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Original Article

Immune Cell Phenotypes, Inflammatory Proteins and Epilepsy: A Mendelian Randomization Study to Investigate Causal Pathways

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Abstract

Background and objectives: Emerging evidence implicates immune dysregulation and neuroinflammation in the pathogenesis of epilepsy, yet the causal mechanisms remain unclear. This study aimed to investigate the causal effects of immune cells and inflammatory proteins on epilepsy and evaluate the mediating role of inflammatory proteins.

Methods: This study utilized the largest available genome-wide association study data on immune cell phenotypes and inflammatory proteins as exposures, and epilepsy genome-wide association study data from the FinnGen dataset as outcomes. Five Mendelian randomization (MR) methods were applied within a two-sample MR framework to assess causal effects. Furthermore, a two-step MR analysis was conducted to quantify the proportion of epilepsy and its subtypes influenced by immune cells through inflammatory proteins.

Results: The two-sample MR analysis identified 32 immune cell phenotypes associated with epilepsy risk (19 risk-increasing, e.g., $CD19^+$ B cells; 13 protective, e.g., regulatory T cell subsets). Subtype analyses revealed 30 immune phenotypes associated with generalized epilepsy and 26 with focal epilepsy. Eight inflammatory proteins showed suggestive causal effects on epilepsy: C-C chemokine ligand 23, C-X-C motif chemokine ligand 6, C-X-C motif chemokine ligand 11, and vascular endothelial growth factor A increased epilepsy risk, while interleukin-13 (IL-13), leukemia inhibitory factor receptor, tumor necrosis factor, and osteoprotegerin conferred protection. Mediation analysis indicated that inflammatory proteins mediated 6.3–13.5% of the immune effects on epilepsy. Specifically, $CD14^+CD16^+$ monocytes increased epilepsy risk through elevated C-C chemokine ligand 23 levels (8.5% mediation), while effector memory double-negative ($CD4^-CD8^-$) T cells reduced epilepsy risk via upregulation of IL-13 (6.3%). Sensitivity analyses confirmed the robustness of these findings (P heterogeneity/pleiotropy > 0.05). Although no associations reached Bonferroni-corrected significance, the findings implicate B cells, monocytes, regulatory T cells, and cytokines (e.g., IL-13, leukemia inhibitory factor receptor) in the pathogenesis of epilepsy, with inflammatory proteins acting as partial mediators.

Conclusions: These results enhance our understanding of immune-inflammatory pathways in epilepsy and highlight potential therapeutic targets. Future studies should validate these findings across diverse populations and further elucidate the molecular mechanisms underlying the identified associations.

Keywords: Immune cell; Inflammatory protein; Epilepsy; Pathogenesis; Mendelian randomization; Causal relationship.

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Introduction

Epilepsy represents a chronic and debilitating neurological condition marked by recurrent seizures caused by abnormal synchronized neuronal discharges.[1] Seizures, the hallmark of epilepsy, present with diverse and complex clinical presentations, although they often occur in a consistent or stereotypical manner in individual patients. The condition can affect individuals of any age, with the highest incidence observed in infants under one year of age

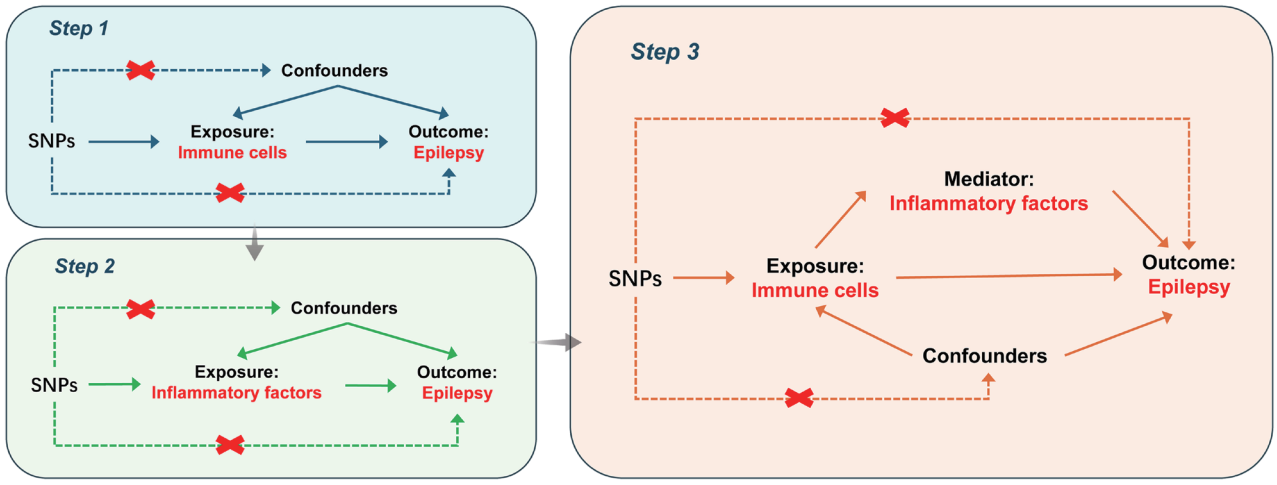

Fig. 1. Study flow chart. SNP, single-nucleotide polymorphism.

and adults over 50 years.[2] Epilepsy significantly impairs both the physiological and psychosocial well-being of patients and poses direct or indirect risks to their lives. Currently, it represents a major global public health challenge, affecting approximately 70 million people worldwide.[2]

The underlying mechanisms of epilepsy remain incompletely understood; however, increasing evidence highlights the critical roles of immune dysregulation and neuroinflammation in its pathogenesis.[3,4] Aberrant immune responses and neuroinflammatory activation have been consistently observed in both animal models of epilepsy and in epileptogenic brain regions of human patients.[5,6] Several inflammatory mediators released by immune cells are known to lower the neuronal excitability threshold, thereby facilitating seizure activity.[7] Therefore, elucidating the roles of specific immune phenotypes and inflammatory mediators in epilepsy is critical for advancing our comprehension of its pathophysiology and guiding the development of targeted therapeutic strategies.

