $p = 6.4\times10^{-5}$ vs the epilepsy controls; OR = 26.5, 95% CI = 7.4–95.7, $p = 4.3\times10^{-5}$ vs the healthy controls) (Fig 1D, E). The relationships between the significant HLA subtypes and anti-LGI1 encephalitis are illustrated in Fig 2. In short, the DRB1*07:01–DQB1*02:02 haplotype of HLA class II represented the strongest susceptibility locus for anti-LGI1 encephalitis, and the B*44:03 and C*07:06 alleles of HLA

class I also showed significant association with the disease.

Lack of Susceptibility Locus in HLA for Anti-NMDAR Encephalitis

Further, the anti-NMDAR encephalitis group yielded no specific association with any HLA alleles (Supplementary Table 4). Although the A*02:06 and B*40:06 alleles showed high frequencies in anti-NMDA encephalitis, the differences were not statistically significant (Tables 2 and 3). In addition, the high frequency of the DRB1*07:01–DQB1*02:02 haplotype in anti-LGI1 encephalitis was not observed in anti-NMDAR encephalitis (only one of 17 patients). C*07:06 and B*44:03 were detected in one and two anti-NMDAR encephalitis patients, respectively.

HLA–LGI1 Binding Prediction and Computational Docking

The association of the HLA subtypes with anti-LGI1 encephalitis led us to prove it in established HLA peptide binding prediction algorithms. Strikingly, algorithms using both quantitative matrices and artificial neural networks for HLA class II anticipated that the DRB1*07:01 would have the closest affinity with the LGI1 sequence over all of the available HLA class II alleles. When predicted by an algorithm using quantitative matrices (ProPred),[32] DRB1*07:01 achieved the highest score (9.4) of the 14 HLA-DR alleles, and the target sequence was 'FLFTPSLQL', which is at the 87th amino acid position from the LGI1 protein N-terminus. When it was predicted by an algorithm using artificial neural networks (NetMHCII),[33] DRB1*07:01 had the highest affinity (3.7 nM) with the same core sequence FLFTPSLQL of the available HLA-DR and HLA-DQ alleles (though DQB1*02:02 was not included). Therefore, the sequence FLFTPSLQL, which is part of the leucine-rich repeat (LRR) domain of the LGI1 protein, possesses a high probability to be a ligand of DRB1*07:01. In the HLA class I peptide binding prediction using artificial neural networks

(NetMHC)[31], A*31:01 showed the highest predicted affinity, at 2.4 nM, where a lower value signifies higher affinity. Although direct comparison of binding affinity between HLA class I and II alleles is not reasonable, the HLA class I binding results revealed that none of the other 13 HLA-A, 18 HLA-B, and 10 HLA-C alleles except for A*31:01 had higher affinity than 3.7 nM, which was found in DRB1*07:01. The predicted affinity of B*44:03 with the LGI1 protein was 145.32 nM, while a prediction for C*07:06 was not available on the prediction server.

From this view, we next attempted to perform *in silico* docking of the ligand into DRB1*07:01. The computational docking program calculated that the sequence FLFTPSLQL is docked on the heterodimer consisting of DRB1*07:01 and DRA1*01:01, with a docking score (ΔG) of -12.9 kcal/mol (Fig 3).

DISCUSSION

Here, we identified strong evidence of an association between anti-LGI1 encephalitis and the HLA subtypes. This result suggests a unique pathogenesis of anti-LGI1 encephalitis that is different from anti-NMDAR encephalitis. It is likely that the majority of anti-LGI1 encephalitis develops only in limited populations with specific HLA subtypes. In addition, further studies on the epitope of LGI1 might reveal whether or not specific antigens that share the epitope structure are capable of provoking an initial immune response.

From the results, we found plenty of alleles that represented a major proportion of the patients with anti-LGI1 encephalitis. In fact, these alleles are genetically related in the general Korean population by linkage disequilibrium, which means that alleles at different loci are conserved during recombination, and this is largely due to their vicinity. Consequently, they appear simultaneously more often than expected in random cases. Specifically, the DRB1*07:01–DQB1*02:02 haplotype has an RLD value of 1.00 both in epilepsy and healthy controls,[26,27] which implies that all individuals with DQB1*02:02 also have DRB1*07:01. This relationship was also observed in the anti-LGI1 encephalitis patients in the present study. RLD values of the C*07:06–B*44:03 haplotype were 1.00 in epilepsy controls and 0.85 in healthy controls, while the values for the B*44:03–DRB1*07:01 haplotype were 0.49 and 0.38, respectively.[26,28] These alleles also showed similar closeness in anti-LGI1 encephalitis. Previous studies investigating the HLA susceptibility of autoimmune disease encountered a similar problem of multiple HLA determinants connected by linkage disequilibrium, and the researchers struggled to identify the causative HLA factor that was truly responsible for the disease using statistical methods or genome-wide association analyses.[44-46] Due to the small number of patients and high collinearity between HLA subtypes in this study, it is difficult to assess independent relationships of HLA factors with the disease. Among the HLA subtypes that were shown to be significant in this study,

however, we suggest that HLA class II may be a more susceptible factor in anti-LGI1 encephalitis. HLA class II genes are usually related to immune-mediated conditions characterized by autoantibodies, such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes, and celiac disease; in contrast, HLA class I genes are associated with diseases that do not feature autoantibodies, including ankylosing spondylitis and Behcet's disease.[13,47] As anti-LGI1 encephalitis is an autoantibody-related disease,[4] HLA-DRB1 or DQB1 has a greater chance of being a causative gene.

Whereas anti-LGI1 is associated with unique HLA subtypes, anti-NMDAR encephalitis is not. The HLA distribution in anti-LGI1 encephalitis was largely homogenous, as characterized by the DRB1*07:01–DQB1*02:02 haplotype in 10 of the 11 patients and the C*07:06–B*44:03–DRB1*07:01–DQB1*02:02 haplotype in seven patients (Fig 1F). Moreover, two patients (no. 3 and 4) had exactly the same alleles (Supplementary Table 2), which correspond to two conserved haplotypes of HLA-A*33:03–C*07:06–B*44:03–DRB1*07:01–DQB1*02:02 (haplotype frequency of 2.99% in Korean general population) and HLA-A*11:01–C*04:01–B*15:01–DRB1*04:06–DQB1*03:02 (haplotype frequency of 1.24%).[26-28] There is approximately a 0.074% (approximately 38,000 people in South Korea) probability, which is not impossible, for any Korean to have these two haplotypes randomly by simple calculation. By contrast, anti-NMDAR encephalitis revealed an indistinct and heterogeneous pattern of HLA genotypes. However, it is still possible that anti-NMDAR encephalitis might be associated with minor or other HLA loci or with non-HLA genes if anti-NMDAR encephalitis has a genetic origin. In fact, one case report demonstrated that 3-year-old male patients with anti-NMDAR encephalitis had a microdeletion at the short arm of chromosome 6, including HLA-DPB1 and HLA-DPB2, which supported the hypothesis that anti-NMDAR encephalitis might have susceptibility to minor or other HLA loci.[48] However, there is much evidence that anti-NMDAR encephalitis may be associated with nongenetic

factors; approximately 38% of all anti-NMDAR encephalitis cases are associated with tumors,[6] and herpes simplex virus-1 encephalitis can trigger anti-NMDAR encephalitis.[11,12]

