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Genome-Wide Association Study Identifying a Novel Gene Related to a History of Febrile Convulsions in Patients With Focal Epilepsy

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Background and Purpose The risk factors for developing epilepsy following febrile convulsion (FC) have been studied extensively, but the underlying genetic components remain largely unexplored. Our objective here was to identify the risk loci related to FC through a genome-wide association study of Korean epilepsy patients.

Methods We examined associations between a history of FC and single-nucleotide polymorphisms (SNPs) in data obtained from 125 patients with focal epilepsy: 28 with an FC history and 97 without an FC history.

Results Among 288,394 SNPs, 5 candidate SNPs showed $p<1\times10^{-4}$. Regional association plots of these SNPs identified a novel locus adjacent to *PROX1* that is implicated in hippocampal neurogenesis and epileptogenesis. The allele frequencies of the SNPs upstream of *PROX1* including two candidate SNPs (rs1159179 and rs7554295 on chromosome 1) differed significantly between the groups with and without an FC history. In contrast, the allele frequencies of the SNPs inside *PROX1* showed no differences, indicating dysregulated expression of *PROX1* rather than a functional alteration in the PROX1 protein.

Conclusions This novel discovery of SNPs upstream of *PROX1* suggests that the dysregulated expression of *PROX1* contributes to the development of focal epilepsy following FC. We propose that these SNPs are potential genetic markers for focal epilepsy following FC, and that *PROX1* represents a potential therapeutic target of antiseizure medications.

Keywords febrile convulsion; focal epilepsy; genome-wide association study; polymorphism, single nucleotide; prospero-related homeobox 1 protein.

INTRODUCTION

A febrile convulsion (FC) is a seizure occurring with fever in childhood in the absence of central nervous system infection and any other evidence of acute symptomatic seizures.[1] FC is the most common form of seizure in childhood, and it usually shows a benign course. However, the probability of it progressing to epilepsy is twofold higher in patients with FC than in the general pediatric population, with roughly 15% of children with epilepsy having had prior febrile seizures.[2-6] Several risk factors for epilepsy following FC have been investigated widely, including preterm birth history, developmental delay, FC frequency, multiple seizure attacks during febrile illness, and electroencephalograms showing epileptiform discharges.[6] While specific epilepsy syndromes such as genetic epilepsy with febrile seizures plus are attributed to genetic mutations such as *SCN1A*, *SCN1B*, *GABA*, and *STX1B*, the genetic associations between FC and epilepsy in the broader epilepsy population remain unclear.[7,8]

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Recent genome-wide association studies (GWASs) evaluating the genetic contributions to epilepsy have identified several loci associated with focal epilepsy, and generalized epilepsy across different ancestries.[9-11] Two Danish studies that applied GWASs to individuals with FC in a European population identified 11 loci related to FC, but some of these genes were also found in genetic studies of the broader epilepsy population.[12,13] The single-ancestry characteristic of the populations analyzed in these studies also underscores the need for research involving East Asian populations, given the genetic diversity across ancestries.[14]

We aimed to use a GWAS to identify significant single-nucleotide polymorphisms (SNPs) and loci in Korean patients with focal epilepsy and a history of FC. We controlled for confounding factors related to focal epilepsy by focusing exclusively on focal epilepsy patients, comparing those linked to FC with others with different etiologies. We enrolled focal epilepsy patients with and without a history of FC as case and control groups, respectively, since the most-prevalent type of epilepsy eventually diagnosed in patients with a history of FC is known as focal epilepsy rather than generalized epilepsy in Korean populations.[6,15] Moreover, we restricted our cohort to individuals of Korean descent in order to minimize inflation from ethnicity variability and to identify novel loci specific to East Asian populations.

METHODS

Study subjects

We retrospectively reviewed data collected from 125 patients with focal epilepsy who visited the epilepsy clinic in Severance Hospital, Yonsei University College of Medicine and obtained blood samples between June 2016 and November 2018. Each participant in the study was of Korean ancestry and had no familial relationship with any of the other participants. Twenty-eight of the participants had a history of FC (18 females and 10 males), and the control group consisted of 97 individuals had no history of FC (45 females and 52 males) (Supplementary Table 1 in the online-only Data Supplement). Epileptologists diagnosed patients with focal epilepsy based on their clinical pattern or electroencephalography localization according to the seizure-type classification of the International League Against Epilepsy.[16] Patients with progressive epilepsy syndrome or epileptic encephalopathy were excluded from both study groups. We explained the details of this genetic study and then obtained written consent for genetic screening from each participant or their responsible family member. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea (IRB No. 3-2016-0096).

