Virologica Sinica 39 (2024) 347–350

Contents lists available at ScienceDirect

Virologica Sinica

journal homepage: www.keaipublishing.com/en/journals/virologica-sinica
www.virosin.org

Letter

Association analysis of genetic variants in critical patients with COVID-19 and validation in a Chinese population

Yi Yin [a,b,c,d], Yi Zhang [b,c], Lelin Sun [b], Shuqiang Wang [e], Yong Zeng [f], Bo Gong [b,c], Lulin Huang [b,c,*], Yongquan He [b,c,*], Zhenglin Yang [a,b,c,d,*]

[a] Center for Natural Products Research, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610213, China
[b] Sichuan Provincial Key Laboratory for Human Disease Gene Study, Center for Medical Genetics, Department of Laboratory Medicine, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610072, China
[c] Research Unit for Blindness Prevention of Chinese Academy of Medical Sciences (2019RU026), Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610072, China
[d] University of Chinese Academy of Sciences, Beijing, 100049, China
[e] Infectious Disease Department, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610072, China
[f] Department of Ophthalmology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610072, China

Dear Editor,

Genome-wide association studies (GWASs) have reported a genetic association between certain populations and the severity of COVID-19. In severe patients, changes in the locus 3p21.31 (including *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*) are associated with COVID-19 hospitalization (Ellinghaus et al., 2020). Moreover, variations in 9p34.2 region (including genes related to the ABO blood grouping) can affect both susceptibility and severity of COVID-19; in particular, individuals with blood group A may have an increased risk of COVID-19 infection, while those with blood group O may have a protective effect (Ellinghaus et al., 2020; Shelton et al., 2021). Variants in *DNAH7/SLC39A10*, *CLUAP1*, *DES/SPEG*, *STXBP5/STXBP5-AS1*, *TOMM7*, *WSB1*, *CPQ*, and *PCDH15* are associated with an increased risk of the COVID-19 mortality (Hu et al., 2021). In the United Arab Emirates, the single-nucleotide polymorphisms (SNPs) rs10507497 (in the intron of *KIAA0564*), rs7715119 (in the intron of *PDE8B*), rs72953026 (at the 5′ end of *GRM5-AS1*), rs7605851 (in the intron of *THSD7B*), rs7595310 (at the 3′ end of *STK39*), rs10140801 (in the intron of *FBXO34-AS1*), rs11659676 (at the 3′ end of *U6*), and rs599976 (at the 5′ end of *METTL21C*) were found to be associated with COVID-19 severity (Mousa et al., 2021). In our previous GWAS on a Chinese cohort, we found that the A allele of rs2069837 (in the intron of *IL6*) leads to serious COVID-19 symptoms, whereas the G allele of rs2069837 can provide protection by reducing serum interleukin (IL) 6 levels (Gong et al., 2022).

In this study, to better understand the genetic heterogeneity of critical COVID-19, we searched COVID-19-associated SNPs reported globally (samples N > 100) (Supplementary Table S1) and validated them in the aforementioned Chinese population. The flowchart illustrating the process of searching, screening, inclusion, and association analysis in this study is presented in Fig. 1. In total, 100 SNPs related to severe or critical COVID-19 were identified and listed (Supplementary Table S2). The data covered almost all major ethnicities (European, American, South Asian, East Asian, and African) across almost all continents (Asia, the Americas, and Europe). Although most of the included studies recruited patients with COVID-19, some utilized data from existing databases [e.g. Andolfo et al. performed an in-depth genetic analysis by exploiting GWAS meta-analysis data from the COVID-19 Host Genetics Initiative (Andolfo et al., 2021)]. Most of the included studies were performed in Europe, with half of the identified SNPs originating from the 11 included European studies that collectively recruited nearly one million individuals (Ellinghaus et al., 2020; Nikoloudis et al., 2020; Shikov et al., 2020; Andolfo et al., 2021; Cantalupo et al., 2021; Hu et al., 2021; Zhang et al., 2021; Degenhardt et al., 2022; Ruter et al., 2022; Yang et al., 2022; Zecevic et al., 2022). Two studies included global populations and contributed 31 SNPs (COVID-19 Host Genetics Initiative, 2021; Kousathanas et al., 2022).