The present study focused on the LRR domain of the LGI1 protein, which may contain the epitope for the antibody–antigen interaction of anti-LGI1 encephalitis, using the bioinformatics technique. Anti-LGI1 antibodies have been demonstrated to inhibit LGI1–ADAM22 interaction and to induce the reduction of AMPA receptor clusters.[10] LGI1 protein consists of the LRR and EPTP domains, and the EPTP domain mediates binding of the LGI1 protein to ADAM22 protein. Since the LRR domain is frequently involved in the formation of protein–protein interactions,[49] it can be proposed that the LRR domain also plays a role in LGI1–ADAM22 interaction. A previous study using cell-based binding assay showed that autoantibodies from anti-LGI1 encephalitis patients bound to both LRR and EPTP domains, which indicates that their epitopes are distributed to both domains of LGI1.[10] Focal loci in the LGI1 protein that participate in the antibody–antigen interaction as epitopes may be revealed in the future studies.

In summary, our study investigated the genetic predisposition of autoimmune encephalitis in adult patients and found that the C*07:06–B*44:03–DRB1*07:01–DQB1*02:02 allele(s) or haplotype is associated with anti-LGI1 encephalitis, but anti-NMDAR encephalitis has no susceptibility locus in HLA. Further studies in a larger number of patients and various populations are required to confirm these results because HLA alleles vary among diverse ethnic groups. Elaborate case-control studies using same sequence-based method are required since the healthy controls were genotyped by the method of low-resolution which contains a potential batch effect, although we used the epilepsy controls genotyped by the same method with the disease group. Additionally, a molecular-based assay or high-density SNP–based mapping approach for HLA genes is beneficial to identify the precise loci and to elucidate the underlying mechanism.

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Author contributions

T.-J.K., S.-T.L., J.M., K.-I.P., K.-H.J., K.-Y.J., M.K., S.K.L., and K.C. contributed to study concept and design. All authors contributed to data acquisition and analysis. T.-J.K., S.-T.L., and K.C. drafted the manuscript.

Potential Conflicts of interest

T.-J.K., S.-T.L., K.-H.J., M.K., S.K.L., and K.C. have a patent pending on the use of HLA typing in anti-LGI1 encephalitis.

List of Abbreviations: Anti-LGI1, anti-leucine-rich glioma-inactivated 1; anti-NMDAR, anti-N-methyl-D-aspartate receptor; HLA, human leukocyte antigen; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LD, linkage disequilibrium value; RLD, relative linkage disequilibrium

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FIGURE LEGENDS

Figure 1: Carrier frequencies of significant alleles and haplotypes in autoimmune encephalitis (anti-LGI1 and anti-NMDAR encephalitis) and control groups (epilepsy controls and healthy controls). We compared carrier frequencies of (A) DRB1*07:01–DQB1*02:02, (B) DRB1*07:01, (C) DQB1*02:02, (D) B*44:03, (E) C*07:06 and (F) C*07:06–B*44:03–DRB1*07:01–DQB1*02:02 between the anti-LGI1 encephalitis versus control groups. ** p values of less than 0.001. * p values of less than 0.05.

Figure 2: Visualization of significant HLA alleles in anti-LGI encephalitis patients. Bold solid lines between DQB1*02:02 and DRB1*07:01 alleles represent absolute linkage disequilibrium in healthy controls (relative linkage disequilibrium (RLD) value = 1.00) and dotted lines between DRB1*07:01 and B*44:03 mean moderate linkage disequilibrium in healthy controls (RLD value = 0.38). There is high degree of linkage disequilibrium between C*07:06 and B*44:03 with RLD value = 0.85 in healthy controls. HLA subtypes are listed in order of chromosomal location.

Figure 3: Computational docking of LGI segment FLFTPSLQL to HLA-DRB1*07:01 heterodimer. (A) The *in silico* docking runs resulted in the placement of the LGI1 segment within the peptide-binding groove between HLA-DRB1*07:01 and HLA-DRA1 with docking scores (ΔG) of -12.9 kcal/mol. Mesh in the HLA surface indicates close contact between atoms with the LGI1 protein segment. (B) Ribbon structure of ligand-binding domains.

TABLES

Table 1. Summarized clinical features of the enrolled patients

		Anti-LGI1 encephalitis	Anti-NMDAR encephalitis
Number of patients		11	17
Age, median (range)		64 (35–73)	25 (17–66)
Sex, female		5 (45%)	11 (65%)
Symptoms or signs	Seizure	8 (73%)	8 (47%)
	FBDS	6 (55%)	0
	Hyponatremia	4 (36%)	0
	Memory dysfunction	8 (73%)	3 (18%)
	Confusion	9 (82%)	15 (88%)
	Psychiatric symptoms	4 (36%)	13 (76%)
	Dyskinesia/dystonia	0	11 (65%)
	Autonomic instability	0	4 (24%)
CSF*	Pleocytosis	1 (11%)	10 (59%)
	Protein increase	2 (22%)	3 (18%)
Brain MRI	Limbic T2 change	7 (64%)	1 (6%)
	Other abnormalities	0	5 (29%)
Tumor		0	4 (24%)
Favorable outcome, mRS ≤ 1		7 (64%)	9 (53%)

- Data are expressed as the number of relevant patients and (percentage in available patients), unless specified otherwise. Detailed characteristics are described in Supplementary Tables 1.

- Abbreviation: anti-LGI1 = anti-leucine-rich glioma-inactivated 1; anti-NMDAR = anti-N-methyl-D-aspartate receptor; FBDS = faciobrachial dystonic seizures; CSF = cerebrospinal fluid; MRI = brain magnetic resonance imaging; mRS = modified Rankin Scale.

* CSF pleocytosis means white blood cell count ≥ 5 /μL, and CSF protein increase means protein ≥ 45 mg/dL.

