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Causal relationship between immune cells and Guillain-Barré syndrome: a Mendelian randomization study

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Objective: The aim of this study was to investigate the causal effect of immune cell phenotype on GBS using two-sample Mendelian randomization (MR) approach.

Methods: This study used MR to investigate the causal relationship between 731 immune cell phenotypes and GBS. We used Inverse variance weighted, Weighted median, MR Egger, Simple mode, Weighted mode for MR analysis. We also used the Cochran Q test, MR-Egger intercept test, IVW regression and MR-PRESSO, leave-one-out analysis to assess the presence of horizontal pleiotropy, heterogeneity and stability, respectively.

Results: Our study revealed a causal relationship between 33 immune cell phenotypes and GBS. Twenty immunophenotypes were observed to be associated with GBS as risk factors. For example, CD20 on IgD+ CD38dim in the B cell group (OR = 1.313, 95%CI:1.042-1.654, p = 0.021), CD3 on CD4 Treg in Treg cell group (OR = 1.395, 95%CI:1.069–1.819, p = 0.014), CD3 on TD CD8br in Maturation stages of T cell group (OR = 1.486, 95%CI:1.025-2.154, p = 0.037), CD16 on CD14+ CD16+ monocyte in Monocyte group (OR = 1.285, 95%CI:1.018-1.621, p = 0.035), CD33dim HLA DR+ CD11b+%CD33dim HLA DR+ in Myeloid cell group (OR = 1.262, 95%CI:1.020-1.561, p = 0.032), HLA DR+ NK AC in TBNK cell group (OR = 1.568, 95%CI:1.100-2.237, p = 0.013). Thirteen immune phenotypes are associated with GBS as protective factors. For example, CD19 on PB/PC in the B cell group (OR = 0.577, 95%CI:0.370-0.902, p = 0.016), CD4 Treg AC in Treg cell group (OR = 0.727, 95%CI:0.538-0.983, p = 0.038), CD11c + monocyte %monocyte in cDC group (OR = 0.704, 95%CI:0.514-0.966, p = 0.030), CX3CR1 on CD14+ CD16- monocyte in Monocyte group (OR = 0.717, 95%CI:0.548-0.939, p = 0.016), Mo MDSC AC in Myeloid cell group (OR = 0.763, 95%CI:0.619-0.939, p = 0.011), CD45 on granulocyte in TBNK group (OR = 0.621, 95%CI:0.391-0.984, p = 0.042).

Conclusion: The findings suggest that certain specific immune cell phenotypes, particularly B cell and Treg cell subpopulations, are causally associated with GBS, providing potential targets for the clinical treatment of GBS.

KEYWORDS

Mendelian randomization, genome-wide association study, immune cells, Guillain-Barré syndrome, causal relationship

1 Introduction

Guillain-Barré syndrome (GBS) is a peripheral neurological disorder that mainly involves nerve roots and peripheral nerves, and is usually triggered by infections, such as intestinal or respiratory infections (1). The onset of GBS is usually rapid, with rapid progression within hours to days, peaking within 2–4 weeks, and is characterized by symmetrical movement disorders. Typical signs and symptoms include weakness or paralysis of the limbs, sensory deficits, loss of reflexes, pain, autonomic dysfunction, facial paralysis, dysphagia and respiratory distress (2). Most patients with GBS partially improve or recover with treatment, while a few may still have prolonged weakness or other problems (3, 4). Epidemiological studies have shown that the global annual incidence of GBS is approximately 1–2/100,000 population, with high mortality and disability rates, and that it occurs in males and in people over 50 years of age (5, 6).

Unfortunately, the exact pathogenesis of GBS is not yet fully understood and is usually considered to be closely related to factors such as respiratory or intestinal infections, recent immunizations and autoimmune diseases. These factors may induce an abnormal immune system response, causing the immune system to mistakenly attack the peripheral nerves, which in turn destroys the myelin sheath. It is noteworthy that GBS is clinically categorized into demyelinating and axonal forms, namely, acute motor axonal neuropathy antibody-mediated (AIDP) and acute motor sensory axonal neuropathy (AMAN). Among them, anti-ganglioside antibodies, particularly anti-GM1 antibodies, are deeply related to the pathogenesis of AMAN. By contrast, the relationship between AIDP and autoantibodies has not been fully clarified, whereas the phagocytosis of myelin by macrophages is a well-known pathological feature in AIDP (7). In the initial stage of GBS, a large number of lymphocytes and macrophages can be seen infiltrating around the lesion nerve, and after activation, a large number of inflammatory cytokines can be produced, resulting in demyelination and axonal damage (8). Immunotherapy regimens such as plasmapheresis (PE) and intravenous immunoglobulin (IVIG) are considered to be one of the key therapeutic options in the treatment of GBS (9-11). In the field of tumor immunotherapy, GBS is one of the adverse events of concern in immune checkpoint inhibitors (ICIs) (12). Each of these mechanisms involves a complex immune response, and it is urgent to explore the causal relationship between immune cells and GBS as soon as possible (13, 14).

Currently, studies surrounding the association between GBS and immune cells are insufficient. And the direct causal relationship between them is highly susceptible to the confounding factors of clinical research and becomes elusive. Therefore, this study took advantage of the fact that genetic variants are randomly assigned to individuals before birth, and conducted a two-sample MR analysis using Genome-wide association study (GWAS) data to further search for a causal relationship between immune cell causal relationship with GBS.

2 Materials and methods

2.1 Study design

This study assessed the potential causal relationship between 731 immune cell phenotypes and GBS using two-sample MR analysis. This study should be guided by three basic assumptions: (1) genetic variation

is directly related to exposure; (2) there are no potential confounders between genetic variation and exposure and outcome; and (3) genetic variation does not affect outcome through pathways other than exposure. The comprehensive design of this work is shown in Figure 1.

2.2 Data source for the GWAS

The GWAS data for 731 immune cell phenotypes and GBS were obtained from the IEU OPENGWAS database, which is publicly available (15). The 731 immune cell phenotypic data contained four immunomorphological features, namely absolute cell count (AC, n=118), relative cell count (RC, n=192), median fluorescence intensity (MFI, n=389), and morphological parameters (MP, n=32). Specifically, they are subdivided into seven major groups: B cell, T regulatory cells (Treg), classical dendritic cells (cDC), Lymphocyte subsets (TBNK), Maturation stages of T cell, Myeloid cell and Monocyte. Specific information is provided in Table 1.

2.3 Instrumental variables selection

Suitable Instrumental Variables (IVs) were obtained separately from different datasets for MR analysis. For IVs with immune cell characteristics associated with GBS we set the *p*-value threshold to 5×10^{-6} . We set the parameters to $r^2 < 0.1$ and kb = 10,000 for linkage disequilibrium (LD) analyses, and excluded the effect of confounding factors. To prevent alleles from influencing the results, palindromic SNPs were removed by palindromic sequence detection. F > 10 were included for MR analysis to exclude bias in weak IVs.

2.4 Statistical analysis

In this study, five complementary methods were used for MR analysis: Inverse variance weighted (IVW), Weighted median, MR Egger, Simple mode, Weighted mode. IVW as the primary method of analysis, with p < 0.05 considered statistically significant and in the same direction as the results of the other methods of analysis, we then considered a causal relationship between exposure and outcome. We checked the heterogeneity of the IVs using the Cochran Q test, with Q_pval>0.05 indicating no heterogeneity. The MR-Egger intercept test, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test were used to detect horizontal multiplicity and outliers, setting p < 0.05. Robustness and symmetry were further assessed by leave-one-out analysis to test whether individual SNPs contributed to the causal effect. All statistical analyses in this study were performed using the R package "TwoSampleMR."