Next, we tried to validate the previously reported SNPs (Table 1) in our Chinese population based on their linkage disequilibrium (LD) pattern ($r^2 \geq 0.6$). The tagging SNPs with a *P*-value <0.05 were listed in Table 1, and all validated SNPs were presented in Supplementary Table S2). In total, 38 tagging SNPs in 12 genes (with the same LD and $P < 0.05$) were found in our Chinese population dataset. The previously reported rs1712779 (in *NEXP2*) with $P = 4.04 \times 10^{-8}$ (OR_T allele = 0.49) showed perfect LD with four SNPs in the Chinese population dataset with $P < 0.05$. Additionally, rs2109069 (in *DPP9*), rs11919389 (in *RPL24*), rs35951367 (in *CTCF*), and

* Corresponding authors.
E-mail addresses: huangluling@yeah.net (L. Huang), yongquanhe2012@163.com (Y. He), yangzhenglin@cashq.ac.cn (Z. Yang).

https://doi.org/10.1016/j.virs.2024.02.004

Available online 23 February 2024

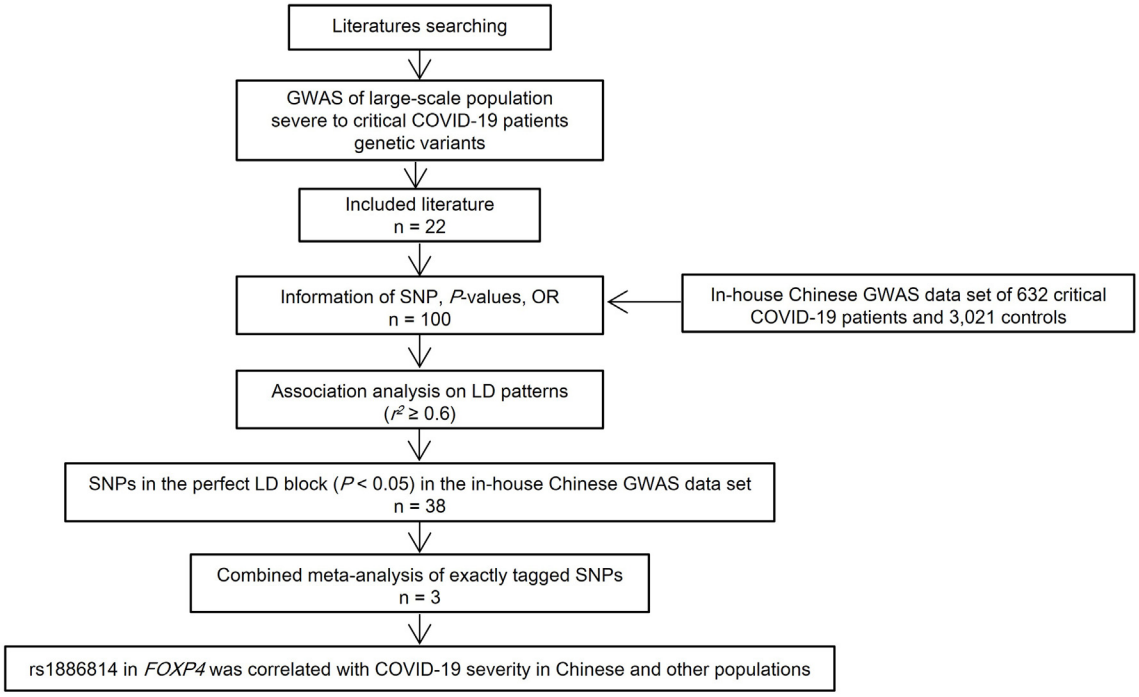

Fig. 1. The flowchart for research strategy.

rs9845542 (in *XCR1*) exhibited perfect LD with those of rs12610495 (in *DPP9*), rs3804778 (in *PCNP*), rs6789719 (near *XCR1* and *FLT1P1*), and rs6789719 (near *XCR1* and *FLT1P1*) in our Chinese population dataset, respectively. Furthermore, the LDs of rs1173773 (in *NPR3*), rs1853837 (*FOXP4-AS1*), and rs1331359 (*RNU2-47P* and *TYRP1*) were tagged in 11, 4, and 5 SNPs in the Chinese dataset, respectively. Finally, two SNPs (rs4496814 and rs9384403) in our dataset exhibited perfect LDs with rs140092351 (in *miR1202*). However, after the Bonferroni correction (Table 1), only the SNPs rs12610495 (tagging rs2109069, *DPP9*) and rs4628342, rs1412074, rs1929425, rs1331346 and rs10116714 (tagging rs1331359, *RNU2-47P/TYRP1*) showed a significant association in the Chinese population dataset. These six significant associated SNPs highlight the importance of *DPP9*, *RNU2-47P* and *TYRP1* in the outcome of SARS-CoV-2 infection in the Chinese population.