Table 2. Carrier frequencies of selected alleles and haplotypes in autoimmune encephalitis patients as well as epilepsy controls and healthy controls

HLA allele or haplotype	Autoimmune encephalitis	Epilepsy controls	Healthy controls
Anti-LGI1 encephalitis			
DRB1*07:01	10/11 (91%)	22/210 (10%)	64/485 (13%)
DQB1*02:02	10/11 (91%)	18/210 (9%)	58/485 (12%)
B*44:03	8/11 (73%)	23/210 (11%)	78/485 (16%)
C*07:06	7/11 (64%)	12/210 (6%)	30/485 (6%)
A*33:03	7/11 (64%)	56/210 (27%)	140/485 (29%)
A*30:01	3/11 (27%)	5/210 (2%)	31/485 (6%)
A*31:01	3/11 (27%)	20/210 (10%)	50/485 (10%)
B*13:02	3/11 (27%)	5/210 (2%)	32/485 (7%)
Haplotype #1*	10/11 (91%)	18/210 (9%)	58/485 (12%)
Haplotype #2*	7/11 (64%)	12/210 (6%)	28/485 (6%)
Haplotype #3*	7/11 (64%)	10/210 (5%)	27/485 (6%)
Anti-NMDAR encephalitis			
A*02:06	7/17 (41%)	27/210 (13%)	68/485 (14%)
B*40:06	4/17 (24%)	17/210 (8%)	37/485 (8%)

- Data are expressed as the number of patients and (percentage)

- Abbreviation: HLA = human leukocyte antigen; anti-LGI1 = anti-leucine-rich glioma-inactivated 1; anti-NMDAR = anti-N-methyl-D-aspartate receptor.

* Haplotype #1 = DRB1*07:01–DQB1*02:02; Haplotype #2 = C*07:06–B*44:03; Haplotype #3 = C*07:06–B*44:03–DRB1*07:01–DQB1*02:02

Table 3. Statistical analysis of selected alleles and haplotypes in autoimmune encephalitis patients versus epilepsy controls and healthy controls

HLA allele or haplotype	AE versus epilepsy controls		AE versus healthy controls	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Anti-LGI1 encephalitis				
DRB1*07:01	85.5 (10.4–699.6)	**3.4×10^{-7}**	65.8 (8.3–522.5)	**1.0×10^{-6}**
DQB1*02:02	106.7 (12.9–881.3)	**3.2×10^{-8}**	73.6 (9.3–585.7)	**1.9×10^{-7}**
B*44:03	21.7 (5.4–87.6)	**3.4×10^{-4}**	13.9 (3.6–53.6)	**2.8×10^{-3}**
C*07:06	28.9 (7.4–112.5)	**6.4×10^{-5}**	26.5 (7.4–95.7)	**4.3×10^{-5}**
A*33:03	4.8 (1.4–17.1)	0.33	4.3 (1.2–15.0)	0.46
A*30:01	15.4 (3.1–75.9)	0.11	5.5 (1.4–21.7)	0.80
A*31:01	3.6 (0.9–14.5)	> 0.99	3.3 (0.8–12.7)	> 0.99
B*13:02	15.4 (3.1–75.9)	0.20	5.3 (1.3–21.0)	> 0.99
Haplotype #1*	106.7 (12.9–881.3)	**1.3×10^{-8}**	73.6 (9.3–585.7)	**7.6×10^{-8}**
Haplotype #2*	28.9 (7.4–112.5)	**1.8×10^{-5}**	28.6 (7.9–103.4)	**7.7×10^{-6}**
Haplotype #3*	35.0 (8.8–139.5)	**7.0×10^{-6}**	29.7 (8.2–107.7)	**6.2×10^{-6}**
Anti-NMDAR encephalitis				
A*02:06	4.7 (1.7–13.5)	0.14	4.3 (1.6–11.7)	0.17
B*40:06	3.5 (1.0–11.9)	> 0.99	3.7 (1.2–12.0)	> 0.99

- Abbreviations: HLA = human leukocyte antigen; AE = autoimmune encephalitis; OR = odds ratio; CI = confidence interval; anti-LGI1 = anti-leucine-rich glioma-inactivated 1; anti-

NMDAR = anti-N-methyl-D-aspartate receptor.

- Bold text indicates a statistically significant difference.

- The *p* values are the results of correction using Bonferroni's method for multiple comparisons. For the correction, *p* values were multiplied by the number of detected alleles for each HLA locus.

- For haplotype comparisons, the *p* values were corrected by a factor 6, considering four combinations and two subgroups.

* Haplotype #1 = DRB1*07:01–DQB1*02:02; Haplotype #2 = C*07:06–B*44:03; Haplotype #3 = C*07:06–B*44:03–DRB1*07:01–DQB1*02:02

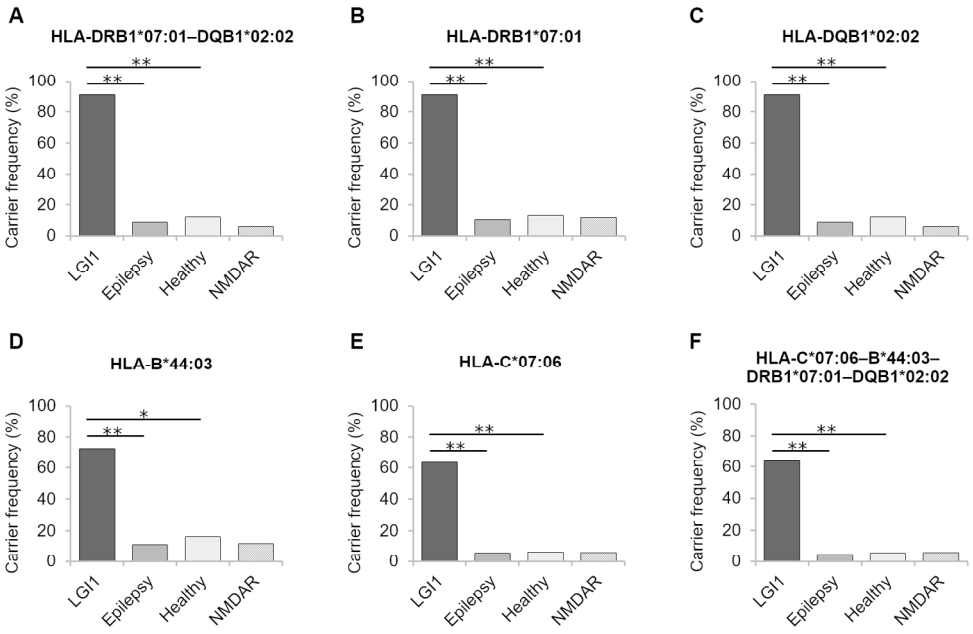

Figure 1: Carrier frequencies of significant alleles and haplotypes in autoimmune encephalitis (anti-LGI1 and anti-NMDAR encephalitis) and control groups (epilepsy controls and healthy controls). We compared carrier frequencies of (A) DRB1*07:01–DQB1*02:02, (B) DRB1*07:01, (C) DQB1*02:02, (D) B*44:03, (E) C*07:06 and (F) C*07:06–B*44:03–DRB1*07:01–DQB1*02:02 between the anti-LGI1 encephalitis versus control groups. ** p values of less than 0.001. * p values of less than 0.05.
Fig 1A
160x105mm (300 x 300 DPI)

