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Genome-Wide Association Study Identifies IFIH1 and HLA-DQB1*05:02 Loci Associated With Anti-NMDAR Encephalitis

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Abstract

Background and Objectives

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare autoimmune neurologic disorder, the genetic etiology of which remains poorly understood. Our study aims to investigate the genetic basis of this disease in the Chinese Han population.

Methods

We performed a genome-wide association study and fine-mapping study within the major histocompatibility complex (MHC) region of 413 Chinese patients with anti-NMDAR encephalitis recruited from 6 large tertiary hospitals and 7,127 healthy controls.

Results

Our genome-wide association analysis identified a strong association at the IFIH1 locus on chromosome 2q24.2 (rs3747517, $p = 1.06 \times 10^{-8}$, OR = 1.55, 95% CI, 1.34–1.80), outside of the human leukocyte antigen (HLA) region. Furthermore, through a fine-mapping study of the MHC region, we discovered associations for 3 specific HLA class I and II alleles. Notably, HLA-DQB1*05:02 ($p = 1.43 \times 10^{-12}$; OR, 2.10; 95% CI 1.70–2.59) demonstrates the strongest association among classical HLA alleles, closely followed by HLA-A*11:01 ($p = 4.36 \times 10^{-7}$; OR, 1.52; 95% CI 1.29–1.79) and HLA-A*02:07 ($p = 1.28 \times 10^{-8}$; OR, 1.87; 95% CI 1.50–2.31). In addition, we uncovered 2 main HLA amino acid variation associated with anti-NMDAR encephalitis including HLA-DQβ1-126H ($p = 1.43 \times 10^{-12}$; OR, 2.10; 95% CI 1.70–2.59), exhibiting a predisposing effect, and HLA-B-97R ($p = 3.40 \times 10^{-8}$; OR, 0.63; 95% CI 0.53–0.74), conferring a protective effect. Computational docking analysis suggested a close relationship between the NR1 subunit of NMDAR and DQB1*05:02.

Discussion

Our findings indicate that genetic variation in IFIH1, involved in the type I interferon signaling pathway and innate immunity, along with variations in the HLA class I and class II genes, has substantial implications for the susceptibility to anti-NMDAR encephalitis in the Chinese Han population.

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Glossary

AA = amino acid; **APCs** = antigen-presenting cells; **CTD** = C-terminal domain; **dsRNA** = double-stranded RNA; **eQTL** = expression quantitative trait loci; **GSA** = global screening array; **GWAS** = genome-wide association study; **HLA** = human leukocyte antigen; **HSV-1** = herpes simplex virus type 1; **LD** = linkage disequilibrium; **MAF** = minor allele frequency; **MHC** = major histocompatibility complex; **NMDAR** = N-methyl-d-aspartate receptor; **QC** = quality control; **SNPs** = single nucleotide polymorphisms.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, a rare autoimmune neurologic disorder associated with antibodies against the GluN1 subunit of NMDAR, was initially reported in 2007.[1] The estimated incidence is approximately 0.03 per 100,000 person-years[2] and possibly underestimated. It is characterized by memory dysfunction, seizures, psychiatric symptoms, behavioral changes, and a reduced level of consciousness.[3] While ovarian teratomas and viral infections, primarily herpes simplex virus type 1 (HSV-1), have been identified as potential triggers for anti-NMDAR encephalitis,[3] many patients have no identifiable immunologic trigger, prompting speculation regarding a genetic predisposition to this disorder.

Human leukocyte antigen (HLA) represents a prominent genetic factor associated with autoimmune diseases, contributing to approximately half of the known genetic predispositions.[4] Nevertheless, current studies focused on the HLA correlation with anti-NMDAR encephalitis[5-8] and have yielded inconsistent results concerning genetic susceptibility, with only weak associations identified, such as the DRB1*16:02 allele in the Chinese population and B*07:02 allele in Germany.[6,8] Therefore, apart from investigating HLA susceptibility in anti-NMDAR encephalitis, the possible role of other non-HLA loci in the pathogenesis of this disease also warrants further investigation. Notably, a recent genome-wide association study (GWAS) conducted in Germany identified novel genetic susceptibility loci (LRRK1, ACP2, and NR1H3) outside the HLA region for anti-NMDAR encephalitis.[9] However, larger scale studies are still required to validate these findings more comprehensively.

Given the rarity of anti-NMDAR encephalitis and the genetic diversity observed across different populations, our understanding of the genetic basis underlying this disease remains limited. In this study, we performed a GWAS using 413 cases and 7,127 healthy controls to validate the previous findings and identify novel genetic susceptibility loci for this disease. Furthermore, we also performed a fine-mapping study of the MHC region to systematically investigate the HLA variants within this region in relation to anti-NMDAR encephalitis.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Study approvals were obtained from the Institutional Review Board at West China Hospital of Sichuan University. All participants gave written informed consent that was approved by the ethical committee of each hospital before sample collection.

Study Design and Subjects

We performed a case-control association study. Cases (n = 413) were Chinese Han and enrolled from 6 large tertiary hospitals (West China Hospital, SiChuan University [n = 207], Chengdu Shangjin Nanfu Hospital [n = 87], the Third Affiliated Hospital of Sun Yat-Sen University [n = 101], Beijing Tiantan Hospital [n = 10], Sichuan Provincial People's Hospital [n = 6] and the First Hospital Affiliated to Zhengzhou University [n = 2]) in China. All patients were hospitalized at the Department of Neurology between January 2012 and April 2022 and fulfilled published diagnostic consensus criteria for definite anti-NMDAR encephalitis[10]: (1) the presence of one or more of the following symptoms with a rapid onset (<3 months): abnormal (psychiatric) behavior, cognitive dysfunction, seizures, movement disorder, speech dysfunction, disturbance of consciousness, autonomic dysfunction, central hypoventilation, and other signs of encephalitis; (2) detection of anti-NMDAR antibodies in the CSF using a cell-based assay (Euroimmun, Lübeck, Germany); and (3) reasonable exclusion of alternative causes. Diagnosis was confirmed by at least 2 neurologists specialized in autoimmune encephalitis. All healthy controls (n = 7,127) were obtained from the GWAS of IgA vasculitis.[11] These healthy controls were recruited from the Chinese Han population through collaboration with multiple hospitals in China. Controls were clinically assessed as being without systemic disorders, autoimmune disorders, and a family history of autoimmune disorders (including first, second, and third-degree relatives).

