

Table S2: List of genes recently associated with COVID-19 susceptibility and severity.

Gene	Variants	Source	Publication
<i>SLC6A2</i>	rs35081325	HGI	not published in a peer review journal
<i>CXCR6</i>		HGI	
<i>CCR1</i>		HGI	
<i>OAS1</i>	rs4766664	HGI	
<i>OAS2</i>		HGI	
<i>OAS3</i>		HGI	
<i>DPP9</i>	rs2277732	HGI	
<i>TYK2</i>	rs7956615	HGI	
<i>IFNAR2</i>	rs13050728	HGI	
<i>IL10RB</i>		HGI	
<i>IFNAR1</i>		HGI	
<i>IFNAR2</i>		HGI	
<i>FOXP4</i>	rs1853837	HGI	
<i>TLR3</i>		Human Genetic Effort (HGE)	Zhnag et al, Science 2020
<i>UNC93B1</i>		Human Genetic Effort (HGE)	
<i>TICAM1</i>		Human Genetic Effort (HGE)	
<i>TBK1</i>		Human Genetic Effort (HGE)	
<i>IRF3</i>		Human Genetic Effort (HGE)	
<i>IRF7</i>		Human Genetic Effort (HGE)	
<i>LZTFL1</i>		Genomicc UK	Castineira et al MedriXiv
<i>CCHCR1</i>		Genomicc UK	
<i>HLA-DPB1</i>		Genomicc UK	
<i>VSTM2A</i>		Genomicc UK	
<i>HAS2-AS1</i>		Genomicc UK	
<i>IGF1</i>		Genomicc UK	
<i>ABO</i>			

Table S3: Details of the comparisons defined between Target and Reference populations.

		Target 1	Reference 1		Target 2	Reference 2
Population specific	C1	Relaxed (+)	Costrained (-)	vs	Costrained (-)	Relaxed (+)
	C2	Costrained (-)	Relaxed (+)	vs	Relaxed (+)	Costrained (-)
Population specific vs ancestry related	C3	Relaxed (+)	Costrained (-)	vs	Costrained (-)	Costrained (-)
	C4	Costrained (-)	Relaxed (+)	vs	Relaxed (+)	Relaxed (+)
	C5	Costrained (-)	Costrained (-)	vs	Relaxed (+)	Costrained (-)
	C6	Relaxed (+)	Relaxed (+)	vs	Costrained (-)	Relaxed (+)
Ancestry related	C7	Relaxed (+)	Relaxed (+)	vs	Costrained (-)	Costrained (-)
	C8	Costrained (-)	Costrained (-)	vs	Relaxed (+)	Relaxed (+)

Table S 4: Summary statistics of the phenotype information available for the TOV cohort.

		Gender		Outcome		
Disease Severity group	n	M (n)	F (n)	Survived (n)	Deceased (n)	Age (mean)
Asymptomatic/Paucisymptomatic (1)	52	25	27	52	0	37.5
Severe (2)	73	45	28	60	13	60.4
Critical/life-threatening (3)	64	40	24	21	43	68.4
total	189	110	79	133	56	57.73

Table S5: Comparison between scores distribution of target populations versus reference populations.

Reference	Target	P-value DSC	P-value SSC
EUR	CAR	1.33E-06	7.79E-07
EUR	FVG	3.17E-02	3.65E-08
EUR	VBI	3.78E-03	3.84E-07
AFR	QGP	4.64E-07	4.36E-01
SAS	QGP	2.97E-05	5.35E-01

Table S6: Enrichment tests in target populations versus reference populations.

Reference	Target	DSC score		SSC score	
		Costrained p-value	Relaxed p-value	Costrained p-value	Relaxed p-value
EUR	CAR	2.08E-06	6.81E-04	1.38E-01	7.11E-04
EUR	FVG	2.27E-03	7.70E-02	3.19E-01	7.80E-06
EUR	VBI	2.27E-03	1.93E-03	2.82E-01	3.68E-06
AFR	QGP	3.72E-03	4.17E-01	1.00E+00	8.60E-01
SAS	QGP	3.51E-02	2.52E-01	7.51E-01	8.60E-01

Table S7: DSC and SSC scores for *FLNA*, *MUC5AC* and *ABCA7* in all 1000Genomes superpopulations.