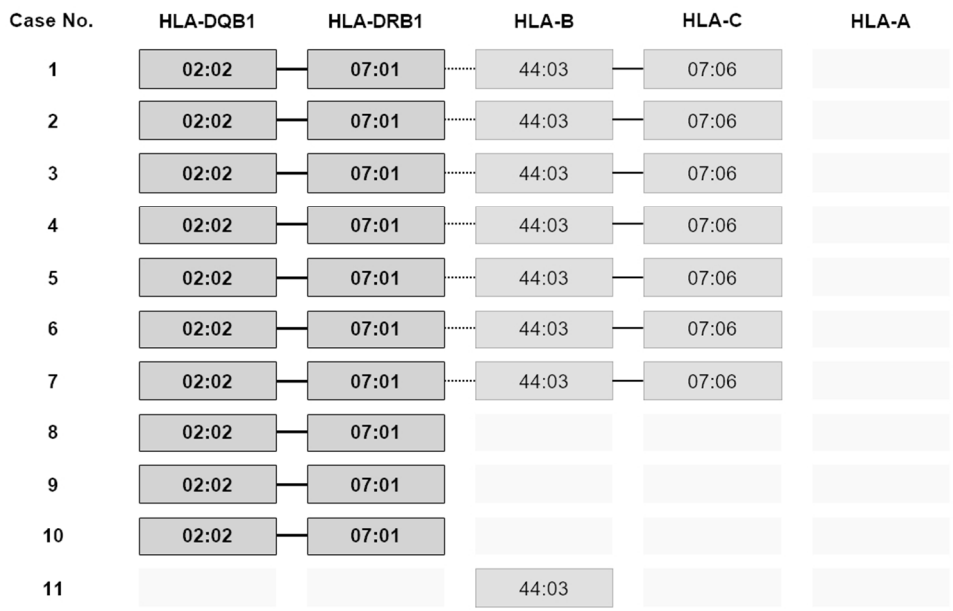

Figure 2: Visualization of significant HLA alleles in anti-LGI encephalitis patients. Bold solid lines between DQB1*02:02 and DRB1*07:01 alleles represent absolute linkage disequilibrium in healthy controls (relative linkage disequilibrium (RLD) value = 1.00) and dotted lines between DRB1*07:01 and B*44:03 mean moderate linkage disequilibrium in healthy controls (RLD value = 0.38). There is high degree of linkage disequilibrium between C*07:06 and B*44:03 with RLD value = 0.85 in healthy controls. HLA subtypes are listed in order of chromosomal location.

Fig 2
92x59mm (300 x 300 DPI)

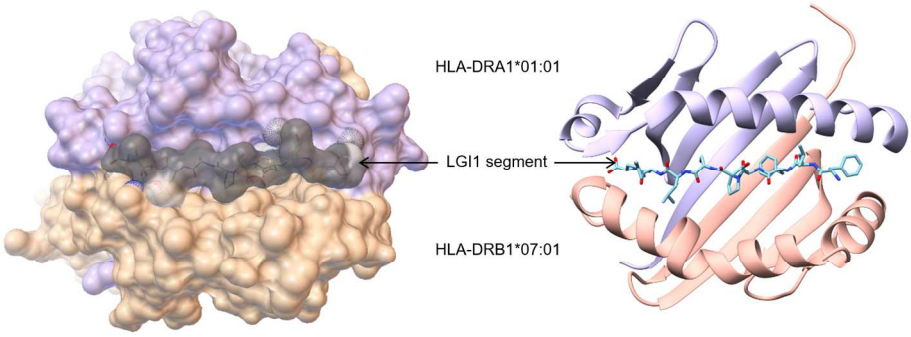

Figure 3: Computational docking of LGI segment FLFTPSLQL to HLA-DRB1*07:01 heterodimer. (A) The in silico docking runs resulted in the placement of the LGI1 segment within the peptide-binding groove between HLA-DRB1*07:01 and HLA-DRA1 with docking scores (ΔG) of -12.9 kcal/mol. Mesh in the HLA surface indicates close contact between atoms with the LGI1 protein segment. (B) Ribbon structure of ligand-binding domains.
Fig 3
170x62mm (300 x 300 DPI)

SUPPLEMENTARY TABLES

Supplementary Table 1. Clinical manifestations of the enrolled patients

Patient, Sex/Age	Symptoms, signs and clinical features	CSF	MRI	Outcome: mRS worst → final (duration of follow-up)
Anti-LGI1 encephalitis				
1, M/61	FBDS, seizure, confusion	Normal	T2 HSI in the left mTL	3 → 1 (28 mon)
2, F/73	FBDS, seizure, hyponatremia, confusion, abnormal behavior	Normal	Normal	4 → 4* (1 mon)
3, F/48	FBDS, seizure, memory impairment, confusion, nausea	Normal	Parenchymal swelling and T2 HSI at bilateral mTL	3 → 2 (49 mon)
4, F/73	Seizure, memory impairment, personality change, confusion, abnormal behavior	Protein 84	Normal	4 → 2 (2 mon)
5, M/68	Seizure, hyponatremia, memory impairment, confusion, somnolence	Normal	bilateral hippocampal HSI	2 → 1 (13 mon)
6, M/44	Seizure, memory impairment, confusion	Normal	Normal	2 → 1 (1 mon)
7, F/64	FBDS, hyponatremia, memory impairment	Not done	Normal	2 → 0 (24 mon)
8, F/73	FBDS, memory impairment, confusion	WBC 5	T2 HSI in the bilateral mTL	3 → 0 (37 mon)
9, M/64	Seizure, confusion, abnormal behavior	Normal	T2 HSI in left mTL	2 → 1 (36 mon)
10, M/69	Hyponatremia, memory impairment, confusion, abnormal behavior, visual hallucination, somnolence, insomnia	Protein 55	bilateral hippocampal HSI	3 → 0 (11 mon)
11, M/35	FBDS, seizure, memory impairment, psychosis, auditory hallucination	Not done	T2 HSI with atrophic change in left hippocampus	4 → 2 (8 mon)
Anti-NMDAR encephalitis				
12, F/28	Orofacial dyskinesia, autonomic instability, auditory and visual hallucination, insomnia, meningeal irritation symptoms, fever, ovarian teratoma	WBC 59	No significant finding (empty sella)	5 → 4 (16 mon)**
13, F/17	Orofacial and limb dyskinesia, autonomic instability, psychosis, confusion, abnormal behavior, ovarian teratoma	WBC 58	Leptomeningeal enhancement	5 → 3 (6 mon)**
14, F/18	Seizure, confusion, abnormal behavior, ovarian teratoma	Normal	Leptomeningeal enhancement	4 → 0 (14 mon)
15, F/25	Orofacial dyskinesia, dystonia, autonomic instability, confusion, abnormal behavior	WBC 20	Normal	5 → 2 (15 mon)
16, M/29	Seizure, psychosis, confusion, mood change, dystonia, meningeal irritation symptoms	Protein 56	Normal	5 → 2 (21 mon)
17, M/44	Dyskinesia, seizure, confusion, personality change	Normal	Normal	5 → 2 (15 mon)
18, M/24	Orofacial and limb dyskinesia, autonomic dysfunction, hypoventilation, catatonia, confusion,	Normal	Normal	5 → 0 (43 mon)