Mendelian randomization (MR) is a robust analytical approach that utilizes genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and outcomes.[8] This methodology is based on Mendel's second law, which states that genetic variants are randomly assigned during gamete formation.[8] This randomization helps minimize the influence of reverse causation and confounding, common limitations in conventional observational studies.[9] MR has become an increasingly utilized tool in recent epidemiological research for exploring causal associations between epilepsy and various risk factors.[10,11] Notably, accumulating evidence from MR analyses has suggested potential causal links between epilepsy and immune cell phenotypes or inflammatory mediators.[12–14]

In this study, we leveraged novel genetic datasets to perform MR analyses aimed at elucidating the causal effects of circulating immune cells and inflammatory proteins on epilepsy. Given that inflammatory proteins are primarily produced through immune cell activity, we also conducted mediation analyses to assess the potential intermediary role of these proteins in the pathogenic pathways linking immune cells to epileptogenesis. These analyses are intended to advance our comprehension of the immunological and inflammatory mechanisms underlying epilepsy and to identify promising targets for therapeutic intervention.

Materials and methods

Study design

This study was designed around three key components, as depicted in Figure 1. The first component investigates the causal effects of 731 immune cell phenotypes on epilepsy and its subtypes. The second component examines the causal associations between epilepsy and 91 inflammatory proteins. The third component utilizes the two-step Mendelian randomization approach to conduct mediation analysis, estimating the extent to which inflammatory proteins mediate the effects of immune cell phenotypes on epilepsy. In the MR analysis, single nucleotide polymorphisms (SNPs) were employed as IVs, which must satisfy three key assumptions: (1) SNPs are strongly associated with the exposure; (2) SNPs are independent of confounding factors; and (3) SNPs influence the outcome solely through the exposure, without any direct effect on the outcome itself.

This study complied with the STROBE-MR reporting guidelines. Ethical approval was not required, as the analysis was based on publicly available genome-wide association studies (GWAS) summary statistics and did not involve access to individual-level data.

Data sources

The GWAS summary statistics for immune-related traits are accessible through the GWAS Catalog, with identifiers ranging from GCST90001391 to GCST90002121.[15] These datasets were generated from a Sardinian population cohort comprising 3,757 individuals, covering 731 distinct immunophenotypes. In parallel, GWAS summary statistics for inflammatory protein markers are also available in the GWAS Catalog, with reference numbers GCST90274758 to GCST90274848. These datasets originate from a large-scale protein quantitative trait locus analysis, which investigated 91 inflammation-associated proteins in a European-ancestry cohort of 14,824 participants.[16]

Regarding epilepsy-related genetic data, the GWAS summary statistics were extracted from the FinnGen project's tenth data release. FinnGen represents a comprehensive genomic initiative that has analyzed more than 500,000 biological samples from the Finnish population, correlating genetic variants with clinical outcomes to advance the understanding of disease etiology and ge-

netic risk factors.[17] In this study, the exposure and outcome data were sourced from two distinct, non-overlapping cohorts.

Instrument selection

In accordance with established methodologies,[15] IVs for each immune trait and inflammatory protein were selected at a significance threshold of $P < 5 \times 10^{-5}$. To eliminate the effects of linkage disequilibrium, all IVs were required to meet the criteria of $r^2 < 0.001$ and a physical distance > 10,000 kb. Furthermore, the F-statistic was calculated for each IV to assess its strength of association with the exposure. Variants with an F-statistic below 10, indicating weak correlation or limited explanatory power, were excluded to ensure IV robustness.[18]

MR analysis

We employed five distinct methods—inverse variance weighted (IVW), weighted median, MR-Egger, weighted mode, and simple mode—to perform two-sample MR analysis. These analyses evaluated the causal effects of 731 immune cell phenotypes and 91 inflammatory proteins on epilepsy. The IVW method served as the primary analytical approach. Statistical significance required an IVW *P*-value < 0.05 and consistent effect direction across the other four MR methods. MR results were quantified using odds ratios (ORs) accompanied by 95% confidence intervals (CIs).

Additionally, a two-step Mendelian randomization approach was employed for mediation analysis to explore whether immune cells influence epilepsy risk by modulating inflammatory protein levels. First, the total causal effect (β_total) of immunophenotypes on epilepsy risk was established using primary MR analysis. Subsequently, a two-step mediation framework was constructed: (1) MR analysis evaluating immunophenotypes as exposures associated with inflammatory protein levels (β1, $P < 0.05$), followed by (2) MR assessment of inflammatory proteins as exposures influencing epilepsy risk (β2, $P < 0.05$). The mediation effect was quantified using the product-of-coefficients approach: β_mediation = β1 × β2. The direct effect was calculated as: β_direct = β_total - β_mediation. Directional consistency was confirmed between the mediation and total effects. The proportion mediated was computed as (β_mediation/β_total) × 100%.

