

Large-scale phenotyping of patients with long COVID post-hospitalization reveals mechanistic subtypes of disease

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Supplementary Materials

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Supplementary methods

Cytokine immunoassay

To validate key results from the Olink analysis, we performed conventional immunoassays on contemporaneously collected plasma samples, available from 58 individuals. We measured G-CSF (CSF3), IL2, TFF2, TNF α and IL1R2 by electrochemiluminescence (ECL, Mesoscale Diagnostics (MSD), Rockville, Maryland, USA). Custom R-plex (IL1R2 cat:K151ANVR-2, TFF2 cat: F21ACM-3) and U-plex (G-CSF, IL-2 cat: K15067M-1) MSD kits were used in addition to the Proinflammatory Panel 1 V-plex kit, for measurement of TNF α . Samples were thawed at room temperature and analysed, according to manufacturer's protocol (Available from: <https://www.mesoscale.com/>). MSD U-plex plates consisted of 96 wells with 2 spots, coated with a capture antibody and linker for G-CSF or IL2 respectively. The R-plex custom plate consisted of 96 wells with 1 spot coated with streptavidin. A solution of biotinylated capture antibody for IL1R2 or TFF2 was incubated on each R-plex plate to enable measurement of the chosen analytes. The V-plex kit consisted of a 96-well plate, precoated with a TNF α capture antibody. Samples were then incubated neat followed by the addition of a labelled detection antibody. MSD plates were measured on a MESO QuickPlex SQ 120 Reader (MSD) and cytokine concentrations were calculated using a reference standard and assigned pg/ml. Samples with values below the limit of detection (LLOD) were excluded from the validation analysis since assays perform poorly at these concentrations. Data were log2 transformed prior to analysis.

ELISA was used to measure IL3RA, (Abcam, Cambridge, United Kingdom, cat: ab300317). Samples were thawed at room temperature and added to the wells neat following the manufacturers' instructions for the kit. ELISA plates were quantified on a FLUOstar Omega (BMG labtech) at 450nm and cytokine concentrations were determined using the reference standard. Values below the limit of detection (LLOD) were excluded from the validation analysis since assays perform poorly at these concentrations. Data were log2 transformed prior to analysis.

Nasal Angiopoietin-2, CXCL-10, Galectin-9, GM-CSF, IL-1 α , IL-33, TSLP, CXCL11, VEGF, CCL2, CXCL11, GDF-15, HGF, Thrombomodulin and IL-15 were measured by custom Luminex discovery bead-based ELISA (Biotechne, Minneapolis, United States, configuration Ubdal728; cat:LXSAHM-15). IFN γ , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-19, IL-12p70, IL-13 and TNF α were measured using the Proinflammatory Panel 1 V-plex kit, which uses an MSD electrochemiluminescence multiplex assay (Mesoscale Diagnostics, Rockville, Maryland, USA, cat K15049D-1). Trefoil factor 2 (TFF2), Tissue Plasminogen Activator (tPA), Follistatin and TGF α were measured using an R-plex custom electrochemiluminescence multiplex assay (MSD; cat: F21ACN-3 & F21ACZ-3).

Nasal samples were thawed at room temperature and analysed at a fixed dilution of 1 in 2 using the R-plex and Luminex assays, and neat using the Proinflammatory Panel 1 V-plex kit. Plates were

prepared and analysed according to the manufacturers protocol¹⁻³. MSD V-plex plates consisted of 96 wells with 10 spots, each precoated with a capture antibody for the given analyte, and to which neat sample was added and incubated. The R-plex custom plate consisted of 96 wells with 4 spots coated with streptavidin. A solution of biotinylated capture antibody for each analyte was incubated on each R-plex plate to enable measurement of the chosen analytes. Nasal fluid was then added and incubated, followed by the addition of a labelled detection antibody. MSD plates were measured on a MESO QuickPlex SQ 120 Reader (MSD) and cytokine concentrations were calculated using a reference standard and assigned pg/ml. For the Luminex assay, samples were incubated on a 96 well plate with addition of beads labelled with the analyte capture antibody. Luminex plates were read on a BioPlex200 instrument (Bio-Rad, UK) and cytokine concentrations were derived from the reference standard and assigned pg/ml. All values at or below the LLOD were replaced with LLOD. All values at or above the upper limit of detection (ULOD) were replaced with ULOD.

Viral antigen measurements from sputum

Sputum samples were thawed at room temperature and sputum plugs were extracted and weighed. Eight millilitres of PBS were added per mg of sputum to create a solution and samples were centrifuged at 400g for 10 minutes at 4°C. Four volumes of PBS supernatant were then removed and stored at -80°C. Another 4 volumes were removed for the addition of 4 volumes of 0.1% dithiothreitol (DTT), creating a 1 in 2 dilution, and stored at -80°C. DTT was added to reduce matrix effects and enable measurement of sputum proteins, and this method has been previously validated⁴. Sputum diluted in DTT was used for the measurement of viral Spike (S) and Nucleopcapsid (N) antigens using a S plex SARS-CoV-2 N kit and SARS-CoV-2 S kit (MSD). The kits used ECL to detect antigen concentrations and plates consisted of 96 wells containing 1 spot coated with a streptavidin bound biotinylated capture antibody. Plates were blocked with MSD Blocker A, followed by the addition of sputum samples in DTT, analysed at a fixed dilution of 1 in 2. After sample incubation a TURBO-BOOST detection antibody was added followed by the addition of a TURBO-TAG which enables higher sensitivity of the assay⁵. All values below the lower limit of detection (LLOD) were replaced with LLOD if MSD software was unable to calculate a value.

