Cell Reports, Volume *38*

Supplemental information

SARS-CoV-2 Nsp13 encodes for an HLA-E-stabilizing peptide that abrogates inhibition of NKG2A-expressing NK cells

Quirin Hammer, Josefine Dunst, Wanda Christ, Francesca Picarazzi, Mareike Wendorff, Pouria Momayyezi, Oisín Huhn, Herman K. Netskar, Kimia T. Maleki, Marina García, Takuya Sekine, Ebba Sohlberg, Valerio Azzimato, Myriam Aouadi, Karolinska COVID-19 Study Group, Severe COVID-19 GWAS Group, Frauke Degenhardt, Andre Franke, Francesco Spallotta, Mattia Mori, Jakob Michaëlsson, Niklas K. Björkström, Timo Rückert, Chiara Romagnani, Amir Horowitz, Jonas Klingström, Hans-Gustaf Ljunggren, and Karl-Johan Malmberg

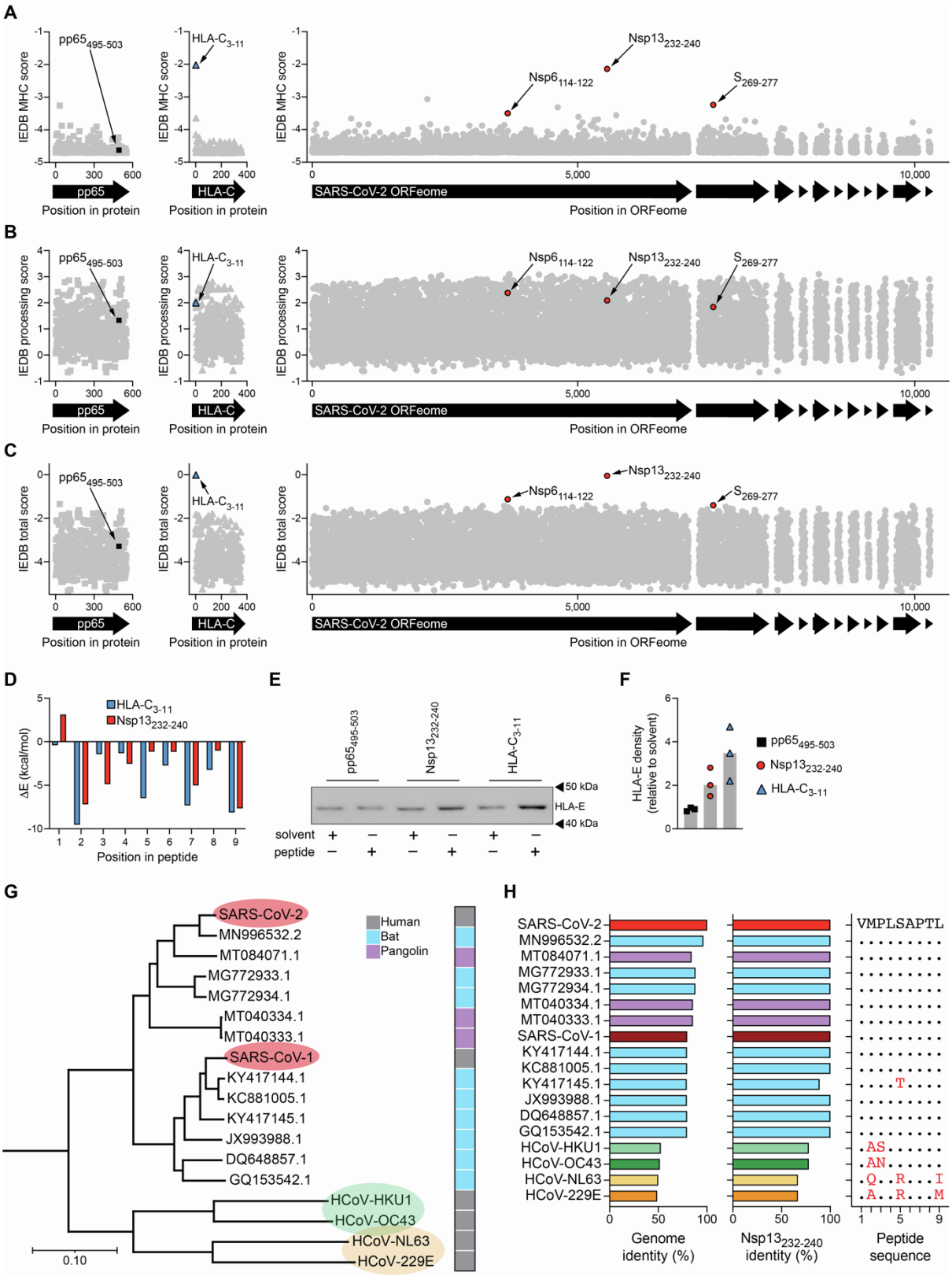


Figure S1. SARS-CoV-2 Nsp13 encodes for an HLA-E-stabilizing peptide. Related to Figure 1.

(**A-C**) *In silico* epitope predictions using the IEDB analysis resource. Left: pp65 protein. Middle: HLA-C*01:02 protein. Right: SARS-CoV-2 ORFeome (isolate Wuhan-Hu-1).

(A) Predicted HLA-E*01:01 binding scores. (B) Predicted proteasomal cleavage and transport scores. (C) Total scores combining HLA-E binding and processing. (**D**) Decomposed contributions of single amino acids to delta energy of binding as indicator of theoretical affinity determined by MD simulations (n=3 independent simulations). (**E-F**) Stability of HLA-E/peptide complexes as determined by cellular thermal shift assays using protein isolates from K562/HLA-E cells. (E) Cellular thermal shift assay and western blot analysis on HLA-E protein isolated form K562/HLA-E cells after incubation with the indicated peptides or corresponding solvent controls. Protein stability was assessed at 65 °C and detected by an anti-HLA-E antibody. (F) Densitometry of HLA-E signal ratio between indicated peptides and corresponding solvent controls. (n=3 independent experiments). (**G**) Phylogenetic relationships between the genomes of SARS-CoV-2, SARS-CoV-1, common cold-causing HCoVs, and sarbecovirus isolates from bats and pangolins as determined by Clustalω. Scale bar indicating nucleotide substitution per site. (**H**) Sequence identities relative to SARS-CoV-2. Left: genome identity as determined by Clustalω. Middle: $Nsp13_{232\text{-}240}$ peptide sequence identity. Right: $Nsp13_{232\text{-}240}$ amino acid sequence comparison between viruses. Sequence alterations relative to SARS-CoV-2 are highlighted in red. Data are mean (D) or mean and individual datapoints (F).