2.5 Reverse MR analysis

We investigated whether immune cell characteristics are affected by GBS using inverse MR analysis, further validating the directionality of the causal effect. We performed a reverse MR analysis with GBS as the exposure factor and the above immune cell profile as the outcome to further validate the directionality of the causal effect of immune cell profile and GBS.



GWAS data	Sample size	Population	Data sources	SNP(n)	Year
Immune cells	3,757	European	ebi-a-GCST0001391- ebi-a-GCST0002121	About 2,000,000	2020
Guillain-Barré syndrome	215,931	European	finn-b-G6_GUILBAR	16,380,463	2021

TABLE 1 Summary information on GWAS data.

3 Results

3.1 Causal relationship between immune cells and GBS

A total of 33 immune cell phenotypes were identified by the IVW method as being causally associated with the development of GBS, setting p < 0.05. The 33 immune cell types included 20 risk factors and 13 protective factors. There were 9 cases in the Treg cell group, 7 cases in the B cell group, 5 cases in the Maturation stages of T cell group, 4 cases in the TBNK group, 3 cases in the cDC cell group, 3 cases in the Monocyte group and 2 cases in the Myeloid cell group. Twenty immunophenotypes were found to be associated with GBS as risk factors using the IVW method. For example, in the B cell group, CD20 on IgD+ CD38naïve (OR = 1.412, 95%CI:1.001–1.991, p = 0.049), CD20 on IgD+ CD38dim (OR = 1.313, 95%CI:1.042-1.654, p = 0.021), IgD-CD38dim %B cell (OR = 1.500, 95%CI:1.031-2.183, *p* = 0.034), IgD+ CD24+ %B cell (OR = 1.648, 95%CI:1.031–2.634, *p* = 0.037). In the Treg cell group, CD25 on activated Treg (OR = 1.913, 95%CI:1.020-3.589, *p* = 0.043), CD3 on activated and secreting Treg (OR = 1.293, 95%CI:1.020–1.638, *p* = 0.034), CD3 on CD39+ CD4+ (OR = 1.294, 95%CI:1.043–1.606, *p* = 0.019), CD3 on CD4 Treg (OR = 1.395, 95%CI:1.069-1.819, p = 0.014), CD3 on secreting Treg (OR = 1.292, 95%CI:1.040-1.606, p = 0.021), CD39+ CD8br %T cell (OR=1.361, 95%CI:1.009-1.837, p = 0.044). In the Maturation stages of T cell group, CD3 on CM CD8br (OR = 1.460, 95%CI:1.012–2.107, *p* = 0.043), CD3 on EM CD4+ (OR = 1.245, 95%CI:1.000-1.550, *p* = 0.049), CD3 on TD CD8br (OR = 1.486, 95%CI:1.025-2.154, *p* = 0.037), CM CD4+ %T cell (OR = 1.762, 95%CI:1.019-3.046, *p* = 0.043), HVEM on naive CD4+ (OR = 1.451, 95%CI:1.104-1.907, p = 0.007). In the Monocyte group, CD16 on CD14+ CD16+ monocyte (OR = 1.285, 95%CI:1.018-1.621, *p*=0.035), CD40 on CD14+ CD16+ monocyte (OR = 1.171, 95%CI:1.015–1.352, p = 0.030). In the Myeloid cell group, CD33dim HLA DR+ CD11b+%CD33dim HLA DR+ (OR = 1.262, 95%CI:1.020–1.561, *p* = 0.032). In TBNK group, FSC-A on NK (OR = 1.296, 95%CI:1.000–1.680, *p* = 0.049), HLA DR+ NK AC (OR = 1.568, 95%CI:1.100–2.237, *p* = 0.013), as shown in Figure 2 and Supplementary Table S1. Thirteen immune cell phenotypes as protective factors associated with GBS. For example, in the B cell group, CD19 on PB/PC (OR=0.577, 95%CI:0.370-0.902, *p*=0.016), IgD+ CD24- %lymphocyte (OR = 0.554, 95%CI:0.332–0.924, *p* = 0.024), CD8dim %leukocyte (OR = 0.621, 95%CI:0.405-0.953, *p* = 0.029), Transitional AC (OR = 0.704, 95% CI: 0.524 - 0.946, p = 0.020). In the Treg cell group, CD127 on CD28- CD8br (OR=0.727, 95%CI:0.541-0.976, *p* = 0.034), CD28+ CD45RA- CD8dim %T cell (OR = 0.863, 95%CI:0.771-0.966, p = 0.010), CD4 Treg AC (OR = 0.727, 95%CI:0.538-0.983, p = 0.038). In the cDC group, CD11c + monocyte %monocyte (OR = 0.704, 95%CI:0.514–0.966, p = 0.030), CD62L– myeloid DC AC (OR = 0.694, 95%CI:0.493–0.978, p = 0.037), CD86 on monocyte (OR = 0.737, 95%CI:0.544–0.999, p = 0.049). In the Monocyte group, CX3CR1 on CD14+CD16– monocyte (OR = 0.717, 95%CI:0.548–0.9939, p = 0.016). In the Myeloid cell group, Mo MDSC AC (OR = 0.763, 95%CI:0.619–0.939, p = 0.011). In the TBNK group, CD45 on granulocyte (OR = 0.621, 95%CI:0.391–0.984, p = 0.042), as shown in Figure 3 and Supplementary Table S2.

3.2 Sensitivity analysis

Further sensitivity analyses of the results of the significant causal relationship between immune cell phenotype and GBS using Cochran's *Q* test showed that Q_pval was >0.05 in all cases and there was no significant heterogeneity, no outliers were found in the MR-PRESSO results, and there was no level of The intersection of the MR-Egger regression pleiotropy (pval >0.05) as shown in Figures 4, 5 and Supplementary Table S3. Leave-one-out analyses provide some evidence of the robustness of the results of this part of the study, as shown in Figures 6, 7.

3.3 Inverse MR analysis results

To investigate the causal relationship between GBS and immune phenotypes, we used inverse MR to study the effect of GBS on immune phenotype cells. The results showed that there was no causal relationship between GBS and any of the 33 immune cells mentioned above.

4 Discussion

The GBS usually develops after infection and affects the peripheral nervous system, resulting in muscle weakness and sensory abnormalities, with the condition progressing gradually from mild muscle weakness to severe generalized paralysis. In recent years, the scientific hypothesis that "the immune system attacks the nervous system to cause disease" has gradually come to the forefront of researchers' minds as studies on the pathogenesis of GBS continue to deepen. This study analyzed the potential causal relationship between 731 immune cell phenotypic markers and GBS using MR methods based on a large amount of publicly available genetic data. The results of the analysis showed that a total of 33 immune cell phenotypes were included in this study, 20 immune cell phenotype markers were considered as risk factors for the development of GBS and 13 immune cell phenotype markers were considered as protective factors for the development of GBS. There were 9 cases in