Genome-wide association study

We genotyped samples from all participants in 2019 with the GeneChip Human Mapping 500K Array Set (Affymetrix) using the standard protocol recommended by the manufacturer. We performed quality control and genotyped SNPs following the protocols used in previous studies.[17,18] We assessed population stratification using HapMap Phase III data from four ethnic populations (European, African, Japanese, and Han Chinese), followed by principal-components analysis (PCA) with the SmartPCA software (EIGENSOFT).[19] We checked the sex of samples by calculating the mean homozygosity rate across the X chromosome. In brief, all of the included samples passed the following quality-control criteria: population stratification PCA score within 6 standard deviations (SDs), genotype call rate >0.96, consistency between estimated and reported sex, and absence of excessive heterozygosity (more than the mean plus 3 SDs or less than the mean minus 3 SDs).

The total number of SNPs was 440,398: 430,623 were located in autosomes, 155 in the pseudoautosomal region of the X chromosome, and 9,620 in the X chromosome. The quality-control criteria for the SNPs were as follows: minor allele frequency (MAF) >0.01 and a genotype call rate >0.95 in both groups, as well as Hardy–Weinberg equilibrium with $p>1\times10^{-4}$ in the control group. A total of 288,394 SNPs passed the quality-control analysis, and each SNP was annotated with genes based on the Affymetrix gene annotation database and UCSC Genome Browser (https://genome.ucsc.edu/).

Phenome-wide association study

We applied a phenome-wide association study (PheWAS) to each candidate SNP and produced a Manhattan plot using the UK Biobank ICD PheWeb tool (https://pheweb.org/UKB-SAIGE/).

Statistical analyses

We used PLINK software for quality-control and association analyses.[20] Additive model and logistic regression analyses were used for association analyses, since all participants were of Korean descent and from a single center with no batch effect. We used R software (version 4.2.0) to conduct chi-square tests, Fisher's exact tests, and Student's *t*-tests, and to produce quantile–quantile and Manhattan plots. We used LocusZoom software to construct regional association plots (http://csg.sph.umich.edu/locuszoom/).[21]

Allele frequency in the normal population

We obtained the allele frequencies of SNPs in the Korean population from the Korea Centers for Disease Control and Prevention and in the European population from the 1000 Genomes Project phase3 (https://www.ncbi.nlm.nih.gov/snp/).

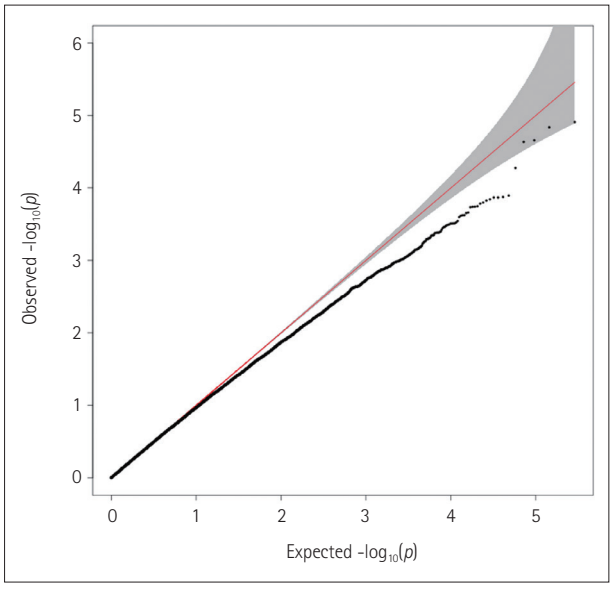

Fig. 1. Quantile-quantile plot after applying quality control to GWAS data. The plot was drawn with GWAS data obtained from 28 focal epilepsy patients with an FC history and 97 without an FC history. Probability values were calculated using allelic association tests. Black points are the results for all SNPs after applying quality-control criteria to GWAS data. The red line represents y=x. FC, febrile convulsion; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

RESULTS

Genome-wide association study

We performed a GWAS involving 28 epilepsy patients with an FC history and 97 epilepsy patients without an FC history. All of the included individuals passed the stringent quality-control criteria, including the absence of a significant sex difference between the two groups in a chi-square test (p=0.146). A quantile–quantile plot was constructed to visualize the distribution of observed versus expected p values to verify the quality of SNPs, which provided some evidence of significant associations (Fig. 1).