Genotyping, Quality Control, and GWAS Association Analysis

Genomic DNA was extracted from blood samples following the instructions of the Blood Genomic DNA Extraction Kit RC1001 (Concert, Xiamen). All samples were genotyped using the Illumina global screening array (GSA). GSAMD-24v3.0 EA was used for cases and GSA-24 v1.0 BeadChip for

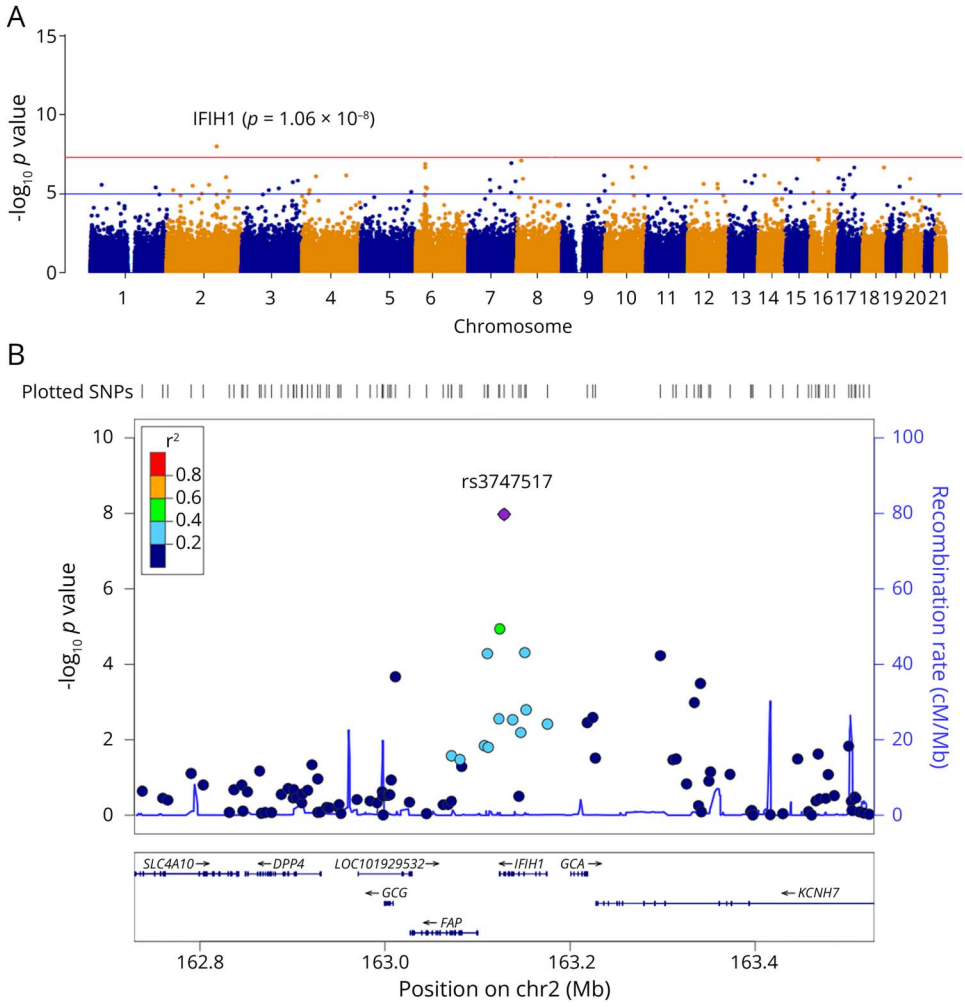
Table 1 Sample Characteristics

Characteristics	Anti-NMDAR (n = 413)	Controls (n = 7,127)
Median (range)/Mean age[a] (±SD), y	28 (3–75)/29.6 ± 13.8	33.7 ± 15.2
Female	221 (53.5)	3,610 (50.7)
Age at onset, y		
≤12	11 (2.7)	NA
13-17	57 (13.8)	NA
≥18	345 (83.5)	NA
Main clinical symptoms at acute phase		
Epileptic seizures	290 (70.2)	NA
Psychiatric symptoms	336 (81.4)	NA
Cognitive disorder	208 (50.4)	NA
Sleep disorders	101 (24.5)	NA
Movement disorders	103 (24.9)	NA
Ataxia	14 (3.4)	NA
Aphasia	60 (14.5)	NA
Limb weakness	20 (4.8)	NA
Decreased level of consciousness	127 (30.8)	NA
Death	8 (1.9)	NA
Tumor	51 (12.3)	NA
Ovarian teratoma	39 (76.4)	NA
Others[b]	12 (23.6)	NA
ICU Admission	77 (18.6)	NA
Abnormal brain MRI[c]	183 (45.7)	NA
Abnormal EEG[d]	299 (76.5)	NA

Abbreviation: NA = not applicable.
Data are n (%), median (range), or mean (±SD).
[a] Cases: mean age at onset; controls: mean age.
[b] There were 12 patients with other tumors (3 lung neoplasm, 2 thyroid cancer, 1 pancreas cancer, 3 colon cancer, 1 lymphoma, 1 rectal cancer, and 1 renal cancer).
[c] MRI data were available for 400 patients.
[d] EEG data were available for 391 patients.

controls. We conducted systematic quality control on the raw genotyping data to exclude unqualified samples and single nucleotide polymorphisms (SNPs). All genotype analyses were performed using GenomeStudio v2.0 and PLINK version 1.07 software. Samples with a low SNP call rate below 95% as well as individuals closely related based on estimated identity-by-descent (PI_HAT >0.25) were excluded from further analysis. Samples were also excluded because of abnormal heterozygosity (> mean ±3 SD) or genotyping call rate <95%. Principal component analysis (PCA) was conducted using the Plink 1.9 program to investigate the population structure, extracting 20 principal components from the variance-standardized relationship matrix. In the PC1 vs PC2 coordinate, the average distance from the centroid is 0.01456, with the standard deviation of 0.0068. We used the average distance plus 3 times SD as the threshold value (0.03496) to identify outliers, and 586 samples were removed. Sex and the first principal component were used as covariates in the subsequent regression analysis while the first 5 eigenvalues were 19.138, 2.65926, 2.5213, 2.45009, and 2.36265. After excluding SNPs on sex chromosomes and mitochondrial SNPs, SNPs were also excluded if they had a call rate <95% in cases or controls, minor allele frequency (MAF) < 1% in the population, or deviation from the Hardy-Weinberg equilibrium in the controls ($p_{\mathrm{hwe}} < 1 \times 10^{-4}$). Logistic regression was use for case-control association analyses. Conditional analysis was conducted to determine independent association signals. For the newly identified risk loci, regional association plots were generated using LocusZoom.[12] We identified expression quantitative trait loci (eQTL) using GTEx (version 8) and