Statistics and reproducibility

Performance of the adjusted penalised ridge logistic regression

The AUC of the final models were >0.6 for all symptom outcomes and the classification errors were all <0.4 (Extended Data Fig. 9). These metrics indicate that the model assigned symptom groups correctly based on the identified variables more frequently than would be expected by chance (in which case: $AUC \leq 0.5$ and $Classification\ error \geq 0.5$). The cognitive impairment model was weighted due to the imbalance in group size (60 Vs 233), preventing misclassification to the majority class (Recovered), and the sensitivity of the weighted model was 0.98. Since the objective was not a predictive model, the accuracy metrics were considered adequate for extracting associations between symptoms and variables.

The small effect sizes reported in PLR were small, which can be explained by how the model derives coefficients. PLR shrinks correlated mediator coefficients towards each other to account for combined effects and prevent colinear inflation⁶. Thus, the effect sizes do not necessarily diminish the potential mechanistic significance of our findings, as inflammatory proteins are expected to mediate effects in combination.

Validation of results through alternative analytical approaches

PLS and univariate analyses were used to support the reliability of PLR findings, but were not used to draw conclusions. PLR enables relationships between mediators to be accounted for without false discovery^{7,8}. In highly correlated data such as ours, PLR has been shown to consistently outperform PLS, which tends to overestimate coefficient variance^{9,10}. Thus PLR was used for the primary analysis and to draw conclusions.

Supplementary tables

Cardiorespiratory	Neuropsychiatric	Gastrointestinal
Atrial fibrillation	Migraine	Inflammatory Bowel disease
Ischaemic heart disease	Previous Cerebrovascular Accident (CVA)	Irritable bowel syndrome
Congestive heart failure	Dementia	Peptic ulcer disease
Coronary heart disease	Multiple sclerosis	Chronic liver disease
Valvular heart disease	Depression	Any other chronic gastrointestinal disorder
Chronic Obstructive Pulmonary Disease (COPD)	Anxiety	
Asthma	Previous treatment by mental health professional	
Interstitial lung disease	Any other chronic neurological disorder	
Bronchiectasis		
Previous pulmonary embolus		
Previous Tuberculosis infection		
Lung carcinoma		
Any other chronic cardiac or lung disorder		

Supplementary Table 1. Comorbidities included as covariates in analysis. Details of patient questionnaire items used to assign patient comorbidity status relevant to long COVID symptom outcomes. Relevant comorbidities were included as covariates in the model for each symptom group. All comorbidities recorded by the PHOSP-COVID patient questionnaire were included as covariates for the Fatigue model, including the response ‘Yes’ to variable ‘any other comorbidity?’.

Targeted aetiology	Drug	Mechanisms of action relevant to long COVID inflammatory profiles	Clinical trial identifier
Viral persistence	Nirmatrelvir/ritonavir (Paxlovid)	Anti-SARS-CoV-2	NCT05668091 NCT05595369 NCT05576662 NCT05823896 NCT05852873
	Remdesivir	Anti-SARS-CoV-2	NCT04978259 NCT05911906
	Favipiravir	Anti-SARS-CoV-2	NCT04448119
	Rintatolimod (Ampligen)	TLR3 agonist and antiviral action through induction of interferons	NCT05592418
Autoimmunity and/or chronic inflammation	Anakinra	IL-1 signalling blockade	NCT05926505
	Infliximab	TNF signalling blockade	NCT05220280
	Imatinib	JAK inhibition and suppression of vascular ¹¹ and macrophage/TNF α dependent ¹² inflammation	NCT05220280
	Baricitinib	Anti-SARS-CoV-2 effects Inhibits multiple cytokines including IL-1, IL-6 and G-CSF ¹³⁻¹⁵	NCT05858515
	Ibudilast	Phosphodiesterase inhibition and reduction of monocyte derived cytokines	NCT05513560
	Cannabidiol Xltanplus Naltrexone	Agonist to PPAR γ and CBD receptors expressed by immune cells to suppress NF κ B, TNF α , IL-1 and IL-6 signalling. ¹⁶	NCT04997395 NCT05467904 NCT04604704 NCT05430152 NCT05946551
	Methylprednisolone	Broad suppression of immune responses, including vascular inflammation	NCT05986422
	Montelukast	Leukotriene receptor antagonist which can suppress IL-1 and IL-6 in a range of tissues. ¹⁷	NCT04695704
	Colchicine	Inhibits neutrophil derived inflammation and suppresses N- κ B inflammatory pathways including IL-1 and TNF α ¹⁸	NCT05648734 STIMULATE-ICP /ISRCTN10665760
Complement and/or Thrombosis	Pentoxifylline	Vasodilation and suppression of vascular inflammation ¹⁹	NCT05513560
	Rivaroxaban	Anticoagulation	STIMULATE-ICP /ISRCTN10665760

Supplementary Table 2. Drugs repurposed for long COVID. Trials listed are those using drugs already licensed in other disease, which have potential to target long COVID aetiologies consistent with observed inflammatory signatures. Trials were identified by searching clinicaltrials.gov, September 2023.

