

1 **Supplementary Table 1.** Demographic and clinical characteristics of participants in The
2 COVID Mind Study at Yale and the IDCPR EPICC cohort.

Variable		The COVID Mind Study at Yale Cohort				EPICC Cohort		
		Never- COVID Control (n=22)	Neurologic Long COVID (n=31)	Recovered Controls (n=7)	p value	BRACE Not Impaired (N=44)	BRACE Impaired (N=29)	p value
Age	Median [IQR]	47.5 [33-55]	53 [40-61]	41 [31-48]	0.260	43 [36.5- 53]	38 [30-50]	0.346
	Mean $\pm$ SD	45.6 $\pm$ 13.16	49.5 $\pm$ 12.92	40.4 $\pm$ 13.67		44.8 $\pm$ 11.09	41.7 $\pm$ 15.06	
Sex	Female	6 (27.3%)	21 (67.7%)	5 (71.4%)	0.008	14 (32%)	18 (62%)	0.016
	Male	16 (72.7%)	10 (32.3%)	2 (28.6%)		30 (68%)	11 (38%)	
Active Duty	Yes	—	—	—		24 (54.5%)	14 (48.3%)	0.639
Race & Ethnicity	White	7 (31.8%)	25 (80.6%)	3 (42.9%)	0.001	31 (70.5%)	19 (65.5%)	0.081
	Black/African American	10 (45.5%)	5 (16.1%)	2 (28.6%)		1 (2%)	6 (21%)	
	Hispanic	4 (18.2%)	1 (3.2%)	0 (0.0%)		7 (16%)	3 (10%)	
	Asian	1 (4.5%)	0 (0.0%)	2 (28.6%)		3 (7%)	1 (3%)	
	Multiple	—	—	—		2 (4.5%)	0 (0%)	
BMI	Median [IQR]	27.3 [25.5- 31.7]	28.8 [25.5- 31.8]	25.5 [23.2- 27.0]	0.626	30.2 [27.0- 34.2]	27.4 [24.1- 32.2]	0.146
	Mean $\pm$ SD	28.2 $\pm$ 4.73	29.8 $\pm$ 7.2	27.9 $\pm$ 9.8		30.4 $\pm$ 5.56	28.4 $\pm$ 5.53	
Days from COVID-19 to blood draw	Median [IQR]	—	323 [137- 413]	319 [243- 436]		202 [188.5- 360.2]	253 [193- 376]	
	Range	—	81-701	68-460		167-588	169-585	
No. COVID- 19 episodes	1	—	—	—		39 (88.6%)	18 (62.1%)	<0.01
	2	—	—	—		5 (11.4%)	11 (37.9%)	
Acute COVID-19 Care	Home	—	21 (67.7%)	6 (85.7%)	0.149	35 (79.5%)	27 (93.1%)	0.297
	Hospital floor	—	6 (19.4%)	0 (0.0%)		8 (18.2%)	2 (6.9%)	
	ICU	—	4 (12.9%)	0 (0.0%)		—	—	
	Unknown	—	0 (0.0%)	1 (14.3%)		—	—	
	Asymptomatic	—	—	—		1 (2.3%)	0 (0%)	
Vaccination Status*	Fully vaccinated	—	3 (9.7%)	3 (42.9%)	<0.001	35 (79.5%)	24 (82.8%)	1.000
	Partially vaccinated	—	0 (0.0%)	1 (14.3%)		—	—	
	Unvaccinated	—	28 (90.3%)	0 (0.0%)		9 (20.5%)	5 (17.2%)	
	Unknown	—	0 (0.0%)	3 (42.9%)		—	—	