Figure 1 Association Plots for Anti-NMDAR Encephalitis



(A) Manhattan plot of the genome-wide association results. The genome-wide *p*-value from logistic regression analysis of 379,039 SNPs in 378 cases and 6,576 controls are presented. The x-axis represents the chromosomal position, and the y-axis represents the −log10 of the *p*-value for each SNP. The red line denotes the genome-wide significance threshold ($p = 5.0 \times 10^{-8}$). (B) Regional association plot for Chr2q24.2 centering on the lead SNP rs3747517, located in an exonic region of IFIH1; regional association plot are *p* values (−log10 scale) of the association tests for genotyped SNPs in our sample. The *p*-value of the significant genotyped SNPs are shown by the purple diamond. The top significant SNPs were given rsIDs. The color of each SNP spot reflects its r^2 value with the rsID (from blue to red). SNPs = single nucleotide polymorphisms.

BRAINEAC data sets.[13,14] For this study, we defined genome-wide level significant association as $p < 5 \times 10^{-8}$ and suggestive evidence of association as $p < 5 \times 10^{-5}$.

HLA Imputation and Association Analysis

We extracted 6,422 genotyped SNPs located within the MHC region (chromosome 6: 29–34 Mb) from the GSA chips for subsequent analysis. Imputation was performed using a Han MHC reference panel comprising 29,948 variants built by deep sequencing for 10,689 healthy Han Chinese subjects.[15] This MHC reference panel contains 8 HLA genes (HLA-A, HLA-B, HLA-C, HLADRB1, HLA-DQA1, HLA-DQB1, HLA-DPA1, and HLA-DPB1), amino acid (AA) polymorphisms, and SNPs. SNP2HLA and Beagle software were used to impute SNPs, two-digit and four-digit HLA alleles, and HLA AAs.[16,17] We applied post-imputation quality control (QC) criteria of MAF > 0.01 and imputation quality ($r^2 > 0.3$). Subjects and SNPs with call rates of <95% and/or Hardy Weinberg equilibrium $p < 1.0 \times 10^{-4}$ were excluded.

After the QC procedures, 27,013 variants including 25,859 SNPs, 341 alleles (103 2-digit and 238 4-digit), and 813 AA polymorphisms remained for further analysis. For the association study, the biallelic variants were encoded as allele 1 and allele 2, and the multiallelic variants including multi-residue positions and HLA alleles were encoded as the presence or absence of an individual allele. To evaluate independent signals among variants of the HLA allele or AA polymorphisms, we conducted a stepwise regression analysis using the PLINK version 1.07 software.[18] The process involved conditioning on the top variant as a covariate and iteratively identifying subsequent variants until no variants met the significance threshold.[18] To avoid missing potentially significant associations, we used a stringent criterion of a genome-wide significance threshold ($p = 5.0 \times 10^{-8}$) and also applied a study-wide significance threshold ($p = 1.85 \times 10^{-6}$) based on Bonferroni adjustment for the total number of tested variants ($p = 0.05/27{,}013$).

Prediction of NR1-HLA Binding and in Silico Docking

To investigate the binding of NR1 peptides to HLA class II molecules, we used the online tool NetMHCIIpan 4.0.[19,20]

Table 2 Association of HLA Alleles and Amino Acid Polymorphisms With Anti-NMDAR Encephalitis Susceptibility

HLA variant	Position (hg19)	A1/A2	Case (n = 378) MAF	Control (n = 6,576) MAF	OR (95% CI)	*p* Value
HLA allele						
HLA-DQB1*05:02	32631061	P/A	0.15	0.08	2.10 (1.70–2.59)	1.43×10^{-12}
HLA-DRB1*16:02	32552064	P/A	0.09	0.04	2.26 (1.73–2.96)	9.93×10^{-10}
HLA-A*11:01	29911991	P/A	0.29	0.20	1.56 (1.33–1.84)	6.82×10^{-8}
HLA-A*02:07	29911991	P/A	0.15	0.09	1.73(1.41–2.14)	1.27×10^{-7}
HLA-C*06:02	31238192	P/A	0.04	0.09	0.40 (0.28–0.58)	6.42×10^{-7}
HLA-DPB1*05:01	33049368	P/A	0.46	0.37	1.47 (1.27–1.70)	2.59×10^{-7}
HLA-DQA1*02:01	32608306	P/A	0.04	0.09	0.42 (0.29–0.60)	1.51×10^{-6}
Amino acid variation						
HLA-DQβ1-126H	32629932	P/A	0.15	0.08	2.10 (1.70–2.59)	1.43×10^{-12}
HLA-DQβ1-57S	32632688	P/A	0.15	0.08	2.10 (1.70–2.59)	1.54×10^{-12}
HLA-B-97R	31324201	A/P	0.27	0.38	0.59 (0.50–0.70)	4.14×10^{-10}
HLA-DRβ1-28E	32552086	P/A	0.14	0.24	0.53 (0.43–0.65)	1.14×10^{-9}
HLA-DPβ1-35L	33048539	P/A	0.56	0.45	1.57 (1.35–1.82)	1.70×10^{-9}

Abbreviations: CI = confidence interval; MAF = minor allele frequency; OR = estimated odds ratio.
This table shows a summary of post-imputation of HLA association with anti-NMDAR encephalitis, including the top 5 amino acids in HLA-DRB1, HLA-DQB1, HLA-B, and HLA-DPB1, and four-digit alleles with $p < 1.85 \times 10^{-6}$. A1, effective allele, A2, alternative allele, the letter 'A' stands for 'Absent', the letter 'P' stands for 'Present.'
MAF = allele counts/2n.