CD16 on CD14+ CD16+ monocyte	nsnp 16	MR Egger	pval 0.444	⊷ •−•	OR(95% CI) 1.155 (0.807 to 1.653
	16	Weighted median	0.157	֥	1.265 (0.914 to 1.752)
	16	Inverse variance weighted	0.035		1.285 (1.018 to 1.621)
	16	Simple mode	0.771		1.083 (0.638 to 1.841)
	16	Weighted mode	0.111	H	1.262 (0.964 to 1.652)
CD20 on IgD+ CD38- naive	10	MR Egger	0.095		1.789 (0.980 to 3.264)
	10	Inverse variance weighted	0.010		1.662 (1.132 to 2.499)
	10	Simple mode	0.093		1.715 (0.977 to 3.010)
	10	Weighted mode	0.028		1.715 (1.145 to 2.570)
CD20 on IgD+ CD38dim	22	MR Egger	0.639	+ -	1.086 (0.774 to 1.523)
	22	Weighted median	0.663		1.076 (0.774 to 1.495)
	22	Inverse variance weighted	0.021		1.313 (1.042 to 1.654)
	22	Simple mode	0.128	• • •	1.625 (0.891 to 2.962)
	22	Weighted mode	0.521	H=	1.109 (0.812 to 1.515)
CD25 on activated Ireg	9	MK Egger	0.663		1.273 (0.450 to 3.606)
	9	Inverse variance weighted	0.043		1.913 (1.020 to 3.589)
	9	Simple mode	0.309	→	1.840 (0.612 to 5.532)
	9	Weighted mode	0.180	→ →	1.933 (0.802 to 4.661)
CD3 on activated & secreting Treg	13	MR Egger	0.434	—	1.188 (0.784 to 1.799)
	13	Weighted median	0.083		1.312 (0.965 to 1.782)
	13	Inverse variance weighted	0.034		1.293 (1.020 to 1.638)
	13	Simple mode	0.664		1.150 (0.622 to 2.125)
CD3 on CD39+ CD4+	13	Weighted mode	0.085		1.284 (0.935 to 1.762)
ODD OF ODDAT ODAT	13	Weighted median	0.125		1.244 (0.941 to 1.643)
	13	Inverse variance weighted	0.019		1.294 (1.043 to 1.698)
	13	Simple mode	0.888		1.035 (0.650 to 1.648)
	13	Weighted mode	0.154		1.238 (0.940 to 1.632)
CD3 on CD4 Treg	8	MR Egger	0.282		1.348 (0.822 to 2.211)
	8	Weighted median	0.072		1.338 (0.974 to 1.836)
	8	Inverse variance weighted	0.014		1.395 (1.069 to 1.819)
	8	Simple mode	0.137		1.743 (0.911 to 3.334)
	8	Weighted mode	0.117	H •	1.346 (0.972 to 1.865)
CD3 on CM CD8br	10	MR Egger	0.621		1.210 (0.585 to 2.501)
	10	Weighted median	0.204		1.356 (0.847 to 2.169)
	10	inverse variance weighted	0.043		1.460 (1.012 to 2.107)
	10	Simple mode	0.050		2.00/ (1.154 to /.222)
CD3 on EM CD4+	15	MR Ecoer	0.332		1.306 (0.785 to 2.173)
GBO OF ENGLISH.	15	Weighted median	0.113		1.280 (0.943 to 1.736)
	15	Inverse variance weighted	0.049		1.245 (1.001 to 1.550)
	15	Simple mode	0.327		1.283 (0.793 to 2.074)
	15	Weighted mode	0.095		1.313 (0.974 to 1.769)
CD3 on secreting Treg	14	MR Egger	0.603	H0-H	1.108 (0.760 to 1.615)
	14	Weighted median	0.146	H	1.249 (0.925 to 1.686)
	14	Inverse variance weighted	0.021		1.292 (1.040 to 1.606)
	14	Simple mode	0.550		1.171 (0.707 to 1.940)
	14	Weighted mode	0.217	+	1.221 (0.903 to 1.652)
CD3 on TD CD8br	14	MR Egger	0.203		1.750 (0.776 to 3.946)
	14	Weighted median	0.032		1.688 (1.046 to 2.724)
	14	Simple mode	0.037		1.466 (1.025 to 2.154)
	14	Weighted mode	0.071	→ →	1.699 (1.002 to 2.882)
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+	13	MR Eoger	0.040		1.654 (1.083 to 2.525)
	13	Weighted median	0.039		1.360 (1.015 to 1.821)
	13	Inverse variance weighted	0.032		1.262 (1.020 to 1.561)
	13	Simple mode	0.249		1.317 (0.844 to 2.055)
	13	Weighted mode	0.056	→ •→	1.382 (1.025 to 1.864)
CD39+ CD8br %T cell	15	MR Egger	0.773		1.077 (0.656 to 1.769)
	15	Weighted median	0.198	÷••••	1.355 (0.853 to 2.152)
	15	Inverse variance weighted	0.044		1.361 (1.009 to 1.837)
	15	Simple mode	0.172	• •••	1.656 (0.833 to 3.289)
	15	Weighted mode	0.269		1.406 (0.787 to 2.512)
CD40 on CD14+ CD16+ monocyte	16	MR Egger	0.131		1.218 (0.957 to 1.551)
		vapiohted median	0.011		1.242 (1.018 to 1.515)
	16	Inverse parionen	0.033	1	1 1 2 2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	16 16	Inverse variance weighted	0.030		1.325 (0.090 to 1.332)
	16 16 16	Inverse variance weighted Simple mode Weighted mode	0.030		1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473)
CM CD4+ %T cell	16 16 16 16 11	Inverse variance weighted Simple mode Weighted mode MR Eccer	0.033 0.030 0.079 0.035 0.647		1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596)
CM CD4+ %T cell	16 16 16 16 11 11	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median	0.033 0.030 0.079 0.035 0.647		1.325 (0.989 to 1.325) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596) 1.922 (0.954 to 3.871)
CM CD4+ %T coll	16 16 16 16 11 11 11	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted	0.033 0.030 0.079 0.035 0.647 0.068 0.043		1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596) 1.922 (0.954 to 3.871) 1.762 (1.019 to 3.046)
CM CD4+ %T cell	16 16 16 16 11 11 11 11	Inverse variance weighted Simple mode Weighted mode MRE Egger Weighted median Inverse variance weighted Simple mode	0.033 0.030 0.079 0.035 0.647 0.068 0.043 0.328		1.771 (1.015 to 1.352) 1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596) 1.922 (0.954 to 3.871) 1.762 (1.019 to 3.046) 1.876 (0.566 to 6.222)
CM CD4+ %/T coll	16 16 16 11 11 11 11 11 11	Weighted mode Weighted mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode Weighted mode	0.033 0.030 0.079 0.035 0.647 0.068 0.043 0.328 0.350		1.771 (1.015 to 1.352) 1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596) 1.922 (0.954 to 3.871) 1.762 (1.019 to 3.066) 1.876 (0.566 to 6.222) 1.738 (0.575 to 5.250)