Among the 440,398 initially analyzed SNPs, 288,394 SNPs were included in the association analyses after applying quality control to the markers, and we constructed a Manhattan plot to provide an overview of all 288,394 SNPs (Fig. 2). In the allelic association tests of the genotype data, the p value was $<1\times10^{-3}$ for 114 SNPs (Supplementary Table 2 in the online-only Data Supplement). We identified five candidate SNPs and three independent loci satisfying the following criteria: p value of $<1\times10^{-4}$ for SNPs in the allelic association test and an independent locus (Table 1).

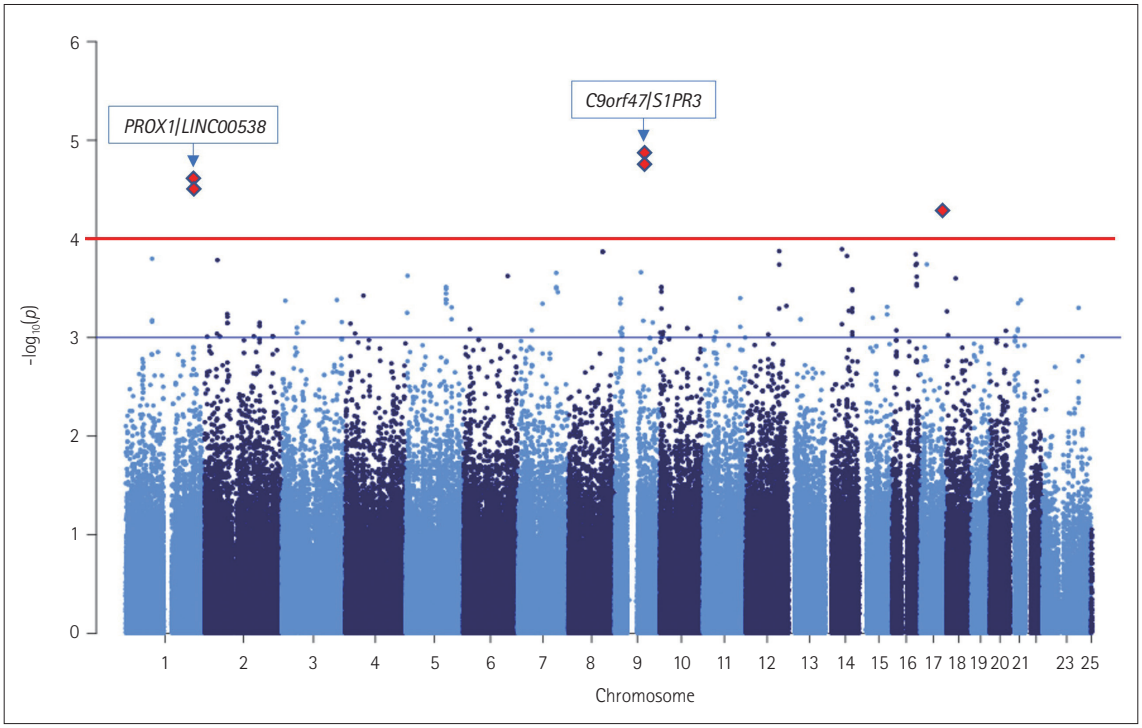

Fig. 2. Manhattan plot of genotype data. The 288,394 SNPs are plotted according to their chromosomal position; the $-\log_{10}(p)$ values were calculated using allelic association tests. The candidate SNPs are highlighted with red dots. The red line indicates the significance threshold for the association analysis ($p=1.0\times10^{-4}$). The blue line indicates $p=1.0\times10^{-3}$. SNP, single-nucleotide polymorphism.

Table 1. Summary of five candidate SNPs

SNP	Chr	Position (GRCh37)	Position (GRCh38)	Nearest genes	Region	MAF		Alleles (major/minor)	OR (95% CI)	*p*
						Cases	Controls			
rs1159179	1	214108641	213935298	*PROX1, LINC00538*	Intron, upstream, downstream	0.5893	0.2216	C/T	4.505 (2.294, 8.846)	0.00001231
rs7554295	1	214110402	213937059	*PROX1, LINC00538*	Intron, upstream, downstream	0.5714	0.2113	T/C	4.439 (2.263, 8.707)	0.00001453
rs7043095	9	91604005	88989090	*C9orf47, S1PR3*	Upstream	0.5893	0.2448	C/T	4.958 (2.367, 10.380)	0.00002196
rs6559331	9	91607869	88992954	*C9orf47, S1PR3*	3'-UTR, intron	0.5893	0.2474	C/T	4.950 (2.360, 10.380)	0.00002314
rs12945260	17	64939792	66943675	None		0.1786	0.0155	C/G	17.410 (4.356, 69.560)	0.00005296