Cardiorespiratory	OR	upper_SE	lower_SE	p-value	
Female	2.05	2.46	1.64	0.0003	***
Cardioresp comorbidity	1.45	1.76	1.15	0.05	*
WHO acute severity: class 6-9	1.44	1.71	1.17	0.06	NS
Age	1.00	1.00	0.99	0.59	NS
Fatigue	OR	upper_SE	lower_SE	p-value	
Any Comorbidity	2.24	2.71	1.77	0.0001	***
Female	2.19	2.64	1.74	0.0002	***
Age	0.98	0.99	0.98	0.05	NS
WHO acute severity: class 6-9	1.38	1.66	1.11	0.10	NS
Anxiety/depression	OR	upper_SE	lower_SE	p-value	
Neuro/Psych comorbidity	4.30	5.46	3.14	6.90E-08	*****
Female	2.08	2.56	1.60	0.002	**
WHO acute severity: class 6-9	1.52	1.86	1.18	0.06	NS
Age	0.98	0.99	0.98	0.09	NS
Gastrointestinal	OR	upper_SE	lower_SE	p-value	
Female	3.00	3.71	2.29	3.23E-06	*****
GI Comorbidity	1.53	2.08	0.98	0.23	NS
WHO acute severity: class 6-9	0.95	1.18	0.73	0.83	NS
Age	1.00	1.01	0.99	0.86	NS
Cognitive impairment	OR	upper_SE	lower_SE	p-value	
Female	2.01	2.63	1.40	0.02	*
Neuro/Psych comorbidity	2.02	2.76	1.27	0.05	*
Age	1.02	1.03	1.01	0.14	NS
WHO acute severity: class 6-9	1.12	1.45	0.79	0.71	NS

Supplementary Table 3. The effect of clinical covariates on symptom outcome. The unadjusted odds ratio (OR) and standard error (SE) associated with clinical variables and each symptom outcome. An unadjusted, non-regularized logistic regression was used. The significance value from the binomial generalized linear model is shown: $*$ = $p<0.05$, $**$ = $p<0.01$, $***$ = $p<0.001$, $*****$ = $p<0.0001$.

Healthy control demographics		
	Nasal fluid (n=25)	BALF (n=9)
COVID status	Samples collected prior to COVID-19 pandemic	Samples collected prior to COVID-19 pandemic
Age (years) Mean (SD)	39.5 (12.2)	38.1 (13.3)
Female sex n (%)	14 (56)	2 (22)
Non-smoker n (%)	25 (100)	9 (100)
White ethnicity n (%)	14 (56)	7 (77.8)

Supplementary Table 4. Demographics of healthy control participants. Nasal fluid from convalescent patients were compared to pre-pandemic nasal samples from healthy controls. Sputum from convalescent patients were compared to Broncho-alveolar lavage fluid (BALF) collected from individuals before the emergence of SARS-CoV-2. Data is shown as n (%) or mean (SD).

		Recovered (n=31)	Long COVID (n=33)	Missing data
Age, years Mean (SD)		59.32 (13.9)	54.8 (11.4)	5 (7.8)
Female sex n (%)		15 (50)	17 (58.6)	5 (7.8)
WHO acute severity n (%)	Class 3-4	4 (12.9)	7 (25)	5 (7.8)
	Class 5	18 (58.1)	11 (39.3)	
	Class 6	8 (25.8)	9 (32.1)	
	Class 7-9	1 (3.2)	1(3.6)	

Supplementary Table 5. Demographics of study participants with nasal inflammatory mediators measured (n=64). Data are n (% of cohort with complete data) or mean (SD). Missing data is shown as n (% of all individuals with inflammatory mediators measured).

		Recovered (n=16)	Long COVID (n=23)
Age, years Mean (SD)		57.5 (15.9)	61.7 (8.8)
Female sex n (%)		3 (18.8)	8 (34.8)
WHO acute severity n (%)	Class 3-4	4 (25.0)	6 (26.1)
	Class 5	7 (43.8)	4 (17.4)
	Class 6	3(18.8)	5 (21.7)
	Class 7-9	2 (12.5)	8 (34/8)

Supplementary Table 6. Demographics of study participants with Sputum samples available (n=40). Data are n (% of cohort with complete data) or mean (SD). There was no missing data in this cohort.

Symptom group	Questionnaire	Response type	Threshold score
Cardiorespiratory*	MRC dyspnoea scale	Numerical scale	Score >1
	Dyspnoea-12	Numerical scale	Score >= 12
	Palpitations	Yes/No	Yes
	Chest pain	Yes/No	Yes
Fatigue	FACIT Fatigue scale	Numerical scale	Score < 40
Anxiety/depression*	PHQ-9	Numerical scale	>= 10
	GAD-7	Numerical scale	>8
Cognitive impairment	Montreal Cognitive Assessment (MoCA)	Numerical scale	Score < 26
GI symptoms	Stomach pain	Yes/No	'Yes' to at least 2 symptoms.
	Constipation	Yes/No	
	Diarrhoea	Yes/No	
	Weight loss	Yes/No	
	Nausea and/or vomiting	Yes/No	
Recovered	Do you feel fully recovered from COVID-19?	Yes/No	Yes

Supplementary Table 7. Clinical questionnaires used to define symptom groups. The MoCA assessment was administered by a healthcare worker and the remaining scores were self-reported. All non-numerical scores were self-reported and patients were given the option to provide a binary response 'YES' or 'NO'. *Patients were placed in this symptom group if they met the threshold score for at least one variable in this category.

Supplementary Table 8. Univariate analysis of 368 Olink mediators measured. Each mediator was analysed, comparing values between recovered and symptom groups using the two-sided Wilcoxon-signed ranks test. The table is available in Appendix 1.