CM CD4+ %T cell FSC-A on NK	16 16 16 11 11 11 11 11 11 11 11	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted modan Inverse variance weighted Simple mode Weighted moda MR Egger	0.033 0.030 0.079 0.035 0.647 0.068 0.043 0.328 0.328 0.350		1.771 (1.015 to 1.352) 1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.596) 1.922 (0.954 to 3.871) 1.762 (0.956 to 6.222) 1.738 (0.575 to 5.250) 1.210 (0.820 to 1.766)
CM CD4+ %T cell FSC-A on NK	16 16 16 11 11 11 11 11 11 13 13	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted modan Inverse variance weighted Simple mode Weighted moda MR Egger Weighted modan	0.033 0.030 0.079 0.035 0.047 0.068 0.043 0.328 0.350 0.358 0.358 0.212		1.771 (1018 6) 1.322 1.325 (0 969 to 1.775) 1.233 (1033 to 1.473) 1.484 (0 290 to 7.596) 1.922 (0 954 to 3.871) 1.762 (1019 to 3.046) 1.876 (0 566 to 6 222) 1.738 (0.575 to 5.250) 1.210 (0 820 to 1.766) 1.259 (0.876 to 1.810)
CM CD4+ %T coll FSC-A on NK	16 16 16 11 11 11 11 11 13 13 13	Negrovaniance weighted Simple mode Weighted mode MR Egger Weighted moden Inverse variance weighted Simple mode Weighted mode MR Egger Weighted moden	0.033 0.030 0.079 0.035 0.067 0.068 0.043 0.328 0.350 0.358 0.358 0.358 0.212 0.050		1.771 (1018 6 1-392) 1.325 (0.989 to 1.775) 1.233 (1.033 to 1.473) 1.484 (0.290 to 7.569) 1.922 (0.954 to 3.871) 1.762 (1.019 to 3.046) 1.876 (0.566 to 6.222) 1.738 (0.575 to 5.250) 1.210 (0.820 to 1.786) 1.259 (0.876 to 1.810) 1.296 (1.000 to 1.680) 1.296 (1.000 to 1.680)
CM CD4+ %T cell FSC-A on NK	16 16 16 11 11 11 11 11 13 13 13 13 13	Negativa radance weighted Simple mode Weighted moda MR Egger Weighted modan Inverse variance weighted Simple mode MR Egger Weighted modan Inverse variance weighted Simple mode	0.033 0.030 0.035 0.647 0.068 0.043 0.328 0.350 0.350 0.358 0.212 0.050 0.180		1.171 (1018 6) 1.322 1.325 (0.989 6) 1.775) 1.233 (1.033 6) 1.473) 1.484 (0.290 6) 7.509 1.922 (0.954 6) 3.871) 1.762 (1.019 6) 3.046] 1.762 (1.019 6) 3.046] 1.763 (0.566 6) 6.222] 1.738 (0.575 6) 5.250) 1.210 (0.820 6) 1.8100 1.259 (0.876 6) 1.8100 1.266 (1.000 6) 1.6800 1.480 (0.862 fo 2.540)
CM CD4+ %T cell FSC-A on NK	16 16 16 11 11 11 11 13 13 13 13 13 13 13 13	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted modan Inverse variance weighted Simple mode WR Egger Weighted modan Inverse variance weighted Simple mode Weighted mode	0.033 0.079 0.035 0.647 0.068 0.043 0.328 0.350 0.388 0.212 0.050 0.180 0.148		1.171 (1018 6 1.322) 1.325 (0.989 10.1775) 1.233 (1.033 to 1.473) 1.484 (0.200 to 7.566) 1.922 (0.954 to 3.871) 1.762 (1.019 to 3.046) 1.876 (0.566 to 6.222) 1.738 (0.575 to 5.250) 1.210 (0.820 to 1.766) 1.259 (0.876 to 1.810) 1.296 (1.000 to 1.680) 1.480 (0.882 to 2.540) 1.303 (0.932 to 1.823)
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC	16 16 16 11 11 11 11 13 13 13 13 13 13 13 13 13	Negaroanance weighted Simple mode Vieighted mode MR Egger Weighted modan Inverse variance weighted Simple mode MR Egger Weighted modan Inverse variance weighted Simple mode Weighted moda	0.033 0.039 0.079 0.035 0.647 0.068 0.043 0.350 0.350 0.358 0.212 0.050 0.150 0.148 0.166		1.171 (1018 6 1.322) 1.325 (0.989 6 1.775); 1.233 (1033 6 1.473); 1.484 (0.290 6 7.596); 1.922 (0.554 6 3.871); 1.782 (1019 6 3.048); 1.876 (0.556 6 6 2.222); 1.210 (0.820 6 1.786); 1.259 (0.875 6 6 1.810); 1.296 (1.000 6 1.880); 1.480 (0.882 6 2.540); 1.303 (0.992 6 1.833); 1.850 (0.874 6 3.115); 1.850
CM CD4+ %T cell FSC-A on NK HLA.DR+ NK AC	16 16 18 11 11 11 11 13 13 13 13 13 13 13 13 9 9 9	Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda Inverse variance weighted Simple mode MR Egger Weighted moda Simple mode Weighted mode Weighted mode MR Egger Weighted moda	0.033 0.079 0.035 0.047 / 0.068 0.043 0.328 0.350 0.350 0.358 0.212 0.050 0.180 0.180 0.180 0.180		1.171 (1018 61 322) 1.232 (0.088 061 0.175) 1.232 (1.038 10 - 1473) 1.484 (0.230 10 - 568) 1.422 (0.544 0.5 817) 1.726 (1.017 10 - 3.046) 1.876 (0.568 10 - 522) 1.276 (0.578 10 - 525) 1.276 (0.578 10 - 525) 1.296 (1.000 10 - 1860) 1.480 (0.687 10 - 156) 1.480 (0.682 10 - 2.540) 1.480 (0.682 10 - 2.540) 1.480 (0.682 10 - 2.540) 1.480 (0.682 10 - 2.540) 1.480 (0.682 10 - 2.540) 1.487 (0.682 10 -
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC	16 16 16 11 11 11 11 13 13 13 13 13 13 13 13 13	Negrostiance weighted Simple mode Vieighted mode MR Epper Neighted median Inverse variance weighted Simple mode Weighted mode MR Epper Neighted median Inverse variance weighted Simple mode Weighted mode MR Epper	0.033 0.079 0.035 0.647 0.647 0.043 0.328 0.350 0.355 0.212 0.056 0.212 0.056 0.212 0.056 0.212 0.180 0.180 0.185 0.024 0.013		1.17 (1018 61 322) 1.28 (0.086 161 175) 1.28 (0.086 161 175) 1.28 (0.086 161 175) 1.28 (0.056 161 272) 1.28 (0.057 61 05 260) 1.27 (0.056 16 622) 1.27 (0.082 161 786) 1.26 (0.076 161 810) 1.26 (0.077 161 810) 1.26 (0.077 161 810) 1.27 (0.077 161 810) 1
CM CD4+ %T cell FSC-A on NK HLA.DR+ NK AC	16 16 18 11 11 11 11 11 13 13 13 13 13 13 13 9 9 9 9	Negrotaniance weighted Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode MR Egger	0.033 0.079 0.079 0.035 0.068 0.043 0.328 0.320 0.350000000000		1.171 (1016) 61 322 (2016) 1236 (1020) 123