To address multiple testing, Bonferroni correction was applied to adjust the significance thresholds. The corrected thresholds were set at 0.0000684 (0.05/731) for immune cells and 0.0005495 (0.05/91) for inflammatory proteins. P-values below these corrected thresholds were interpreted as indicating definitive causal effects, while those above the corrected thresholds but below 0.05 were considered suggestive of potential causal effects. This rigorous approach ensures robust and reliable identification of causal relationships while minimizing the risk of false positives.

Sensitivity analysis

To ensure the robustness and validity of our findings, we implemented a comprehensive sensitivity analysis framework. First, between-instrument heterogeneity was assessed using Cochrane's Q test. When significant heterogeneity ($P < 0.05$) was detected, a random-effects IVW model was employed to account for potential variability across genetic instruments. To address biases from horizontal pleiotropy, we employed two complementary analytical approaches: (1) MR-Egger regression, where a non-zero intercept ($P < 0.05$) indicated directional pleiotropy; and (2) Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) analysis, which systematically identified and removed outlier variants with disproportionate influence on the causal estimates. Additionally, leave-one-out analyses were conducted by sequentially excluding individual IVs and recalculating the IVW estimates to detect influential variants and assess the consistency of the results. All analyses were performed using R software (version 4.3.1). The TwoSampleMR and MR-PRESSO packages were employed for data analysis and visualization.

Results

Causal effects of immune traits on epilepsy

Our study revealed potential correlations between 32 immune cell types and epilepsy, including seven B cell types, three myeloid cell types, four monocyte types, four maturation stages of T cell types, four TBNK types, eight regulatory T cell (Treg) types, and two conventional dendritic cells types (Fig. 2). IVW results showed that 19 immune cell types, including $CD14^+$ $CD16^+$ monocyte absolute count (AC) (OR = 1.038, 95% CI: 1.004–1.073, $P = 0.027$), CD28 on CD4 Treg (OR = 1.022, 95% CI: 1.001–1.044, $P = 0.044$), natural killer (NK) AC (OR = 1.047, 95% CI: 1.007–1.088, $P = 0.020$), and human leukocyte antigen-DR isotype on plasmacytoid dendritic cell (OR = 1.021, 95% CI: 1.003–1.040, $P = 0.026$) were positively associated with the risk of epilepsy. Conversely, 13 immune cell types, including IgD^+ $CD38^-$ AC (OR = 0.935, 95% CI: 0.888–0.983, $P = 0.009$), effector memory double-negative (EM DN $CD4^-CD8^-$) %DN (OR = 0.971, 95% CI: 0.946–0.997, $P = 0.031$), $CD14^-$ $CD16^-$ AC (OR = 0.982, 95% CI: 0.966–0.999, $P = 0.038$), and $CD28^-$ $CD25^{++}$ CD8br AC (OR = 0.969, 95% CI: 0.944–0.995, $P = 0.021$) were negatively associated with the risk of epilepsy. Moreover, MR studies on the two major subtypes of epilepsy indicated that 30 immune cell types were causally associated with generalized epilepsy (File S1: Fig. S2), and 26 immune cell types were causally associated with focal epilepsy (File S1: Fig. S1). It is noteworthy that certain immune cell types may have promotive or inhibitory effects on multiple types of epilepsy. After adjusting for multiple testing using the Bonferroni correction method, no immunophenotypes were detected at the corrected threshold for significance.

Causal effects of inflammatory proteins on epilepsy

A total of 13 circulating inflammatory proteins were identified as potentially causally linked to epilepsy and its subtypes (Fig. 3). C-C chemokine ligand 23 (CCL23, OR = 1.069, 95% CI: 1.011–1.131, $P = 0.019$), C-X-C motif chemokine ligand 11 (CXCL11, OR = 1.076, 95% CI: 1.006–1.150, $P = 0.032$), CXCL6 (OR = 1.048, 95% CI: 1.003–1.095, $P = 0.038$), and vascular endothelial growth factor A (VEGF_A, OR = 1.073, 95% CI: 1.025–1.123, $P = 0.003$) may promote the onset of epilepsy, while interleukin-13 (IL-13, OR = 0.948, 95% CI: 0.901–0.998, $P = 0.040$), leukemia inhibitory factor receptor (LIF-R, OR = 0.916, 95% CI: 0.852–0.984, $P = 0.017$), osteoprotegerin (OPG, OR = 0.923, 95% CI: 0.859–0.992, $P = 0.030$), and tumor necrosis factor (TNF, OR = 0.929, 95% CI: 0.874–0.987, $P = 0.018$) have the potential to inhibit the occurrence of epilepsy. Furthermore, CXCL6 (OR = 1.060, 95% CI: 1.001–1.122, $P = 0.045$) exhibited a promotive effect, while IL-13 (OR = 0.902, 95% CI: 0.846–0.962, $P = 0.002$), LIF-R (OR = 0.897, 95% CI: 0.830–0.969, $P = 0.006$), and TNF (OR = 0.922, 95% CI: 0.856–0.994, $P = 0.034$) exerted inhibitory effects in focal epilepsy. Additionally, eukaryotic initiation factor 4E binding protein 1 (OR = 0.695, 95% CI: 0.533–0.906, $P = 0.007$) and IL-12B (OR = 0.815, 95% CI: 0.671–0.990, $P = 0.039$) were negatively