Additionally, three SNPs were exactly tagged in both the reported studies and our Chinese data set (Table 2). The *P*-values in the previous study and our Chinese population were, 4.04×10^{-8} and 2.828×10^{-2} for rs10831496 (in *GRM5*), 4.08×10^{-13} and 4.029×10^{-2} for rs10774671 (in *OAS1*), and $2.41 \times 10^{-}8$ and 2.405×10^{-2} for rs1886814 (in *FOXP4*). Moreover, rs10831496 (in *GRM5*) was only observed in the Chinese populations (Li et al., 2021), while rs10774671 (in *OAS1*) and rs1886814 (in *FOXP4*) were found both in Chinese (Li et al., 2022) and other populations (COVID-19 Host Genetics Initiative, 2021; Banday et al., 2022). At least two SNPs in LD ($r^2 \geq 0.6$) were found near all three SNPs. The results of our meta-analysis, combining previous data on three aforementioned SNPs, are presented in Table 2. We found that rs10831496 (in *GRM5*) and rs10774671 (in *OAS1*) showed both negative and positive directions in the meta-analysis, while rs1886814 (in *FOXP4*) only showed a positive direction. This result suggested that rs1886814 is associated with COVID-19 severity.

Understanding the genetic variants in individuals with or susceptible to COVID-19 can help to prevent and control the disease. Genetic divergence, particularly in differentiated loci, between human ancestries, plays a major role in determining an individual's immune response to viral infections. Furthermore, a large-scale genetic study identified significant genetic variations associated with protein coding in populations with geographically diverse ancestries (Randolph et al., 2021). In the current study, we summarized and reviewed COVID-19-related SNP data from relevant GWASs conducted globally resulting in the identification of 100 contributing loci in approximately 107 genes. When we validated these loci using data from a Chinese population of critical COVID-19 patients, we found 38 loci that showed associations. Additionally, we confirmed a significant association between six loci in *DPP9* or near *RNU2-47P* and *TYRP1* and the Chinese population.

In summary, after validating the Chinese population data with the data of previously reported 100 contributing loci, we noted that 38 SNPs within or near 12 genes (namely *NXPE2*, *GRM5*, *OAS1*, *DPP9*, *RPL24*, *CTCF*, *XCR1*, *NPR3*, *FOXP4*, *FOXP4-AS1*, *TYRP1*, and *miR1202*) are significantly associated with the severity of COVID-19, with a *P*-value of <0.05. Our Chinese population dataset showed exact tagging for three SNPs (rs1886814 in *FOXP4*, rs10831496 in *GRM5*, and rs10774671 in *OAS1*). After the Bonferroni correction, only six SNPs were found to be significantly associated with the critical illness of COVID-19 in the Chinese population. These SNPs are rs12610495 in *DPP9* (tagging rs2109069) and rs4628342, rs1412074, rs1929425, rs1331346, and rs10116714 near *RNU2-47P* and *TYRP1* (tagging rs1331359). Specifically, the SNP of rs12610495 in *DPP9* was recently reported by Pairo-Castineira et al. and identified as a genetic variant associated with the critical illness of COVID-19 (Pairo-Castineira et al., 2023). Compared to the healthy control group or bacterial infected patients, the expression of *DPP9* in the peripheral blood of severe patients with SARS-Cov-2 infection has also been confirmed to increase (Wang et al., 2021). Allele G of rs12610495 can decrease the expression of *DPP9* in lung tissue, leading to increased expression of the NLPR1 inflammasome and an increased risk of COVID-19 severity and idiopathic pulmonary fibrosis (Wang et al., 2021). Additionally, the SNP rs2109069 within *DPP9* ($P = 0.032$, OR = 1.33 for A allele) also showed a significant association with COVID-19 severity in the Huoshenshan cohort (Li et al., 2021). Since we conducted an association analysis of several studies involving individuals from diverse ancestries, the heterogeneity in strong GWAS signals may be explained by ancestry-specific effects (Pairo-Castineira et al., 2021). By combining our Chinese dataset with data from other sources, our work

Table 1
Association analysis results for SNPs in the Chinese population ($P < 0.05$).