	abnormal behavior			
19, F/23	Orofacial dyskinesia psychosis, catatonia, confusion, abnormal behavior	Normal	Normal	5 → 0 (10 mon)
20, F/19	Dystonia, catatonia, seizure, psychosis, confusion, abnormal behavior	WBC 6, Protein 49	Normal	4 → 3 (19 mon)
21, F/27	Confusion, memory impairment, language disturbance, somnolence	WBC 24	Normal	4 → 2 (2 mon)
22, M/23	Catatonia, seizure, psychosis, confusion, meningeal irritation symptoms	WBC 9	T2 HSI along the sulci at right cerebral hemisphere	4 → 1 (35 mon)
23, F/22	Limb dyskinesia, psychosis, seizure, confusion, behavior change	WBC 95	Normal	3 → 2 (8 mon)
24, F/21	Catatonia, seizure, confusion, ovarian cystic and fibrous mass	WBC 6	T2 HSI lesions, bilateral (Lt>Rt) insula, hippocampi and anterior temporal lobes	3 → 1 (2 mon)
25, F/28	Orofacial dyskinesia, confusion, abnormal behavior, visual hallucination, depression, somnolence, meningeal irritation symptoms	Normal	Normal	3 → 1 (1 mon)
26, M/66	Psychosis, confusion, memory impairment, meningeal irritation symptoms, fever	WBC 23, Protein 64	T2 HSI of bilateral caudate nucleus	2 → 0 (97 mon)
27, M/45	Psychosis, seizure, confusion, memory impairment, abnormal movement, auditory hallucination, meningeal irritation symptoms	WBC 24	Normal	1 → 0 (62 mon)
28, F/33	Dystonia, paraphasia, meningeal irritation symptoms	Normal	Normal	1 → 0 (1 mon)

- Abbreviation: CSF, cerebrospinal fluid; MRI, brain magnetic resonance imaging; mRS, modified Rankin Scale; M, male; F, female; FBDS, faciobrachial dystonic seizures; HSI, high signal intensity; mTL, medial temporal lobe; WBC, white blood cell; mon, month(s)

- All patients had no symptoms (mRS = 0) in premorbid state.

- CSF units: WBC in /μL and Protein in mg/dL

* Due to the previous rib fracture

** Being admitted in hospital from onset to now

Supplementary Table 2. HLA genotypes of the patients

Patient no.	HLA-A	HLA-C	HLA-B	HLA-DRB1	HLA-DQB1
Anti-LGI1 encephalitis					
1	30:01/33:03	06:02/**07:06**	13:02/**44:03**	**07:01**/**07:01**	**02:02**/**02:02**
2	33:03/33:03	03:02/**07:06**	**44:03**/58:01	03:01/**07:01**	02:01/**02:02**
3	11:01/33:03	04:01/**07:06**	15:01/**44:03**	04:06/**07:01**	**02:02**/03:02
4	11:01/33:03	04:01/**07:06**	15:01/**44:03**	04:06/**07:01**	**02:02**/03:02
5	24:02/33:03	**07:06**/07:02	38:02/**44:03**	**07:01**/08:03	**02:02**/03:01
6	26:02/33:03	03:04/**07:06**	**44:03**/48:01	**07:01**/09:01	**02:02**/03:03
7	26:01/31:01	**07:06**/08:01	15:18/**44:03**	**07:01**/12:01	**02:02**/03:02
8	30:01/31:01	03:03/06:02	13:02/35:01	**07:01**/09:01	**02:02**/03:03
9	24:02/30:01	06:02/15:02	13:02/40:06	**07:01**/09:01	**02:02**/03:03
10	02:07/31:01	01:02/08:01	40:06/46:01	**07:01**/09:01	**02:02**/03:03
11	02:01/33:03	03:03/14:03	35:01/**44:03**	11:01/13:02	03:01/06:04
Anti-NMDAR encephalitis					
12	01:01/02:01	06:02/08:01	48:01/57:01	04:03/07:01	03:02/03:03
13	02:06/11:01	01:02/04:01	15:01/55:02	04:06/11:01	03:01/03:02
14	02:01/24:02	01:02/14:02	27:05/51:01	01:01/04:10	04:02/05:01
15	02:06/24:02	01:02/07:02	07:02/55:02	01:01/15:01	05:01/06:02
16	02:01/24:02	01:02/08:01	40:06/54:01	08:03/11:06	03:01/06:01
17	11:01/31:01	03:03/14:02	35:01/51:01	04:05/16:02	03:02/05:02
18	11:01/31:01	07:02/07:02	38:02/40:01	11:01/15:02	03:01/05:01
19	26:01/31:01	01:02/14:02	51:01/54:01	14:05/15:01	05:03/06:02
20	02:06/26:01	03:04/08:03	40:06/48:01	04:03/09:01	03:02/03:03
21	11:01/31:01	01:02/03:04	40:02/59:01	04:05/15:01	04:01/06:02
22	02:01/33:03	08:01/14:03	40:06/44:03	04:10/08:03	04:02/06:01
23	02:06/24:02	03:03/03:04	35:01/40:02	14:01/15:01	05:03/06:02
24	30:01/33:03	06:02/07:06	13:02/44:03	07:01/13:01	02:02/06:03
25	02:01/02:06	01:02/03:02	27:05/58:01	01:01/13:02	05:01/06:09
26	26:02/33:03	03:02/03:03	15:01/58:01	13:02/14:06	03:01/06:09
27	02:06/26:01	03:03/08:01	35:01/40:06	09:01/12:01	03:01/03:03
28	02:01/02:06	01:02/07:04	15:18/54:01	04:05/04:06	03:02/04:01