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Supplementary Table 8

	p value				
Assay	Cardiorespiratory	Fatigue	GI	Anxiety/ Depression	Cognitive
ACTN4	0.81050	0.79739	0.58587	0.81237	0.06346
ADA	0.88396	0.82789	0.58551	0.75619	0.49407
ADAM23	0.00682	0.00422	0.01834	0.00177	0.06026
ADGRE2	0.17803	0.27543	0.18735	0.39009	0.76286
AGER	0.15862	0.10577	0.29673	0.01256	0.19039
AGRN	0.92491	0.98035	0.95297	0.95531	0.91193
AGRP	0.41477	0.48829	0.19986	0.49593	0.56046
ALDH3A1	0.00247	0.00077	0.03121	0.00529	0.09081
AMBN	0.64560	0.73426	0.73014	0.91974	0.48710
AMN	0.12211	0.07642	0.54577	0.12229	0.32401
ANGPT1	0.43706	0.52978	0.30031	0.15403	0.41563
ANGPTL2	0.02766	0.02436	0.06211	0.00992	0.03074
ANGPTL4	0.13889	0.10379	0.21442	0.17346	0.93979
ANXA11	0.89512	0.79669	0.92964	0.75448	0.12503
AOC1	0.98301	0.91544	0.36056	0.70887	0.56934
ARHGEF12	0.68997	0.80717	0.82973	0.78684	0.22774
ARNIT	0.42597	0.56220	0.69986	0.79074	0.24464
ARTN	0.86670	0.76789	0.99805	0.46119	0.75165
ATP5F1	0.66350	0.84314	0.38571	0.82488	0.18530
AXIN1	0.89391	0.96149	0.89556	0.74744	0.40151
B4GALT1	0.16695	0.49533	0.59201	0.51084	0.85162
BACH1	0.50149	0.69635	0.65882	0.40903	0.12169
BANK1	0.81952	0.70486	0.96656	0.99961	0.51226
BCL2L1	0.25462	0.22514	0.16587	0.33901	0.89594
BCR	0.88511	0.97933	0.87956	0.81981	0.51556
BID	0.63722	0.60413	0.98084	0.78373	0.33113
BSG	0.86519	0.89895	0.48466	0.73836	0.55625
BTN2A1	0.69610	0.91296	0.99204	0.88575	0.41707
BTN3A2	0.80565	0.94480	0.37344	0.90235	0.27145
CLQA	0.28580	0.27994	0.08466	0.31555	0.02585
CASP2	0.44400	0.60466	0.62207	0.73586	0.36638
CLL1	0.33783	0.21097	0.24419	0.17599	0.10149
CLL13	0.04120	0.03952	0.12308	0.06138	0.32732
CLL17	0.24628	0.47709	0.23560	0.16263	0.54107
CLL20	0.29954	0.14704	0.19836	0.05802	0.22522
CLL21	0.77664	0.48870	0.39429	0.19249	0.34646
CLL22	0.10054	0.11941	0.03880	0.02273	0.08510
CLL23	0.54279	0.65320	0.23553	0.76989	0.49939
CLL24	0.92245	0.73379	0.86432	0.58731	0.35225
CLL25	0.81414	0.60697	0.90836	0.47221	0.19985
CLL26	0.21044	0.30852	0.81697	0.19416	0.11313
CLL28	0.11729	0.03393	0.74824	0.20374	0.99272
CLL3	0.98270	0.90274	0.73175	0.72319	0.94503
CLL4	0.55245	0.29619	0.84891	0.38402	0.57163
CLL7	0.50114	0.47034	0.66015	0.38114	0.32808
CON2	0.54704	0.55934	0.69115	0.25212	0.57046
CD160	0.39574	0.25103	0.74370	0.45075	0.33703
CD200	0.11874	0.32724	0.38657	0.14413	0.30127
CD200R1	0.65203	0.74189	0.40629	0.81344	0.74297
