Genetic Predisposition in Anti-LGI1 and Anti-NMDA Receptor Encephalitis

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We performed a genome-wide association study in 1,194 controls and 150 patients with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR, n = 96) or anti-leucine-rich glioma-inactivated1 (anti-LGI1, n = 54) autoimmune encephalitis. Anti-LGI1 encephalitis was highly associated with 27 single-nucleotide polymorphisms (SNPs) in the HLA-II region (leading SNP rs2858870 $p = 1.22 \times 10^{-17}$, OR = 13.66 [7.50–24.87]). Potential associations, below genome-wide significance, were found with rs72961463 close to the doublecortin-like kinase 2 gene (*DCLK2*) and rs62110161 in a cluster of zinc-finger genes. HLA allele imputation identified association of anti-LGI1 encephalitis with HLA-II haplotypes encompassing DRB1*07:01, DQA1*02:01 and DQB1*02:02 ($p < 2.2 \times 10^{-16}$) and anti-NMDAR encephalitis with HLA-I allele B*07:02 ($p = 0.039$). No shared genetic risk factors between encephalitides were identified.

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In many patients with autoimmune encephalitis, which can cause subacute memory dysfunction, psychiatric symptoms, seizures, and loss of consciousness, antibodies against synaptic epitopes can be found in serum and cerebrospinal fluid.

The two most common antigens are the ionotropic glutamate receptor, *N*-methyl-D-asparate receptor (NMDAR), and the secreted, soluble, synaptic protein, leucin-rich glioma-inactivated1 (LGI1), which clusters pre- and postsynaptic receptors.[1] Together, they define the two most common autoimmune encephalitis subtypes, which (1) are more common than any individual viral encephalitis,[2] (2) respond favorably to immunotherapy, and (3) were shown experimentally to be directly caused by autoantibodies.[3] In some patients with anti-NMDAR encephalitis, ectopic expression of the antigen

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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TABLE 1. Cohort Characteristics

	NMDAR-E	LGI1-E	controls
Number	96	54	1,194
%-Female	80.2%	42.6%	45.1%
Mean age (± SD)	30.3 (± 13.3)	62.7 (± 11.0)	54.1 (± 14.3)
Mean AAO (± SD)	29.0 (± 13.3)	62.0 (± 10.9)	NA
Prodromal symptoms	42%	50%	NA
Epileptic seizures	73%	76%	NA
Psychiatric symptoms	92%	57%	NA
Movement disorders	45%	11%	NA
Autonomic dysfunction	39%	12%	NA
Abnormal EEG	75%	78%	NA
Abnormal MRI	57%	74%	NA
CSF Pleocytosis	70%	14%	NA
Oligoclonal bands	70%	31%	NA
Tumor	17% (94% ovarian teratoma)*	2% (one esophageal cancer)	NA
Steroids, ivIG, plasma exchange and tumor resection if applicable	99%	94%	NA
Rituximab, Cyclophosphamide or both	47%	40%	NA
ICU treatment necessary	42%	7%	NA
Time from onset until first treatment in days median (range)	16.5 (1-1638)	17.5 (1-1035)	NA
Last follow up in days from diagnosis median (range)	297 (16-2728)	325 (15-3797)	NA

Descriptive statistics for the three cohorts in this study: healthy controls, anti-NMDAR encephalitis (NMDAR-E) patients, and anti-LGI1 encephalitis (LGI1-E) patients. Control samples are part of the PopGen control cohort, a population-based biobank in northern Germany.[19] SD = standard deviation; AAO = age at onset; NA = not applicable; * = 1 patient with small-cell lung cancer.

in ovarian teratomas is the likely cause. So far, in the majority of patients, no environmental or genetic risk factors have been identified.[4] We sought to elucidate genetic risk factors for these two biomarker-defined, homogeneous subtypes of autoimmune encephalitis.