- Alleles with bold characters: $p < 0.05$

Supplementary Table 3. Distribution of all the alleles in anti-LGI1 encephalitis patients versus epilepsy and healthy controls

HLA allele	Phenotype frequency			Statistical analysis					
	Anti-LGI1 encephalitis (N=11)	Epilepsy controls (N=210)	Healthy controls (N=485)	Anti-LGI1 encephalitis versus epilepsy controls			Anti-LGI1 encephalitis versus healthy controls		
				OR (95% CI)	*p_uc**	*p*	OR (95% CI)	*p_uc**	*p*
A*02:01	1	69	145	0.2 (0.0–1.6)	0.18	> 0.99	0.2 (0.0–1.8)	0.19	> 0.99
A*02:07	1	24	29	0.8 (0.1–6.3)	1.00	> 0.99	1.6 (0.2–12.7)	0.50	> 0.99
A*11:01	2	40	100	0.9 (0.2–4.5)	1.00	> 0.99	0.9 (0.2–4.0)	1.00	> 0.99
A*24:02	2	86	188	0.3 (0.1–1.5)	0.21	> 0.99	0.4 (0.1–1.6)	0.22	> 0.99
A*26:01	1	20	44	1.0 (0.1–7.8)	1.00	> 0.99	1.0 (0.1–8.0)	1.00	> 0.99
A*26:02	1	12	19	1.7 (0.2–14.0)	0.50	> 0.99	2.5 (0.3–20.2)	0.37	> 0.99
A*30:01	3	5	31	15.4 (3.1–75.9)	0.0045	0.11	5.5 (1.4–21.7)	0.033	0.80
A*31:01	3	20	50	3.6 (0.9–14.5)	0.093	> 0.99	3.3 (0.8–12.7)	0.10	> 0.99
A*33:03	7	56	140	4.8 (1.4–17.1)	0.014	0.33	4.3 (1.2–15.0)	0.019	0.46
C*01:02	1	78	161	0.2 (0.0–1.3)	0.10	> 0.99	0.2 (0.0–1.6)	0.11	> 0.99
C*03:02	1	32	71	0.6 (0.1–4.5)	1.00	> 0.99	0.6 (0.1–4.6)	1.00	> 0.99
C*03:03	2	50	110	0.7 (0.1–3.4)	1.00	> 0.99	0.8 (0.2–3.6)	1.00	> 0.99
C*03:04	1	54	62	0.3 (0.0–2.3)	0.30	> 0.99	0.7 (0.1–5.4)	1.00	> 0.99
C*04:01	2	21	62	2.0 (0.4–9.9)	0.32	> 0.99	1.5 (0.3–7.2)	0.64	> 0.99
C*06:02	3	13	46	5.7 (1.3–24.0)	0.036	0.794	3.6 (0.9–14.0)	0.085	> 0.99
C*07:02	1	29	73	0.6 (0.1–5.1)	1.00	> 0.99	0.6 (0.1–4.5)	1.00	> 0.99
C*07:06	**7**	**12**	**30**	**28.9 (7.4–112.5)**	**2.9×10^{-6}**	**6.4×10^{-5}**	**26.5 (7.4–95.7)**	**1.9×10^{-6}**	**4.3×10^{-5}**
C*08:01	2	26	71	1.6 (0.3–7.7)	0.63	> 0.99	1.3 (0.3–6.1)	0.67	> 0.99
C*14:03	1	11	49	1.8 (0.2–15.4)	0.47	> 0.99	0.9 (0.1–7.1)	1.00	> 0.99
C*15:02	1	16	25	1.2 (0.1–10.1)	0.59	> 0.99	1.8 (0.2–14.9)	0.45	> 0.99
B*13:02	3	5	32	15.4 (3.1–75.9)	0.0045	0.20	5.3 (1.3–21.0)	0.036	> 0.99
B*15:01	2	39	93	1.0 (0.2–4.7)	1.00	> 0.99	0.9 (0.2–4.4)	1.00	> 0.99
B*15:18	1	3	9	6.9 (0.7–72.4)	0.19	> 0.99	5.3 (0.6–45.8)	0.20	> 0.99
B*35:01	2	22	53	1.9 (0.4–9.4)	0.34	> 0.99	1.8 (0.4–8.6)	0.35	> 0.99
B*38:02	1	6	11	3.4 (0.4–31.0)	0.30	> 0.99	4.3 (0.5–36.7)	0.24	> 0.99
B*40:06	2	17	37	2.5 (0.5–12.6)	0.24	> 0.99	2.7 (0.6–12.9)	0.21	> 0.99
B*44:03	**8**	**23**	**78**	**21.7 (5.4–87.6)**	**7.7×10^{-6}**	**3.4×10^{-4}**	**13.9 (3.6–53.6)**	**6.4×10^{-5}**	**2.8×10^{-3}**
B*46:01	1	29	43	0.6 (0.1–5.1)	1.00	> 0.99	1.0 (0.1–8.2)	1.00	> 0.99
B*48:01	1	8	33	2.5 (0.3–22.2)	0.37	> 0.99	1.4 (0.2–11.0)	0.55	> 0.99
B*58:01	1	31	59	0.6 (0.1–4.7)	1.00	> 0.99	0.7 (0.1–5.7)	1.00	> 0.99
DRB1*03:01	1	9	28	2.2 (0.3–19.4)	0.41	> 0.99	1.6 (0.2–13.2)	0.49	> 0.99
DRB1*04:06	2	22	39	1.9 (0.4–9.4)	0.34	> 0.99	2.5 (0.5–12.2)	0.23	> 0.99

DRB1*07:01	**10**	**22**	**64**	**85.5 (10.4–699.6)**	**1.0×10^{-8}**	**3.4×10^{-7}**	**65.8 (8.3–522.5)**	**3.1×10^{-8}**	**1.0×10^{-6}**
DRB1*08:03	1	32	75	0.6 (0.1–4.5)	1.00	> 0.99	0.5 (0.1–4.3)	1.00	> 0.99
DRB1*09:01	4	46	86	2.0 (0.6–7.3)	0.27	> 0.99	2.7 (0.8–9.3)	0.12	> 0.99
DRB1*11:01	1	22	43	0.9 (0.1–7.0)	1.00	> 0.99	1.0 (0.1–8.2)	1.00	> 0.99
DRB1*12:01	1	30	32	0.6 (0.1–4.9)	1.00	> 0.99	1.4 (0.2–11.4)	0.53	> 0.99
DRB1*13:02	1	28	83	0.7 (0.1–5.3)	1.00	> 0.99	0.5 (0.1–3.8)	0.70	> 0.99
DQB1*02:01	1	9	28	2.2 (0.3–19.4)	0.41	> 0.99	1.6 (0.2–13.2)	0.49	> 0.99
DQB1*02:02	**10**	**18**	**58**	**106.7 (12.9–881.3)**	**2.1×10^{-9}**	**3.2×10^{-8}**	**73.6 (9.3–585.7)**	**1.3×10^{-8}**	**1.9×10^{-7}**
DQB1*03:01	2	73	121	0.4 (0.1–2.0)	0.34	> 0.99	0.7 (0.1–3.1)	1.00	> 0.99
DQB1*03:02	3	45	97	1.4 (0.4–5.4)	0.71	> 0.99	1.5 (0.4–5.8)	0.47	> 0.99
DQB1*03:03	4	51	104	1.8 (0.5–6.3)	0.47	> 0.99	2.1 (0.6–7.3)	0.27	> 0.99
DQB1*06:04	1	11	49	1.8 (0.2–15.4)	0.47	> 0.99	0.9 (0.1–7.1)	1.00	> 0.99