CD22	0.37468	0.06172	0.07342	0.10772	0.98531
CD244	0.48867	0.36389	0.37025	0.60590	0.38787
CD276	0.14434	0.07477	0.56531	0.10443	0.07474
CD4	0.17890	0.16687	0.53573	0.47325	0.01188
CD40	0.95801	0.97678	0.71338	0.91925	0.50267
CD40LG	0.96187	0.91378	0.63722	0.73298	0.42694
CD48	0.28831	0.73922	0.80353	0.37027	0.92249
CD58	0.02520	0.04096	0.02191	0.06637	0.07476
CD6	0.89146	0.57233	0.64187	0.86662	0.76058
CD70	0.79132	0.95848	0.51491	0.73210	0.98354
CD79B	0.34973	0.52888	0.78955	0.47941	0.70611
CD83	0.21333	0.11968	0.23895	0.13765	0.24831
CD84	0.74242	0.81049	0.90736	0.81703	0.27693
CDON	0.60270	0.71023	0.08399	0.53347	0.39713
CD5N	0.52534	0.58049	0.37917	0.24733	0.72132
CEACAM21	0.69865	0.88692	0.83027	0.79077	0.83411
CEP164	0.13441	0.08125	0.32200	0.31197	0.07347
CHRD11	0.89258	0.93295	0.76300	0.69617	0.11433
CKAP4	0.67591	0.59597	0.97523	0.80857	0.33515
CKMT1A/B	0.77070	0.57203	0.89919	0.60048	0.19389
CLEC4A	0.66043	0.61813	0.92430	0.70278	0.10373
CLEC4C	0.36007	0.10612	0.16437	0.04408	0.00633
CLEC4D	0.11614	0.04899	0.05339	0.02222	0.05771
CLEC4G	0.16728	0.21228	0.33311	0.19296	0.30057
CLEC7A	0.90046	0.94651	0.54976	0.58563	0.60461
CLIP2	0.79828	0.87317	0.86357	0.76390	0.23238
CLSTN2	0.44331	0.26365	0.47066	0.18189	0.48481
CNTNAP2	0.32335	0.20585	0.08791	0.16280	0.53206
COL9A1	0.91103	0.92553	0.31561	0.82217	0.09467
COLEC12	0.08993	0.07017	0.40892	0.15165	0.06520
CRELD2	0.91940	0.81340	0.74264	0.92743	0.97800
CRHBP	0.27119	0.21505	0.33588	0.16515	0.60723
CRIM1	0.71658	0.94817	0.68905	0.86767	0.48201
CRKL	0.84533	0.91145	0.79392	0.88601	0.16880
CRF1	0.69610	0.68395	0.33959	0.46239	0.50872
CSF1	0.95188	0.47032	0.27476	0.58141	0.55176
CSF3	0.05212	0.02783	0.00109	0.04287	0.52887
CS7	0.74867	0.81811	0.72906	0.85536	0.23753
CTRC	0.15276	0.05795	0.01973	0.31245	0.72123
CTSC	0.42579	0.42549	0.73370	0.60916	0.32719
CTSO	0.13435	0.09827	0.86001	0.33220	0.03305
CXADR	0.40214	0.36947	0.66200	0.50014	0.01361
CXCL1	0.71475	0.70001	0.98919	0.70939	0.18498
CXCL10	0.52192	0.42895	0.59748	0.62459	0.78184
CXCL12	0.84298	0.94123	0.44174	0.99609	0.92844
CXCL14	0.60216	0.70596	0.17801	0.82781	0.35683
CXCL17	0.29083	0.51517	0.28501	0.27376	0.78870
CXCL3	0.89611	0.92349	0.76151	0.94010	0.25128
CXCL6	0.38225	0.27391	0.60203	0.16911	0.18681
CXCL8	0.92946	0.82929	0.63684	0.61213	0.26703
CXCL9	0.25703	0.27071	0.83730	0.28595	0.37746
DAG1	0.61444	0.69272	0.80763	0.77870	0.48989
DAPP1	0.64370	0.81907	0.65425	0.85852	0.32896