Panel	Trait	nSNP	OR (95%CI)	P-value
B cell	IgD+ CD38- AC	17	0.9346 (0.8884-0.9832)	0.0089
B cell	CD19 on IgD+ CD38-	31	1.0174 (1.0007-1.0343)	0.0408
B cell	CD19 on IgD+ CD38dim	24	1.0208 (1.0019-1.0400)	0.0307
B cell	CD19 on IgD+	27	1.0163 (1.0006-1.0324)	0.0423
B cell	CD25 on IgD+ CD38br	13	0.9450 (0.9019-0.9902)	0.0177
B cell	CD25 on IgD- CD38-	22	1.0338 (1.0039-1.0646)	0.0262
B cell	CD25 on IgD- CD38br	19	0.9238 (0.8775-0.9725)	0.0025
Myeloid cell	CD33dim HLA DR- AC	24	0.9824 (0.9702-0.9947)	0.0052
Myeloid cell	Basophil AC	23	0.9825 (0.9701-0.9951)	0.0066
Myeloid cell	HLA DR on CD33br HLA DR+ CD14	25	1.0216 (1.0071-1.0363)	0.0034
Maturation stages of T cell	Naive CD4+ %CD4+	35	0.9713 (0.9440-0.9993)	0.0447
Maturation stages of T cell	Naive CD8br AC	27	0.9652 (0.9418-0.9892)	0.0047
Maturation stages of T cell	CM DN (CD4-CD8-) AC	4	1.0540 (1.0192-1.0901)	0.0022
Maturation stages of T cell	EM DN (CD4-CD8-) %DN	28	0.9713 (0.9458-0.9974)	0.0315
Monocyte	CD14+ CD16+ monocyte AC	20	1.0381 (1.0042-1.0730)	0.0271
Monocyte	CD14- CD16- AC	24	0.9824 (0.9660-0.9990)	0.0383
Monocyte	CD16+ monocyte %monocyte	22	1.0475 (1.0041-1.0927)	0.0316
Monocyte	CD64 on CD14- CD16-	16	1.0826 (1.0361-1.1312)	0.0004
TBNK	HLA DR+ CD4+ %lymphocyte	21	1.0659 (1.0165-1.1177)	0.0083
TBNK	B cell %lymphocyte	34	1.0421 (1.0060-1.0795)	0.0217
TBNK	NK AC	22	1.0467 (1.0072-1.0878)	0.0201
TBNK	Granulocyte AC	24	0.9572 (0.9175-0.9987)	0.0435
Treg	CD39+ CD4+ %T cell	31	0.9796 (0.9641-0.9954)	0.0115
Treg	CD28+ CD45RA- CD8dim AC	36	1.0089 (1.0027-1.0151)	0.0050
Treg	CD28- CD25++ CD8br AC	25	0.9692 (0.9438-0.9952)	0.0205
Treg	CD28 on CD4 Treg	24	1.0218 (1.0006-1.0435)	0.0439
Treg	CD127 on granulocyte	31	1.0319 (1.0028-1.0618)	0.0313
Treg	CD25 on CD45RA+ CD4 not Treg	22	1.0287 (1.0083-1.0495)	0.0055
Treg	CD4 on resting Treg	13	0.9423 (0.8961-0.9909)	0.0206
Treg	CD4 on CD39+ secreting Treg	22	1.0192 (1.0000-1.0387)	0.0498
cDC	HLA DR on plasmacytoid DC	23	1.0213 (1.0025-1.0404)	0.0260
cDC	HLA DR on DC	19	1.0325 (1.0097-1.0558)	0.0050

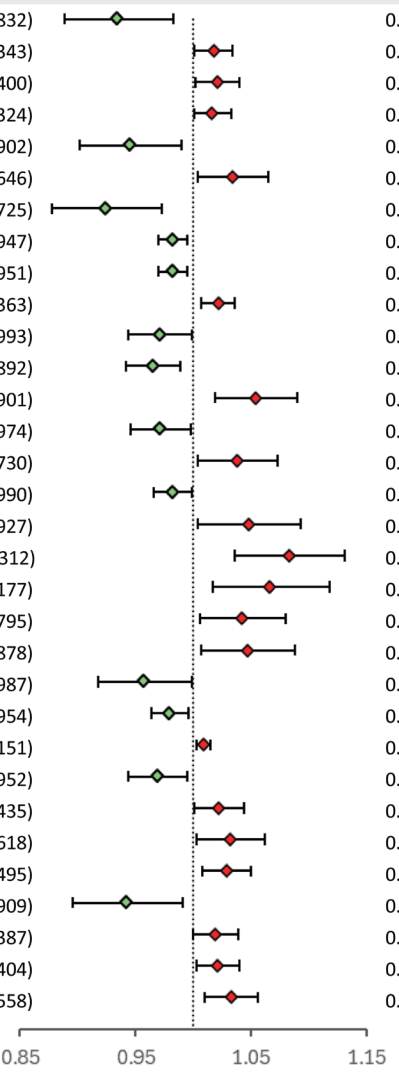

Fig. 2. Causal effects between immunophenotypes and epilepsy. AC, absolute count; CD, cluster of differentiation; cDC, conventional dendritic cells; CI, confidence interval; CM, central memory; DC, dendritic cell; DN, double-negative; EM, effector memory; HLA-DR, human leukocyte antigen-DR isotype; Ig, immunoglobulin; NK, natural killer; nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; TBNK, T-cell, B-cell, and natural killer cell panel; Treg, regulatory T cells.

correlated with the risk of generalized epilepsy, while CD5 (OR = 1.280, 95% CI: 1.031–1.591, $P = 0.026$) and interleukin 10 receptor subunit beta (OR = 1.172, 95% CI: 1.045–1.315, $P = 0.007$) showed positive correlations. After applying the Bonferroni correction for multiple testing, no circulating inflammatory proteins were found to have a definitive causal effect on epilepsy.