Query						Results							
Nearest Gene	SNP	Ref	Alt	*P*	OR	Nearest Gene	SNP (LD; $r^2 \geq 0.6$)	Ref	Alt	*P*	OR	L95	U95
NXPE2	rs1712779	T	A	1.138×10^{-8}	0.49	*NXPE2*	rs4938118	A	G	6.162×10^{-3}	1.340	1.086	1.652
							rs10891738	G	A	3.142×10^{-2}	1.255	1.020	1.545
							rs1712791	G	A	9.827×10^{-3}	1.307	1.066	1.603
							rs11215191	T	C	4.233×10^{-2}	1.235	1.007	1.516
GRM5	rs10831496	A	G	4.04×10^{-8}	1.66	*GRM5*	rs1499172	C	A	3.331×10^{-2}	0.845	0.724	0.987
							rs7119749	A	G	3.399×10^{-2}	0.834	0.705	0.987
							rs10831496	A	G	2.828×10^{-2}	0.828	0.699	0.980
OAS1	rs10774671	G	A	4.08×10^{-13}	1.200	*OAS1*	rs10774671	G	A	4.029×10^{-2}	0.842	0.713	0.993
							rs1131476	G	A, C, and T	4.207×10^{-2}	0.843	0.715	0.994
							rs2660	G	A	3.961×10^{-2}	0.841	0.713	0.992
						OAS1 and *OAS3*	rs10774679	C	T	2.74×10^{-2}	0.830	0.703	0.980
							rs10735079	G	A	3.778×10^{-2}	0.839	0.711	0.990
DPP9	rs2109069	G	A	9.68×10^{-22}	1.049	*DPP9*[a]	rs12610495	A	G	3.671×10^{-4}	1.401	1.163	1.688
RPL24	rs11919389	T	C	3.46×10^{-15}	0.941	*PCNP*	rs3804778	C	T	4.211×10^{-2}	0.8493	0.7254	0.9943
CTCF	rs35951367	T	C	3.2×10^{-19}	1.32	*XCR1* and *FLT1P1*	rs6789719	G	A	4.111×10^{-2}	0.7082	0.5078	0.9877
XCR1	rs9845542	G	A	4.2×10^{-20}	1.33								
NPR3	rs1173773	T	C	4.94×10^{-8}	NA	*NPR3*	rs3828586	A	G	4.210×10^{-2}	1.183	1.006	1.391
							rs973079	G	A	1.966×10^{-2}	1.218	1.032	1.438
							rs7716901	T	G	1.508×10^{-2}	1.251	1.044	1.499
							rs3792752	A	G	1.658×10^{-2}	1.247	1.041	1.494
							rs3811965	C	T	1.286×10^{-2}	1.258	1.05	1.508
							rs11740452	G	A	1.387×10^{-2}	1.256	1.047	1.506
							rs1173736	A	G	2.154×10^{-2}	1.234	1.031	1.478
							rs3792751	C	T	9.315×10^{-3}	1.271	1.061	1.524
							rs751432	T	G	9.254×10^{-3}	1.256	1.058	1.491
							rs10075794	T	C	1.143×10^{-2}	1.247	1.051	1.481
							rs2270915	A	C, G, and T	7.091×10^{-3}	1.265	1.066	1.502
miR1202	rs140092351	G	16mer	4.60×10^{-8}	1.30	*miR1202*	rs4496814	G	A	4.257×10^{-2}	0.829	0.692	0.994
							rs9384403	C	T	4.885×10^{-2}	0.836	0.699	0.999
FOXP4	rs1886814	A	C	2.41×10^{-8}	1.106	*LINC01276*	rs2496644	A	C	3.755×10^{-3}	1.241	1.072	1.436
						FOXP4	rs1886813	A	G	2.999×10^{-2}	1.169	1.015	1.347
							rs1886814	A	C	2.405×10^{-2}	1.180	1.022	1.362
							rs9381074	T	A	1.557×10^{-2}	1.194	1.034	1.378
FOXP4-AS1	rs1853837	C	A	2.51×10^{-10}	1.28	*LINC01276* and *FOXP4*	rs2495239	A	G	8.573×10^{-3}	1.210	1.050	1.395
						FOXP4	rs1886814	A	C	2.405×10^{-2}	1.180	1.022	1.362
							rs9381074	T	A	1.557×10^{-2}	1.194	1.034	1.378
						LINC01276	rs2496644	A	C	3.755×10^{-3}	1.241	1.072	1.436
RNU2-47P and *TYRP1*	rs1331359	G	A	8.69×10^{-6}	1.26	*RNU2-47P* and *TYRP1*[a]	rs4628342	G	A	4.222×10^{-4}	1.293	1.121	1.492
							rs1412074	G	A	9.744×10^{-4}	1.271	1.102	1.467
							rs1929425	T	C	5.586×10^{-4}	1.287	1.115	1.485
							rs1331346	T	C	3.392×10^{-4}	1.294	1.124	1.491
							rs10116714	A	G	6.287×10^{-4}	1.279	1.111	1.473