Patients and Methods

Study Population

Two hundred forty-one patients with NMDAR (n = 166) or LGI1 (n = 75) antibodies were recruited by the German Network for Research on Autoimmune Encephalitis (GENERATE). All contributing scientists are listed in Supplementary Table 1. All participants gave written informed consent. Initial institutional review board approval was given by the ethical advisory board University of Lübeck (reference number: 13-162) and consecutively by 48 other regional ethics advisory boards. One hundred fifty patients with autoimmune encephalitis (anti-NMDAR: 96, anti-LGI1: 54) remained for genome-wide association study (GWAS) analysis. Patients were included if they fulfilled recently published criteria for definite autoimmune anti-NMDAR or anti-LGI1 encephalitis.[5] Detailed clinical characteristics of the study population are provided in Table 1 and Supplementary Table 2.

Genome-Wide Association Analysis

Samples were genotyped with Illumina Infinium Global Screening Array. Thorough quality control procedures were conducted, see Supplementary Table 3. Genotyped single-nucleotide polymorphisms (SNPs) were imputed using Michigan Imputation Server.[6] Tests for marker-disease association

were performed separately for both phenotypes using plink1.9.[7] We used a logistic model and incorporated sex, age, and first four dimensions of a principle component analysis (PCA) as covariates.

Analyzing HLA-Region

We investigated disease associations in the human MHC region, here defined as chr6:29,000,000 to 34,000,000. We imputed four-digit human leukocyte antigen (HLA) alleles with SNP2HLA,[8] based on 6,213 genotyped markers with minor allele frequency (MAF) above 0.025 in our study. We used the T1DGC reference panel.[8]

Association analyses for HLA alleles were conducted with PyHLA,[9] separately for anti-NMDAR and anti-LGI1 encephalitis. An additive, logistic model including sex, age, and first four PCA dimensions was used. p values were adjusted for multiple testing with false discovery rate (FDR) step-up method. Additionally, we tested for interaction between HLA alleles and examined phased haplotypes in individuals.

Results

We conducted a genome-wide association study (GWAS) in 150 patients and 1,194 controls. Sample characteristics are reported in Table 1. We performed logistic regression in both diseases together as well as separately incorporating sex, age, and the first four dimensions of a PCA as covariates. Joint analysis of both diseases degraded association findings of the separate analysis and did not yield any additional significant results.

Genome-wide analysis in anti-NMDAR as well as anti-LGI1 encephalitis showed minimal genomic inflation with λ being 0.9414 and 0.8839, indicating that no significant population stratification was present.

We identified a strong disease association in anti-LGI1 encephalitis patients with the SNP, rs2858870, located in the HLA region (odds ratio [OR] = 13.66 [95% confidence interval {CI} = 7.50–24.87]; $p = 1.22 \times 10^{-17}$; Fig A,B; Table 2A). In close vicinity to rs2858870, another 26 SNPs were associated with comparable significance (ie, $P<1 \times 10^{-16}$). Conditional analyses including any one of the top five SNPs diminished association scores beyond genome-wide significance ($p < 5 \times 10^{-8}$) for all other SNPs. Thus, the strong linkage disequilibrium in this region hindered the identification of a single causal SNP. Two other distinct regions showed association scores just below the genome-wide significance threshold ($p < 5 \times 10^{-8}$) with leading SNPs rs72961463 close to the doublecortin-like kinase 2 gene (*DCLK2*) on chromosome 4 (OR = 13.19 [5.11–34.04]; $p = 9.84 \times 10^{-8}$) and rs62110161 in a cluster zinc-finger of genes on chromosome 19 (OR = 4.11 [2.36–7.15]; $p = 5.87 \times 10^{-7}$; Fig C,D). Annotation of these SNPs with HaploReg v4.1[10] and GTEx[11] reported rs62110161 to be an expression quantitative trait locus (eQTL) associated with genes *ZNF528* and *CTD-3018O17.3* while rs72961463 was no eQTL. In contrast, we could not identify any significantly disease-associated variants for anti-NMDAR encephalitis. Additional analyses in patient subgroups defined by disease onset and presence of tumor also remained inconclusive.