Mediation analysis of inflammatory factors

We employed a two-step Mendelian randomization approach to conduct a mediation analysis to further explore the mediating role of inflammatory proteins. Six inflammatory proteins (VEGF_A, IL-13, CCL23, LIF-R, CXCL11, OPG) were identified as mediators between immune cells and epilepsy (Table 1). $CD14^+$ $CD16^+$ monocyte AC and human leukocyte antigen-DR isotype on plasmacytoid dendritic cell were found to promote the occurrence of epilepsy through increased CCL23, with mediation effects accounting for 8.5% and 6.5%, respectively. NK AC was found to promote epilepsy, with 13.5% of the effect mediated through CXCL11. On the other hand, EM DN ($CD4^-CD8^-$) %DN exerted a protective effect on epilepsy through promoting IL-13 (6.3%); $CD14^-$ $CD16^-$ AC inhibited the occurrence of epilepsy through promoting LIF-R (12.4%); $CD28^-$ $CD25^{++}$ CD8br AC exerted a protective effect on epilepsy through promoting OPG (7.3%).

The mediating effects of inflammatory proteins were also observed in the analysis of different subtypes of epilepsy. For focal epilepsy, CD127 on CD8br exerted a detrimental effect by decreasing IL-13 (13.6%), while $CD14^-$ $CD16^-$ AC exerted a protective effect by increasing LIF-R (10.4%). For generalized epilepsy, naive-mature B cell %lymphocyte and $CD16^-CD56$ on NK exerted a detrimental effect by increasing CD5, whereas CD4 on $CD45RA^+$ $CD4^+$ exerted a protective effect by decreasing CD5. Furthermore, $CD14^+$ $CD16^+$ monocyte %monocyte promoted the occurrence of

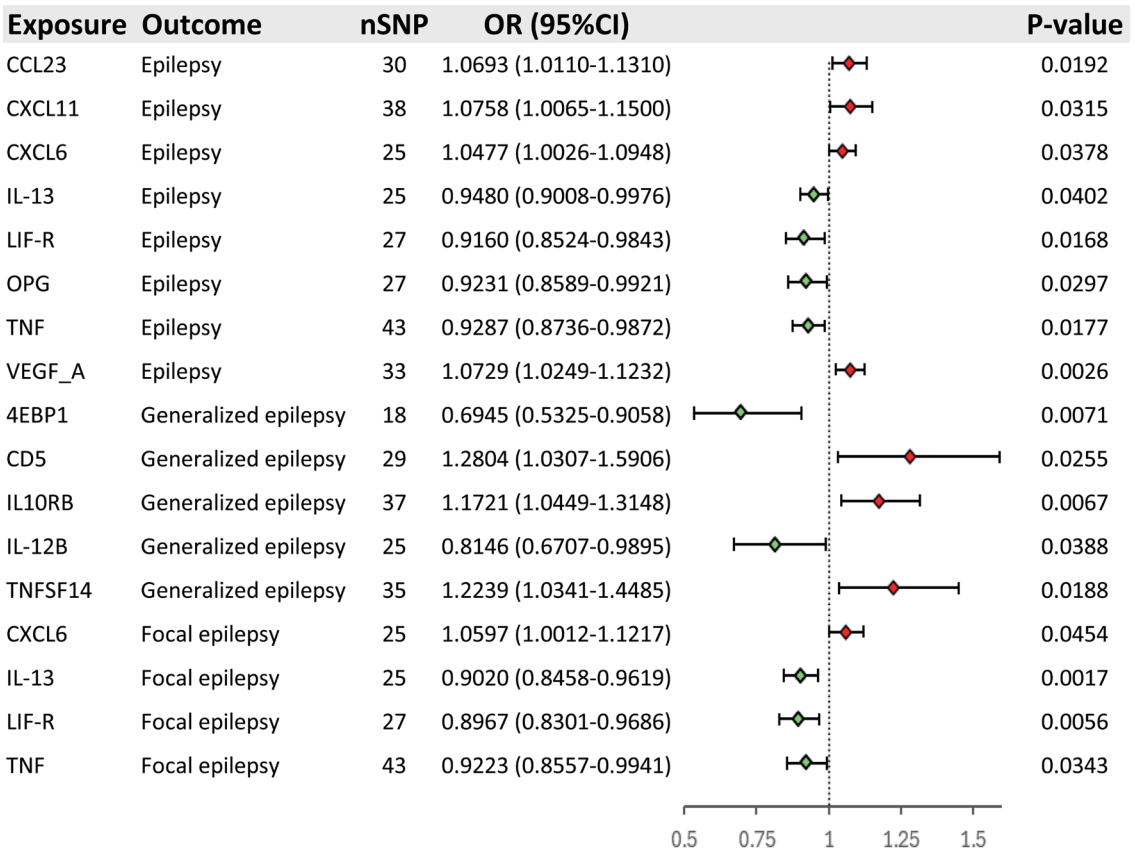

Fig. 3. Causal effects between inflammatory proteins and epilepsy. CD, cluster of differentiation; CI, confidence interval, CCL, C-C chemokine ligand; CXCL, C-X-C motif chemokine ligand; IL, interleukin; IL10RB, interleukin 10 receptor subunit beta; LIF-R, leukemia inhibitory factor receptor; nSNP, number of single-nucleotide polymorphisms; OPG, osteoprotegerin; OR, odds ratio; TNF, tumor necrosis factor; TNFSF, tumor necrosis factor superfamily protein; VEGF_A, vascular endothelial growth factor A; 4EBP1, eukaryotic initiation factor 4E binding protein 1.