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC	16 16 16 11 11 11 11 13 13 13 13 13 13 9 9 9 9 9	Negros analoce weighted Simple mode Weighted moda MR Egger Weighted moda Inverse variance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode Simple mode Weighted mode Simple mode	0.033 0.079 0.035 0.647 0.068 0.043 0.328 0.358 0.328 0.358 0.328 0.359 0.328 0.359 0.430 0.430 0.430 0.430 0.430 0.450 0.655 0.655		1.117 (10156 132) 1.236 (0.986 tol. 1775) 1.236 (10165 tol. 1775) 1.236 (10165 tol. 1775) 1.236 (1016 tol. 1066) 1.246 (1026 tol. 7566) 1.256 (1016 tol. 1266) 1.256 (0.875 tol. 1260) 1.256 (0.875 tol. 1260) 1.256 (0.875 tol. 1810) 1.256 (0.875 tol. 1810) 1.256 (0.875 tol. 1810) 1.256 (0.875 tol. 1810) 1.266 (0.875 tol. 1810) 1.267 (0.105 tol. 1810) 1.267
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+	16 16 16 11 11 11 11 13 13 13 13 13 13 13 13 13	Neese valance weighted Neese valance weighted Simple mode Weighted mode MR Egger Weighted mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Neese valance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode	0.030 0.079 0.035 0.647 0.068 0.043 0.356 0.358 0.359 0.358 0.359 0.358 0.3590		1.17 (1018) 61 322 1.280 (0.980 tel 0.175 1.282 (0.980 tel 0.175 1.282 (0.954 tel 0.375) 1.444 (0.280 tel 7.865 1.420 (0.954 tel 0.871 1.782 (1018 tel 3.867 1.787 (0.168 tel 0.822) 1.280 (0.875 tel 5.255) 1.210 (0.820 tel 7.865 1.210 (0.820 tel 7.865 1.210 (0.820 tel 7.865 1.210 (0.820 tel 7.865 1.250 (0.820 tel 8.23) 1.266 (1.000 tel 1.802) 1.365 (1.000 tel 1.802) 1.365 (1.000 tel 3.802) 1.365 (1.000 tel 3.802) 1.375 (1.000
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on haive CD4+	16 16 16 11 11 11 13 13 13 13 13 13 13 13 13 9 9 9 9	Negarod metalance weighted Simple mode Weighted mode MR Egger Weighted moda Inverse variance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode Inverse variance weighted Simple mode MR Egger Weighted mode MR Egger Weighted mode Weighted mode Weighted mode MR Egger Weighted mode MR Egger	0.033 0.079 0.035 0.647 0.068 0.043 0.380 0.380 0.380 0.380 0.212 0.050 0.148 0.148 0.168 0.048 0.013 0.065 0.0550 0.0550 0.05500000000		1.171 (1016) 61 322 (1026) 61 7175 1232 (1026) 61 7175 1232 (1026) 61 7175 1232 (1026) 61 756 1222 (0246) 53 76 1222 (0246) 53 76 1222 (0246) 53 76 1226 (1026) 53 76 1226 (1026) 53 76 1226 (1026) 53 76 1256 (1027) 53 76 1266 (10
CM CD4+ %T cell FSC-A on NK HLA.DR+NK AC HVEM on naive CD4+	16 16 16 17 11 11 11 11 13 13 13 13 13 13 9 9 9 9 9	Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda	0.033 0.079 0.035 0.047 0.0647 0.068 0.329 0.32900000000000000000000000000000000000		1.171 (10156 132) 1.236 (0.986 to 1.775) 1.236 (10165 to 1.275) 1.236 (10165 to 1.275) 1.236 (1016 to 1.265) 1.236 (1016 to 1.265) 1.276 (1.056 to 6.222) 1.276 (0.257 to 1.230) 1.276 (0.257 to 1.230) 1.276 (0.257 to 1.230) 1.266 (0.276 to 2.234) 1.566 (0.274 to 2.116) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.116) 1.267 (0.294 to 2.264) 1.266 (0.274 to 2.166) 1.266 (0.274
CM CD4+ %T cell FSC-A on NK HLA.DR+ NK AC HVEM on naive CD4+	16 16 16 11 11 11 13 13 13 13 13 13 13 13 13 9 9 9 9	Negroot and and weighted Simple mode Weighted mode MR Egger Weighted moda Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda MR Egger Weighted moda MR Egger Weighted moda MR Egger Weighted moda Simple mode Weighted moda	0.033 0.079 0.035 0.047 0.064 0.047 0.328 0.328 0.328 0.328 0.336 0.350 0.050 0.00000000		1.171 (10186 13.22) (10186 10.175) 1.232 (10186 10.175) 1.232 (10186 10.175) 1.232 (10136 10.230 10.756) 1.232 (10136 10.236) 1.242 (1018 10.236) 1.252 (1018 10.236) 1.256 (1018 10.236) 1.256 (1018 10.236) 1.256 (1018 10.236) 1.266 (1018 10.237) 1.256 (1018 10.237) 1.257 (1018 10.237)
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+ EQC-C02864m V/48 cvall	16 16 16 11 11 11 11 11 13 13 13 13 13 13 13 13	Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda Inverse variance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger	0.033 0.079 0.035 0.047 0.0647 0.328 0.350 0.358 0.358 0.358 0.358 0.212 0.368 0.358 0.358 0.358 0.358 0.358 0.480 0.180 0.180 0.180 0.552 0.065 0.055 0.048 0.055 0.048 0.055 0.048 0.055 0.048 0.055 0.048 0.055 0.048 0.055 0.048 0.055 0.048 0.055		1.117 (10156 132) 1.236 (0.986 to 1.75) 1.236 (1016 to 1.75) 1.236 (1016 to 1.75) 1.236 (1016 to 1.75) 1.236 (1016 to 1.86) 1.252 (0.954 to 3.87) 1.252 (0.954 to 3.87) 1.256 (0.975 to 5.22) 1.256 (0.975 to 5.25) 1.256 (0.975 to 5.25) 1.257 (
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+ IgD- CD38dim %B cell	16 16 16 11 11 11 11 11 13 13 13 13 13 13 13 13	Negroot analose weighted Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode MR Egger Nighted mode MR Egger Weighted mode MR Egger Weighted mode Weighted mode Weighted mode MR Egger Weighted mode MR Egger	0.033 0.079 0.035 0.047 0.068 0.047 0.328 0.350 0.356 0.356 0.356 0.356 0.356 0.450 0.480 0.013 0.065 0.0550 0.0550 0.0550 0.05500000000		1.171 (10156132) 1.236 (0.986 te) 1.75; 1.236 (10165 te) 1.75; 1.236 (10165 te) 1.75; 1.236 (10165 te) 1.75; 1.236 (1016 te) 3.66; 1.260 (1016 te) 3.66; 1.276 (1016 te) 3.66; 1.276 (1016 te) 3.66; 1.216 (1016 te) 3.66; 1.216 (1016 te) 3.66; 1.216 (1016 te) 3.66; 1.256 (1016 te) 3.66;
CM CD4+ %/T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+	16 16 16 11 11 11 13 13 13 13 13 13 13 13 9 9 9 9	Negroot and and on weighted Simple mode Weighted mode MR Egger Weighted mode Simple mode Simple mode Weighted mode MR Egger Weighted mode	0.033 0.079 0.035 0.047 0.047 0.047 0.328 0.350 0.358 0.350 0.358 0.350 0.358 0.350 0.480 0.480 0.480 0.0550 0.0550 0.05500000000		1.117 (1018 b) 322 1.226 (0.286 b) 1.757 1.236 (1018 b) 1.757 1.236 (1018 b) 1.757 1.236 (1018 b) 1.757 1.236 (1018 b) 1.246 1.226 (1018 b) 1.246 1.226 (1018 b) 1.246 1.226 (1018 b) 1.246 1.226 (1018 b) 1.246 1.256 (1018 b) 1.246 1.256 (1018 b) 1.246 1.256 (1018 b) 1.246 1.256 (1018 b) 1.257 1.257 (1018 b) 1.257 (1018 b) 1.257 1.257 (1018 b) 1.257 1.257 (1