SARS-CoV-2 variant*	Ancestral	—	—	—		2 (4.5%)	1 (3.4%)	0.689
	Alpha	—	—	—		1 (2.3%)	1 (3.4%)	
	Delta	—	—	—		23 (52.3%)	19 (65.5%)	
	Omicron	—	—	—		18 (40.9%)	8 (27.6%)	
Co-morbidities	Smoking (current or former)	14 (63.6%)	10 (32.3%)	2 (28.6%)	0.068	18/42 (42.9%)	3/27 (11.1%)	0.007
	Alcohol use	9 (40.9%)	0 (0.0%)	0 (0.0%)	<0.001	8/42 (19%)	6/27 (22%)	0.767
	Hypertension	2 (9.1%)	6 (19.4%)	1 (14.3%)	0.683	10/41 (24%)	4/27 (15%)	0.379
	Type 2 Diabetes (T2D)	3 (13.6%)	3 (9.7%)	0 (0.0%)	0.710	3 (7%)	2 (7%)	1.000
	Obesity	6 (27.3%)	9 (29.0%)	1 (14.3%)	0.843	22 (50%)	10/27 (37%)	0.333
	Antidepressant use (12 mo)	0 (0.0%)	2 (6.5%)	2 (28.6%)	0.049	Not collected	Not collected	
CCI Score	Median [IQR]	—	—	—		0.00 [0.00-1.00]	0.00 [0.00-1.00]	
	Range	—	—	—		0.00-6.00	0.00-9.00	
Other	PROMIS cognitive impaired (n=60)	—	—	—		10/38 (26%)	7/22 (32%)	0.768
	DoDSR pre-COVID sera present	—	—	—		8 (18%)	4 (14%)	
Neuro Long COVID symptoms	Cognitive dysfunction	—	25 (81%)	—		—	—	
	Fatigue/PEM	—	24 (77%)	—		—	—	
	Mood changes	—	24 (77%)	—		—	—	
	Headaches	—	18 (58%)	—		—	—	
	Neuropathy	—	17 (55%)	—		—	—	
	Dizziness/Falls	—	17 (55%)	—		—	—	
	Dysautonomia	—	15 (48%)	—		—	—	
	Poor sleep	—	12 (39%)	—		—	—	

CCI = Charlson Comorbidity Index; PROMIS = Patient Reported Outcomes Measurement System; DoDSR = Department of Defense Serum Repository; BRACE = Brain Baseline Assessment of Cognition and Everyday Functioning; EPICC = Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases With Pandemic Potential; PEM = Post-exertional malaise.

— Data not available.

*Variables refer to first COVID-19 episode if the participant had more than one episode. P values for categorical variables were calculated using exact tests (Fisher's exact test for 2x2 tables and Fisher-Freeman-Halton exact tests for larger contingency tables). Continuous variables were calculated using Welch's ANOVA for Yale cohort and Welch's two-sample t-test for EPICC cohort.