- Abbreviations: HLA = human leukocyte antigen; OR = odds ratio; CI = confidence interval; anti-LGI1 = anti-leucine-rich glioma-inactivated 1.

- Bold text indicates a statistically significant difference.

- The p values are the results of correction using Bonferroni's method for multiple comparisons. For the correction, p values were multiplied by the number of detected alleles for each HLA locus.

* *p_uc*: uncorrected *p* (before correction with Bonferroni's method)

Supplementary Table 4. Distribution of all the alleles in anti-NMDAR encephalitis patients versus epilepsy and healthy controls

HLA allele	Phenotype frequency			Statistical analysis					
				Anti-NMDAR encephalitis versus epilepsy controls			Anti-NMDAR encephalitis versus healthy controls		
	Anti-NMDAR encephalitis (N=17)	Epilepsy controls (N=210)	Healthy controls (N=485)	OR (95% CI)	*p_uc**	*p*	OR (95% CI)	*p_uc**	*p*
A*01:01	1	9	17	1.4 (0.2–11.7)	0.55	> 0.99	1.7 (0.2–13.7)	0.47	> 0.99
A*02:01	6	69	145	1.1 (0.4–3.1)	0.80	> 0.99	1.3 (0.5–3.5)	0.60	> 0.99
A*02:06	7	24	29	4.7 (1.7–13.5)	0.0059	0.14	4.3 (1.6–11.7)	0.0070	0.17
A*11:01	4	40	100	1.3 (0.4–4.2)	0.75	> 0.99	1.2 (0.4–3.7)	0.76	> 0.99
A*24:02	4	86	188	0.4 (0.1–1.4)	0.20	> 0.99	0.5 (0.2–1.5)	0.31	> 0.99
A*26:01	3	20	44	2.0 (0.5–7.7)	0.39	> 0.99	2.1 (0.6–7.8)	0.21	> 0.99
A*26:02	1	12	19	1.0 (0.1–8.4)	1.00	> 0.99	1.5 (0.2–12.2)	0.50	> 0.99
A*30:01	1	5	31	2.6 (0.3–23.3)	0.37	> 0.99	0.9 (0.1–7.1)	1.00	> 0.99
A*31:01	4	20	50	2.9 (0.9–9.8)	0.089	> 0.99	2.7 (0.8–8.5)	0.099	> 0.99
A*33:03	3	56	140	0.6 (0.2–2.1)	0.57	> 0.99	0.5 (0.1–1.9)	0.42	> 0.99
C*01:02	8	78	161	1.5 (0.6–4.1)	0.44	> 0.99	1.8 (0.7–4.7)	0.30	> 0.99
C*03:02	2	32	71	0.7 (0.2–3.4)	1.00	> 0.99	0.8 (0.2–3.5)	1.00	> 0.99
C*03:03	4	50	110	1.0 (0.3–3.2)	1.00	> 0.99	1.0 (0.3–3.3)	1.00	> 0.99
C*03:04	3	54	62	0.6 (0.2–2.2)	0.57	> 0.99	1.5 (0.4–5.2)	0.47	> 0.99
C*04:01	1	21	62	0.6 (0.1–4.5)	1.00	> 0.99	0.4 (0.1–3.3)	0.71	> 0.99
C*06:02	2	13	46	2.0 (0.4–9.8)	0.31	> 0.99	1.3 (0.3–5.7)	0.67	> 0.99
C*07:02	2	29	73	0.8 (0.2–3.8)	1.00	> 0.99	0.8 (0.2–3.4)	1.00	> 0.99
C*07:04	1	1	5	13.1 (0.8–218.7)	0.14	> 0.99	6.0 (0.7–54.4)	0.19	> 0.99
C*07:06	1	12	30	1.0 (0.1–8.4)	1.00	> 0.99	0.9 (0.1–7.4)	1.00	> 0.99
C*08:01	4	26	71	2.2 (0.7–7.2)	0.25	> 0.99	1.8 (0.6–5.7)	0.30	> 0.99
C*08:03	1	4	6	3.2 (0.3–30.5)	0.32	> 0.99	5.0 (0.6–43.9)	0.22	> 0.99
C*14:02	3	27	61	1.5 (0.4–5.4)	0.47	> 0.99	1.5 (0.4–5.3)	0.47	> 0.99
C*14:03	1	11	49	1.1 (0.1–9.3)	1.00	> 0.99	0.6 (0.1–4.3)	1.00	> 0.99
B*07:02	1	12	34	1.0 (0.1–8.4)	1.00	> 0.99	0.8 (0.1–6.4)	1.00	> 0.99
B*13:02	1	5	32	2.6 (0.3–23.3)	0.38	> 0.99	0.9 (0.1–6.9)	1.00	> 0.99
B*15:01	2	39	93	0.6 (0.1–2.7)	0.74	> 0.99	0.6 (0.1–2.5)	0.75	> 0.99
B*15:18	1	3	9	4.3 (0.4–43.9)	0.30	> 0.99	3.3 (0.4–27.7)	0.29	> 0.99
B*27:05	2	10	23	2.7 (0.5–13.3)	0.22	> 0.99	2.7 (0.6–12.4)	0.21	> 0.99
B*35:01	3	22	53	1.8 (0.5–6.9)	0.41	> 0.99	1.7 (0.5–6.3)	0.42	> 0.99
B*38:02	1	6	11	2.1 (0.2–18.7)	0.42	> 0.99	2.7 (0.3–22.1)	0.34	> 0.99
B*40:01	1	18	38	0.7 (0.1–5.3)	1.00	> 0.99	0.7 (0.1–5.7	1.00	> 0.99