Summary of five SNPs with allelic chi-square *p* values <1×10^{-4} from our genotype data.
3'-UTR, three prime untranslated region; Chr, chromosome; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

We also investigated 11 SNPs whose associations with FC were discovered in previous European studies, which identified only 1 SNP (rs6432860) in our set of SNPs.[12,13] The MAF of rs6432860 did not differ significantly between cases and controls, and there were overall discrepancies in the allele frequencies across ancestries in the general population (Supplementary Table 3 in the online-only Data Supplement). The MAF values for cases, controls, and the normal Korean population in this study were 0.125, 0.072, and 0.092, respectively, compared with 0.240, 0.296, and 0.309 in previous European studies.

Fine mapping of identified susceptibility loci

Among the three identified independent loci, we produced regional association plots for two regions to characterize these susceptibility loci where two SNPs with $p<1\times10^{-4}$ are located within 100 kb (Supplementary Fig. 1 in the online-only Data Supplement). Regions up to 200 kb from each susceptibility locus were visualized.

Among the two associated regions, the region where rs1159179 and rs7554295 are located on chromosome 1 is upstream of *PROX1* and downstream of *LINC00538*. We plotted all SNPs annotated with *PROX1* according to their location relative to the gene (Fig. 3). Most of the SNPs located upstream of *PROX1* showed *p* values <0.05, while all SNPs located in the intron or exon of *PROX1* showed *p* values >0.05. The MAF differences of the SNPs upstream of *PROX1* were more pronounced than in the European population (Table 2). The second region, where rs7043095 and rs6559331 are located on chromosome 9, is adjacent to the three prime untranslated region

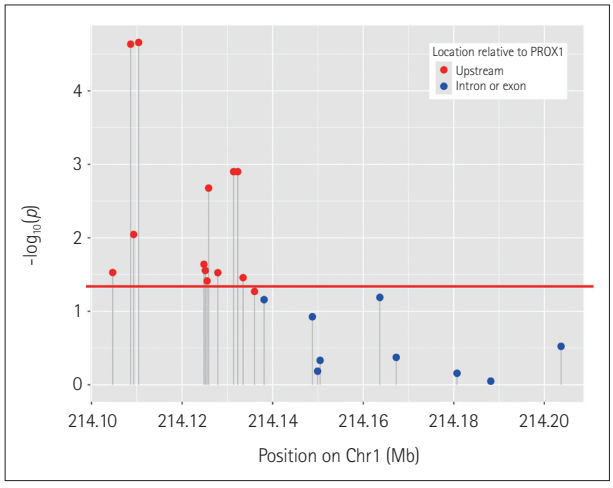

Fig. 3. Regional association plot of all SNPs annotated with *PROX1*. The 22 SNPs annotated with *PROX1* from our genotype data are plotted according to their position on Chr 1 with their -$\log_{10}(p)$ values. The red and blue dots indicate the SNPs located upstream of *PROX1* and inside *PROX1*, respectively. The red line indicates $p=5.0\times10^{-2}$. Chr, chromosome; Mb, megabase; SNP, single-nucleotide polymorphism.