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+	16 16 16 11 11 11 11 11 13 13 13 13 13 13 9 9 9 9	Inverse variance weighted Simple mode Weighted moda MR Egger Weighted moda Inverse variance weighted Simple mode Weighted moda Inverse variance weighted Simple mode Weighted modan Inverse variance weighted Simple mode Weighted modan Inverse variance weighted Simple mode Weighted modan Inverse variance weighted Simple mode	0.033 0.079 0.035 0.047 0.054 0.064 0.326 0.326 0.326 0.326 0.326 0.326 0.328 0.024 0.024 0.043 0.065 0.047 0.047 0.047 0.050 0.047 0.047 0.050 0.0470000000000		1.117 (10156 132) 1.236 (0.986 to 1.775) 1.236 (10165 to 1.275) 1.236 (1016 to 1.275) 1.236 (1016 to 1.265) 1.236 (1016 to 1.266) 1.236 (1016 to 1.266) 1.256 (0.275 to 1.230) 1.256 (0.275 to 1.230) 1.257 (1.136 to 1.450) 1.257 (1.136 to
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+	16 16 16 11 11 11 13 13 13 13 13 13 13 9 9 9 9 9	Neese valance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode Weighted mode MR Egger Weighted mode	0.033 0.079 0.035 0.047 0.047 0.047 0.328 0.320 0.320 0.320 0.320 0.320 0.482 0.482 0.055 0.057 0.057 0.055 0.055 0.0570		1.171 (10186 1322) 1.232 (0.2986 10.175) 1.232 (0.2986 10.175) 1.232 (0.2986 10.175) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2756 10.5 259) 1.210 (0.820 10.1763 1.226 (0.2756 10.5 259) 1.210 (0.820 10.1763 1.226 (0.2756 10.5 259) 1.210 (0.820 10.1763 1.256 (0.1756 10.5 259) 1.333 (0.832 10.5 259) 1.357 (0.1056 10.5 259) 1.359 (0.1056 10.5 25
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HUEM on naive CD4+ [gD= CD38dm %B cell [gD+ CD24+ %B cell]	16 16 16 11 11 11 11 13 13 13 13 13 13 13 13 9 9 9 9	Inverse variance weighted Simple mode Viseghted mode MR Egger Weighted mode Simple mode Viseghted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode Inverse variance weighted Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode Weighted mode MR Egger Weighted mode MR Egger	0.033 0.079 0.035 0.047 0.035 0.047 0.328 0.350 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.452 0.055 0.0570000000000		1.117 (10156) 1327 1.226 (0.286) 60 1.775; 1.236 (0.286) 60 1.775; 1.236 (0.286) 60 1.755; 1.232 (0.254) 60 7.565; 1.222 (0.254) 60 7.565; 1.226 (0.254) 60 7.265; 1.276 (0.256) 60 7.222; 1.278 (0.2756) 7.250; 1.276 (0.2756) 7.250; 1.256 (0.276 1.810) 1.266 (0.276 1.810) 1.267 (0.256 1.224) 1.267 (0.256 1.224)
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+ (gD - CD38dim %B cell IgD+ CD24+ %B cell	16 16 16 11 11 11 11 11 13 13 13 13 13 13 9 9 9 9	Investe variance weighted Simple mode Weighted mode MR Epper Mighted moda Simple mode Weighted moda MR Epper Weighted moda MR Epper Mighted moda MR Epper Weighted moda MR Epper Weighted moda MR Epper Weighted moda MR Epper Weighted moda MR Epper Weighted moda MR Epper Mighted moda	0.030 0.079 0.035 0.047 0.064 0.28 0.350 0.350 0.350 0.212 0.050 0.148 0.148 0.148 0.148 0.148 0.148 0.148 0.148 0.148 0.050 0.148 0.050 0.482 0.055 0.482 0.055 0.482 0.055 0.482 0.055 0.482 0.055 0.043 0.055 0.045 0.055 0.045 0.055 0.045 0.055 0.045 0.055 0.045 0.055 0.045 0.0550 0.0550 0.05500000000		1.171 (10156 132) 1.236 (0.986 to 1.775) 1.236 (10165 to 1.275) 1.236 (10165 to 1.275) 1.236 (1016 to 1.265) 1.236 (1016 to 1.266) 1.236 (1016 to 1.266) 1.256 (1016 to 1.267) 1.256 (1016 to 1.267) 1.257 (1016 to 1.267) 1.256 (1016 to 1.267)
CM CD4+ %T cell FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+ IgD- CD28tdem %B cell IgD+ CD24+ %B cell	16 16 16 11 11 11 13 13 13 13 13 13 13 13 9 9 9 9	Nvese valance weighted Simple mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Simple mode Simple mode Weighted mode MR Egger Weighted mode	0.033 0.079 0.035 0.047 0.047 0.328 0.320 0.328 0.320 0.320 0.350 0.482 0.055		1.171 (10156 1322) 1.232 (0.2986 10.175) 1.232 (0.2986 10.175) 1.232 (0.2986 10.175) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2954 10.3 601) 1.232 (0.2756 10.2 201) 1.230 (0.2756 10.2 201) 1.230 (0.2756 10.2 201) 1.230 (0.2756 10.2 201) 1.230 (0.276 10.1 201) 1.256 (0.276 10.1 201) 1.257 (0.205 10.2 201) 1.257
CM CD4+ %/T coll FSC-A on NK HLA DR+ NK AC HVEM on naive CD4+ IgD- CD38dem %8 cell IgD+ CD24+ %8 cell	16 16 16 11 11 11 11 11 13 13 13 13 13 13 13 9 9 9 9	Inverse variance weighted Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode Simple mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Simple mode Weighted mode MR Egger Weighted mode Simple mode Weighted mode Weighted mode Weighted mode Weighted mode MR Egger Weighted mode Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode MR Egger Weighted mode	0.033 0.079 0.035 0.047 0.035 0.047 0.328 0.350 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.358 0.452 0.054 0.065 0.055 0.055 0.055 0.059 0.047 0.065 0.059 0.047 0.065 0.059 0.059 0.059 0.059 0.059 0.059 0.059		1.117 (10156) 1.327 1.236 (0.986) 60 1.775; 1.236 (10166) 60 1.775; 1.236 (10166) 1.756; 1.236 (1016) 2.086; 1.236 (1016) 2.086; 1.256 (1016) 2.086; 1.256 (1016) 2.086; 1.256 (1016) 2.086; 1.256 (1016) 2.087; 1.256 (1016) 2.087;