The human NR1 sequence was retrieved from the UNIPROT database (accession number NP_015566.1) and uploaded into the tool. Subsequently, DQB1*05:02 was selected and compared to predict the binding epitopes within the protein. The AutoDock Vina software was used, as previously described, for predicting the tertiary structure and docking.[6,20] Owing to the crystallographic structure of DQB1*05:02 not being experimentally determined, we generated its structure through homology modeling using Swiss-Model and DQB1*02:02 as a template (Protein Data Bank code 6PX6).[21] The docking grid encompassed the entire peptide-binding cleft with the number of torsions being set to zero.[20] We also performed AA structure prediction to determine the position of the AA variant on the HLA-DQB1 (Protein Data Bank code 1JK8)[22] or HLA-B (Protein Data Bank code 1 A1M)[23] protein using the RCSB Protein Data Bank (RCSB.org).[24]

Data Availability

Genetic data that support the findings are available from the corresponding author on reasonable request.

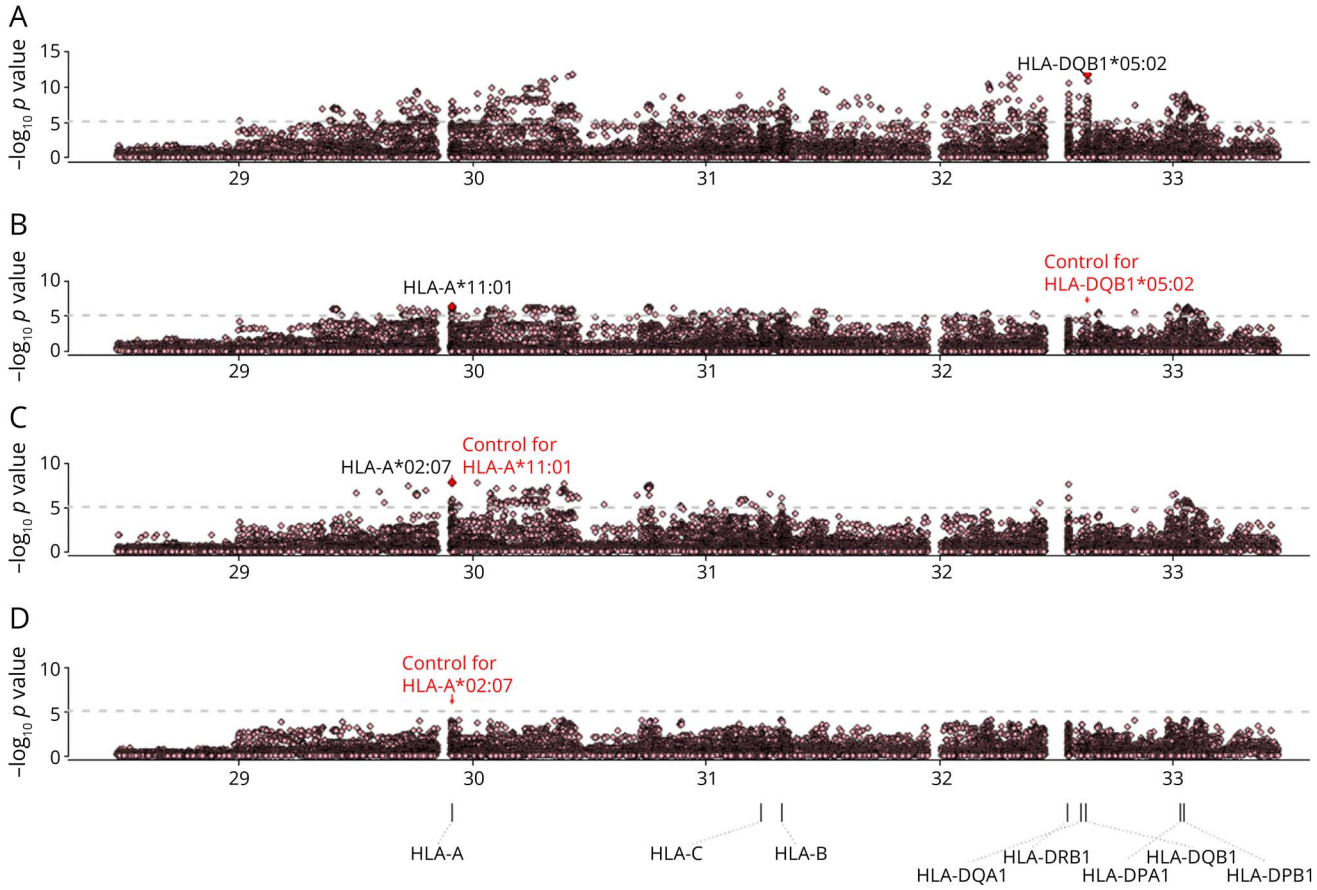
Results

GWAS Association Results of Non-HLA Variants

We performed genotyping using Illumina GSA chips on 413 cases and 7,127 healthy controls. Sample characteristics are reported in Table 1, and characteristics of patients with post–herpes simplex virus (post-HSV) infectious anti-NMDAR encephalitis are presented in eTable 1. After quality control, genotype data for 379,039 variants in 378 cases and 6,576 controls remained for association analysis. The genomic inflation factor (λ_{GC}) was 1.14, indicating a minimal impact of population stratification. Manhattan plots and quantile-quantile plots are presented in Figure 1A and eFigure 1, respectively.

We identified one novel non-HLA variant rs3747517 ($p = 1.06 \times 10^{-8}$, OR = 1.55, 95% CI 1.34–1.80) that achieved genome-wide significance ($p < 5 \times 10^{-8}$) (eTable 2). This variant is located at the extronic region of IFIH1 on chromosome 2q24.2 and represents a missense mutation (NM_022168:exon13:c.2528A>G: p.H843R) in IFIH1, which is a widely recognized gene related to autoimmune disorders.[25] Notably, a regional association plot revealed multiple SNPs in linkage disequilibrium (LD) with rs3747517 ($r^2 > 0.2$) situated within the IFIH1 locus (Figure 1B). Conducting a conditioning analysis on rs3747517 yielded no further independent associations (data not shown). Our analysis of eQTL data from the GTEx and BRAINEAC data sets demonstrated a significant correlation between rs3747517 genotypes and the expression levels of IFIH1 in the anterior cingulate cortex and cerebellar cortex ($p = 0.016$ and $p = 7.90 \times 10^{-5}$; eFigure 2 and eTable 3). Additional analyses of subpopulations defined by teratoma, post-HSV infectious anti-NMDAR encephalitis and age at onset younger than 18 years yielded no

Figure 2 Conditional Analysis of Classical HLA Alleles Associated With Anti-NMDAR Encephalitis



(A) Association results before conditional analysis, marked with HLA-DQB1*05:02 in the DQB1 locus; (B) conditional analysis by controlling for HLA-DQB1*05:02; (C) conditional analysis by controlling for HLA-DQB1*05:02 and HLA-A*11:01; (D) conditional analysis by controlling for HLA-DQB1*05:02, HLA-A*11:01, and HLA-A*02:07.