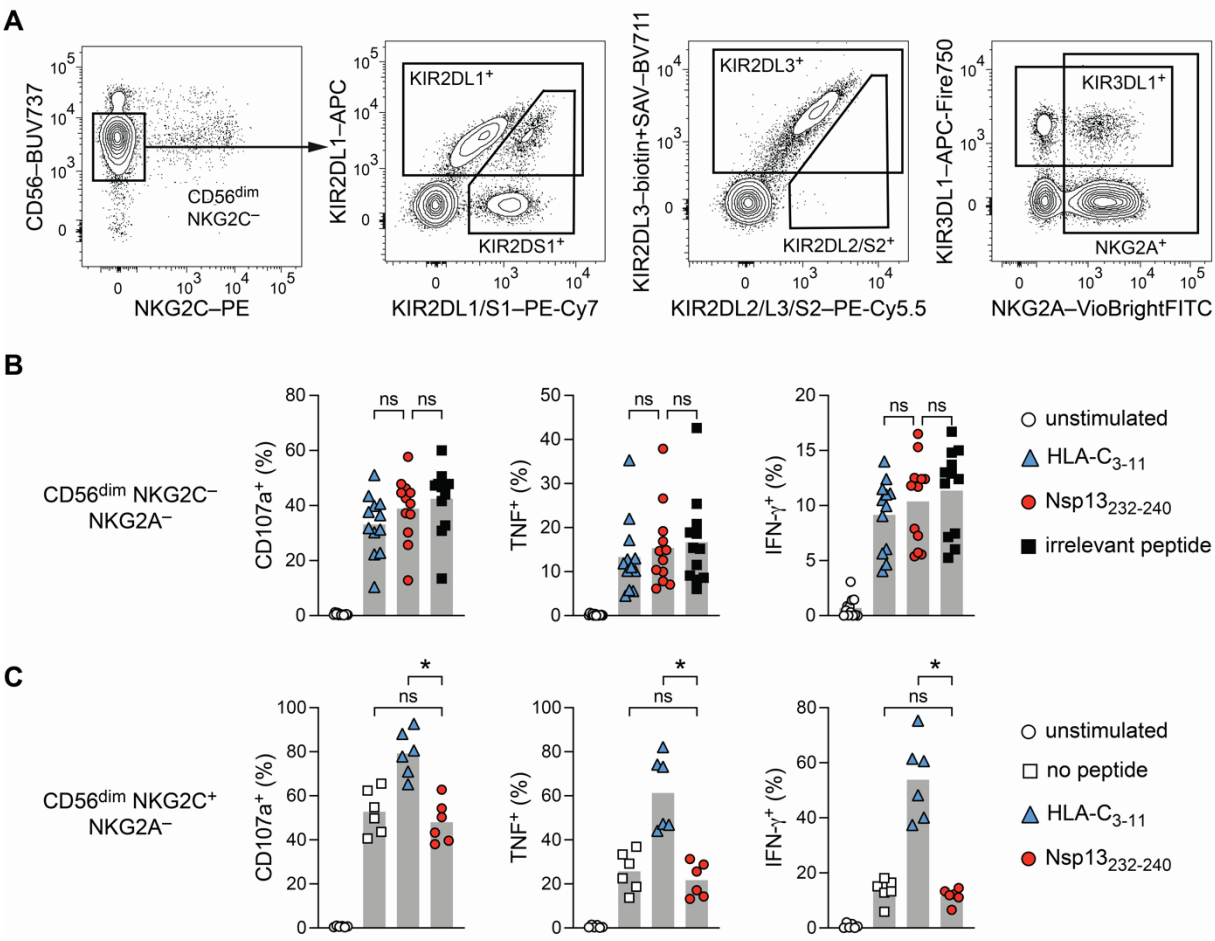
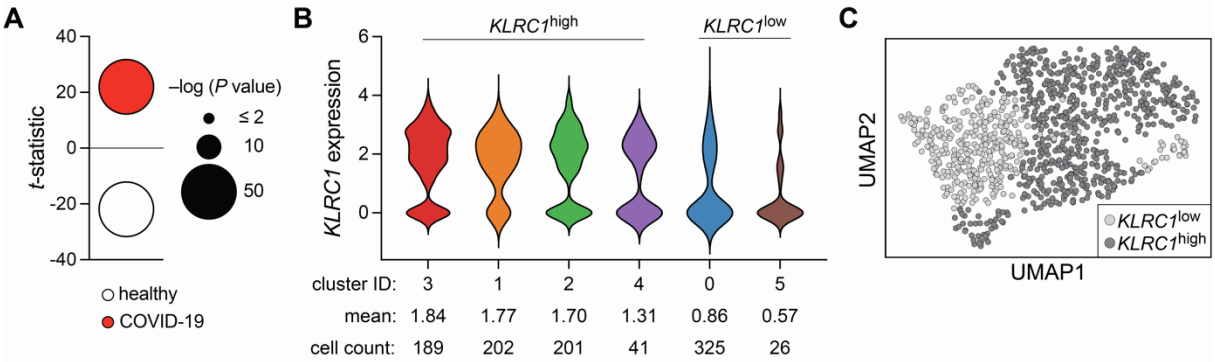


Figure S2. Nsp13$_{232-240}$ presented by HLA-E does not affect NKG2A$^-$ nor NKG2C$^+$ NK cells. Related to Figure 3.

(**A**) Gating strategy for flow cytometric analyses of NK cell subsets. After gating on viable CD14$^-$ CD19$^-$ CD3$^-$ events, CD56^{dim} NKG2C$^-$ NK cells were selected, and Boolean gating was performed on KIR2DS1$^-$ KIR2DL2/S2$^-$ subsets. (**B**) Summaries of activation of CD56^{dim} NKG2C$^-$ NKG2A$^-$ NK cells upon co-culture with peptide-pulsed K562/HLA-E target cells. Left: degranulation. Middle: TNF expression. Right: IFN-γ expression (n=12 donors in 5 independent experiments). (**C**) Summaries of activation of adaptive CD56^{dim} NKG2C$^+$ NKG2A$^-$ NK cells upon co-culture with peptide-pulsed K562/HLA-E target cells. Left: degranulation. Middle: TNF expression. Right: IFN-γ expression (n=6 donors in 5 independent experiments). Data are mean and individual datapoints (B and C). Statistical significance was tested using Friedman test with Dunn's multiple comparison test (B and C). *P < 0.05.