FIGURE 2

Forest plot for the causal effect of 20 immune cell features as risk factors for GBS using 5 methods including MR Egger, Weighted median, Inverse variance weighted, Simple mode, Weighted mode.

exposure	nsnp	method	pval			OR(95% CI)
CD11c+ monocyte %monocyte	11	MR Egger	0.104	· • • · · · ·		0.563 (0.302 to 1.049)
	11	Weighted median	0.028			0.615 (0.399 to 0.950)
	11	Inverse variance weighted	0.030			0.704 (0.514 to 0.966)
	11	Simple mode	0.166		•	0.606 (0.314 to 1.170)
	11	Weighted mode	0.053			0.602 (0.382 to 0.947)
CD127 on CD28- CD8br	12	MR Egger	0.476		-	0.841 (0.532 to 1.329)
	12	Weighted median	0.298		-	0.804 (0.532 to 1.213)
	12	Inverse variance weighted	0.034	⊢ ⊷ -		0.727 (0.541 to 0.976)
	12	Simple mode	0.327			0.726 (0.394 to 1.338)
	12	Weighted mode	0.295		4	0.799 (0.535 to 1.192)
CD19 on PB/PC	13	MR Egger	0.375	H-0		0.700 (0.329 to 1.491)
	13	Weighted median	0.276	- +		0.692 (0.357 to 1.342)
	13	Inverse variance weighted	0.016			0.577 (0.370 to 0.902)
	13	Simple mode	0.634	· · · · ·		0.801 (0.328 to 1.955)
	13	Weighted mode	0.380			0.731 (0.373 to 1.433)
CD28+ CD45RA- CD8dim %T cell	15	MR Egger	0.065	нон		0.874 (0.767 to 0.996)
	15	Weighted median	0.052	нен		0.857 (0.733 to 1.001)
	15	Inverse variance weighted	0.010			0.863 (0.771 to 0.966)
	15	Simple mode	0.730		_	0.952 (0.726 to 1.249)
	15	Whishted mode	0.071		•	0.969 (0.753 to 1.000)
	10	MD Farmer	0.071			0.852 (0.735 to 1.000)
CD4 Ireg AC	13	MR Egger	0.532			0.003 (0.025 to 1.384)
	13	Weighted median	0.121			U.728 (U.488 to 1.087)
	13	Inverse variance weighted	0.038			0.727 (0.538 to 0.983)
	13	Simple mode	0.430		-	0.774 (0.419 to 1.431)
	13	Weighted mode	0.154			0.745 (0.509 to 1.089)
CD45 on granulocyte	10	MR Egger	0.529	· • • • • • • • • • • • • • • • • • • •		0.668 (0.201 to 2.219)
	10	Weighted median	0.115	· • • +		0.616 (0.337 to 1.125)
	10	Inverse variance weighted	0.042	_ ⊢ ●{		0.621 (0.391 to 0.984)
	10	Simple mode	0.195		-	0.569 (0.259 to 1.253)
	10	Weighted mode	0.147			0.590 (0.308 to 1.133)
CD62L- myeloid DC AC	10	MR Egger	0.057	H		0.540 (0.314 to 0.929)
	10	Weighted median	0.029			0.676 (0.475 to 0.961)
	10	Inverse variance weighted	0.037			0.694 (0.493 to 0.978)
	10	Simple mode	0.648			0.842 (0.412 to 1.719)
	10	Weighted mode	0.048			0.679 (0.488 to 0.946)
CD86 on monocuto	7	MR Egger	0.325		_	0.786 (0.510 to 1.212)
obce en menecyte	7	Weighted median	0.020			0.703 (0.472 to 1.044)
	7		0.000			0.702 (0.472 to 1.044)
	7	Circula made	0.050			0.737 (0.344 to 1.000)
	-	Simple mode	0.145			0.542 (0.264 to 1.111)
	7	Weighted mode	0.113			0.688 (0.463 to 1.022)
CD8dim %leukocyte	11	MR Egger	0.351			0.628 (0.249 to 1.585)
	11	Weighted median	0.107			0.625 (0.353 to 1.107)
	11	Inverse variance weighted	0.029			0.621 (0.405 to 0.953)
	11	Simple mode	0.125			0.511 (0.233 to 1.122)
	11	Weighted mode	0.193		-	0.592 (0.284 to 1.236)
CX3CR1 on CD14+ CD16- monocyte	19	MR Egger	0.408			0.786 (0.450 to 1.372)
	19	Weighted median	0.062	— ⊷ –∔		0.720 (0.509 to 1.017)
	19	Inverse variance weighted	0.016	He-H		0.717 (0.548 to 0.939)
	19	Simple mode	0.550			0.843 (0.488 to 1.458)
	19	Weighted mode	0.206			0.778 (0.534 to 1.132)
IgD+ CD24- %lymphocyte	12	MR Egger	0.875			0.859 (0.137 to 5.406)
.g_ 0,	12	Weighted median	0.030			0.464 (0.232 to 0.928)
	12	Inverse variance weighted	0.024			0.554 (0.332 to 0.924)
	12	Simple mode	0.024			0.334 (0.332 to 0.324)
	12	Simple mode	0.200			0.480 (0.165 to 1.399)
	12	weighted mode	0.227			0.432 (0.119 to 1.563)
M- MD00 A0	15	MR Egger	0.063	H		0.678 (0.466 to 0.985)
M8 MDSC AC	15	Weighted median	0.081	H.		0.777 (0.586 to 1.031)
MO MDSC AC		Inverse variance weighted	0.011	H H H		0.763 (0.619 to 0.939)
MO MUSE AC	15					0.812 (0.544 to 1.212)
MO MUSE AC	15 15	Simple mode	0.325		-	
	15 15 15	Simple mode Weighted mode	0.325		·	0.746 (0.557 to 0.999)
Transitional AC	15 15 15 20	Simple mode Weighted mode MR Egger	0.325 0.069 0.220		1	0.746 (0.557 to 0.999) 0.759 (0.496 to 1.162)
Transitional AC	15 15 15 20 20	Simple mode Weighted mode MR Egger Weighted median	0.325 0.069 0.220 0.395		- 	0.746 (0.557 to 0.999) 0.759 (0.496 to 1.162) 0.825 (0.531 to 1.284)
Transitional AC	15 15 20 20 20 20	Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted	0.325 0.069 0.220 0.395 0.020		- 	0.746 (0.557 to 0.999) 0.759 (0.496 to 1.162) 0.825 (0.531 to 1.284) 0.704 (0.524 to 0.946)
Transitional AC	15 15 15 20 20 20 20 20	Simple mode Weighted mode MR Egger Weighted median Inverse variance weighted Simple mode	0.325 0.069 0.220 0.395 0.020 0.143			0.746 (0.557 to 0.999) 0.759 (0.496 to 1.162) 0.825 (0.531 to 1.284) 0.704 (0.524 to 0.946) 0.567 (0.274 to 1.173)

FIGURE 3

Forest plot for the causal effect of 13 immune cell characteristics as protective factors for GBS using 5 methods including MR Egger, Weighted median, Inverse variance weighted, Simple mode, Weighted mode.



HLA DR+. (S) FSC-A on NK. (T) HLA DR+ NK AC.

the Treg cell group, 7 cases in the B cell group, 5 cases in the Maturation stages of T cell group, 4 cases in the TBNK group, 3 cases in the cDC cell group, 3 cases in the Monocyte group and 2 cases in the Myeloid cell group.

Treg cells play an important role in maintaining immune homeostasis and suppressing inflammation, and a reduction in their numbers or dysfunction may be importantly linked to the pathogenesis of GBS. Patients with AMAN and AIDP, a common subtype of GBS, have significantly fewer peripheral Tregs in the acute phase of the disease (16). Immunosuppressive subpopulations of CD4+ T helper cells reduce autoimmune and inflammatory responses and are widely used in the treatment of neurological disorders such as GBS (17). It has been shown that patients with GBS treated with lymphoid progenitor exchange (LPE) have a significant decrease in the



Funnel plot of 13 immune cell characteristics as protective factors for GBS. (A) CD19 on PB/PC. (B) IgD+ CD24– %lymphocyte. (C) CD8dim %leukocyte. (D) Transitional AC. (E) CD127 on CD28– CD8br. (F) CD28+ CD45RA– CD8dim %T cell. (G) CD4 Treg AC. (H) CD11c + monocyte %monocyte. (I) CD62L– myeloid DC AC. (J) CD86 on monocyte. (K) CX3CR1 on CD14+ CD16– monocyte. (L) Mo MDSC AC. (M) CD45 on granulocyte.



percentage of Th1 and Th17 cells and an increase in Th2 and Treg cells in the peripheral blood among the CD4+ T-lymphocyte subsets (18). It follows that the role of Th17 cells in GBS should not be overlooked, and these cells promote GBS by mediating inflammatory and autoimmune responses (19).The results of another similar study suggest that during the acute phase of the clinical course of GBS, although there is a decline in the number and proportion of CD4 + CD25 + T cells, this decline is reversible, suggesting that the number and function of Treg cells may be only temporarily suppressed rather than permanently impaired (20). IVIG promotes proliferation of CD4 + CD25 + Foxp3 + and other Treg cells and secretion of antiinflammatory cytokines IL-10 and TGF- β 1 in GBS patients (21). Experimental autoimmune neuritis (EAN) is an animal model of AIDP that induces T-cell-mediated neuritis via myelin epitopes P0 or



(C) CD8dim %leukocyte. (D) Transitional AC. (E) CD127 on CD28– CD8br. (F) CD28+ CD45RA– CD8dim %T cell. (G) CD4 Treg AC. (H) CD11c + monocyte.
 (K) CD3cH = 000 CD24– %gmphocyte.
 (C) CD8dim %Leukocyte. (D) Transitional AC. (E) CD127 on CD28– CD8br. (F) CD28+ CD45RA– CD8dim %T cell. (G) CD4 Treg AC. (H) CD11c + monocyte.
 (K) CX3CR1 on CD14+ CD16– monocyte. (L) Mo MDSC AC. (M) CD45 on granulocyte.