B*40:02	2	27	37	0.9 (0.2–4.2)	1.00	> 0.99	1.6 (0.4–7.3)	0.63	> 0.99
B*40:06	4	17	37	3.5 (1.0–11.9)	0.058	> 0.99	3.7 (1.2–12.0)	0.042	> 0.99
B*44:03	2	23	78	1.1 (0.2–5.0)	1.00	> 0.99	0.7 (0.2–3.1)	1.00	> 0.99
B*48:01	2	8	33	3.4 (0.7–17.3)	0.17	> 0.99	1.8 (0.4–8.3)	0.34	> 0.99
B*51:01	3	41	79	0.9 (0.2–3.2)	1.00	> 0.99	1.1 (0.3–3.9)	0.75	> 0.99
B*54:01	3	25	55	1.6 (0.4–5.9)	0.45	> 0.99	1.7 (0.5–6.0)	0.43	> 0.99
B*55:02	2	4	26	6.9 (1.2–40.6)	0.066	> 0.99	2.4 (0.5–10.8)	0.24	> 0.99
B*57:01	1	1	2	13.1 (0.8–218.7)	0.14	> 0.99	15.1 (1.3–175.2)	0.098	> 0.99
B*58:01	2	31	59	0.8 (0.2–3.5)	1.00	> 0.99	1.0 (0.2–4.3)	1.00	> 0.99
B*59:01	1	7	20	1.8 (0.2–15.7)	0.47	> 0.99	1.5 (0.2–11.5)	0.52	> 0.99
DRB1*01:01	3	21	64	1.9 (0.5–7.3)	0.40	> 0.99	1.4 (0.4–5.0)	0.49	> 0.99
DRB1*04:03	2	14	31	1.9 (0.4–9.0)	0.34	> 0.99	2.0 (0.4–8.9)	0.31	> 0.99
DRB1*04:05	3	30	83	1.3 (0.3–4.7)	0.72	> 0.99	1.0 (0.3–3.7)	1.00	> 0.99
DRB1*04:06	2	22	39	1.1 (0.2–5.3)	0.70	> 0.99	1.5 (0.3–6.9)	0.64	> 0.99
DRB1*04:10	2	5	12	5.5 (1.0–30.6)	0.089	> 0.99	5.3 (1.1–25.6)	0.077	> 0.99
DRB1*07:01	2	22	64	1.1 (0.2–5.3)	0.70	> 0.99	0.9 (0.2–3.9)	1.00	> 0.99
DRB1*08:03	2	32	75	0.7 (0.2–3.4)	1.00	> 0.99	0.7 (0.2–3.3)	1.00	> 0.99
DRB1*09:01	2	46	86	0.5 (0.1–2.2)	0.54	> 0.99	0.6 (0.1–2.8)	0.75	> 0.99
DRB1*11:01	2	22	43	1.1 (0.2–5.3)	0.70	> 0.99	1.4 (0.3–6.2)	0.66	> 0.99
DRB1*11:06	1	0	1	1.1 (0.9–1.2)	0.075	> 0.99	30.3 (1.8–505.6)	0.067	> 0.99
DRB1*12:01	1	30	32	0.4 (0.0–2.9)	0.48	> 0.99	0.9 (0.1–6.9)	1.00	> 0.99
DRB1*13:01	1	4	9	3.2 (0.3–30.5)	0.32	> 0.99	3.3 (0.4–27.7)	0.29	> 0.99
DRB1*13:02	2	28	83	0.9 (0.2–4.0)	1.00	> 0.99	0.6 (0.1–2.9)	0.75	> 0.99
DRB1*14:01	1	10	29	1.3 (0.2–10.4)	0.58	> 0.99	1.0 (0.1–7.7)	1.00	> 0.99
DRB1*14:05	1	19	33	0.6 (0.1–5.0)	1.00	> 0.99	0.9 (0.1–6.7)	1.00	> 0.99
DRB1*14:06	1	4	8	3.2 (0.3–30.5)	0.32	> 0.99	3.7 (0.4–31.6)	0.27	> 0.99
DRB1*15:01	4	26	70	2.2 (0.7–7.2)	0.25	> 0.99	1.8 (0.6–5.8)	0.30	> 0.99
DRB1*15:02	1	14	32	0.9 (0.1–7.1)	1.00	> 0.99	0.9 (0.1–6.9)	1.00	> 0.99
DRB1*16:02	1	4	6	3.2 (0.3–30.5)	0.32	> 0.99	5.0 (0.6–43.9)	0.22	> 0.99
DQB1*02:02	1	18	58	0.7 (0.1–5.3)	1.00	> 0.99	0.5 (0.1–3.5)	0.71	> 0.99
DQB1*03:01	5	73	121	0.8 (0.3–2.3)	0.79	> 0.99	1.3 (0.4–3.6)	0.78	> 0.99
DQB1*03:02	5	45	97	1.5 (0.5–4.6)	0.54	> 0.99	1.7 (0.6–4.8)	0.34	> 0.99
DQB1*03:03	3	51	104	0.7 (0.2–2.4)	0.77	> 0.99	0.8 (0.2–2.8)	1.00	> 0.99
DQB1*04:01	2	30	80	0.8 (0.2–3.7)	1.00	> 0.99	0.7 (0.2–3.0)	1.00	> 0.99
DQB1*04:02	2	13	35	2.0 (0.4–9.8)	0.31	> 0.99	1.7 (0.4–7.8)	0.36	> 0.99
DQB1*05:01	4	31	82	1.8 (0.5–5.8)	0.31	> 0.99	1.5 (0.5–4.8)	0.51	> 0.99
DQB1*05:02	1	14	21	0.9 (0.1–7.1)	1.00	> 0.99	1.4 (0.2–10.9)	0.54	> 0.99
DQB1*05:03	2	24	46	1.0 (0.2–4.8)	1.00	> 0.99	1.3 (0.3–5.7)	0.67	> 0.99

DQB1*06:01	2	40	89	0.6 (0.1–2.6)	0.75	> 0.99	0.6 (0.1–2.6)	0.75	> 0.99
DQB1*06:02	4	23	67	2.5 (0.8–8.3)	0.13	> 0.99	1.9 (0.6–6.1)	0.28	> 0.99
DQB1*06:03	1	4	9	3.2 (0.3–30.5)	0.32	> 0.99	3.3 (0.4–27.7)	0.29	> 0.99
DQB1*06:09	2	17	36	1.5 (0.3–7.2)	0.64	> 0.99	1.7 (0.4–7.6)	0.38	> 0.99

- Abbreviations: HLA = human leukocyte antigen; OR = odds ratio; CI = confidence interval; anti-NMDAR = anti-N-methyl-D-aspartate receptor.

- The p values are the results of correction using Bonferroni's method for multiple comparisons. For the correction, p values were multiplied by the number of detected alleles for each HLA locus.

* *p_uc*: uncorrected *p* (before correction with Bonferroni's method)