Next, we imputed four-digit HLA alleles with SNP2HLA.[8] We identified 11 HLA alleles associated with anti-LGI1 encephalitis, all of them belonging to the MHCII gene family. The most significant associations were found for HLA-DQA1*02:01 (OR = 13.36 [7.34–24.33]; $p_{adj} = 1.38 \times 10^{-16}$), HLA-DRB1*07:01 (OR = 13.36 [7.34–24.33]; $p_{adj} = 1.61 \times 10^{-16}$), and HLA-DQB1*02:02 (OR = 10.01 [5.74–17.45]; $p_{adj} = 3.76 \times 10^{-15}$). Further associated HLA alleles were DQA1*01:02, DQA1*05:01, DQB1*02:01, DQB1*03:03, DQB1*06:02, DPB1*03:01, DRB1*03:01, and DRB1*15:01 (Table 2B). After adjustment for multiple testing by FDR step-up routine, we also found one significant association for anti-NMDAR encephalitis with MHCI allele HLA-B*07:02 (OR = 2.01 [1.23–3.29]; $p_{adj} = 0.039$). This association was stronger in the patient subgroup with later disease onset (age at onset $\geq$ median of 23.5 years; OR = 2.32 [1.34–4.00]; $p = 0.0175$), but was missing in the subgroup with earlier disease onset (OR = 1.20 [0.32–4.43]; $p_{adj} = 0.84$).

A closer look at individual haplotypes revealed that in anti-LGI1 encephalitis cases, as well as healthy controls and anti-NMDAR encephalitis patients, DRB1*07:01 and DQA1*02:01 always occurred together. This haplotype (H1) was highly associated with anti-LGI1 encephalitis (OR = 7.20 [4.84–10.71]; $p < 2.2 \times 10^{-16}$) and was also recently reported based on selective HLA genotyping in smaller cohorts of Dutch and Korean anti-LGI1 patients.[4,12] We identified two new haplotypes (H2 and H3) associated with anti-LGI1 encephalitis. Haplotype 2 (H2) is composed of DRB1*07:01, DQA1*02:01, and DQB1*02:02, while haplotype 3 (H3) constitutes of DRB1*07:01, DQA1*02:01, and DQB1*03:03 (H2: OR = 6.80 [4.48–10.33], $p < 2.2 \times 10^{-16}$; H3: OR = 3.42 [1.84–6.32], $p = 9.65 \times 10^{-5}$). Because of the complete correlation of DRB1*07:01 and DQA1*02:01 in patients and controls alike, the relative contribution of the alleles could not be determined in this study.

Discussion

This is the first GWAS comparing antibody-defined autoimmune encephalitis subtypes and controls. The main finding is the strong association of anti-LGI1 encephalitis with SNPs rs2858870, and potential associations with rs72961463 and rs62110161, especially

TABLE 2. Identified Associations

A

Phenotype	SNP					Cases			Controls				
	rsID	CHR	BP [GRCh37]	A1	A2	#A1	#A2	MAF	#A1	#A2	MAF	P-Value	OR [95% CI]
LGI-E	**rs72961463**	**4**	**150,935,250**	**A**	**G**	8	100	0.0741	20	2,368	0.0084	9.84E-08	13.19 [5.11-34.04]
LGI-E	**rs2858870**	**6**	**32,572,251**	**C**	**T**	**53**	**55**	**0.4907**	**276**	**2,112**	**0.1156**	**1.22E-17**	**13.66 [7.50-24.87]**
LGI-E	**rs62110161**	**19**	**52,906,348**	**C**	**T**	22	86	0.2037	158	2,230	0.0662	5.87E-07	4.11 [2.36-7.15]