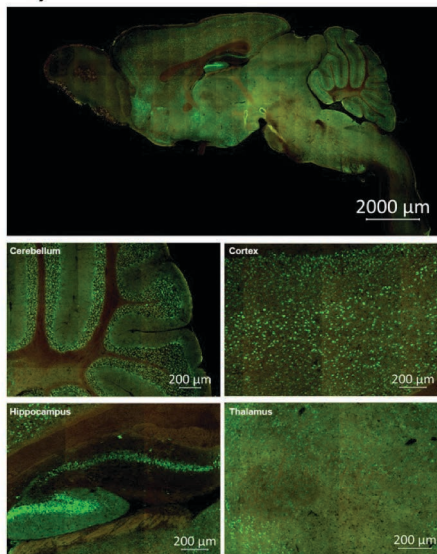
3

4

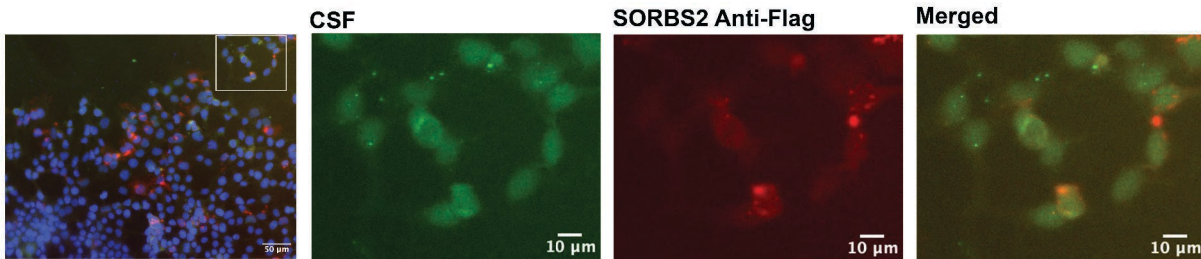
5

6 **Supplementary Figure 1**

A) **Case_nLC_Y10**



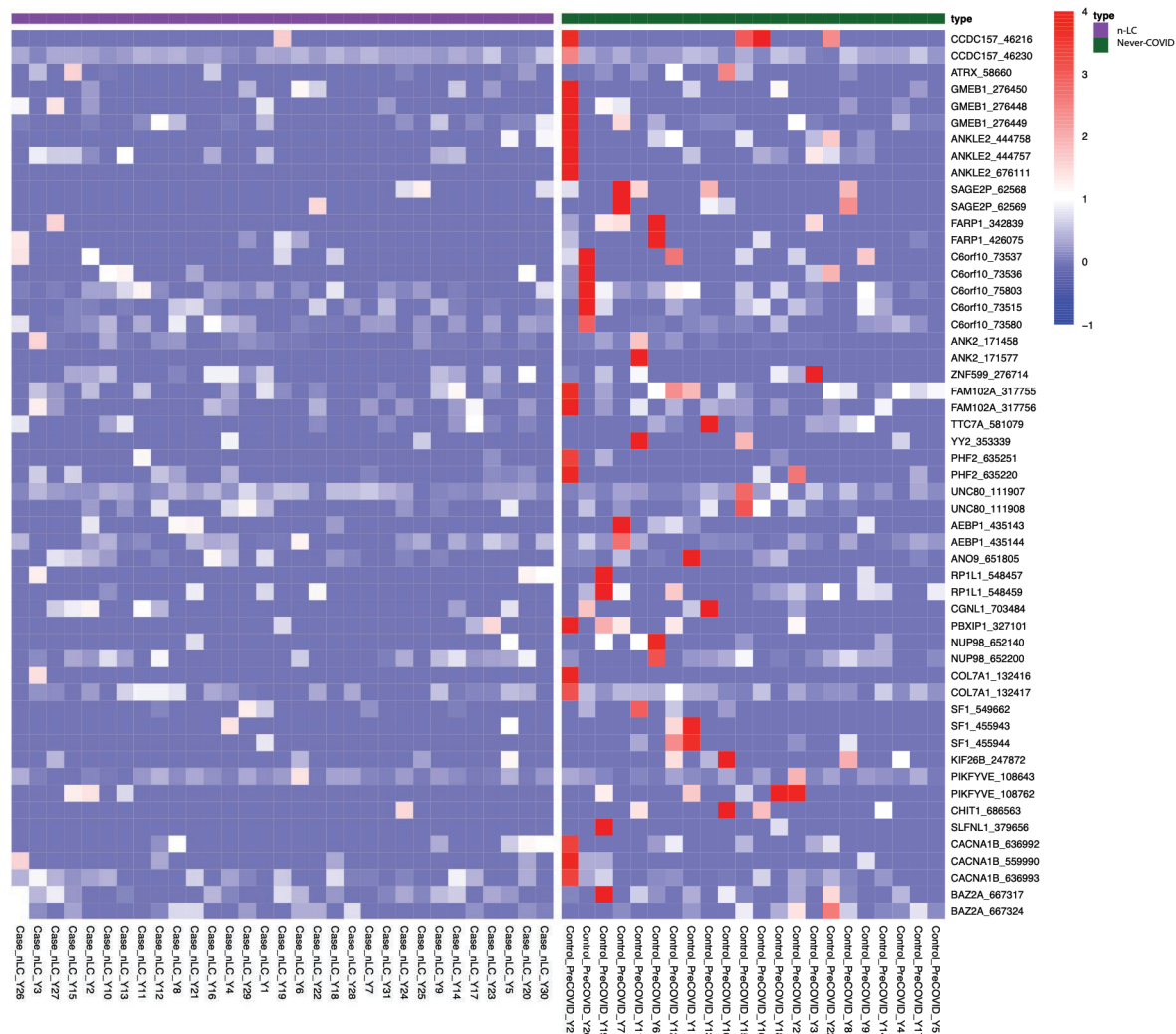
B) **Case_nLC_Y21**



7
8 **Supplementary Figure 1. A) Case example showing pronounced neuropil reactivity.**
9 Mouse sagittal brain sections were incubated with patient CSF (1:4) and detected with
10 anti-human IgG (green). The composite whole-brain image (top; scale bar, 2,000 μm) is
11 accompanied by higher-magnification fields (bottom; cerebellum, cortex, hippocampus,
12 thalamus; scale bars, 200 μm). This case exhibited intense cytoplasmic staining in the
13 nucleus accumbens and deep cerebellar nuclei, together with robust neuropil labeling in
14 the dentate gyrus extending along mossy fiber tracts.