P2 as the primary antigen (22). Pathologically, EAN is characterized by rupture of the blood-nerve barrier and accumulation of autoreactive T cells and macrophages in the peripheral nervous system through chemotaxis and demyelination (23). *In vitro* activation of anti-CD3 and anti-CD28 antibodies allows IFN- γ to generate CD4+CD25+ regulatory T cells (iTregs) from CD4+CD25– T cells in GBS patients (24). The above further corroborates the association of Treg cell subtypes such as CD25 on activated Treg, CD3 on activated and secreting Treg, CD3 on CD4 Treg and GBS in the results.

B cells are involved in GBS pathogenesis through autoantibody production, antigen presentation, and inflammatory regulation. Flow cytometry results showed that the percentage of memory B cells was significantly higher in GBS patients than in healthy controls. Correlation analyses showed that an increase in the percentage of memory B cells was positively correlated with the clinical severity of GBS patients (25). This was similarly corroborated in another study, suggesting that peripheral blood DN (IgD- CD27-) B-cell values were significantly elevated (26). The decrease in the percentage of circulating memory B cells after administration of immunotherapies such as PE and IVIG to GBS patients suggests that the reduction of memory B cells is involved in the recovery process of the disease or is one of the key factors for clinical improvement. For example, the percentage of CD4+/CD8+ T cells and the percentage of CD4+CD45RA+T cells were increased, the percentage of CD8+T cells and CD4 + CD45RO + T cells were significantly decreased, and the number of CD19 + B cells was reduced after IVIG treatment in GBS patients (27). It also promotes the differentiation of CD40activated B cells into plasmoblasts and accelerates immunoglobulin synthesis and secretion (28). Large numbers of plasmoblasts may be a potential biomarker for rapid clinical recovery. CD19 can be used as a B-cell target to treat autoimmune neuropathies (29). It has also been shown that an anti-CD20 monoclonal antibody (rituximab) may be a potential target for the treatment of GBS (30). The results of the present study are broadly similar to the above, CD19 on PB/PC, CD20 on IgD+ CD38- naive, CD20 on IgD+ CD38dim are associated with GBS.

Myeloid cells are a group of cells that play an important role in the immune system and include mainly granulocytes, monocytes, macrophages, dendritic cells and mast cells. These cells are derived from hematopoietic stem cells in the bone marrow and are formed through a series of differentiation processes that are also closely linked to the pathogenesis of GBS. Antigen-presenting cell activity of myeloid dendritic cells may contribute to the maintenance of T-cell activation in GBS, with increased numbers of CD11c(+) myeloid DCs versus CD123(+) plasma cell-like DCs in patients with GBS before treatment with high-dose IVIG (31). Another study showed that plasma cell-like DCs were significantly elevated in the acute phase of GBS, and their levels were positively correlated with the severity of disease in GBS patients, and the expression of TLR9 and surface co-stimulatory molecules were significantly elevated in plasma cell-like DCs, suggesting that plasma cell-like DCs are involved in the pathogenesis of GBS (32). Atorvastatinmodified DCs can be induced into tolerogenic DCs, which improve the symptoms of EAN in rats by down-regulating Th1/Th17 levels and increasing the number of Treg and NKR-P1+ cells (33). Although DCs-based immunotherapy is still at the stage of animal experiments, the results of existing studies suggest that DCs have a promising application in the clinical treatment of GBS (34). CD16+56, CD4+ and CD8+ levels were lower and IgG levels were higher in children with GBS spectrum disease variant than in the control group, suggesting that both cellular and humoral immune functions were disturbed in children with GBS spectrum disease variant and were involved in the development of the disease (35). Single-cell RNA sequencing of peripheral blood mononuclear cells (PBMC) from patients with GBS revealed a new clonally-expanded CD14+ CD163+ monocyte subset in the peripheral blood of patients with AIDP and it was enriched for cellular responses to IL1 and chemokine signaling pathways (36). In addition, the researchers found that the neutrophil/lymphocyte ratio (NLR) may be an independent risk factor for GBS and a predictor of severe dysfunction, severe frailty and short-term prognosis (37). Macrophages can be divided into two main phenotypes, pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2), which play a decisive role in the initiation and development of GBS. Macrophages may induce inflammatory or anti-inflammatory effects in M1 and M2 by secreting pro- or antiinflammatory cytokines (TNF- α , IL-12, IL-10, etc.), and induce activation of T cells to mediate immune responses or to promote GBS disease recovery. Currently, the role of macrophages in, e.g., GBS cannot be explained simply by the M1-M2 dichotomy, and how macrophages are involved in degeneration and regeneration of the peripheral nervous system, how macrophage polarization can be shifted toward the M2 phenotype, and how to improve the outcome of GBS need to be explored in further studies (38). The relevant results of the present study on myeloid cell categories are in general agreement with the literature, suggesting that the phenotypes: CD11c + monocyte %monocyte, CX3CR1 on CD14+ CD16- monocyte, CD16 on CD14+ CD16+ monocyte, etc., may be closely related to the GBS.

In addition, reverse MR analyses were performed for further validation of the positive results of this study. The results showed that there was no causal relationship between GBS and any of the 33 immune cells. The reason for this may be that genetic variants predominantly precede disease, and the sequence of the two cannot usually be reversed.

In summary, this work differs from traditional observational studies that address the relationship between one or more immune cells and GBS. It used MR analysis with SNPs as IVs to investigate causal associations between 731 immune cell phenotypes and GBS, reducing confounding variables, reverse causation, and other factors interfering with the results. The results suggest a causal link between 33 immune cell manifestations and GBS. They may play a defensive or pathogenic role by activating different immune functions, and the B-cell and Treg cell groups dominate the exposure factors for GBS. These findings provide a theoretical basis for the development of early detection reagents and late treatment strategies.

In this study, Mendelian randomization (MR) analysis was used to investigate the relationship between GBS and immune cell phenotypes. Although this analysis provides important information on causality, the following limitations exist. For example, the data on 731 immune cell phenotypes and GBS were derived from studies of European populations, and the presence of similar genetic variants in other populations needs to be further explored. If the selected SNPs affect multiple biological pathways, their effects on immune cell function may not be exclusive, potentially introducing a horizontal confounding bias, which in turn affects the accuracy of the MR analysis. Synergistic effects between different immune cell phenotypes were not discussed in this study, and their impact on the findings cannot be ignored. Due to these limitations, future clinical studies with more ethnic groups, more comprehensive genotypic data, and more scientific methods of statistical analyses are needed to enhance the ability of MR in explaining the relationship between GBS and immune cell phenotypes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

HL: Methodology, Writing – original draft, Writing – review & editing. SS: Writing – original draft, Writing – review & editing. BC: Writing – original draft, Writing – review & editing. SY: Writing – original draft, Writing – review & editing. XZ: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1446472/ full#supplementary-material

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