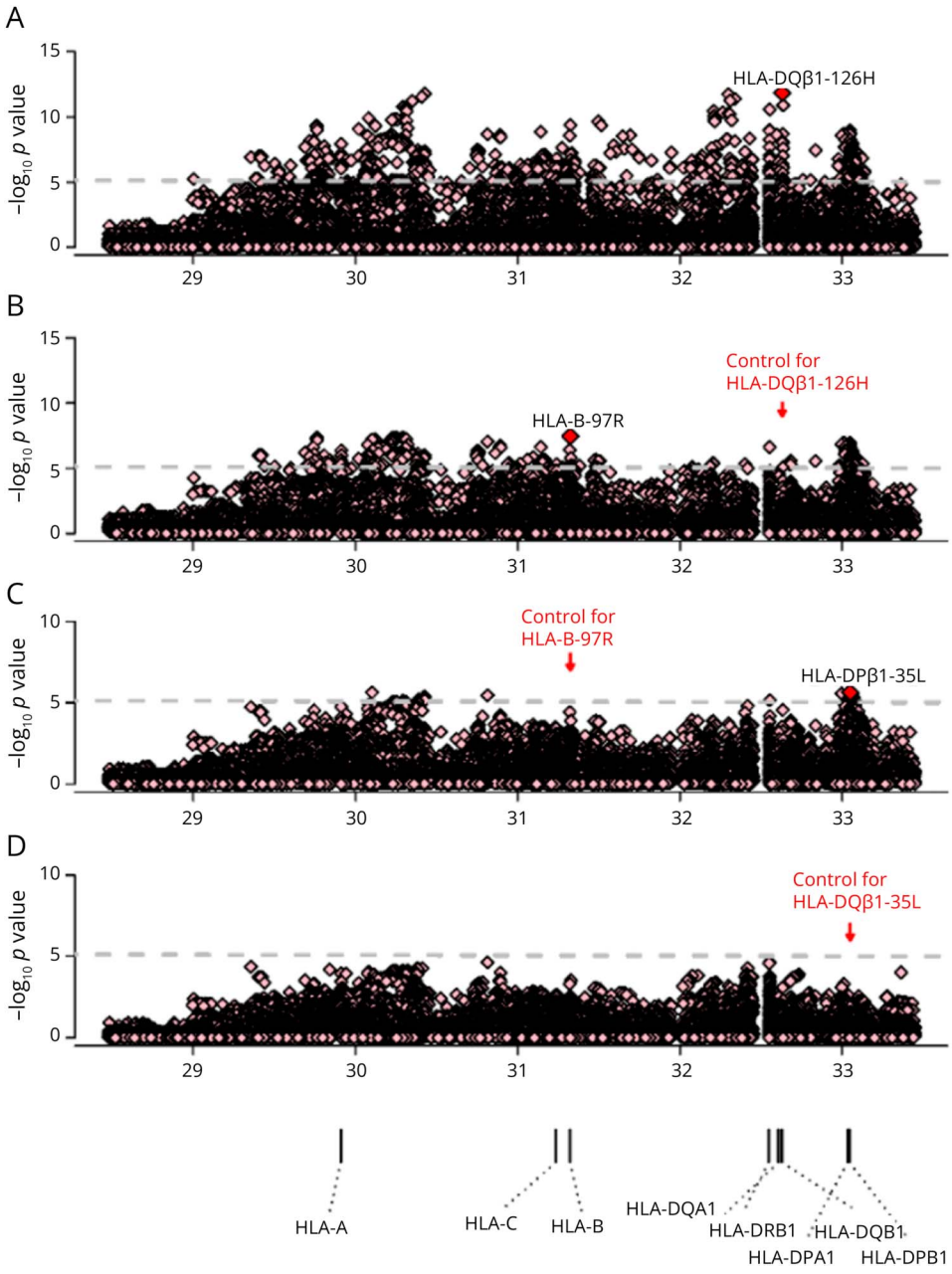
genome-wide significant associations (eTable 4). After excluding these patients with post-HSV infectious anti-NMDAR encephalitis,we still observed a significant IFIH1 association (eTable 4). Stratification analysis by sex was conducted using the SNP rs3747517 to explore gender-related differences in controls and cases. However, no nominal heterogeneity was observed between male and female patientss after stratifying by sex (eTable 4).

We subsequently evaluated whether other non-HLA SNPs previously identified as having significant association with anti-NMDAR encephalitis displayed any notable trends in our data set. A genome-wide association study in Germany reported 2 significant associations,[9] one mapping within the LRRK1 gene (rs10902588, $p = 1.78 \times 10^{-8}$) and a second centered on the ACP2 and NR1H3 genes in a larger region of high linkage disequilibrium (rs75393320, $p = 3.78 \times 10^{-8}$). Despite the absence of robust evidence suggesting an association between the LRRK1 locus and anti-NMDAR encephalitis in our Han Chinese cohorts (eTable 5), we did observe a few SNPs at the LRRK1 locus that exhibited nominal significance ($p < 0.05$). These findings suggest a potential link between the LRRK1 and anti-NMDAR encephalitis. We were unable to analyze the significant association of rs75393320 with this disease, owing to the low frequency of these alleles below 1% in the eastern Asian population.

Association Results of HLA Variants With Anti-NMDAR Encephalitis Susceptibility

In our association analysis, we observed that 5 directly genotyped SNPs (rs2508008, rs9468731, rs139999228, rs1150770, and rs1264562) within the MHC region achieved suggestive genome-wide significance ($p < 5 \times 10^{-5}$), mainly mapped to the intergenic region of RPP21 and HLA-E (eTable 6). Through imputation analysis, we systematically explored HLA variants in the MHC region, identifying 919 SNPs, 34 AA variants, and 10 classical HLA alleles (two-digit or four-digit) in the HLA class I and II gene region, all reaching significant levels in the study (eTable 7). The strongest associations were detected in class II, especially in the HLA-DQB1 region.