D

Cohort	Oxygen supplementation Total n (% of cohort)	Mechanical ventilation Total n (% of cohort)	Non-invasive n (% of mechanical)	Invasive n (% of mechanical)	ECMO n (% of mechanical)	OR (95% CI)	*P* value
Italy	276 (18.0)	1,260 (82.0)	933 (74.0)	320 (25.4)	7 (0.6)	0.49 (0.29-0.83)	0.008
Spain	897 (63.3)	519 (36.7)	122 (23.5)	381 (73.4)	16 (3.1)	0.95 (0.64-1.42)	0.796
Germany	109 (45.2)	132 (54.8)	21 (15.9)	86 (65.2)	25 (18.9)	1.01 (0.37-2.79)	0.985
Meta	1,282 (40.2)	1,911 (59.8)	1,076 (56.3)	787 (41.2)	48 (2.5)	0.77 (0.56-1.04)	0.088

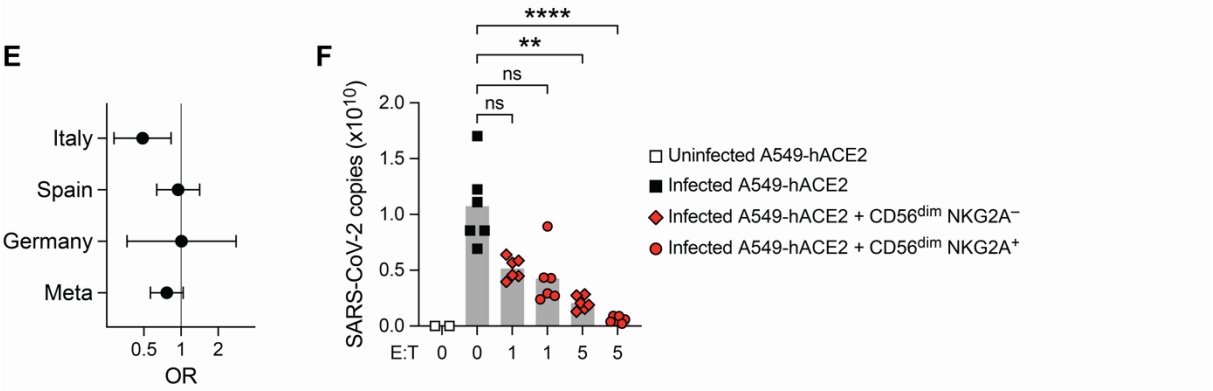


Figure S3. NKG2A-expressing NK cells are activated in patients with COVID-19 and proficiently suppress SARS-CoV-2 replication *in vitro*. Related to Figure 4.

(**A-C**) Single cell-RNA-sequencing analysis of NK cells from BALF (Liao et al., 2020). (A) *t*-statistic characterizing the separation of NK cells from BALF of healthy donors and patients with COVID-19 using a previously described signature of inflammatory NK cell responses (Yang et al., 2019). (B) Leiden clusters sorted according to mean *KLRC1* expression and grouped into *KLRC1*^{high} (clusters 3, 1, 2, and 4) and *KLRC1*^{low} (clusters 0 and 5) bins. (C) UMAP plot as in **Figure 4E** overlaid with *KLRC1* bins. (**D-E**) Genetic Association Analysis of *HLA-B –21* in patients with COVID-19 with respiratory failure. (D) Summary table of genetic association of the –21*M/M* genotype with COVID-19 respiratory severity in three distinct cohorts and a meta-analysis (Severe Covid-19 GWAS Group et al., 2020). ECMO (Extracorporeal membrane oxygenation). (E) Forest plot depicting the odds ratio (OR) of –21*M/M* carriership with

the requirement for mechanical ventilation in the indicated cohorts. Meta (meta-analysis). (**F**) A549-hACE2 were infected with SARS-CoV-2 (isolate SARS-CoV-2/human/SWE/01/2020) and co-cultured with sorted $CD56^{dim}$ $NKG2A^{-}$ or $CD56^{dim}$ $NKG2A^{+}$ NK cells at 1 h post-infection as in **Figure 4G**. Absolute virus copies in adherent A549-hACE2 were quantified at 24 h post-infection by RNA extraction and RT-qPCR using the CDC nCoV-2019 N1 assay (n=6 NK cell donors in 2 independent experiments). Data are either distributions (B), OR and 95% CI (E), or mean and individual datapoints (F). Statistical significance was tested using student's t-test (A), logistic regression (D and E), or Friedman test with Dunn's multiple comparison test (F). $^{**}P < 0.01$ and $^{****}P < 0.0001$.

Table S1. Characteristics of patients with COVID-19 from the Karolinska COVID-19 Immune Atlas. Related to Figure 4.

Re-analysis of NK cell activation was performed on a previously described cohort of patients (Maucourant et al., 2020). Moderate and severe groups were combined and two patients excluded due low cell counts. Further details can be found at https://covid19cellatlas.com/#/project/cohort.

Clinical characteristics		Patients with moderate COVID-19	Patients with severe COVID-19
Group size	n	10	17
Risk factors	Age, median (range)	56.5 (18-76)	58 (40-78)
	Sex, n female/male	3/7	3/14
	BMI, median (range)	27.63 (23-35.06)	29 (23-55)
	Smoking – current, n (%)	1 (10)	2 (12)
	Smoking – prior, n (%)	2 (20)	5 (29)
	Smoking – non-smoker, n (%)	2 (20)	9 (53)
	Smoking – unknown, n (%)	5 (50)	1 (6)
Preexisting conditions	None, n (%)	4 (40)	5 (29)
	Diabetes mellitus, n (%)	3 (30)	5 (29)
	Hypertension, n (%)	2 (20)	6 (35)
	Coronary heart disease, n (%)	– (–)	2 (12)
	Asthma, n (%)	1 (10)	2 (12)
Viremia at sampling	n (%)	4 (40)	8 (47)
Symptoms on admission	Fever, n (%)	10 (100)	17 (100)
	Cough, n (%)	9 (90)	14 (82)
	Dyspnea, n (%)	10 (100)	17 (100)
	Body ache, n (%)	3 (30)	9 (53)
	Gastrointestinal, n (%)	1 (10)	3 (18)
Days from symptom onset	To admission, median (range)	8.5 (4-14)	9 (3-14)
	To sampling, median (range)	13.5 (6-19)	14 (5-24)
Peak oxygen therapy	None, n (%)	2 (20)	0 (0)
	Low flow <10 L/min, n (%)	6 (60)	0 (0)
	Low flow 10-15 L/min, n (%)	1 (10)	3 (18)
	High flow, n (%)	1 (10)	1 (6)
	Ventilator, n (%)	0 (0)	12 (71)
	ECMO, n (%)	0 (0)	1 (6)
Treatment prior to sampling	Anticoagulant	10 (100)	15 (88)
	Corticosteroids	2 (20)	12 (71)
	Antibiotics	3 (30)	12 (71)
	Antivirals	0 (0)	1 (6) Remdesivir
	Cytokine inhibitors	0 (0)	2 (12) Anakinra, Tocilizumab
Clinical course	Days on ICU, median (range)	0 (0)	14 (0-45)
	Days intubated, median (range)	0 (0)	11 (0-45)
	Days hospitalized, median (range)	8 (5-39)	21 (10-57)
	SOFA score at sampling, median (range)	1 (0-2)	6 (2-12)
Outcome	Discharged, n (%)	10 (100)	12 (71)
	Death, n (%)	0 (0)	4 (24
	Unknown, n (%)	0 (0)	1 (6)