generalized epilepsy by decreasing IL-12B (8.7%), while CD4 on $CD45RA^+$ $CD4^+$ inhibited its occurrence by decreasing tumor necrosis factor superfamily protein 14 (8.0%).

Sensitivity analysis

We excluded immune cells and inflammatory proteins exhibiting horizontal pleiotropy as identified by MR-Egger regression and MR-PRESSO analysis, ensuring that our results were not influenced by horizontal pleiotropy ($P > 0.05$; File S2: Tables S4, S6, S8, S12). Assessment of between-variant heterogeneity using Cochran's Q test indicated no substantial heterogeneity across our MR analyses ($P > 0.05$; File S2: Tables S4, S6, S8, S12). Furthermore, scatter plots, forest plots, funnel plots, and leave-one-out plots were also employed to further demonstrate the reliability of our results (File S1). Concordant causal directions were observed across five complementary MR methods (IVW, weighted median, MR-Egger, weighted mode, simple mode), with detailed results shown in scatter plots. Funnel plots demonstrated no evidence of influential outliers, with all scatter points exhibiting symmetrical distribution patterns around the IVW estimate axis. Sensitivity analyses revealed no outlier SNPs influencing results in leave-one-out testing. Considering the potentially overly stringent nature of Bonferroni correction, we additionally performed a false discovery rate adjustment for multiple testing. Unfortunately, no significant findings remained after correction.

Discussion

In this study, we employed MR analysis to investigate the causal relationship between peripheral immune cells and epilepsy, and to determine whether this relationship is mediated through inflammatory proteins. The results revealed suggestive causal associations between 32 immune phenotypes and epilepsy. Among these immune phenotypes, 13 were associated with reduced epilepsy risk, while 19 were linked to increased risk. Furthermore, we identified potential causal relationships between eight out of 91 investigated inflammatory proteins and epilepsy incidence — four demonstrating positive associations and four showing negative correlations. Mediation analysis demonstrated that five inflammatory proteins mediated the effects of six immune cells on epilepsy, accounting for 6.3% to 13.5% of the total effect.

We found that several phenotypes of CD19-positive B lymphocytes are causally associated with epilepsy and its subtypes, contributing to increased susceptibility to epilepsy. Hansen *et al*.[19,20] also found increased expression of $CD19^+$ B cells in temporal lobe epilepsy caused by autoantibody-negative limbic encephalitis, which correlates with patients' memory impairments. Furthermore, our mediation analysis identified that within the B lymphocyte phenotype, naive-mature B cell % lymphocyte can promote generalized epilepsy by upregulating CD5. CD5 is a cysteine-rich scavenger receptor family glycoprotein that exhibits constitutive expression across mature T lymphocytes and specific B cell sub-

Table 1. The mediating effect of inflammatory proteins between immune cell phenotypes and epilepsy

Outcome	Exposure	Mediator	Total effect (β)	Indirect effect (β1*β2)	Direct effect (β-β1*β2)	Proportion (β1*β2/β)
Epilepsy	IgD^+ $CD38^-$ AC	VEGF_A	−0.0676	0.0507 × 0.0704	−0.0712	–
	EM DN ($CD4^-CD8^-$) %DN	IL-13	−0.0292	0.0344 × −0.0534	−0.0273	6.29%
	$CD14^+$ $CD16^+$ monocyte AC	CCL23	0.0347	0.0472 × 0.0670	0.0342	8.46%
	$CD14^-$ $CD16^-$ AC	LIF-R	–0.0178	0.0252 × −0.0877	−0.0156	12.43%
	NK AC	CXCL11	0.0457	0.0845 × 0.0731	0.0395	13.52%
	$CD28^-$ $CD25^{++}$ CD8br AC	OPG	−0.0313	0.0285 × −0.0800	−0.0290	7.29%
	CD28 on CD4 Treg	LIF-R	0.0216	0.0207 × −0.0877	0.0234	–
	HLA DR on plasmacytoid DC	CCL23	0.0210	0.0205 × 0.0670	0.0197	6.52%
	HLA DR on DC	LIF-R	0.0320	0.0221 × −0.0877	0.0339	–
	HLA DR on CD33br HLA DR^+ $CD14^-$	OPG	0.0214	0.0162 × −0.0800	0.0227	–
Focal epilepsy	CD127 on CD8br	IL-13	0.0523	−0.0691 × −0.1031	0.0451	13.63%
	CD8 on NKT	IL-13	−0.0527	−0.0396 × −0.1031	−0.0567	–
	$CD14^-$ $CD16^-$ AC	LIF-R	−0.0265	0.0252 × −0.1090	−0.0238	10.36%
	CD8 on NKT	TNF	−0.0527	−0.0325 × −0.0809	−0.0553	–
Generalized epilepsy	CD4 on $CD45RA^+$ $CD4^+$	4EBP1	−0.0995	−0.0295 × −0.3646	−0.1102	–
	Naive-mature B cell %lymphocyte	CD5	0.1798	0.0445 × 0.2472	0.1688	6.12%
	CD16-CD56 on NK	CD5	0.1044	0.0253 × 0.2472	0.0982	5.98%
	CD4 on $CD45RA^+$ $CD4^+$	CD5	−0.0995	−0.0309 × 0.2472	−0.0918	7.67%
	$CD14^+$ $CD16^+$ monocyte %monocyte	IL-12B	0.1076	−0.0456 × −0.0205	0.0983	8.69%
	TCRgd %T cell	TNFSF14	−0.0816	0.0463 × 0.2020	−0.0909	–
	CD4 on $CD45RA^+$ $CD4^+$	TNFSF14	−0.0995	−0.0392 × 0.2020	−0.0916	7.97%