Figure 3 Conditional Analysis of HLA Amino Acid Residues Associated With Anti-NMDAR Encephalitis

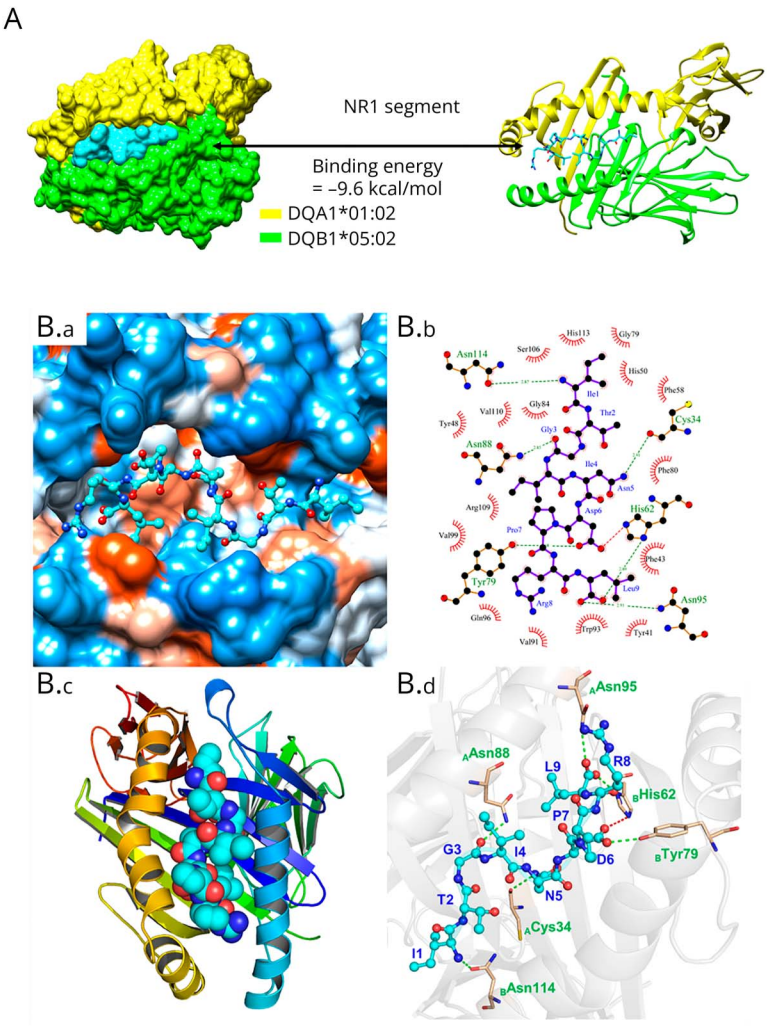


(A) Association results before conditional analysis, marked with HLA-DQβ1-126H; (B) conditional analysis by controlling for HLA-DQβ1-126H; (C) conditional analysis by controlling for HLA-DQβ1-126H and HLA-B-97R; (D) conditional analysis by controlling for HLA-DQβ1-126H, HLA-B-97R, and HLA-DPβ1-35L.

In regard to classical HLA alleles, the carrier frequencies of HLA-DQB1*05:02, DRB1*16:02, HLA-A*11:01, and HLA-A*02:07 in patients were 26.7% (101/378), 15.6% (59/378), 48.4% (183/378), and 27.5% (104/378), respectively (eTable 8). These frequencies were higher in anti-NMDAR encephalitis compared with healthy control groups. The strongest association was observed in the HLA-DQB1*05:02 allele ($p = 1.43 \times 10^{-12}$; OR, 2.10; 95% CI 1.70–2.59), followed by HLA-DRB1*16:02 ($p = 9.93 \times 10^{-10}$; OR, 2.26; 95% CI 1.73–2.96). Possible strong associations were observed with HLA-A*11:01, A*02:07, and DPB1*05:01, predisposing to anti-NMDAR encephalitis ($p = 6.82 \times 10^{-8}$; OR, 1.56; 95% CI 1.33–1.84; $p = 1.27 \times 10^{-7}$; OR1.73; 95% CI 1.41–2.14; $p = 2.59 \times 10^{-7}$; OR, 1.47; 95% CI 1.27–1.70). No significant association was observed for classical alleles in the HLA-B, DQA1, or DRA1 locus (Table 2 and eTable 7).

Table 2 presents the significant AA variation associated with anti-NMDAR encephalitis. The most significant associations were observed at position 126 of DQβ1, where the histidine (H) residue conferred a predisposing effect ($p = 1.43 \times 10^{-12}$; OR, 2.10; 95% CI 1.70–2.59), and at position 57 with serine (S), also demonstrating a predisposing effect ($p = 1.54 \times 10^{-12}$; OR, 2.10; 95% CI 1.70–2.59). These AA residues were in complete linkage disequilibrium (LD) with HLA-DQB1*05:02 and showed an identical signal. Strong

Figure 4 Molecular Modeling of Interactions Between NR1 Peptide and the DQB1*05:02 Protein



(A) Computational docking of the NR1 peptide "ITGINDPRL" to a heterodimer of HLA-DQB1*05:02 and HLA-DQA1*01:02. Mesh in the HLA surface indicates close contact between atoms with the NR1 protein segment. (B) Model of interaction of the NR1 segment with HLA-DQB1*05:02: (a) the binding of the NR1 segment to the hydrophobic surface of HLA-DQB1*05:02, with blue and orange denoting the hydrophilic and hydrophobic parts of the protein surface, respectively; (b) two-dimensional binding mode of the NR1 segment to HLA-DQB1*05:02 molecule, with green dashed lines indicating hydrogen bonding and red cogwheel-like indicating hydrophobic interactions; (c) location of the NR1 segment in the three-dimensional structure of the HLA-DQB1*05:02; (d) three-dimensional binding mode of the NR1 segment to HLA-DQB1^{a}05:02, with green dashed lines indicating hydrogen bonding interactions.

associations were also observed in HLA-B at position 97 with an absence of an arginine residue ($p = 4.14 \times 10^{-10}$; OR, 0.59; 95% CI 0.50–0.70) and in HLA-DRβ1 at position 28 with a glutamic acid residue ($p = 1.14 \times 10^{-9}$; OR, 0.53; 95% CI 0.43–0.65), which showed protective effects.