Table S2. Gene set of inflammatory NK cell responses. Related to Figure 4.

List of genes indicative of inflammatory responses of NK cells ("inflamed" cluster) obtained from Yang et al., 2019. Genes integrated into an inflammatory score are marked with *.

Genes		
PMAIP1*	*EHD4**	*GZMK**
IFIT3*	*PTGER4*	*FCER1G**
IFIT2*	*APOL6**	*EFHD2**
CCL3*	*KLRB1**	*ZBTB20**
CCL3L1	*FTH1**	*RAC2**
CCL3L3	*XIST*	*SBF2*
TNF	*NANS**	*CTSW**
NFKBIZ*	*ZEB2-AS1**	*CORO1A**
CCL4*	*TMSB4X**	*GZMA**
OASL*	*CD7**	*CLIC1**
ISG15*	*CDKN1A**	*BTG1**
GCA	*DDX3Y**	*IGFBP7**
PPP1R15A	*ARHGAP11B*	*SFT2D2**
CCL4L2	*ZBP1**	*CLEC2B**
IFIT1*	*NR4A2**	*CMC1**
RPS4Y1*	*MT2A**	*ARPC5**
LTA	*TTTY15*	*CLIC3**
TNFAIP3*	*ACTB**	*CFL1**
FOS*	*HERC5**	*CTD-2037K23.2*
CCL4L1	*PRF1**	*CD160**
ZC3HAV1*	*C20orf24*	*KLF9*
CD69*	*DDIT4**	*BTG2**
AC069363.1	*LINC-PINT*	*ZEB2*
LAX1*	*ANKRD28**	*RHOB**
HELB*	*FGR**	*PPP2R5C**
YBX1*	*TNIP1**	*MIA3**
ETV3*	*MYL12B**	*ANXA2**
CCL5*	*RBM39**	*ELF1**
RP1-40E16.12	*RGS1*	*C1orf162**
MYL12A*	*TXNIP**	*PRDM1*

Supplementary Author list 1. The Karolinska COVID-19 Study Group. Authors including their affiliation.

Mira Akber[1], Soo Aleman[2], Lena Berglin[1], Helena Bergsten[1], Niklas K. Björkström[1], Susanna Brighenti[1], Demi Brownlie[1], Marcus Buggert[1], Marta Butrym[1], Benedict J. Chambers[1], Puran Chen[1], Martin Cornillet[1], Angelica Cuapio[1], Isabel Diaz Lozano[1], Lena Dillner[2], Therese Djärv[3], Majda Dzidic[1], Johanna Emgård[1], Lars I. Eriksson[4], Malin Flodström-Tullberg[1], Hedvig Glans[2], Jean-Baptiste Gorin[1], Sara Gredmark-Russ[1], Jonathan Grip[4], Quirin Hammer[1], Alvaro Haroun-Izquierdo[1], Elisabeth Henriksson[1], Laura Hertwig[1], Sadaf Kalsum[1], Tobias Kammann[1], Jonas Klingström[1], Efthymia Kokkinou[1], Egle Kvedaraite[1], Hans-Gustaf Ljunggren[1], Marco Giulio Loreti[1], Magdalini Lourda[1], Kimia T. Maleki[1], Karl-Johan Malmberg[1], Nicole Marquardt[1], Johan Mårtensson[4], Christopher Maucourant[1], Jakob Michaëlsson[1], Jenny Mjösberg[1], Kirsten Moll[1], Jagadeeswara Rao Muvva[1], Pontus Nauclér[2], Anna Norrby-Teglund[1], Laura M. Palma Medina[1], Tiphaine Parrot[1], André Perez-Potti[1], Björn P. Persson[4], Lena Radler[1], Dorota Religa[5], Emma Ringqvist[1], Olga Rivera-Ballesteros[1], Olav Rooyackers[4], Johan K. Sandberg[1], John Tyler Sandberg[1], Takuya Sekine[1], Ebba Sohlberg[1], Tea Soini[1], Anders Sönnerborg[2], Kristoffer Strålin[2], Benedikt Strunz[1], Mattias Svensson[1], Janne Tynell[1], Christian Unge[3], Renata Varnaite[1], Andreas von Kries[1], David Wulliman[1].

[1] Center for Infectious Medicine, Department of Medicine Huddinge, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

[2] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden.

[3] Department of Emergency Medicine, Karolinska University Hospital, Stockholm, Sweden.

[4] Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden.

[5] Theme Aging, Karolinska University Hospital, Stockholm, Sweden.

Supplementary Author list 2. The Severe COVID-19 GWAS group. Authors including their affiliation.