	p value				
Assay	Cardiorespiratory	Fatigue	GI	Anxiety/ Depression	Cognitive
DBNL	0.76030	0.87345	0.77722	0.96391	0.21269
DEC1	0.99616	0.92540	0.80225	0.95365	0.64329
DFFA	0.90772	0.83129	0.95000	0.91430	0.15786
DGK2	0.82598	0.88376	0.82069	0.99150	0.70551
DNAJA2	0.97392	0.87844	0.99916	0.77042	0.20067
DNER	0.00003	0.00001	0.01092	0.00032	0.00944
DNP1	0.47652	0.53786	0.42248	0.32019	0.07042
DPP10	0.11769	0.17225	0.14428	0.23071	0.00120
EDAR	0.67918	0.96758	0.40317	0.44669	0.38539
EGF	0.75595	0.92703	0.52980	0.73981	0.46932
EGLN1	0.92596	0.96095	0.67836	0.75284	0.35623
EIF4G1	0.61444	0.73940	0.85761	0.71377	0.19182
EIF5A	0.91448	0.67234	0.51616	0.65895	0.81210
ENAH	0.03529	0.03732	0.18537	0.13088	0.47099
ENPP5	0.00180	0.00111	0.00332	0.01386	0.26779
ENPP7	0.36629	0.08887	0.36062	0.02311	0.58890
EPCAM	0.51881	0.22133	0.39332	0.47327	0.04468
EPHA1	0.73446	0.74895	0.72429	0.74395	0.92558
EPO	0.11360	0.07243	0.04896	0.13858	0.18916
ERBB3	0.21359	0.07990	0.17998	0.03600	0.57568
ESM1	0.04378	0.09839	0.57950	0.11824	0.44494
F2R	0.86867	0.89939	0.93347	0.96558	0.19518
FABP1	0.09780	0.04344	0.18692	0.10097	0.19690
FABP9	0.81897	0.46472	0.11185	0.76814	0.79631
FASLG	0.48894	0.94121	0.33906	0.93614	0.72449
FCAR	0.11046	0.08793	0.11389	0.01831	0.14251
FCRL2	0.00293	0.10854	0.32256	0.02807	0.01962
FCRL3	0.77297	0.60954	0.62518	0.99689	0.41049
FCRL6	0.24074	0.12174	0.09997	0.12150	0.74445
FGF19	0.25839	0.34651	0.43930	0.66190	0.04267
FGF2	0.64817	0.55188	0.49732	0.76860	0.20144
FGF5	0.17195	0.22741	0.62300	0.21645	0.16461
FB1	0.82480	0.80470	0.98766	0.68592	0.32881
FKBP1B	0.56154	0.63221	0.80949	0.59658	0.34283
FLT3LG	0.25954	0.31118	0.08794	0.30724	0.77572
FOXO1	0.55474	0.58116	0.81734	0.67558	0.28818
FST	0.09078	0.05310	0.00669	0.02038	0.27647
FSTL3	0.23858	0.11635	0.36917	0.33868	0.72562
FXYD5	0.82539	0.78012	0.90285	0.95870	0.16845
GAL	0.01603	0.02869	0.10848	0.03077	0.16354
GALNT3	0.25258	0.27420	0.14132	0.35037	0.47725
GBP2	0.80051	0.82359	0.84081	0.59038	0.30437
GLOD4	0.61767	0.70342	0.59001	0.62362	0.07496
GMFR	0.66064	0.89587	0.64895	0.81251	0.12164
GOPC	0.95990	0.92676	0.77377	0.98700	0.28983
GZMA	0.86758	0.99520	0.47443	0.90308	0.50017
GZMB	0.64036	0.58856	0.29889	0.85265	0.38703
HCL1	0.39968	0.38747	0.43445	0.47268	0.29080
HEXIM1	0.89562	0.77487	0.86576	0.83054	0.21701
HGF	0.06673	0.08213	0.16002	0.05715	0.16600
HLA-DRA	0.45796	0.44349	0.17830	0.33423	0.31156
HLA-E	0.39252	0.40686	0.66894	0.23763	0.23019
HPICAL1	0.96253	0.97496	0.90708	0.84741	0.21785
HSD11B1	0.49529	0.32016	0.83609	0.65609	0.19206
HSPA1A	0.89465	0.95714	0.75364	0.95257	0.19635
ICA1	0.79437	0.68853	0.76627	0.73118	0.41204
ICAM4	0.00707	0.00217	0.00019	0.01482	0.21762
ID5	0.04207	0.00685	0.05753	0.02714	0.84990
IFNG	0.77626	0.65786	0.18128	0.91349	0.69687
IFNGR1	0.10281	0.19129	0.19401	0.18824	0.85291
IFNL1	0.12425	0.14114	0.08654	0.18509	0.99994
IKBK	0.83311	0.92925	0.94088	0.82683	0.26364
IL10	0.35088	0.45059	0.35165	0.50533	0.42664
IL10RA	0.46051	0.48410	0.08872	0.52353	0.28862
IL10RB	0.81198	0.70537	0.78142	0.70190	0.87329
IL11	0.47436	0.36722	0.33577	0.40359	0.30424
IL12B	0.02439	0.18488	0.09372	0.02292	0.08305
IL12RB1	0.54960	0.86952	0.78623	0.95107	0.11312
IL13	0.39729	0.59793	0.96109	0.77746	0.90692
IL15	0.65545	0.38851	0.88991	0.70165	0.80262
IL15RA	0.28688	0.57540	0.70160	0.21707	0.65753
IL16	0.59918	0.35501	0.66511	0.76015	0.15824
IL17A	0.44131	0.85921	0.53035	0.73366	0.06560
IL17C	0.73756	0.92777	0.43157	0.76296	0.93863
IL17D	0.98945	0.56410	0.15484	0.92585	0.48894
IL17F	0.19861	0.22145	0.24855	0.32190	0.00482
IL17RB	0.68807	0.80511	0.53850	0.58016	0.20951
IL18	0.80079	0.94748	0.75615	0.77879	0.88351
IL18R1	0.03539	0.01671	0.19124	0.03602	0.71183
IL1A	0.42265	0.08455	0.17520	0.09415	0.28182
IL1B	0.51424	0.56077	0.98701	0.55059	0.45982
IL1R2	0.00607	0.00061	0.05391	0.00021	0.22766
IL1RL2	0.07020	0.01231	0.06117	0.10291	0.15499
IL1LRN	0.08592	0.02898	0.18443	0.02180	0.61730
IL2	0.00461	0.00437	0.32610	0.01797	0.10340
IL20	0.75320	0.74782	0.99652	0.94728	0.21397
IL20RA	0.02912	0.02579	0.01513	0.00611	0.05010
IL22RA1	0.71832	0.84800	0.90914	0.94268	0.86560
IL24	0.11303	0.14630	0.17197	0.24022	0.51283
IL2RB	0.37711	0.64271	0.51092	0.91406	0.76761
IL32	0.56962	0.70641	0.49781	0.88340	0.09267
IL33	0.30230	0.66156	0.49291	0.94038	0.56826
IL3RA	0.71710	0.84522	0.82663	0.99573	0.38109
IL4	0.73380	0.86763	0.83791	0.91104	0.34974
IL4R	0.58148	0.82322	0.59560	0.94100	0.27248
IL5	0.32461	0.64367	0.76792	0.35519	0.63577
IL5RA	0.04583	0.04989	0.10622	0.01435	0.71320
IL6	0.00864	0.00558	0.00039	0.00220	0.04438
IL7	0.38783	0.54027	0.53250	0.18562	0.38897
IRAK1	0.88895	0.79620	0.98977	0.69511	0.36582
IRAK4	0.81657	0.82785	0.96926	0.66349	0.16427
ISM1	0.01991	0.02421	0.05177	0.14262	0.34449