AC, absolute count; CCL, C-C chemokine ligand; CD, cluster of differentiation; DC, dendritic cell; DN, double-negative; EM, effector memory; HLA-DR, human leukocyte antigen-DR isotype; Ig, immunoglobulin; IL, interleukin; LIF-R, leukemia inhibitory factor receptor; NK, natural killer; OPG, osteoprotegerin; TCR, T cell receptor; TNF, tumor necrosis factor; TNFSF, tumor necrosis factor superfamily protein; VEGF_A, vascular endothelial growth factor A; 4EBP1, eukaryotic initiation factor 4E binding protein 1.

sets, with the capability to modulate intracellular signaling strength induced by antigen receptors in T and B cells.[21] Prayson *et al*.[22] reported the presence of $CD5^+$ T lymphocyte infiltration in the brain tissue of patients with refractory epilepsy caused by Rasmussen's encephalitis. Our study unveiled that CD5 increases susceptibility to generalized epilepsy, with three types of immune cells (naive-mature B cell % lymphocyte, CD16-CD56 on NK cells, and CD4 on $CD45RA^+$ $CD4^+$ cells) capable of modulating CD5 levels to impact epilepsy risk.

Previous studies have indicated monocyte infiltration in the brain tissue of epilepsy patients, which can promote inflammatory responses and exacerbate neuronal damage.[23] Our study found that various monocyte phenotypes can increase the risk of epilepsy, while certain monocyte phenotypes can also decrease this risk. This suggests that monocytes may have dual effects on epilepsy, with the impact depending on monocyte phenotype. Yamanaka *et al*.[24] discovered that levels of intracellular cytokines in peripheral blood monocytes of patients with epilepsy were higher than those in normal control groups, suggesting that inflammatory factors play an intermediary role between monocytes and epilepsy. CCL23 is a chemokine that inhibits the production and release of polymorphonuclear leukocytes and monocytes,[25] and participates in inflammatory responses by stimulating the production of adhesion molecules and pro-inflammatory cytokines.[26] Several studies have reported the role of CCL23 in the inflammatory response associated with Alzheimer's disease, cerebral hemorrhage, and acute brain injury.[27–29] We found that CCL23 promotes epilepsy, and that $CD14^+$ $CD16^+$ monocyte AC increases epilepsy risk by enhancing CCL23 levels. Leukemia inhibitory factor and ciliary neurotrophic factor are neurotrophic factors that exert their effects via receptor complexes involving the LIF-R, playing crucial roles in neuron survival and maintenance.[30] We discovered that LIF-R can decrease susceptibility to epilepsy, and $CD14^-$ $CD16^-$ AC reduces epilepsy risk by enhancing LIF-R. Rosell *et al*.[31] found a rapid, intense, and transient upregulation of leukemia inhibitory factor in the brain after epileptic seizures, accompanied by high expression of LIF-R in the hippocampus. These changes may relate to neuronal damage repair after seizures. Additionally, within the monocyte phenotype, we also discovered that $CD14^+$ $CD16^+$ monocyte % monocyte promotes the occurrence of generalized epilepsy by reducing IL-12B.

Treg cells can suppress immune responses, and their protective role in epilepsy has been demonstrated.[32,33] Similarly, in our study, we found that various Treg cell phenotypes confer protective effects against epilepsy. $CD39^+$ $CD4^+$ % T cells and $CD28^-$ $CD25^{++}$ CD8br AC protect against focal epilepsy; $CD39^+$ CD8br % T cells, $CD28^-$ CD8br AC, and CD4 on resting Treg cells protect against generalized epilepsy. Moreover, through mediation analysis, we

discovered that OPG can reduce susceptibility to epilepsy and that $CD28^{-}$ $CD25^{++}$ CD8br AC can upregulate OPG. OPG, together with receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL), constitutes the RANKL/RANK/OPG axis, which is primarily involved in regulating bone metabolism.[34] However, research has also reported the neuroprotective effects of OPG after brain injury.[35] Additionally, we observed that certain Treg cell subtypes may promote epilepsy, suggesting a dual role of Treg cells in epilepsy. IL-13 is an anti-inflammatory cytokine that can ameliorate neuroinflammation and promote functional recovery after brain injury.[36,37] Qi *et al*.[38] found elevated levels of IL-13 in the hippocampus of epileptic rats after vagus nerve stimulation therapy, indicating a protective role of IL-13 in epilepsy. Our findings are consistent with this, and we further discovered that CD127 on CD8br promotes epilepsy by downregulating IL-13. Furthermore, several studies have reported alterations in NK cells, $CD4^{+}$ T cells, and $CD8^{+}$ T cells in the peripheral blood of epilepsy patients.[39–41] In our study, we also found that the phenotype of NK cells, maturation stages of T cells, and conventional dendritic cells can influence susceptibility to epilepsy.