B

Phenotype	HLA Allele	Cases			Controls			P_{adj}-value	OR [95% CI]
		pos	neg	freq	pos	neg	freq		
LGI1-E	**DQA1*02:01**	53	55	0.4907	282	2,106	0.1181	**1.38E-16**	**13.36 [7.34-24.33]**
LGI1-E	**DRB1*07:01**	53	55	0.4907	282	2,106	0.1181	**1.61E-16**	**13.36 [7.34-24.33]**
LGI1-E	**DQB1*02:02**	40	68	0.3704	190	2,198	0.0796	**3.76E-15**	**10.01 [5.74-17.45]**
LGI1-E	**DQB1*03:03**	14	94	0.1296	117	2,271	0.0490	**0.0028**	**3.06 [1.60-5.86]**
LGI1-E	**DQA1*05:01**	11	97	0.1019	605	1,783	0.2534	**0.0052**	**0.37 [0.19-0.69]**
LGI1-E	**DQA1*01:02**	11	97	0.1019	501	1,887	0.2098	**0.0258**	**0.45 [0.24-0.85]**
LGI1-E	**DQB1*02:01**	3	105	0.0278	278	2,110	0.1164	**0.0326**	**0.23 [0.07-0.72]**
LGI1-E	**DPB1*03:01**	3	105	0.0278	271	2,115	0.1136	**0.0391**	**0.22 [0.07-0.69]**
LGI1-E	**DRB1*03:01**	3	105	0.0278	275	2,113	0.1152	**0.0444**	**0.23 [0.07-0.73]**
LGI1-E	**DQB1*06:02**	6	102	0.0556	329	2,059	0.1378	**0.0453**	**0.38 [0.16-0.87]**
LGI1-E	**DRB1*15:01**	6	102	0.0556	336	2,052	0.1407	**0.0467**	**0.37 [0.16-0.86]**
NMDAR-E	**B*07:02+**	34	156	0.1789	309	2,047	0.1312	**0.0390**	**2.01 [1.23-3.29]**
NMDAR-E: earlier onset	**B*07:02+**	13	79	0.1413	309	2,047	0.1312	0.8383	1.20 [0.32-4.43]
NMDAR-E: later onset	**B*07:02+**	21	77	0.2143	309	2,047	0.1312	**0.0175**	**2.32 [1.34-4.00]**

A Applying a logistic model, we tested SNPs for association with disease status in anti-LGIl encephalitis. Association testing included 54 cases and 1,194 controls. Adjustment for sex, age, and population stratification (first four dimensions of a PCA) was performed. We found a substantially associated region on chromosome 6 with leading SNP rs2858870, here highlighted in bold. Two other regions slightly missing genome-wide significance threshold of $p < 5 \times 10^{-8}$ were identified on chromosome 4 and 19 with leading SNPs rs72961463 and rs62110161, respectively.

B Results from detailed association tests of the HLA-region for anti-LGIl encephalitis (LGI1-E, n = 54), anti-NMDAR encephalitis (NMDAR-E, n = 96) and earlier onset (age of onset < 23.5 yr, n = 47) as well as later onset anti-NMDAR patients (age of onset > 23.5 yr, n = 49) compared to healthy controls (n = 1,194). Allele counts and frequencies (freq) are given for all significantly associated ($p_{adj} < 0.05$) HLA alleles. Presence of specific HLA alleles are noted as positive counts (pos) while absence of the same as negative counts (neg). We used a logistic model with adjustment for age, sex, and first four PCA dimensions to test for allele associations with disease status. *p* values are corrected for multiple testing using FDR step-up method. Adjusted *p* values below the significance threshold of 0.05 are highlighted in bold. [+]For this gene, not in all samples allele calls could be imputed with satisfying certainty, reducing sample sizes slightly A1 = minor allele, A2 = major allele; adj = adjusted; BP = base-pair position (GRCh37); CHR = chromosome; CI = 95% confidence interval; MAF = minor allele frequency; OR = odds ratio: pos = positive (occurrence of HLA allele); neg = negative (absence of HLA allele)