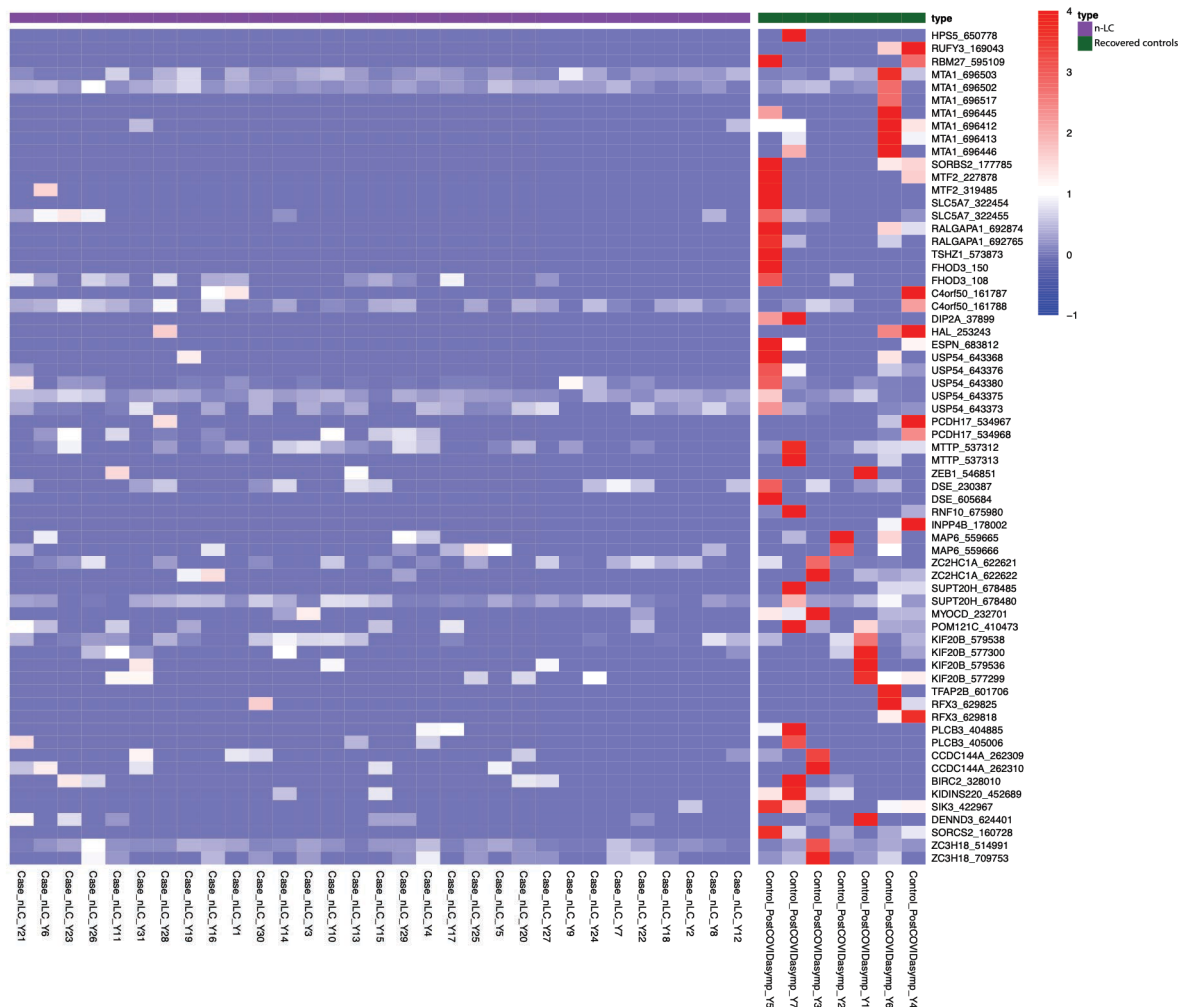
B) SORBS2, which was enriched in an n-LC patient above both Never-COVID and recovered controls by PhIP-Seq, was not validated by the HEK293 overexpression cell-based assay. Cells transfected with FLAG-tagged SORBS2 were immunostained with patient CSF (1:10) and a rabbit anti-FLAG antibody. Cells were then counterstained with anti-human IgG 488 (green) and anti-rabbit IgG 594 (red). No colocalization was observed between the patient CSF immunostaining and SORBS2 overexpression in the HEK293 cells.

Supplementary Figure 2



Supplementary Figure 2. Reciprocal analysis of human PhIP-Seq reactivity in Never-COVID CSF controls compared to neurological Long-COVID (n-LC) CSF cases. Heatmap showing peptide-level enrichment in cerebrospinal fluid (CSF) from Never-COVID control samples relative to patients with neurological Long-COVID (n-LC). Each row corresponds to a unique peptide, and each column represents an individual CSF sample. Color intensity denotes the $\log_{10}$ -transformed fold change relative to n-LC. Peptides were enriched in only 1 or 2 control samples at most, and the peptides enriched in Never-COVID controls were distinct from those enriched in n-LC.