Aaron Blandino Ortiz[1], Adolfo de Salazar[2,3], Adolfo Garrido Chercoles[4], Adriana Palom[5,6], Agustín Albillos[7,8], Agustín Ruiz[9,10], Alba-Estela Garcia-Fernandez[11], Albert Blanco-Grau[11], Alberto Mantovani[12,13], Alberto Zanella[14,15], Aleksander Rygh Holten[16,17], Alena Mayer[18], Alessandra Bandera[14,15], Alessandro Cherubini[15], Alessandro Protti[12,13], Alessio Aghemo[12,13], Alessio Gerussi[19,20], Alexander Popov[21], Alfredo Ramirez[22,23,24,25,26], Alice Braun[18], Almut Nebel[27], Ana Barreira[6], Ana Lleo[12,13], Ana Teles[28,29], Anders Benjamin Kildal[30], Andre Franke[27,31], Andrea Biondi[32], Andrea Caballero-Garralda[11], Andrea Ganna[33], Andrea Gori[15,34], Andreas Glück[35], Andreas Lind[36], Anja Tanck[27], Anke Hinney[37], Anna Carreras Nolla[38], Anna Latiano[39], Anna Ludovica Fracanzani[14,15], Anna Peschuck[27], Annalisa Cavallero[40], Anne Ma Dyrhol-Riise[17,41], Antonella Ruello[42], Antonio Julià[5], Antonio Muscatello[15], Antonio Pesenti[14,15], Antonio Voza[12,13], Ariadna Rando-Segura[43,44], Aurora Solier[45], Beatriz Cortes[38], Beatriz Mateos[7,8], Beatriz Nafria-Jimenez[4], Benedikt Schaefer[46,47], Bettina Heidecker[18], Björn Jensen[48], Carla Bellinghausen[49], Carlo Maj[50], Carlos Ferrando[51,52], Carmen de la Horra[53,54,55,56,57], Carmen Quereda[58], Carsten Skurk[18], Charlotte Thibeault[18], Chiara Scollo[59], Christian Herr[60], Christoph D Spinner[61], Christoph Gassner[27,62], Christoph Lange[63,64,65], Cinzia Hu[15], Cinzia Paccapelo[66], Clara Lehmann[67,68,69], Claudio Angelini[70], Claudio Cappadona[13], Clinton Azuure[28,29], Cristiana Bianco[15], Cristina Cea[11], Cristina Sancho[71], Dag Arne Lihaug Hoff[72,73], Daniela Galimberti[14,15], Daniele Prati[15], David Ellinghaus[27,74], David Haschka[75], David Jiménez[45], David Pestaña[76], David Toapanta[52], Douglas Maya-Miles[8,54,55], Eduardo Muñiz-Diaz[77], Eike M Wacker[27], Elena Azzolini[12,13], Elena Sandoval[52], Eleonora Binatti[19,20], Elio Scarpini[14,15], Elisa T Helbig[18], Eloisa Urrechaga[78,79], Elvezia Maria Paraboschi[12,13], Emanuele Pontali[80], Enric Reverter[52], Enrique J Calderón[53,54,55,56,57], Enrique Navas[58], Erik Solligård[81,82], Ernesto Contro[83], Eunate Arana[84], Eva C Schulte[85,86,87], Fátima Aziz[52], Federico Garcia[2,3], Félix García Sánchez[88], Ferruccio Ceriotti[15], Filippo Martinelli-Boneschi[89,90], Flora Peyvandi[91,92], Florian Kurth[18,93], Florian Tran[27,35], Florian Uellendahl-Werth[27], Francesco Blasi[94,95], Francesco Malvestiti[14], Francisco J Medrano[53,54,56,57,96], Francisco Mesonero[7,8], Francisco Rodriguez-Frias[5,8,44,97], Frank Hanses[98,99], Frauke Degenhardt[27], Fredrik Müller[17,36], Georg Hemmrich-Stanisak[27], Giacomo Bellani[100,101], Giacomo Grasselli[14,15], Gianni Pezzoli[102], Giorgio Costantino[14,15], Giovanni Albano[42], Giulia Cardamone[103], Giuseppe Bellelli[101,104], Giuseppe Citerio[101,105], Giuseppe Foti[100,101], Giuseppe Lamorte[15], Giuseppe Matullo[106], Guido Baselli[66], Hayato Kurihara[70], Heinz Zoller[46,47], Hesham ElAbd[27], Holger Neb[107], Ilaria My[12], Ingo Kurth[108], Isabel Hernández[9,10], Isabell Pink[109], Itziar de Rojas[9,10], Iván Galván-Femenia[38], Jan C Holter[17,36], Jan Egil Afset[72,110], Jan Heyckendorf[63,64,65], Jan Kässens[27], Jan Kristian Damås[111,112], Jan Rybniker[67,68,113,114], Janine Altmüller[115], Jatin Arora[116,117,118,119,120], Javier Ampuero[53,54,55,121], Javier Fernández[52,122], Javier Martín[123], Jeanette Erdmann[124,125,126], Jesus M Banales[8,127,128,129], Joan Ramon Badia[130], Joaquin Dopazo[131], Jochen Schneider[61], Johannes R Hov[17,132,133,134], Jon Lerga-Jaso[135], Jonas Bergan[136], Jordi Barretina[137], Jörn Walter[138], Jose Hernández Quero[2,139], Josune Goikoetxea[140], Juan Delgado[53,54,55,56,57], Juan M Guerrero[53,54,55], Julia Fazaal[141], Julia Kraft[18], Julia Schröder[141], Kari Risnes[112,142], Karina Banasik[74], Karl Erik Müller[143], Karoline I Gaede[144,145,146], Kerstin U Ludwig[141], Koldo Garcia-Etxebarria[8,129], Kristian