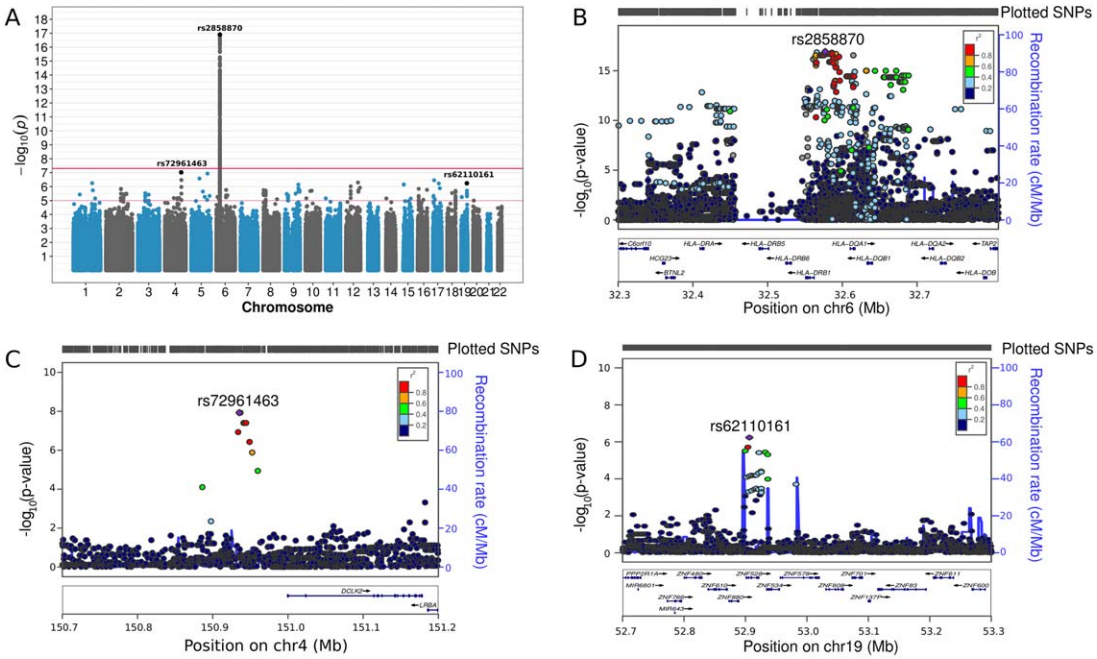

FIGURE 1: Manhattan plot and regional plot chromosome 6 in anti-LGI1 encephalitis. (A) Results of association analysis in 54 anti-LGI1 encephalitis patients and 1,194 healthy controls. The negative logarithms of marker-wise *p* values are plotted against their genomic base-pair position. (B) Associations with anti-LGI1 encephalitis for markers on chromosome 6 in the genomic region from 32.2 to 32.8Mb. Additionally, r^2 metrics for pairwise linkage disequilibrium as well as recombination rate and genes located in this region are featured. The most significantly associated marker rs2858870 (chr6: 32,572,251; OR = 13.66 [95% CI = 7.50–24.87]; $p = 1.22 \times 10^{-17}$) is located in an intergenetic region between MHCII genes HLA-DRB1 and HLA-DQA1. (C) Genomic region 150.7 to 151.2Mb on chromosome 4 with leading SNP rs72961463 (chr4: 150,935,250; OR = 13.19 [5.11–34.04]; $p = 9.48 \times 10^{-8}$), located upstream of DCLK2. (D) Genomic region 52.7 to 53.3Mb on chromosome 19 with leading SNP rs62110161 (chr19: 52,906,348; OR = 4.11 [2.36–7.15]; $p = 5.87 \times 10^{-7}$), located in an intronic region of ZNF528. SNPs = single-nucleotide polymorphisms. [Color figure can be viewed at www.annalsofneurology.org]

considering the small sample size attributed to the rarity of the disease.

rs72961463 is located in the vicinity of *DCLK2*. *DCLK2* is mainly expressed in multiple brain regions (GTEx), promotes neuronal development and survival, and its deficiency in mice leads to hippocampal dysmaturation and epilepsy.[13,14] rs62110161 is located in a cluster of poorly characterized zinc-finger genes with unclear biological function.

SNP-wise analysis of anti-NMDAR encephalitis yielded no genome-wide significant associations.