50 **Supplementary Figure 3**



51

52 **Supplementary Figure 3. Reciprocal analysis of human PhIP-Seq reactivity in**

53 **recovered CSF controls compared to neurological long-COVID (n-LC) CSF cases.**

54 Heatmap showing peptide-level enrichment in cerebrospinal fluid (CSF) from recovered

55 control samples relative to patients with neurological Long-COVID (n-LC). Each row

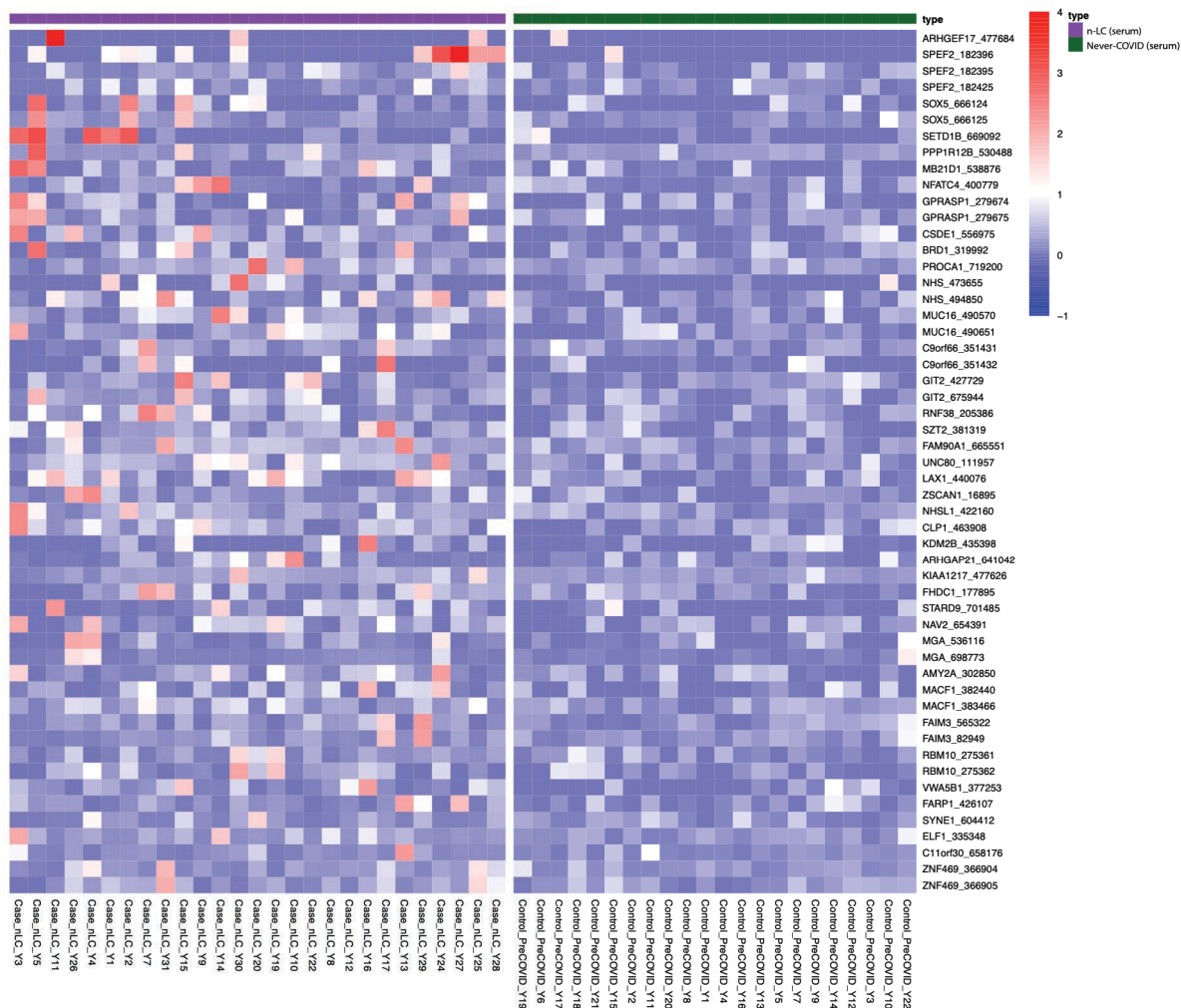
56 corresponds to a unique peptide, and each column represents an individual CSF sample.