Tonby[17,41], Lars Heggelund[143,147], Lars Wienbrandt[27], Laura Izquierdo-Sanchez[8,129,148], Laura Rachele Bettini[32], Lauro Sumoy[137], Leif Erik Sander[18], Lena J Lippert[18], Leonardo Terranova[15], Lindokuhle Nkambule[149,150], Lisa Knopp[48], Lise Tuset Gustad[81,151], Luca Valenti[14,15], Lucia Garbarino[152], Luigi Santoro[15], Luigia Scudeller[66], Luis Bujanda[8,127,129], Luis Téllez[7,8], Luisa Roade[6,8,44], Mahnoosh Ostadreza[15], Maider Intxausti[71], Malte C Rühlemann[27,153], Manolis Kogevinas on behalf of the COVICAT study group[56,154,155,156], Manuel Romero-Gómez[8,157], Mar Riveiro-Barciela[6,8,44], Marc M Berger[158], Marco Schaefer[159], Mareike Wendorff[27], Mari EK Niemi[33], María A Gutiérrez-Stampa[160], Maria Buti[6,8,44], Maria Carrabba[66], Maria E. Figuera Basso[27], Maria Grazia Valsecchi[161], María Hernandez-Tejero[52], Maria JGT Vehreschild[162], Maria Manunta[15], Marialbert Acosta-Herrera[123], Mariella D'Angiò[32], Marina Baldini[66], Marina Cazzaniga[163], Mario Cáceres[135,164], Marit M Grimsrud[17,133,134], Markus Cornberg[165], Markus M Nöthen[141], Marta Marquié[9,10], Massimo Castoldi[42], Mattia Cordioli[33], Maurizio Cecconi[12,13], Mauro D'Amato[128,166], Max Augustin[67,68,69], May Sissel Vadla[167,168], Melissa Tomasi[15], Mercè Boada[9,10], Michael Dreher[169], Michael J Seilmaier[170], Michael Joannidis[171], Michael Wittig[27], Michela Mazzocco[152], Michele Ciccarelli[70], Miguel Rodríguez-Gandía[7,8], Monica Bocciolone[70], Monica Miozzo[14,66], Natale Imaz Ayo[84], Natalia Blay[38], Natalia Chueca[3], Nicola Montano[14,15], Nicole Braun[27,172], Nicole Ludwig[173], Nikolaus Marx[174], Nilda Martínez[175], Ole Bernt Lenning[167,176], Oliver A Cornely[113,114,177,178], Oliver Witzke[179], Onur Özer[28,29], Orazio Palmieri[39], Paola Faverio[101,180], Paoletta Preatoni[70], Paolo Bonfanti[101,181], Paolo Omodei[70], Paolo Tentorio[12], Pedro Castro[52], Pedro M Rodrigues[8,129,148], Pedro Pablo España[78], Per Hoffmann[141], Petra Bacher[27,182], Philip Rosenstiel[27], Philipp Koehler[68,113,177], Philipp Schommers[67,68,69], Phillip Suwalski[18], Pietro Invernizzi[19,20], Rafael de Cid on behalf of the COVICAT study group[38], Raúl de Pablo[1], Ricard Ferrer[183], Robert Bals[60], Roberta Gualtierotti[14,15], Rocío Gallego-Durán[54,55,121], Ronny Myhre[184], Rosa Nieto[45], Rosanna Asselta[12,13], Rossana Carpani[15], Rubén Morilla[53,54,55,56,57], Salvatore Badalamenti[12], Sammra Haider[185], Sandra Ciesek[186,187], Sandra May[27], Sara Bombace[12,13], Sara Marsal[5], Sara Pigazzini[33], Sebastian Klein[171], Selina Rolker[141], Serena Aneli[106], Serena Pelusi[14,15], Sibylle Wilfling[99,188,189], Siegfried Goerg[190], Silvano Bosari[14,15], Simonas Juzenas[27,191], Søren Brunak[74], Soumya Raychaudhuri[116,117,118,119,120,192], Stefan Schreiber[27,35], Stefanie Heilmann-Heimbach[141], Stefano Aliberti[12,13], Stefano Duga[12,13], Stephan Ripke[18], Susanne Dudman[17,36], Tanja Wesse[27], Tenghao Zheng[193], Thomas Bahmer[35], Thomas Eggermann[108], Thomas Illig[21], Thorsten Brenner[158], Tobias L Lenz[28,29], Tom H Karlsen[17,132,133,134], Tomas Pumarola[194,195], Torsten Feldt[48], Trine Folseraas[17,132,133,134], Trinidad Gonzalez Cejudo[196], Ulf Landmesser[197], Ulrike Protzer[85,198], Ute Hehr[188], Valeria Rimoldi[13], Valter Monzani[66], Vegard Skogen[199,200], Verena Keitel[48], Verena Kopfnagel[21], Vicente Friaza[53,54,55,56,57], Victor Andrade[22,24], Victor Moreno[56,201,202,203], Wolfgang Albrecht[27], Wolfgang Peter[159], Wolfgang Poller[18], Xavier Farre[38], Xiaoli Yi[27], Xiaomin Wang[18], Ximo Dopazo[204], Yascha Khodamoradi[162], Zehra Karadeniz[18], COVICAT study group, Covid-19 Aachen Study (COVAS), Pa COVID-19 Study Group, The Humanitas COVID-19 Task Force, and The Humanitas Gavazzeni COVID-19 Task Force.

[1] Department of Intensive Care, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá, Madrid, Spain.

[2] Ibs.ranada Instituto de Investigación Biosanitaria, Granada, Spain.

[3] Microbiology Unit.Hospital Univeristario Clinico San Cecilio, Granada, Spain.
[4] Osakidetza Basque Health Service, Donostialdea Integrated Health Organisation, Clinical Biochemistry Department, San Sebastian, Spain.
[5] Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Hospital Universitari, Barcelona, Spain.
[6] Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain.
[7] Department of Gastroenterology, Hospital Universitario Ramón y Cajal, University of Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain.
[8] Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
[9] Research Center and Memory Clinic.Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya, Spain.
[10] CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute of Health Carlos III, Madrid, Spain.
[11] Department of Biochemistry, University Hospital Vall d'Hebron, Barcelona, Spain.
[12] IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
[13] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.
[14] University of Milan, Milan, Italy.
[15] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
[16] Department of Acute Medicine, Oslo University Hospital, Oslo, Norway.
[17] Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
[18] Charite Universitätsmedizin Berlin, Berlin, Germany.
[19] European Reference Network on Hepatological Diseases (ERN RARE-LIVER), San Gerardo Hospital, Monza, Italy.
[20] Division of Gastroenterology, Center for Autoimmune Liver Diseases, School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.
[21] Hannover Unified Biobank, Hannover Medical School, Hannover, Germany.
[22] Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Medical Faculty, Bonn, Germany.
[23] Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany.
[24] Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany.
[25] German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany.
[26] Department of Psychiatry and Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX, USA.
[27] Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany.
[28] Research Group for Evolutionary Immunogenomics, Max Planck Institute for Evolutionary Biology, Plön, Germany.