Table 2. Summary of all SNPs annotated with *PROX1*

SNP	Chr	Position (GRCh37)	Position (GRCh38)	Region relative to *PROX1*	MAF				Alleles (major/minor)	OR (95% CI)	*p*
					Cases	Controls	Korea	Europe			
rs6696711	1	214104671	213931328	Upstream	0.107	0.245	0.242	0.457	T/C	0.355 (0.139, 0.903)	0.029640*
rs1159179	1	214108641	213935298	Upstream	0.589	0.247	0.338	0.072	C/T	4.950 (2.360, 10.380)	0.000023*
rs1008431	1	214109296	213935953	Upstream	0.304	0.505	0.431	0.530	C/G	0.411 (0.211, 0.801)	0.009009*
rs7554295	1	214110402	213937059	Upstream	0.589	0.245	0.339	0.072	T/C	4.958 (2.367, 10.380)	0.000022*
rs17762150	1	214124818	213951475	Upstream	0.107	0.247	0.231	0.543	C/T	0.333 (0.129, 0.859)	0.022920*
rs17762192	1	214125127	213951784	Upstream	0.107	0.242	0.230	0.457	G/C	0.346 (0.135, 0.891)	0.027900*
rs1367951	1	214125513	213952170	Upstream	0.107	0.237	0.226	0.457	A/G	0.375 (0.148, 0.950)	0.038610*
rs2075425	1	214125854	213952511	Upstream	0.286	0.531	0.445	0.574	G/A	0.346 (0.176, 0.680)	0.002104*
rs340840	1	214127887	213954544	Upstream	0.093	0.232	0.216	0.381	T/G	0.331 (0.122, 0.898)	0.029820*
rs340864	1	214131371	213958028	Upstream	0.268	0.526	0.436	0.558	G/A	0.320 (0.160, 0.640)	0.001257*
rs340863	1	214132290	213958947	Upstream	0.268	0.526	0.435	0.558	G/A	0.320 (0.160, 0.640)	0.001257*
rs7548778	1	214133468	213960125	Upstream	0.089	0.222	0.221	0.381	C/T	0.344 (0.128, 0.927)	0.034840*
rs12733434	1	214135997	213962654	Upstream	0.111	0.237	0.213	0.382	A/C	0.405 (0.162, 1.015)	0.053710
rs12089247	1	214138105	213964762	Intron	0.107	0.217	0.213	0.370	G/A	0.421 (0.165, 1.071)	0.069420
rs1431983	1	214148772	213975429	Intron	0.554	0.438	0.449	0.460	G/T	1.649 (0.880, 3.090)	0.118800
rs4655312	1	214149930	213976587	Intron	0.130	0.108	0.138	0.026	G/A	1.240 (0.485, 3.173)	0.653400
rs17021749	1	214150482	213977139	Intron, exon	0.143	0.108	0.137	0.026	C/T	1.400 (0.566, 3.463)	0.465900
rs340835	1	214163675	213990332	Intron	0.250	0.387	0.347	0.467	G/A	0.526 (0.266, 1.040)	0.064660
rs4655313	1	214167292	213993949	Intron	0.185	0.141	0.165	0.179	A/G	1.384 (0.624, 3.066)	0.423800
rs3767844	1	214180721	214007378	Intron	0.315	0.344	0.335	0.289	A/G	0.881 (0.466, 1.665)	0.696500
rs378414	1	214188173	214014830	Intron	0.107	0.113	0.148	0.035	T/G	0.935 (0.352, 2.487)	0.893500
rs12089523	1	214203699	214030356	Intron, exon	0.054	0.026	0.037	0.023	G/A	2.208 (0.494, 9.876)	0.300100

Summary of 22 SNPs annotated with *PROX1* from our genotype data. The SNPs are listed in numerical position order. Allele frequencies of the Korean and European populations were obtained from the KCDC and the 1000 Genomes Project phase3, respectively.

*$p<0.05$.

Chr, chromosome; CI, confidence interval; KCDC, Korea Centers for Disease Control and Prevention; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

and the intron of *C9orf47* and *S1PR3*.

Phenome-wide association study

We applied a PheWAS to five candidate SNPs and investigated the phenotypes with the most-significant relationships according to neurological categories. The phenotype with the most-significant relationship with rs7043095 was "partial epilepsy" (p=0.013), while the top-ranked phenotype of other SNPs was not related to epilepsy or seizure (Supplementary Fig. 2 in the online-only Data Supplement).

DISCUSSION

This study investigated the genetic components related to FC in patients with focal epilepsy. To avoid including genes related to focal epilepsy in general, we set the control group as focal epilepsy patients who had never experienced FC. Overall, our findings indicate that *PROX1* identified through the GWAS might be genetically relevant to the history of FC in patients with focal epilepsy.

A Danish research group conducted two large genetic investigations of FC using GWASs that were reported on in 2014 and 2022. Their first study identified four loci associated with FC: *SCN2A*, *SCN1A*, *ANO3*, and a region associated with magnesium levels.[22] Their subsequent larger-scale GWAS study identified seven novel loci in addition to the four previously reported loci: *PTGER3*, *IL10*, *BSN*, *ERC2*, *GABRG2*, *HERC1*, and *MAP3K9*.[13] However, some of these reported genes, including *GABRG2*, *SCN1A*, and *SCN2A*, were already known to be associated with epilepsy. We assume that the Danish research group was unable to eliminate the confounding factor of an epilepsy diagnosis, since they enrolled normal children as the control group.