Classical Alleles HLA-DQB1*05:02, A*11:01, and A*02:07 Independently Associated With Anti-NMDAR Encephalitis

We performed conditional analyses to evaluate independent associations with certain classical HLA alleles in the MHC region. HLA-DQB1*05:02 and HLA-DRB1*16:02 were identified as the prominent alleles at the classical II regions of the MHC. After setting conditions on HLA-DQB1*05:02, the association for HLA-DRB1*16:02 was mainly abolished, suggesting a robust LD between these 2 alleles. In addition, conditioning on HLA-DQB1*05:02, the second independent allele was HLA-A*11:01 ($p = 4.36 \times 10^{-7}$; OR, 1.52; 95% CI 1.29–1.79; Figure 2B). Conditioning on both alleles revealed the third independently associated signal with HLA-A*02:07 ($p = 1.28 \times 10^{-8}$; OR, 1.87; 95% CI 1.50–2.31; Figure 2C). Upon conditioning analysis on HLA-DQB1*05:02, A*11:01, and A*02:07, the residual genetic signal within the MHC region was exclusively observed within the DPB1*05:01 ($p = 8.07 \times 10^{-5;}$ OR, 1.35; 95% CI 1.16–1.56). These results clearly indicated that almost all the association signals can be attributed to these specific HLA classical alleles, with DQB1*05:02 possessing the major effect (Figure 2).

HLA-DQβ1-126H and HLA-B-97R Are Major Independent MHC Residues

We also performed conditional analyses to identify independent associations with amino acid variation in MHC genes. Conditioning on HLA-DQβ1-126H showed a strong second association with HLA-B-97R ($p = 3.40 \times 10^{-8}$; OR, 0.63; 95% CI 0.53–0.74; Figure 3B). When both HLA-DQβ1-126H and HLA-B-97R were used as covariates together, we observed a third independent signal at HLA-DPβ1-35L ($p = 2.31 \times 10^{-6}$; OR, 1.43; 95% CI 1.23–1.66; Figure 3C); however, it did not reach a study-wide significance threshold

($p = 1.85 \times 10^{-6}$). Conditioning on HLA-DQβ1-126H, HLA-B-97R and HLA-DPβ1-35L attenuated almost all the AA association signals (Figure 3D). Thus, the major independent MHC signals mapped to HLA-DQβ1-126H and HLA-B-97R (Figure 3). HLA-DQβ1 residue His 126 is located on the junction turn point of 2 β-sheet structures and lies on the β1 domain (eFigure 3A). HLA-B residue Arg 97 is located on the β-sheet structure within the α1 domain (eFigure 3B).

Prediction and Modeling of Binding Between HLA Protein and NR1 Peptide

Given the previous findings indicating that pathogenic autoantibodies targeting NMDAR bind to the NR1 subunit,[26] we tried to predict potential epitopes within this receptor subunit that can be recognized by DQB1*05:02. By analysis using the NetMHCpan 4.0 server, we identified 3 peptides showing strong binding levels to DQB1*05:02, including 'ITGINDPRL', 'IQAVRDNKL', and 'ILLVSDDHE' (eTable 9). Among these 3 predicted epitopes, 'ITGINDPRL' exhibited the highest predicted binding affinity to DQB1*05:02. The position of the target sequence 'ITGINDPRL' is located between 658th and 662nd amino acids from the NR1 protein N-terminus. Computational docking analysis revealed that the target sequence 'ITGINDPRL' fit precisely into the peptide-binding groove between DQB1*05:02 and HLA-DQA1*01:02, with a docking energy (ΔG) of −9.6 kcal/mol (Figure 4A, eFigure 4 and eFigure 5). In the docked structure, the NR1 peptide was located mostly in the hydrophobic cavity of the heterodimer of HLA-DQB1*05:02 and HLA-DQA1*01:02 [Figure 4B (a)]. The peptide primarily occupies a binding cavity composed of A chain residues Cys34, His50, Phe58, Gly79, Phe80, Gly84, Asn88, Val91 and Asn95, as well as B chain residues Tyr41, Phe43, Tyr48, His62, Tyr79, Trp93, Gln96, Val99, Arg109, Val110, His113, and Asn114 [Figure 4B (b-d)]. This in silico *docking* result suggests a positive interaction between the predicted epitope and DQB1*05:02.

Discussion

We conducted a large GWAS and performed a fine-mapping study within the MHC region for anti-NMDAR encephalitis in the Han Chinese population in an attempt to investigate the genetic etiology of this disease. Our study not only identified a novel locus outside the HLA region (IFIH1) but also revealed that alleles and AA polymorphisms in multiple class I and II HLA genes explained most of the susceptibility risk within the MHC region for anti-NMDAR encephalitis.

IFIH1, also known as MDA-5, encodes an interferon-inducible RNA helicase that, along with RIG-I, acts as a cytoplasmic double-stranded RNA (dsRNA) sensor for viral infection detection and subsequent initiation of antiviral responses by the activation of the type I interferon (IFN) pathway.[27,28] Dysfunction of IFIH impairs the activation of downstream innate immune responses. Given HSV-1 being believed to trigger anti-NMDAR encephalitis,[3] we postulated that the presence of the IFIH1 missense variant might interfere with the normal function of the type I interferon (IFN) signaling pathway. Consequently, this disruption could potentially undermine the host defense against HSV-1 in the CNS. MDA5 primarily functions as a cytoplasmic sensor for dsRNA viruses and also detects dsDNA viruses using their dsRNA intermediate replication products. Therefore, it is plausible to speculate that a wider range of dsRNA or dsDNA viruses could potentially act as triggers for the development of anti-NMDAR encephalitis. Beyond its crucial role in antiviral defense, MDA5 has been reported to be involved in autoimmune and autoinflammatory diseases.[29] Taken together, IFIH1 provides a link between host genetics, viruses, and the innate immune response or autoimmunity, which may contribute to our understanding of the pathogenesis of anti-NMDAR encephalitis. Notably, we found a significant IFIH1 association with anti-NMDAR encephalitis. One potential source of bias could stem from the inclusion of a specific subset of patients with post-HSV infectious anti-NMDAR encephalitis in our study. Intriguingly, even upon excluding these patients from the study, we still observed a significant association with IFIH1.