[29] Research Unit for Evolutionary Immunogenomics, Department of Biology, University of Hamburg, Hamburg, Germany.
[30] Department of Anesthesiology and Intensive Care, University Hospital of North Norway, Tromsø, Norway.
[31] University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Germany.
[32] Pediatric Departement and Centro Tettamanti- European Reference Network (ERN) PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM/Ospedale San Gerardo, Italy.
[33] Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland.
[34] Centre for Multidisciplinary Research in Health Science (MACH), University of Milan, Milan, Italy.
[35] Klinik für Innere Medizin I, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany.
[36] Department of Microbiology, Oslo University Hospital, Oslo, Norway.
[37] Department of Child and Adolescent Psychiatry, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.
[38] Genomes for Life-GCAT lab.Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain.
[39] Gastroenterology Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy.
[40] Laboratory of Microbiology, San Gerardo Hospital, Monza, Italy.
[41] Department of Infectious diseases, Oslo University Hospital, Oslo, Norway.
[42] Humanitas Gavazzeni-Castelli, Bergamo, Italy.
[43] Microbiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[44] Universitat Autònoma de Barcelona, Bellatera, Spain.
[45] Department of Respiratory Diseases, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá, Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES), Madrid, Spain.
[46] Medical University of Innsbruck, Department of Medicine I, Gastroenterology, Hepatology and Endocrinology, Innsbruck, Austria.
[47] Christian Doppler Laboratory of Iron and Phosphate Biology at the Department of Medicine I, Medical University of Innsbruck, Innsbruck, Austria.
[48] Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital Duesseldorf, Medical Faculty Heinrich Heine University, Duesseldorf, Germany.
[49] Department of Respiratory Medicine and Allergology, University Hospital, Goethe University, Frankfurt am Main, Germany.
[50] Institute of Genomic Statistics and Bioinformatics, University Hospital Bonn, Medical Faculty University of Bonn, Venusberg-Campus [1], Bonn Germany.
[51] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain.
[52] Hospital Clinic, University of Barcelona, and IDIBAPS, Barcelona, Spain.
[53] University of Sevilla, Sevilla, Spain.
[54] Instituto de Biomedicina de Sevilla (IBIS), Sevilla, Spain.

[55] Hospital Universitario Virgen del Rocío de Sevilla, Sevilla, Spain.
[56] Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.
[57] Consejo Superior de Investigaciones científicas, Sevilla, Spain.
[58] Department of Infectious Diseases, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá, Madrid, Spain.
[59] Department of Transfusion Medicine and Haematology Laboratory, San Gerardo Hospital, Monza, Italy.
[60] Department of Internal Medicine V - Pneumology, Allergology and Intensive Care Medicine, University Hospital Saarland, Homburg/Saar, Germany.
[61] Technical University of Munich, School of Medicine, University Hospital rechts der Isar, Department of Internal Medicine II, Munich, Germany.
[62] Private University in the Principality of Liechtenstein.
[63] Respiratory Medicine & International Health, University of Lübeck, Lübeck, Germany.
[64] Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany.
[65] German Center for Infection Research (DZIF) Clinical Tuberculosis Unit, Borstel, Germany.
[66] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
[67] Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany.
[68] Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany.
[69] German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany.
[70] Humanitas Clinical and Research Center, IRCCS, Milan, Italy.
[71] Osakidetza Basque Health Service, Basurto University Hospital, Respiratory Service, Bilbao, Spain.
[72] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway.
[73] Department of Medicine, Møre & Romsdal Hospital Trust, Ålesund, Norway.
[74] Novo Nordisk Foundation Center for Protein Research, Disease Systems Biology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[75] Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria.
[76] Department of Anesthesiology and Critical Care, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá, Madrid, Spain.
[77] Immunohematology Department, Banc de Sang i Teixits, Autonomous University of Barcelona, Barcelona, Spain.
[78] Osakidetza Basque Health Service, Galdakao Hospital, Respiratory Service, Galdakao, Spain.
[79] Biocruces Bizkaia Health Research Institute.
[80] Department of Infectious Diseases - E..Ospedali Galliera, Genova, Italy.
[81] Geminicenter for Sepsis Research, Institute of Circulation and Medical Imaging (ISB), NTNU, Trondheim, Norway.
[82] Clinic of Anesthesia and Intensive Care, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway.

[83] Accident & Emergency and Emergency Medicine Unit, San Gerardo Hospital, Monza, Italy.
[84] Biocruces Bizkaia Health Research Institute, Barakaldo, Spain.
[85] Institute of Virology, Technical University Munich/Helmholtz Zentrum München, Munich, Germany.
[86] Institute of Psychiatric Phenomics and Genomics, University Medical Center, University of Munich, Munich, Germany.
[87] Department of Psychiatry, University Medical Center, University of Munich, Munich, Germany.
[88] Histocompatibilidad y Biologia Molecular, Centro de Transfusion de Madrid, Madrid, Spain.
[89] Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.
[90] IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy.
[91] University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy.
[92] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy.
[93] Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine, and Department of Medicine I, University Medical Centre Hamburg-Eppendorf, [20359] Hamburg, Germany.
[94] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Respiratory Unit, Milan, Italy.
[95] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Italy.
[96] Internal Medicine Department, Virgen del Rocio University Hospital, Sevilla, Spain.
[97] Biochemistry Department, University Hospital Vall d'Hebron, Barcelona, Spain.
[98] Emergency Department, University Hospital Regensburg, Regensburg, Germany.
[99] Department for Infectious Diseases and Infection Control, University Hospital Regensburg, Regensburg, Germany.
[100] Department Emergency, Anesthesia and Intensive Care, San Gerardo Hospital, Monza, Italy.
[101] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.
[102] Fondazione Grigioni per il Morbo di Parkinson and Parkinson Institute, ASST Gaetano Pini-CTO, Milan, Italy.
[103] Department of Biomedical Sciences, Humanitas University, Milan, Italy.
[104] Acute Geriatric Unit, San Gerardo Hospital, Monza, Italy.
[105] Neurointensive Care Unit, San Gerardo Hospital, Monza, Italy.
[106] Department of Medical Sciences, Università degli Studi di Torino, Turin, Italy.
[107] Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt am Main, Germany.
[108] Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany.
[109] Department of Pneumology, Hannover Medical School, Hannover, Germany.
[110] Department of Medical Microbiology, Clinic of Laboratory Medicine, St.Olavs hospital, Trondheim, Norway.
[111] Department of Infectious Diseases, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway.
[112] Department of Clinical and Molecular Medicine, NTNU, Trondheim, Norway.