57 Color intensity denotes the log₁₀-transformed fold change relative to n-LC. Peptides were

58 enriched in only 1 or 2 control samples at most, and the peptides enriched in recovered

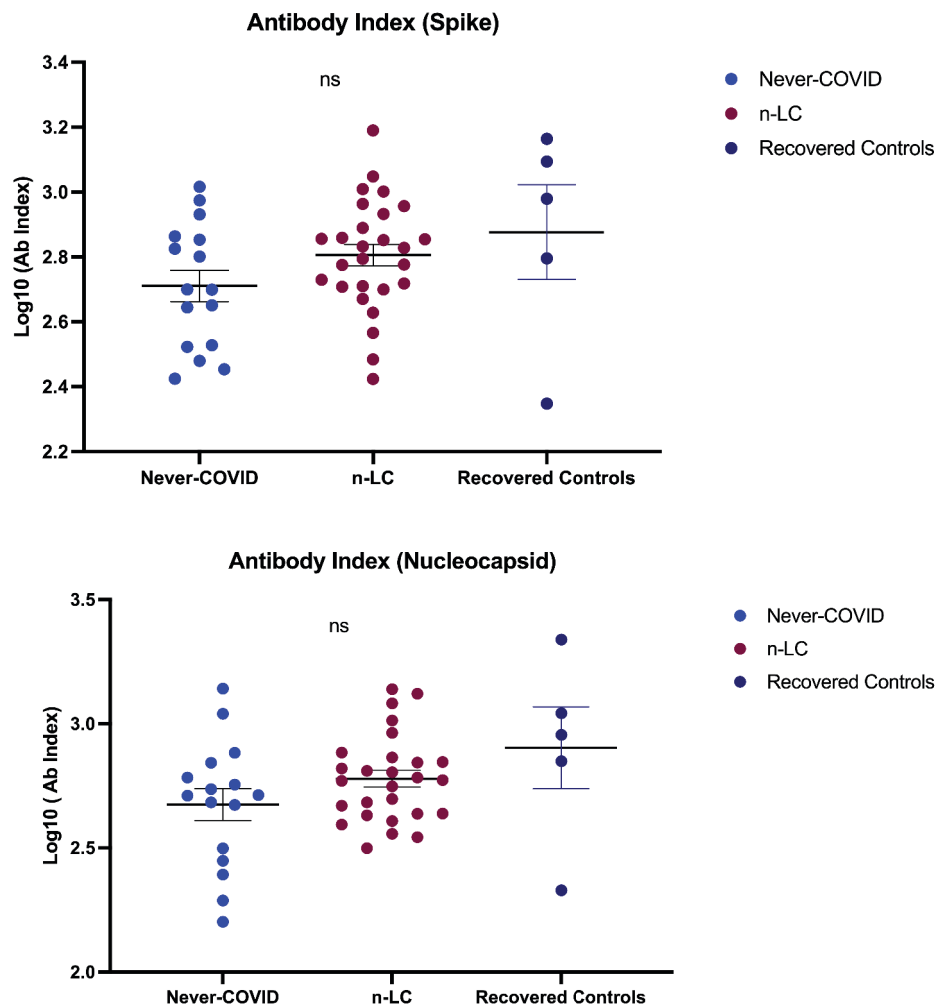
59 controls were distinct from those enriched in n-LC.

Supplementary Figure 4



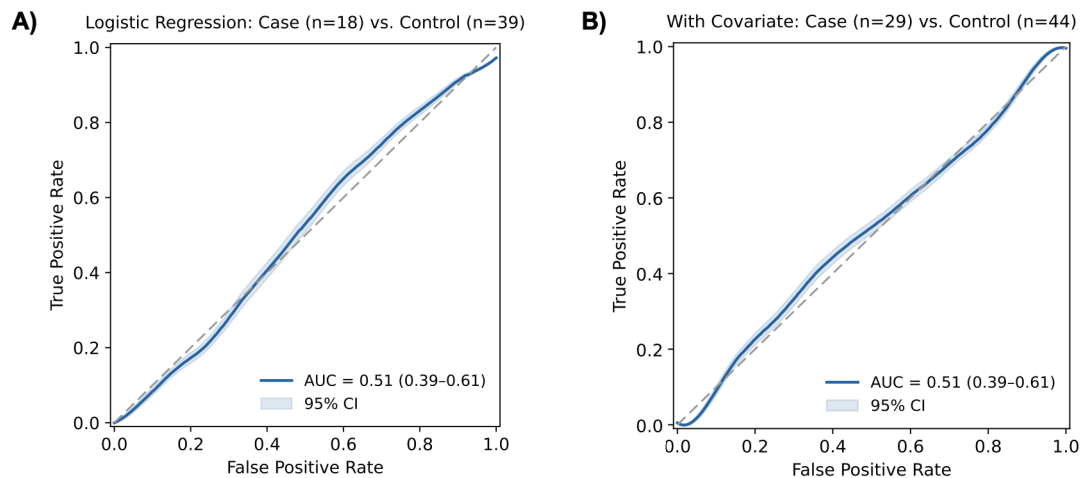
Supplementary Figure 4. Heatmap of human PhIP-Seq reactivity in all n-LC Serum samples compared to Never-COVID controls. This heatmap displays peptide-level enrichment data from human phage immunoprecipitation sequencing (PhIP-Seq) performed on Serum samples from patients with neurological Long-COVID (n-LC) and pre-pandemic healthy controls (Never-COVID). Each row corresponds to a unique peptide, and each column represents an individual Serum sample. Color intensity reflects the degree of peptide enrichment, quantified as the $\log_{10}$ -transformed fold changes in cases relative to controls. Peptides were enriched in only 2-4 patients out of the total n-LC Serum samples above never-COVID controls.