OR, odds ratio; SE, standard error; L95, lower confidence interval; U95, upper confidence interval.
[a] These variants remained significant after multiple testing correction (Bonferroni *P*-value threshold = 1.19×10^{-3}).

Table 2
Results of combined meta-analysis for the three SNPs.

SNP	Genes	Chr:pos (hg38)	Allele1	Allele2	Weight	Z-score	*P*-value	Direction
rs1886814	*FOXP4*	6:41534945	A	C	2052550	6.174	6.64×10^{-10}	+ +
rs10831496	*GRM5*	11:88824823	A	G	4419	1.32	0.1868	+ −
rs10774671	*OAS1*	12:112919388	A	G	2052550	−7.169	7.54×10^{-13}	− +

may provide new insights the underlying factors to the severity of COVID-19. Those findings could serve as a foundation for further targeted experiments aimed at developing therapies specifically for severe cases of COVID-19, going beyond just considering ancestry. Besides the differences between the populations included in this study and the previous GWASs, the limited sample size in the Chinese population could be a significant factor contributing to the weak correlation observed for most of the corresponding SNPs. Additional large-scale, multiethnic, international, collaborative studies focused on host-pathogen interactions and genetic factors in COVID-19 are warranted.

Footnotes

This project was supported by the National Natural Science Foundation of China (81790643, 82121003, and 82271105), the Sichuan Science and Technology Program (2019YFS0368, 2021YFS0404, 2021YFS0369, 2021YFS0388, 2021ZYD0082, 2021YFS0033, and 2022NSFSC1352), the CAMS Innovation Fund for Medical Sciences (2019–12M-5-032), Sichuan Provincial People's Hospital (2021QN13), and 2021 open project of Sichuan Provincial Key Laboratory for Human Disease Genetics Research (2021kflx008). The authors declare that they have no competing interests.

All data needed to evaluate the current conclusions are presented in the paper or will be available from the corresponding authors on reasonable request. Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2024.02.004.

References

Andolfo, I., Russo, R., Lasorsa, V.A., Cantalupo, S., Rosato, B.E., Bonfiglio, F., Frisso, G., Abete, P., Cassese, G.M., Servillo, G., Esposito, G., Gentile, I., Piscopo, C., Villani, R., Fiorentino, G., Cerino, P., Buonerba, C., Pierri, B., Zollo, M., Iolascon, A., Capasso, M., 2021. Common variants at 21q22.3 locus influence MX1 and TMPRSS2 gene expression and susceptibility to severe COVID-19. iScience 24, 102322.

Banday, A.R., Stanifer, M.L., Florez-Vargas, O., Onabajo, O.O., Papenberg, B.W., Zahoor, M.A., Mirabello, L., Ring, T.J., Lee, C.H., Albert, P.S., Andreakos, E., Arons, E., Barsh, G., Biesecker, L.G., Boyle, D.L., Brahier, M.S., Burnett-Hartman, A., Carrington, M., Chang, E., Choe, P.G., et al., 2022. Genetic regulation of OAS1 nonsense-mediated decay underlies association with COVID-19 hospitalization in patients of European and African ancestries. Nat. Genet. 54, 1103–1116.

Cantalupo, S., Lasorsa, V.A., Russo, R., Andolfo, I., D'alterio, G., Rosato, B.E., Frisso, G., Abete, P., Cassese, G.M., Servillo, G., Gentile, I., Piscopo, C., Della Monica, M., Fiorentino, G., Russo, G., Cerino, P., Buonerba, C., Pierri, B., Zollo, M., Iolascon, A., Capasso, M., 2021. Regulatory noncoding and predicted pathogenic coding variants of CCR5 predispose to severe COVID-19. Int. J. Mol. Sci. 22, 5372.