[113] University of Cologne, Medical Faculty and University Hospital Cologne, Department I of Internal Medicine, Cologne, Germany.
[114] University of Cologne, Medical Faculty and University Hospital Cologne, German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany.
[115] Cologne Center for Genomics (CCG), University of Cologne, Cologne, Germany.
[116] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA.
[117] Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
[118] Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA.
[119] Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.
[120] Center for Data Sciences, Brigham and Women's Hospital, Boston, MA, USA.
[121] Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBEREHD), Sevilla, Spain.
[122] European Foundation for the Study of Chronic Liver Failure (EF-CLIF), Barcelona, Spain.
[123] Institute of Parasitology and Biomedicine Lopez-Neyra, Granada, Spain.
[124] Institute for Cardiogenetics, University of Lübeck, Lübeck, Germany.
[125] German Research Center for Cardiovascular Research, partner site Hamburg–Lübeck–Kiel, Lübeck, Germany.
[126] University Heart Center Lübeck, Lübeck, Germany.
[127] Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital, University of the Basque Country (UPV/EHU), CIBERehd, Ikerbasque, San Sebastian, Spain.
[128] Ikerbasque, Basque Foundation for Science, Bilbao, Spain.
[129] Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital, University of the Basque Country (UPV/EHU), San Sebastian, Spain.
[130] Respiratory ICU, Institut Clínic Respiratory, Hospital Clinic, University of Barcelona, and IDIBAPS, Barcelona, Spain.
[131] Bioinformatics Area, Fundación Progreso y Salud, and Instritute of Biomedicine of Sevilla (IBIS), Sevilla, Spain.
[132] Section for Gastroenterology, Department of Transplantation Medicine, Division for Cancer Medicine, Surgery and Transplantation, Oslo University Hospital Rikshospitalet, Oslo, Norway.
[133] Research Institute for Internal Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital Rikshospitalet and University of Oslo, Oslo, Norway.
[134] Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital Rikshospitalet, Oslo, Norway.
[135] Institut de Biotecnologia i de Biomedicina, Universitat Autònoma de Barcelona, Bellaterra (Barcelona), Spain.
[136] Department of Research, Ostfold Hospital Trust, Gralum, Norway.
[137] Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain.

[138] Department of Genetics & Epigenetics, Saarland University, Saarbrücken, Germany.
[139] Department of Infectious Diseases, Hospital Univeristario Clinico San Cecilio, Granada, Spain.
[140] Infectious Diseases Service, Osakidetza, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain.
[141] Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn, Germany.
[142] Department of Research, St Olav Hospital, Trondheim University Hospital, Trondheim, Norway.
[143] Medical Department, Drammen Hospital, Vestre Viken Hospital Trust, Norway.
[144] Research Center Borstel, BioMaterialBank Nord, Germany.
[145] German Center for Lung Research (DZL), Airway Research Center North (ARCN), Germany.
[146] Popgen [2]. network (P^2N), Kiel, Germany.
[147] Department of Clinical Science, University of Bergen, Bergen, Norway.
[148] Biodonostia Health Research Institute, Donostia University Hospital, San Sebastian, Spain.
[149] Analytic & Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA.
[150] Stanley Center for Psychiatric Research & Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA.
[151] Clinic of Medicine and Rehabilitation, Levanger Hospital, Nord-Trondelag Hospital Trust, Levanger, Norway.
[152] HLA Laboratory – E..Ospedali Galliera, Genova, Italy.
[153] Institute for Medical Microbiology and Hospital Epidemiology, Hannover Medical School, Hannover, Germany.
[154] ISGlobal, Barcelona, Spain.
[155] Universitat Pompeu Fabra (UPF), Barcelona, Spain.
[156] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
[157] Digestive Diseases Unit, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain.
[158] Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany.
[159] Stefan-Morsch-Stiftung, Birkenfeld, Germany.
[160] Osakidetza, OSI Donostialdea, Altza Primary Care, Biodonostia Health Research Institute, San Sebastián, Spain.
[161] Center of Bioinformatics, Biostatistics and Bioimaging, School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.
[162] Department of Internal Medicine, Infectious Diseases, University Hospital Frankfurt & Goethe University Frankfurt, Frankfurt am Main, Germany.
[163] Phase [1] Research Centre, ASST Monza, School of Medicine and Surgery, University of Milano-Bicocca, Italy.
[164] ICREA, Barcelona, Spain.
[165] Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany.

[166] Gastrointestinal Genetics Lab, CIC bioGUNE - BRTA, Derio, Spain.
[167] Randaberg Municipality, Norway.
[168] University of Stavanger, Faculty of Health Sciences, Department of Quality and Health Technology, Stavanger, Norway.
[169] Department of Pneumology and Intensive Care Medicine, University Hospital Aachen, Germany.
[170] Munich Clinic Schwabing, Academic Teaching Hospital, Ludwig-Maximilians-University (LMU), Munich, Germany.
[171] Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria.
[172] University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany.
[173] Center of Human and Molecular Biology, Department of Human Genetics, University Hospital Saarland, Homburg/Saar, Germany.
[174] Department of Internal Medicine I, RWTH Aachen University Hospital, Aachen, Germany.
[175] Department of Anesthesiology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain.
[176] Research Department, Stavanger University Hospital.
[177] University of Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany.
[178] Clinical Trials Centre Cologne, ZKS Köln, Cologne, Germany.
[179] Department of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany.
[180] Pulmonary Unit, San Gerardo Hospital, Monza, Italy.
[181] Infectious Diseases Unit, San Gerardo Hospital, Monza, Italy.
[182] Institute of Immunology, Christian-Albrechts-University of Kiel & UKSH Schleswig-Holstein, Kiel, Germany.
[183] Intensive Care Department, Vall d'Hebron University Hospital, SODIR-VHIR research group, Barcelona, Spain.
[184] Norwegian Institute of Public Health, Division of Health Data and Digitalization, Department of Genetics and Bioinformatics (HDGB) Oslo, Norway.
[185] Department of Medicine, Møre & Romsdal Hospital Trust, Molde, Norway.
[186] Institute of Medical Virology, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany.
[187] German Centre for Infection Research (DZIF), External Partner Site Frankfurt, Frankfurt am Main, Germany.
[188] Zentrum für Humangenetik Regensburg, Regensburg, Germany.
[189] Department of Neurology, Bezirksklinikum Regensburg, University of Regensburg, Regensburg, Germany.
[190] Institute of Transfusionsmedicine, University Hospital Schleswig-Holstein (UKSH), Germany.
[191] Institute of Biotechnology, Life Science Centre, Vilnius University, Lithuania.

[192] Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK.
[193] School of Biological Sciences, Monash University, Clayton, VIC, Australia.
[194] Department of Microbiology, University Hospital Vall d'Hebron, Barcelona, Spain.
[195] Autonoma University of Barcelona, Barcelona, Spain.
[196] Biochemistry Unit.Hospital Univeristario Clinico San Cecilio, Granada, Spain.
[197] Charite Universitätsmedizin Berlin, Berlin Institute of Health, Berlin Germany.
[198] German Center for Infection Research (DZIF), Munich partner site, Munich, Germany.
[199] Department of Infectious Diseases, University Hospital of North Norway, Tromsø, Norway.
[200] Faculty of Health Sciences, UIT The Arctic University of Norway, Norway.
[201] Catalan Institute of Oncology (ICO), Barcelona, Spain.
[202] Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain.
[203] Universitat de Barcelona (UB), Barcelona, Spain.
[204] Bioinformatics area, Fiundación progreso y Salud, Andalucia, Spain.