Supplementary Figure 5



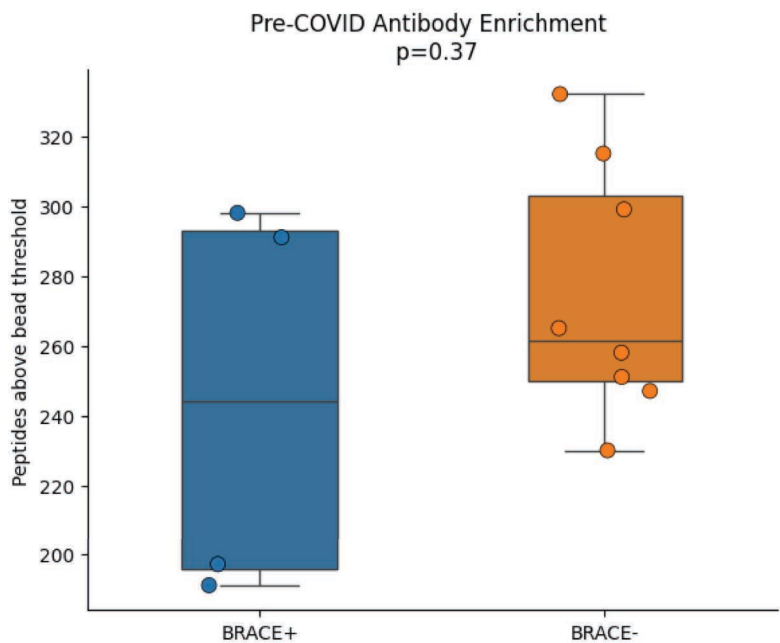
Supplementary Figure 5. No differences in the SARS-CoV-2 antibody levels in CSF and serum between neurological Long-COVID (n-LC) patients and controls. A Luminex bead-based immunoassay was used to quantify antibodies against SARS-CoV-2 Spike and Nucleocapsid proteins in CSF and serum. Antibody Index values were calculated as (CSF MFI/Serum MFI) / (CSF total IgG/Serum total IgG). Comparisons among n-LC patients, recovered controls, and Never-COVID controls showed no significant differences in the Antibody Index (Kruskal-Wallis test; ns = not significant). Data represent individual values with Mean ± SEM.