	p value				
Assay	Cardiorespiratory	Fatigue	GI	Anxiety/ Depression	Cognitive
ITGA11	0.02069	0.00920	0.00501	0.04576	0.21897
ITGA6	0.30610	0.25969	0.46493	0.41824	0.57787
ITGB6	0.10529	0.01330	0.06800	0.02263	0.57576
ITM2A	0.43392	0.44025	0.03707	0.27952	0.90769
JCHAIN	0.21242	0.30833	0.33755	0.40020	0.29174
JUN	0.60591	0.73770	0.90186	0.54598	0.41410
KLRB1	0.87824	0.54583	0.91096	0.63741	0.98693
KLRD1	0.90485	0.62739	0.85535	0.82808	0.22846
KRT19	0.30288	0.62243	0.52674	0.57093	0.11763
KYNU	0.55920	0.72687	0.29571	0.67721	0.87732
LAIR1	0.92249	0.77773	0.85505	0.95134	0.62270
LAMA4	0.85870	0.90148	0.90888	0.97350	0.83613
LAMP3	0.30580	0.44366	0.54161	0.16982	0.89200
LAP3	0.76175	0.95626	0.85006	0.96818	0.20408
LAT	0.84431	0.75217	0.72128	0.57258	0.25189
LGALS4	0.01838	0.00542	0.03572	0.01047	0.00147
LGALS9	0.11114	0.04762	0.06717	0.04943	0.07784
LGMN	0.39877	0.53812	0.99461	0.83329	0.20442
LHPP	0.65095	0.66877	0.51794	0.32508	0.47082
LIFR	0.90884	0.85492	0.71904	0.89604	0.10127
LIRB4	0.67327	0.58763	0.65037	0.81122	0.88355
LRRN1	0.08750	0.02525	0.02424	0.00854	0.01628
LSP1	0.76357	0.85187	0.39659	0.80851	0.32617
LTA	0.63965	0.39778	0.30801	0.61455	0.57550
LTBR	0.76518	0.99299	0.90932	0.91671	0.55356
LTOT1	0.79820	0.82546	0.46830	0.84860	0.83647
LY6D	0.21545	0.21938	0.29174	0.22260	0.75401
LY75	0.71989	0.99188	0.66118	0.85668	0.37517
LY9	0.92118	0.68786	0.75061	0.70852	0.40427
MANF	0.79915	0.87669	0.46672	0.85531	0.15420
MAP2K6	0.57041	0.63270	0.82128	0.75942	0.12603
MAPK9	0.72599	0.96203	0.74085	0.82960	0.06634
MATN2	0.01206	0.01031	0.03138	0.02093	0.03121
MEGF10	0.00017	0.00038	0.02219	0.00720	0.11492
MEPE	0.18730	0.20809	0.08553	0.14826	0.47345
MERTK	0.58114	0.60019	0.57539	0.91007	0.14572
METAP1D	0.76510	0.73720	0.71416	0.68247	0.73618
MGLL	0.75241	0.79834	0.55968	0.70176	0.21015
MGMT	0.75524	0.68917	0.90932	0.93366	0.50860
MICB_MICA	0.06119	0.03011	0.06513	0.05108	0.01171
MILR1	0.75601	0.66411	0.38046	0.42320	0.24704
MLN	0.87811	0.92700	0.80281	0.70079	0.59679
MMP1	0.56133	0.48272	0.42385	0.24432	0.89028
MMP10	0.09400	0.30559	0.83999	0.35975	0.19312
MPIG6B	0.40646	0.45821	0.24364	0.21387	0.14228
MVK	0.14364	0.14770	0.25437	0.13883	0.20066
MYO9B	0.78521	0.85919	0.96601	0.99187	0.51251
MZB1	0.63531	0.38378	0.49808	0.68225	0.94476
NBN	0.76327	0.99320	0.45041	0.79945	0.28917
NC2	0.32005	0.15862	0.70966	0.21631	0.02094
NCK2	0.77806	0.79743	0.84187	0.89728	0.46623
NCLN	0.82640	0.55088	0.26151	0.79362	0.47800
NCR1	0.65426	0.46432	0.55430	0.71656	0.21773
NELL2	0.93322	0.87735	0.90673	0.94929	0.60370
NFASC	0.11402	0.13756	0.60848	0.20852	0.01012
NFATC1	0.83033	0.72949	0.84810	0.90230	0.48961
NFATC3	0.18531	0.09128	0.79878	0.20567	0.79379
NME3	0.90832	0.86319	0.31323	0.67748	0.61244
NPPC	0.15353	0.08467	0.08569	0.21631	0.15566
NRTN	0.85238	0.92649	0.53710	0.85157	0.64691
NTSC3A	0.96389	0.95847	0.95710	0.93194	0.28298
NTF3	0.14486	0.02463	0.05635	0.03163	0.88393
NUB1	0.74942	0.74881	0.58672	0.64988	0.28091
NUDC	0.89480	0.82721	0.81287	0.84820	0.21648
OMD	0.01523	0.00541	0.01163	0.02909	0.75947
OSCAR	0.88233	0.52878	0.53727	0.25819	0.05449
OSM	0.14775	0.08471	0.15268	0.02379	0.07551
PADI2	0.62563	0.67072	0.94648	0.73700	0.02732
PAPPA	0.17062	0.20938	0.15975	0.37382	0.05782
PARP1	0.71163	0.98301	0.52005	0.75854	0.47351
PCDH1	0.60032	0.82133	0.42114	0.42426	0.54729
PDGFB	0.42090	0.52451	0.37719	0.19921	0.48825
PDLM17	0.85548	0.99885	0.87105	0.86580	0.41433
PGF	0.34472	0.30658	0.42319	0.40064	0.95694
PIK3AP1	0.45544	0.47249	0.50780	0.36755	0.05370
PKLR	0.21342	0.21689	0.27021	0.09388	0.27253
PLA2G4A	0.84274	0.74442	0.85506	0.80485	0.32050
PLAUR	0.36019	0.28372	0.20596	0.30307	0.16388
PLXNA4	0.61133	0.74286	0.60984	0.68445	0.27100
PNLIPRP2	0.48718	0.80891	0.45599	0.26328	0.20843
PNPT1	0.79183	0.91934	0.81462	0.81073	0.42459
PON3	0.21361	0.35802	0.55270	0.75240	0.83239
PPP1R9B	0.47268	0.47455	0.46531	0.46252	0.38686
PRDX3	0.91954	0.90862	0.88432	0.86943	0.24940
PRDX5	0.79181	0.71555	0.77104	0.80286	0.12720
PREB	0.64555	0.90374	0.69069	0.88193	0.23439
PRELP	0.07758	0.08238	0.09589	0.08794	0.34416
PRKAB1	0.98417	0.99182	0.84935	0.60733	0.56202
PRKCC	0.75517	0.46957	0.94443	0.66466	0.80422
PROK1	0.00608	0.00029	0.03947	0.00378	0.03596
PRSS8	0.05267	0.07074	0.06217	0.05590	0.32261
PSIP1	0.74734	0.90812	0.48122	0.71728	0.34844