COVID-19 Host Genetics Initiative, 2021. Mapping the human genetic architecture of COVID-19. Nature 600, 472–477.

Degenhardt, F., Ellinghaus, D., Juzenas, S., Lerga-Jaso, J., Wendorff, M., Maya-Miles, D., Uellendahl-Werth, F., Elabd, H., Rühlemann, M.C., Arora, J., Özer, O., Lenning, O.B., Myhre, R., Vadla, M.S., Wacker, E.M., Wienbrandt, L., Blandino Ortiz, A., De Salazar, A., Garrido Chercoles, A., Palom, A., et al., 2022. Detailed stratified GWAS analysis for severe COVID-19 in four European populations. Hum. Mol. Genet. 31, 3945–3966.

Ellinghaus, D., Degenhardt, F., Bujanda, L., Buti, M., Albillos, A., Invernizzi, P., Fernández, J., Prati, D., Baselli, G., Asselta, R., Grimsrud, M.M., Milani, C., Aziz, F., Kässens, J., May, S., Wendorff, M., Wienbrandt, L., Uellendahl-Werth, F., Zheng, T., et al., 2020. Genomewide association study of severe Covid-19 with respiratory failure. N. Engl. J. Med. 383, 1522–1534.

Gong, B., Huang, L., He, Y., Xie, W., Yin, Y., Shi, Y., Xiao, J., Zhong, L., Zhang, Y., Jiang, Z., Hao, F., Zhou, Y., Li, H., Jiang, L., Yang, X., Song, X., Kang, Y., Tuo, L., Huang, Y., Shuai, P., Liu, Y., Zheng, F., Yang, Z., 2022. A genetic variant in IL-6 lowering its expression is protective for critical patients with COVID-19. Signal Transduct. Targeted Ther. 7, 112.

Hu, J., Li, C., Wang, S., Li, T., Zhang, H., 2021. Genetic variants are identified to increase risk of COVID-19 related mortality from UK Biobank data. Hum. Genom. 15, 10.

Kousathanas, A., Pairo-Castineira, E., Rawlik, K., Stuckey, A., Odhams, C.A., Walker, S., Russell, C.D., Malinauskas, T., Wu, Y., Millar, J., Shen, X., Elliott, K.S., Griffiths, F., Oosthuyzen, W., Morrice, K., Keating, S., Wang, B., Rhodes, D., Klaric, L., Zechner, M., et al., 2022. Whole-genome sequencing reveals host factors underlying critical COVID-19. Nature 607, 97–103.

Li, P., Ke, Y., Shen, W., Shi, S., Wang, Y., Lin, K., Guo, X., Wang, C., Zhang, Y., Zhao, Z., 2022. Targeted screening of genetic associations with COVID-19 susceptibility and severity. Front. Genet. 13, 1073880.

Li, Y., Ke, Y., Xia, X., Wang, Y., Cheng, F., Liu, X., Jin, X., Li, B., Xie, C., Liu, S., Chen, W., Yang, C., Niu, Y., Jia, R., Chen, Y., Liu, X., Wang, Z., Zheng, F., Jin, Y., Li, Z., Yang, N., Cao, P., Chen, H., Ping, J., He, F., Wang, C., Zhou, G., 2021. Genome-wide association study of COVID-19 severity among the Chinese population. Cell Discov 7, 76.

Mousa, M., Vurivi, H., Kannout, H., Uddin, M., Alkaabi, N., Mahboub, B., Tay, G.K., Alsafar, H.S., Partnership, U.C.-C., 2021. Genome-wide association study of hospitalized COVID-19 patients in the United Arab Emirates. EBioMedicine 74, 103695.

Nikoloudis, D., Kountouras, D., Hiona, A., 2020. The frequency of combined IFITM3 haplotype involving the reference alleles of both rs12252 and rs34481144 is in line with COVID-19 standardized mortality ratio of ethnic groups in England. PeerJ 8, e10402.