Supplementary Figure 6



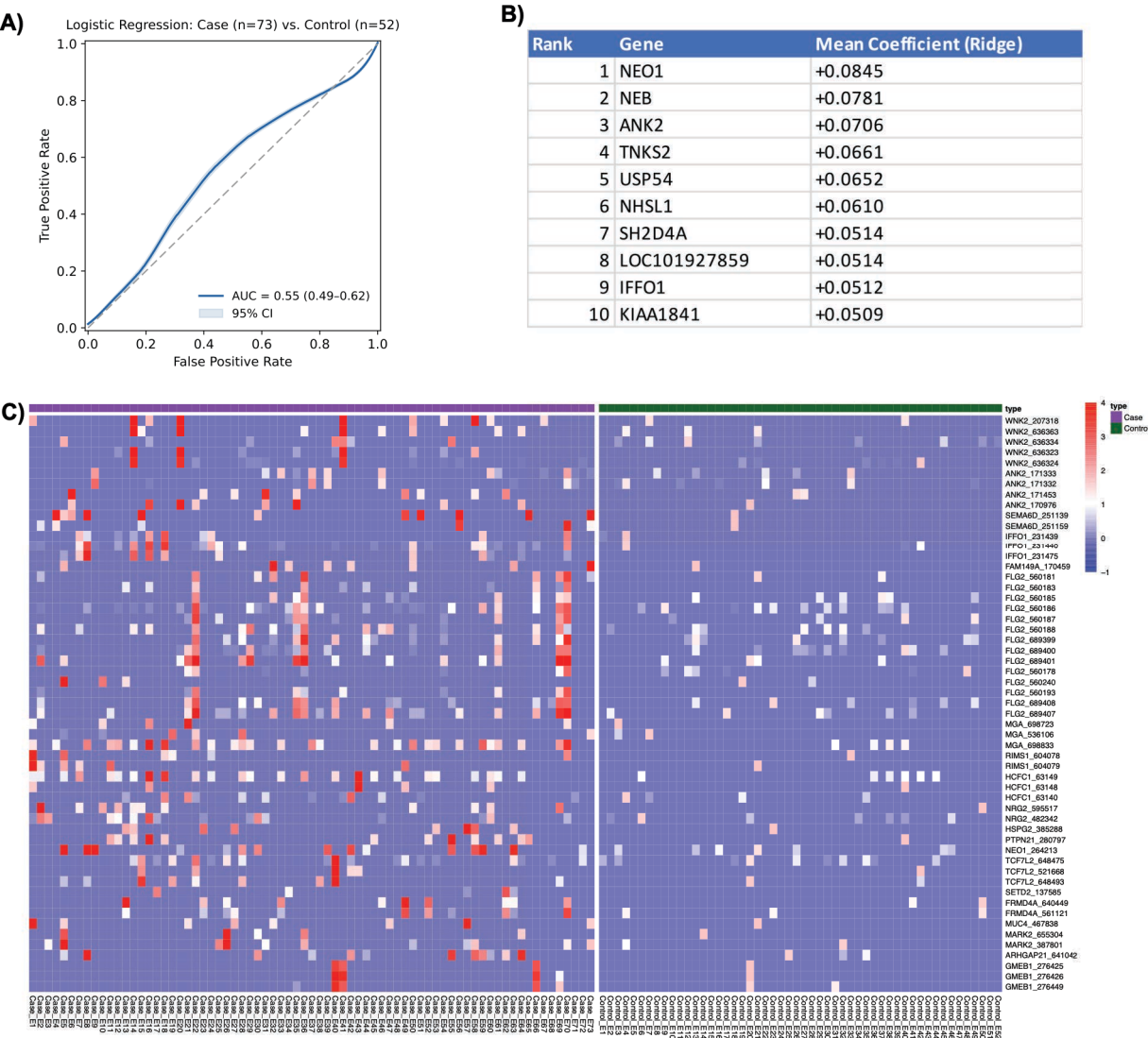
Supplementary Figure 6. Sensitivity analyses restricting to a single SARS-CoV-2 infection or adjusting for number of infections did not alter BRACE+ vs BRACE- classifier performance in the EPICC cohort. A) Ridge logistic regression analysis restricted to participants with one documented SARS-CoV-2 infection episode (BRACE+ n = 18; BRACE- n = 39) showed no discriminatory ability between cognitive-status groups (mean AUC = 0.51). **B)** Ridge logistic regression analysis of the full EPICC cohort (BRACE+ n = 29; BRACE- n = 44), with the number of documented SARS-CoV-2 infection episodes included as a covariate, similarly yielded a mean AUC of 0.51.

Supplementary Figure 7



Supplementary Figure 7. No pre-existing immunological differences between BRACE+ and BRACE- individuals prior to SARS-CoV-2 infection. Autoantibody repertoire breadth, quantified as peptide counts above bead threshold, was compared between BRACE+ (n=4) and BRACE- (n=8) EPICC participants with available pre-infection sera archived in the Department of Defense Serum Repository (DoDSR). Mann-Whitney U test showed no significant difference between the two groups ($p=0.37$), indicating that BRACE+ classification is not attributable to pre-existing baseline immunological differences. The data show individual values, with quartiles indicated. The line inside the box shows the median, and the whiskers extend to the minimum and maximum values.

114 **Supplementary Figure 8**



115

116 **Supplementary Figure 8. A) Logistic regression classifier shows limited**

117 **discrimination between all post-COVID serum cases (with or without cognitive**

118 **impairment) (n = 73) and controls (n = 52) from the EPICC cohort. The ROC curve**

119 **represents the mean classifier performance across 100 repeated five-fold cross-**

120 **validation iterations, with a mean AUC of 0.55. B) Table showing the top genes ranked**

121 **by their logistic regression coefficients. These genes contribute the most to case-**

122 **control classification. C) Heatmap of human PhIP-Seq reactivity in post-COVID serum**

123 **cases compared to controls. This heatmap displays peptide-level enrichment data from**

124 human phage immunoprecipitation sequencing (PhIP-Seq) performed on serum samples
125 from post-COVID patients with or without cognitive impairment above controls. Each row
126 corresponds to a unique peptide, and each column represents an individual serum
127 sample. Color intensity reflects the degree of peptide enrichment, quantified as the $\log_{10}$ -
128 transformed fold changes in cases relative to controls.