The correlation between inflammatory factors and immune responses suggests that certain inflammatory factors may play critical roles in the pathophysiological processes through which immune reactions induce epilepsy. In our study, we identified six types of immune cells that influence epileptogenesis by modulating the levels of five inflammatory proteins. However, the mediating effects of these inflammatory proteins were limited (proportion of effect: 6.3–13.5%), indicating that additional pathways may mediate this pathological process. Consistent with our findings, previous studies have reported other mediators bridging immune responses and epileptogenesis. Research by Chen *et al*.[42] suggests that the paraxanthine/linoleate (18:2n6) ratio might act as a mediator in the causal association between $CD64^{+}$ immune cells ($CD14^{-}CD16^{-}$) and epilepsy, accounting for 5.05% of the observed mediation effect.

In our research, distinct phenotypes of immune cells, such as monocytes and Tregs, exhibit differential impacts on epilepsy, with certain subsets increasing seizure susceptibility while others confer neuroprotection. This dual functionality of immune cells appears intrinsically linked to their subtype differentiation patterns. For example, classical monocytes ($CD14^{++}CD16^{-}$) predominantly mediate innate immune responses through expression of chemokines, scavenger receptors, and pro-inflammatory cytokines, facilitating phagocytosis and tissue migration; intermediate monocytes ($CD14^{++}CD16^{+}$) demonstrate enhanced capacity for antigen processing/presentation and participate in monocyte activation and inflammatory processes; non-classical monocytes ($CD14^{+}CD16^{++}$) primarily execute vascular surveillance and patrolling functions.[43] Furthermore, microenvironmental cues dynamically modulate immune cell functional polarization, with monocyte subsets demonstrating divergent operational plasticity in homeostatic versus pathological states.[44] Macrophages exhibit functional plasticity through microenvironment-driven polarization into pro-inflammatory M1 or anti-inflammatory M2 phenotypes.[45] Factors including activation states, environmental influences, or the functional differentiation of cell subtypes could play significant roles in modulating their effects on epilepsy. Further investigation into the conditions or contexts under which these immune cell phenotypes might promote or suppress epilepsy will advance the mechanistic understanding of epilepsy immunopathology.

Our study employed distinct immune cell profiles and inflammatory proteins as research targets, revealing their potential causal relationships with epileptogenesis and offering novel perspectives and methodological approaches to elucidate the pathological axis of "immune-inflammation-epilepsy". Regrettably, current evidence remains predominantly correlational and insufficient to confirm these immune phenotypes and inflammatory proteins as direct etiological factors in epilepsy. Future validation through large-scale clinical trials and longitudinal follow-up studies will be required to better assess the potential clinical utility of these findings in epilepsy diagnosis and therapeutic strategies.

There are certain limitations in this study that should be noted. Firstly, despite incorporating 731 immune cell phenotypes and 91 inflammatory proteins, numerous immune cell phenotypes and inflammatory proteins could not be analyzed due to data insufficiency. Therefore, future studies will need to include additional immune cell phenotypes and inflammatory proteins for a more systematic and comprehensive analysis. Secondly, the number of significant SNPs in GWAS data for immune cells and inflammatory proteins is limited, so we employed a relatively lenient criterion ($P < 5 \times 10^{-5}$) for selecting IVs. Due to the potential reduction in statistical power caused by weak IVs in MR analysis, subsequent studies will need to utilize more robust IVs to validate our conclusions. Thirdly, the data predominantly originate from individuals of European ancestry, thereby precluding direct extrapolation of the conclusions to other racial or ethnic populations. Subsequent studies are needed to conduct MR analyses using GWAS data from other ethnicities to validate the generalizability of our findings. Fourthly, the immunophenotype data (Sardinian cohort) and inflammatory protein data (European cohort) differ in population structure and measurement protocols. Despite allele alignment and linkage disequilibrium pruning to reduce errors, residual heterogeneity may affect causal estimates, requiring validation in homogeneous populations. Finally, while this study utilized MR analysis to infer causal relationships, the conclusions remain largely correlative in nature and do not explore specific molecular mechanisms. Future investigations will employ multi-omics approaches, including snRNA-seq and RNA-seq data, to systematically characterize key molecular pathways and cellular subpopulations.

Conclusions

By integrating conventional and mediation Mendelian randomization approaches, we identified suggestive causal relationships between immune signatures and epilepsy risk, while uncovering mediating roles of specific inflammatory proteins in this pathological cascade. These findings offer novel perspectives and approaches for delineating the "immune-inflammation-epilepsy" pathogenic axis. Future studies should validate these findings across diverse populations and elucidate the molecular mechanisms underlying the identified associations.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Study concept and design (HT, JW), acquisition of data (GW, ML), analysis and interpretation of data (GW, ML, XS, HW), drafting of the manuscript (GW, ML, HW), critical revision of the manuscript for important intellectual content (HT, JW, XS), administrative, technical, or material support (HT, JW), and study supervision (HT). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

Ethical approval was not required, as the analysis was based on publicly available GWAS summary statistics and did not involve access to individual-level data.

Data sharing statement

The data and data processing utilized in this study can be accessed through the first author or corresponding author upon reasonable request.

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