Pairo-Castineira, E., Clohisey, S., Klaric, L., Bretherick, A.D., Rawlik, K., Pasko, D., Walker, S., Parkinson, N., Fourman, M.H., Russell, C.D., Furniss, J., Richmond, A., Gountouna, E., Wrobel, N., Harrison, D., Wang, B., Wu, Y., Meynert, A., Griffiths, F., Oosthuyzen, W., et al., 2021. Genetic mechanisms of critical illness in COVID-19. Nature 591, 92–98.

Pairo-Castineira, E., Rawlik, K., Bretherick, A.D., Qi, T., Wu, Y., Nassiri, I., Mcconkey, G.A., Zechner, M., Klaric, L., Griffiths, F., Oosthuyzen, W., Kousathanas, A., Richmond, A., Millar, J., Russell, C.D., Malinauskas, T., Thwaites, R., Morrice, K., Keating, S., Maslove, D., et al., 2023. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. Nature 617, 764–768.

Randolph, H.E., Fiege, J.K., Thielen, B.K., Mickelson, C.K., Shiratori, M., Barroso-Batista, J., Langlois, R.A., Barreiro, L.B., 2021. Genetic ancestry effects on the response to viral infection are pervasive but cell type specific. Science 374, 1127–1133.

Ruter, J., Pallerla, S.R., Meyer, C.G., Casadei, N., Sonnabend, M., Peter, S., Nurjadi, D., Linh, L.T.K., Fendel, R., Gopel, S., Riess, O., Kremsner, P.G., Velavan, T.P., 2022. Host genetic loci LZTFL1 and CCL2 associated with SARS-CoV-2 infection and severity of COVID-19. Int. J. Infect. Dis. 122, 427–436.

Shelton, J.F., Shastri, A.J., Ye, C., Weldon, C.H., Filshtein-Sonmez, T., Coker, D., Symons, A., Esparza-Gordillo, J., Andme, C.-T., Aslibekyan, S., Auton, A., 2021. Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity. Nat. Genet. 53, 801–808.

Shikov, A.E., Barbitoff, Y.A., Glotov, A.S., Danilova, M.M., Tonyan, Z.N., Nasykhova, Y.A., Mikhailova, A.A., Bespalova, O.N., Kalinin, R.S., Mirzorustamova, A.M., Kogan, I.Y., Baranov, V.S., Chernov, A.N., Pavlovich, D.M., Azarenko, S.V., Fedyakov, M.A., Tsay, V.V., Eismont, Y.A., Romanova, O.V., Hobotnikov, D.N., Vologzhanin, D.A., Mosenko, S.V., Ponomareva, T.A., Talts, Y.A., Anisenkova, A.U., Lisovets, D.G., Sarana, A.M., Urazov, S.P., Scherbak, S.G., Glotov, O.S., 2020. Analysis of the spectrum of ACE2 variation suggests a possible influence of rare and common variants on susceptibility to COVID-19 and severity of outcome. Front. Genet. 11, 551220.

Wang, L., Balmat, T.J., Antonia, A.L., Constantine, F.J., Henao, R., Burke, T.W., Ingham, A., Mcclain, M.T., Tsalik, E.L., Ko, E.R., Ginsburg, G.S., Delong, M.R., Shen, X., Woods, C.W., Hauser, E.R., Ko, D.C., 2021. An atlas connecting shared genetic architecture of human diseases and molecular phenotypes provides insight into COVID-19 susceptibility. Genome Med. 13, 83.

Yang, Z., Macdonald-Dunlop, E., Chen, J., Zhai, R., Li, T., Richmond, A., Klaric, L., Pirastu, N., Ning, Z., Zheng, C., Wang, Y., Huang, T., He, Y., Guo, H., Ying, K., Gustafsson, S., Prins, B., Ramisch, A., Dermitzakis, E.T., Png, G., et al., 2022. Genetic landscape of the ACE2 coronavirus receptor. Circulation 145, 1398–1411.

Zecevic, M., Kotur, N., Ristivojevic, B., Gasic, V., Skodric-Trifunovic, V., Stjepanovic, M., Stevanovic, G., Lavadinovic, L., Zukic, B., Pavlovic, S., Stankovic, B., 2022. Genome-wide association study of COVID-19 outcomes reveals novel host genetic risk loci in the Serbian population. Front. Genet. 13, 911010.

Zhang, Y., Yang, H., Li, S., Li, W.D., Wang, J., Wang, Y., 2021. Association analysis framework of genetic and exposure risks for COVID-19 in middle-aged and elderly adults. Mech. Ageing Dev. 194, 111433.