We explored 1 of those 11 SNPs (rs6432860) and found that the tendency observed in the European population was not replicated in our data, which instead showed the opposite result. This might be because the SNP in the intron of *SCN1A* is related to epilepsy rather than specifically to FC. Additionally, this discordance probably originated from differences in genetic backgrounds across ancestries, highlighting the need for GWASs involving East Asian populations.

The first potential susceptibility locus of rs1159179 and rs7554295 on chromosome 1 is adjacent to *PROX1* and *LINC00538*. *PROX1*, which was not identified in previous Danish studies, encodes prospero-related homeodomain transcription factor and is expressed in the hippocampus, cortex, and other areas in the brain.[23-25] PROX is a key factor in the generation and differentiation of neural stem cells during adult hippocampal neurogenesis, since it is a target of the Wnt signaling pathway.[26] Moreover, this protein suppresses the Notch pathway to promote the differentiation of neural stem cells and cell-cycle withdrawal.[27] The expression of PROX1 has been shown to decrease under prolonged seizure activities, and activation of the Notch pathway can cause seizure activity in temporal lobe epilepsy.[28,29] Previous studies have indicated that a decrease in *PROX1* expression might activate the Notch pathway and induce seizure activity, since PROX1 plays a role in Notch pathway inhibition. Therefore, this locus may contribute to the risk of epilepsy following FC by influencing brain development and increasing the probability of seizure activity.

The SNPs upstream of *PROX1* showed larger significant differences between patients with focal epilepsy with and without a history of FC, in contrast with the SNPs inside *PROX1*. This finding suggests that the expression level of *PROX1*—rather than the function of the PROX1 protein—is influenced by this genetic difference, since regulatory regions such as promoters are usually located upstream of genes. Given this idea, we suggest that aberrant expression of *PROX1* accompanied by FC is attributable to seizure activities and the development of focal epilepsy. Our study was able to successfully identify a novel *PROX1* for the following reasons: 1) the entire population comprised focal epilepsy patients in order to remove the confounding factor of an epilepsy diagnosis, which contrasts with the approach taken in previous studies, and 2) our study population consisted entirely of individuals of Korean descent, while previous studies focused primarily on European populations.

LINC00538 is a long intergenic non-protein-coding RNA that is presumed to play a role in cell-cycle progression; however, further investigations are needed to determine its function in the brain.[30] The second potential susceptibility locus comprised rs7043095 and rs6559331 on chromosome 9 near *C9orf47* and *S1PR3*, which regulates cell proliferation, motility, apoptosis, and neurite retraction.[31] While the relationships of these two genes with neurological disorders have not been extensively documented, our PheWAS analysis of rs7043095 suggests that this SNP is associated with the progression of focal epilepsy in patients with FC (Supplementary Fig. 2 in the online-only Data Supplement).

Our study had some limitations. Firstly, because both the case and control groups comprised single-ancestry patients with focal epilepsy, the resulting relatively small numbers of cases and controls restricted the statistical power. Accordingly, significance criterion for the probability values ($p< 1\times10^{-4}$) was less stringent than in previous GWAS studies. Secondly, the biological impact of these SNPs has not yet been validated, highlighting the need for future functional studies. Expression quantitative trait loci analysis could help to reveal the relationships between these SNPs and *PROX1* ex-

pression, while gene-editing approaches such as CRISPR could uncover the roles of PROX1 in FC and epileptogenesis. Thirdly, even though our results indicate that *PROX1* might be more strongly associated with epilepsy following FC than with other cases with different etiologies, it is questionable whether these SNPs can be used to distinguish those who are likely to be diagnosed with epilepsy from among patients with a history of FC. This question could be addressed by comparing patients with FC showing a benign course with those with FC who are eventually diagnosed with epilepsy.

In conclusion, we have identified five novel SNPs in patients with focal epilepsy with a history of FC, two of which are located near *PROX1*. These SNPs are potential genetic markers indicative of a history of FC in patients with focal epilepsy. We further speculate that the SNPs upstream of *PROX1* contribute to epileptogenesis following FC, since PROX1 is implicated in adult hippocampal neurogenesis and seizure activity. This highlights *PROX1* as a promising therapeutic target due to its potential role in the pathogenesis of epilepsy.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2024.0296.

Availability of Data and Material

The summary statistics encompassing all SNPs analyzed in this GWAS can be accessed at the Figshare repository using the following DOI (digital object identifier): 10.6084/m9.figshare.25126148.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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