Additionally, we found proof for associations between MHCII alleles DRB1*07:01 and DQA1*02:01 and further haplotypes containing these alleles with anti-LGI1 encephalitis. This association extends and confirms the findings of two recently published, smaller MHC studies of anti-LGI1 encephalitis.[4,12] Neither allele has been previously associated with autoimmune disease (NHGRI-EBI GWAS catalogue). Interestingly, both alleles (H1) as well as DQB1*02:02 (contained in H2) were associated with reduced total IgG levels in a recent large GWAS analysis.[15] Given that LGI1 autoantibodies are largely of the IgG4 subclass, it is intriguing to speculate that in addition to facilitating peptide presentation of LGI1 peptides, these haplotypes might be associated with dysregulation of IgG subclasses potentially favoring pathogenic IgG4-LGI1 autoantibodies.

Detailed analysis of the MHC region in anti-NMDAR encephalitis showed a weak association with MHCI allele B*07:02 originating entirely from the group of adult onset patients (≥median of 23.5 years.). Independent investigations of the HLA-B*07:02 association in additional patient cohorts are needed to corroborate this finding. We found no overlap between association signals in anti-LGI1 and anti-NMDAR encephalitis, suggesting major differences in the genetic and pathophysiological mechanisms involved. The significantly stronger genetic associations in anti-LGI1 encephalitis might reflect differences in heritability and aetiological heterogeneity of anti-NMDAR encephalitis (idiopathic, ovarian-teratoma-associated, and postviral encephalitis).[16] The differential association of both encephalitis subtypes with MHCII versus MHCI alleles can be further hypothesized to result from fundamental

differences between the two antigens: LGI1 is a soluble, constitutively secreted protein, which is easily phagocytosed and presented using MHC class II molecules by antigen-presenting cells in draining cervical lymph nodes as was shown for other central nervous system antigens.[17] NMDA receptors are nonsecreted transmembrane proteins, whose peptides will likely not be presented by MHC class II proteins without previous neuronal damage.[18] Furthermore, disparity of main location of respective autoantibody synthesis are known, which occurs systemically in anti-LGI1 encephalitis and intrathecally in anti-NMDAR encephalitis.

The main limitation of the study is the small number of cases owing to the rarity and relatively recent discovery of autoimmune encephalitis. Power calculations showed that only variants conferring odds ratios greater than 3 to 4 and MAF greater 0.05 could be detected with a statistical power of 80%. In summary, we demonstrate that (1) GWAS analyses in small cohorts of encephalitis patients are feasible and enlightening because of the homogeneous nature of cohorts defined by reliable biomarkers, (2) anti-LGI1 encephalitis has a strong genetic predisposition mediated by the presence of MHCII alleles DRB1*07:01 and DQA1*02:01 and other loci just missing genome wide significance in a sample of only 54 patients, and (3) anti-NMDAR encephalitis in adults has only a minor association with MHCI B*07:02. Any associations observed in our cohort of anti-LGI1 encephalitis patients need to be validated in larger cohorts.

Web Resources

Allele Frequency Net Database (AFND): http://www.allelefrequencies.net/

Genetic Power Calculator: http://zzz.bwh.harvard.edu/gpc/cc2.html

GTEx: www.gtexportal.org

HaploReg v4.1: http://archive.broadinstitute.org/mammals/haploreg/haploreg.php

Michigan Imputation Server: https://imputationserver.sph.umich.edu/index.html

plink1.9: www.cog-genomics.org/plink/1.9/

NHGRI-EBI GWAS catalogue: https://www.ebi.ac.uk/gwas/home

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Author Contributions

Conception and design of the study: S.H.M., G.K., K-P.W., and F.L. Acquisition and analysis of data: S.H.M., A.F., H.P., N.M., K.S.G., T.K., F.T., M.E., J.L., M.K., K-W.S., M.R., C.K., C-G.B., A.K., U.Z., S.E., R.H., K.R., F.T.H., J.H.F., W.L., A.F., G.K., K-P.W., F.L. Drafting the text or preparing the figure: S.H.M., A.F., G.K., K-P.W., F.L.

Potential Conflicts of Interest

Nothing to report.

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