We also performed detailed fine mapping of the MHC region using HLA imputation based on the Chinese Han-MHC reference panel. In this analysis, HLA-DQB1*05:02 showed the strongest association with anti-NMDAR encephalitis, followed by HLA-DRB1*16:02 among the HLA classical II alleles, which has been previously reported in the Han Chinese population using the HLA genotyping approach.[6] Our study further confirms the plausibility and reproducibility of the previous finding from China, which differ significantly from those reported in European cohorts. The observed disparities in HLA associations between our study and that of the German cohort[9] may be attributed to population differences, in addition to the smaller sample size of the latter. In Germany, HLA-DQB1*05:02 and DRB1*16:02 are extremely rare (<1%) compared with the Chinese control cohort in this study (4%–8%). These different HLA-population genetics might as well help to explain differences in anti-NMDAR encephalitis epidemiology as has been observed in Southeast Asian populations[30] compared with European cohorts.[31] In addition, it is noteworthy that the cohort exhibits an approximate 50% representation of both female and male patients, which deviates significantly from the gender distribution observed in European cohorts (approximately 75%:25%).[9] This observed disparity in sex distribution can be partially explained by the higher occurrence of teratoma cases in the European cohort, as well as possible influences from population genetics and geographical predisposition.

The DQB1*05:02 and DRB1*16:02 alleles have also been reported to be associated with an increased risk of several autoimmune diseases such as myasthenia gravis and neuromyelitis optica spectrum disorders.[32,33] It is of interest that these autoimmune diseases are predominantly mediated by autoantibodies, indicating a potential significant involvement

of DQB1*05:02 and DRB1*16:02 in the production of autoantibodies. In our condition analysis, after setting conditions on HLA-DQB1*05:02, the association for HLA-DRB1*16:02 was mainly abolished, suggesting that these 2 signals might be strong LD alleles. HLA alleles DRB1*16:02 and DQB1*05:02 are usually tightly linked because of a strong complete LD, which has also been reported in autoimmune neurologic disorders such as myelin oligodendrocyte glycoprotein-associated disorders.[34]

The MHC class II locus encodes molecules that play a pivotal role in presenting peptide antigens to T cells by antigen-presenting cells (APCs).[35] In general, the disease-associated variants in MHC class II molecules primarily influence the structure of the encoded peptide-binding groove.[36] We predicted the peptide 'ITGINDPRL' of NR1 to bind most strongly to the HLA-DQB1*05:02 heterodimer on the surface of APCs, which might provoke the pathogenesis of anti-NMDAR encephalitis. This target sequence (ITGINDPRL) is situated in the intracellular C-terminal domain (CTD) of NR1, which is essential for multiple forms of neuronal synaptic plasticity.[37] Further study is needed to investigate the role of the epitope with the CTD of NR1 in anti-NMDAR encephalitis. In addition, HLA class I alleles such as HLA-A*11:01 and HLA-A*02:07 showed strong associations with anti-NMDAR encephalitis. HLA class I molecules are crucial for immune-mediated control of viral infections.[38] These HLA class I molecules are primarily responsible for presenting intracellular peptides to circulating $CD8^+$ T cells.[38] However, there are no available data supporting the involvement of $CD8^+$ T cells in the pathogenesis of this disease.

Our investigation has revealed that in addition to the identified HLA alleles, specific AA polymorphisms within the MHC regions, namely HLA-DQβ1-126H and HLA-B-97R, play a significant role as major determinants in the pathogenesis of anti-NMDAR encephalitis. To date, there has been a lack of studies on the AA polymorphisms in MHC regions of anti-NMDAR encephalitis in other populations. The histidine (His) residue at position 126 of the HLA-DQβ1 molecule is situated within the β1 domain, which is primarily expressed on the extracellular region of antigen-presenting cells. This domain plays a crucial role in facilitating interactions with $CD4^+$ T cells during the process of antigen presentation. However, the precise contribution of $CD4^+$ T cells to the pathogenesis and progression of anti-NMDAR encephalitis remains to be fully elucidated. In our study, we observed a protective effect associated with the amino acid position 97 of HLA-B. However, it is worth noting that this same amino acid position has been implicated in conferring susceptibility to certain immune-related disorders, such as ankylosing spondylitis[39] and Behcet disease.[40] The arginine (Arg) residue at position 97 of the HLA-B molecule resides within the binding groove responsible for interacting with antigen peptides.[40] During the antigen-presenting process, HLA-B molecules can pass on the specific signal they receive from the endogenous antigens to the $CD8^+$ T cells.[38] In brief, the HLA AA polymorphisms may affect T helper cell regulation and amplify the immune response downstream by changing the binding affinity with antigen peptides.[36]

This study has several limitations that should be acknowledged. First, despite being the largest study conducted in the Chinese population to date, one limitation lies in the absence of a replication study, thereby increasing the likelihood of false positives. The study's limited sample size hinders the exploration of potential associations between genetic variants and other features of anti-NMDAR encephalitis. Future research should encompass a larger patient cohort to validate our findings, detect novel risk loci, and analyze susceptibility characteristics in subpopulations. Furthermore, because of the extensive LD, high polymorphism, and strong genetic heterogeneity of the MHC region,[41] we could not capture all genetic variants, especially rare variants with MAF below 1%, within the MHC region. Thus, a comprehensive understanding of the genetic architecture of the MHC region for anti-NMDAR encephalitis requires studies with a large sample size. Notably, the associations discovered appears to be specific to a Chinese population. Global meta-analyses of published GWAS in anti-NMDAR encephalitis are needed to clarify unifying and population background-independent associations. Finally, owing to the low carrier frequency (<30%) of most HLA alleles associated with anti-NMDAR encephalitis in patients, further research is needed to investigate additional susceptible mechanisms, such as more non-HLA loci and environmental factors, in the pathogenesis of anti-NMDAR encephalitis. Moreover, further functional studies are also required to unveil the roles of the identified variants.

To summarize, our study indicates that genetic variations in IFIH1, which is associated with type I interferon signaling and plays a vital role in innate immunity, alongside variants located in HLA class I and class II genes, contribute to the susceptibility to anti-NMDAR encephalitis. These findings enhance our understanding of the underlying genetic mechanisms implicated in the development of this disease.

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