	p value				
Assay	Cardiorespiratory	Fatigue	GI	Anxiety/ Depression	Cognitive
PSMG3	0.59224	0.58945	0.47407	0.43241	0.18487
PSPN	0.00259	0.00285	0.00180	0.00616	0.03989
PTH1R	0.25401	0.38421	0.97826	0.38693	0.35331
PTPN6	0.60653	0.69023	0.84636	0.72392	0.20520
PTPRM	0.23476	0.07688	0.10490	0.16590	0.41513
PTX3	0.75589	0.41666	0.95209	0.43829	0.69219
RAB37	0.88470	0.87649	0.81690	0.67719	0.17653
RAB6A	0.97520	0.94274	0.96032	0.94476	0.36601
RABGAP1L	0.98844	0.97635	0.95317	0.84260	0.19538
REG4	0.68286	0.31687	0.12733	0.84751	0.17746
RG58	0.82331	0.74095	0.73522	0.98689	0.85045
ROBO1	0.03838	0.02554	0.12806	0.07874	0.29629
SAMD9L	0.87420	0.74742	0.83245	0.77114	0.16409
SCG3	0.93718	0.85195	0.14041	0.75227	0.42805
SCGB1A1	0.44360	0.38557	0.46258	0.27588	0.30943
SCGB3A2	0.96155	0.86672	0.68536	0.83138	0.61205
SCGN	0.52949	0.81290	0.10211	0.51879	0.19738
SCRN1	0.74156	0.56827	0.44599	0.56541	0.14316
SELPGL	0.36191	0.16550	0.57032	0.11894	0.57895
SERPINB8	0.42102	0.33358	0.83533	0.46359	0.04986
SH2D1A	0.91131	0.96395	0.46210	0.65606	0.46568
SHMT1	0.18048	0.26767	0.37989	0.13829	0.12490
SIGLEC1	0.44610	0.31174	0.28337	0.66789	0.66497
SIGLEC10	0.52200	0.20845	0.26175	0.56077	0.08764
SIRPB1	0.46665	0.80279	0.72181	0.67306	0.84651
SIT1	0.61131	0.30405	0.41240	0.33330	0.30168
SKAP2	0.64336	0.80111	0.55535	0.76536	0.21322
SLAMF1	0.95180	0.74811	0.11661	0.32008	0.34002
SLAMF7	0.44555	0.14955	0.90323	0.66600	0.71165
SLC39A5	0.03029	0.01306	0.33622	0.05671	0.25510
SMOC2	0.10717	0.04595	0.01478	0.09379	0.41787
SMPLDL3A	0.77568	0.63580	0.71227	0.58013	0.02731
SPINK4	0.51873	0.48568	0.56985	0.79871	0.01662
SPINT2	0.64418	0.69247	0.85748	0.85859	0.58541
SPON1	0.98106	0.64321	0.92487	0.68975	0.08693
SPRY2	0.48255	0.47472	0.67408	0.54911	0.57848
SRPK2	0.47795	0.55024	0.34905	0.42289	0.48260
STX8	0.78760	0.83901	0.85177	0.93394	0.49488
SULT2A1	0.04511	0.03213	0.21337	0.06697	0.06940
TANK	0.58516	0.70978	0.66931	0.44914	0.30607
TBC1D5	0.29964	0.40877	0.57374	0.51282	0.16596
TF2	0.09708	0.04517	0.01031	0.02007	0.02108
TGFA	0.19841	0.11956	0.10182	0.08391	0.02977
TGFB1	0.27964	0.43854	0.30544	0.23597	0.21768
TIMP3	0.22704	0.25341	0.13253	0.13253	0.08427
TLR3	0.45321	0.22843	0.68210	0.24247	0.66446
TNF	0.91569	0.65629	0.87709	0.83025	0.05782
TNFAIP8	0.26630	0.27259	0.93154	0.21632	0.43621
TNFRSF11A	0.86222	0.84006	0.70302	0.66859	0.84593
TNFRSF11B	0.98227	0.79912	0.09663	0.93828	0.00679
TNFRSF13B	0.89710	0.65602	0.57291	0.91834	0.62816
TNFRSF13C	0.00971	0.05458	0.28992	0.06921	0.08504
TNFRSF14	0.79302	0.89118	0.81197	0.74853	0.58764
TNFRSF4	0.50628	0.24408	0.40606	0.48060	0.39722
TNFSF10	0.38120	0.66831	0.03206	0.45883	0.79044
TNFSF11	0.19441	0.29855	0.00027	0.31662	0.21489
TNFSF12	0.26095	0.23096	0.43051	0.51900	0.69420
TNFSF13	0.09543	0.09251	0.42452	0.13854	0.73670
TPP1	0.81574	0.77232	0.38706	0.37092	0.45114
TPSAB1	0.09264	0.09192	0.09515	0.49904	0.25362
TPST1	0.72096	0.38019	0.33301	0.28821	0.97819
TRAF2	0.47667	0.70580	0.67011	0.79399	0.19724
TREM2	0.16274	0.08434	0.42661	0.13103	0.39964
TRIM21	0.42562	0.33020	0.14077	0.41659	0.57323
TRIM5	0.71690	0.82289	0.79073	0.83015	0.13667
VASH1	0.63406	0.61275	0.76057	0.59458	0.63513
VEGFA	0.71890	0.72726	0.23710	0.23747	0.77450
VEGFD	0.07368	0.06108	0.45856	0.07470	0.63667
WAS	0.78464	0.94263	0.68391	0.90455	0.57179
WFIKKN2	0.00366	0.00954	0.16165	0.00430	0.81605
WNT9A	0.27161	0.27970	0.53304	0.09789	0.71853
YTHDF3	0.52855	0.65617	0.65820	0.61448	0.53743

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