Gene Name	Score	AFR	AMR	EAS	EUR	SAS
<i>ABCA7</i>	DSC	2.6813	1.6151	2.5922	3.0203	2.1504
	SSC	3.3248	4.0146	3.7889	2.5907	3.9976
<i>FLNA</i>	DSC	-2.1657	-2.0498	-2.2511	-2.3994	-1.8791
	SSC	-3.3509	-3.3736	-3.2086	-3.0729	-3.0966
<i>MUC5AC</i>	DSC	3.4995	2.8133	2.8882	3.4774	3.0323
	SSC	3.2673	4.0639	4.1692	3.6789	4.2443

Table S8: Comparison of Gene Singleton Density between the Covid-19 positive cohort (TOV) and other target and reference populations. All singleton counts have been adjusted considering the sample size of each cohort.

Transcript ID	Gene name	Cohort	P-value	OR	TOV Gene singleton count	TOV Gene singleton density	Cohort Gene singleton count	Cohort Gene singleton density
ENST00000369850	<i>FLNA</i>	CAR	0.630140	1.4201	13	0.00050	6	0.00023
		FVG	0.046901	2.3537	13	0.00050	11	0.00042
		VBI	0.000458	5.8145	13	0.00050	5	0.00019
		QGP	0.000028	4.3237	13	0.00050	229	0.00877
		EUR	0.312323	0.6893	13	0.00050	61	0.00234
		AFR	0.878006	0.9218	13	0.00050	60	0.00230
		SAS	0.200408	0.6464	13	0.00050	61	0.00234
ENST00000263094	<i>ABCA7</i>	CAR	3.2746E-11	10.9752	84	0.00328	5	0.00020
		FVG	3.1278E-23	12.8380	84	0.00328	13	0.00051
		VBI	7.1607E-21	8.5370	84	0.00328	22	0.00086
		QGP	6.2413E-63	17.8135	84	0.00328	359	0.01404
		EUR	4.4467E-10	2.9802	84	0.00328	91	0.00356
		AFR	1.7360E-08	2.5141	84	0.00328	142	0.00555

	SAS	2.3435E-04	1.8442	84	0.00328	138	0.00540
ENST00000621226	CAR	7.4274E-12	7.4508	114	0.00264	10	0.00023
	FVG	1.8836E-31	15.0962	114	0.00264	15	0.00035
	VBI	2.3148E-36	19.6004	114	0.00264	13	0.00030
	QGP	1.5512E-76	15.4443	114	0.00264	562	0.01301
	EUR	3.3142E-06	1.9908	114	0.00264	185	0.00428
	AFR	2.9701E-08	2.2129	114	0.00264	219	0.00507
	SAS	7.2316E-03	1.4702	114	0.00264	235	0.00544

Table S9: Comparison of Coding Singleton Density between the Covid-19 positive cohort (TOV) and other target and reference populations. All singleton counts have been adjusted considering the sample size of each cohort.

Transcript ID	Gene name	Cohort	P-value	OR	TOV CDS singleton count	TOV CDS singleton density	Cohort CDS singleton count	Cohort CDS singleton density
		CAR	0.409653	3.2705	5	0.00063	1	0.00013
		FVG	0.316565	1.9922	5	0.00063	5	0.00063
		VBI	0.013015	11.1693	5	0.00063	1	0.00013
ENST00000369850	FLNA	QGP	0.039803	2.7799	5	0.00063	137	0.01725
		EUR	0.786342	1.1543	5	0.00063	14	0.00176
		AFR	0.787767	1.1814	5	0.00063	18	0.00227
		SAS	0.813561	0.7582	5	0.00063	20	0.00252
		CAR	2.5959E-07	14.3697	44	0.00683	2	0.00031
		FVG	1.0535E-17	43.6709	44	0.00683	2	0.00031
		VBI	2.0060E-16	19.6584	44	0.00683	5	0.00078
ENST00000263094	ABCA7	QGP	1.5606E-40	24.9877	44	0.00683	134	0.02080
		EUR	1.0966E-08	4.0565	44	0.00683	35	0.00543
		AFR	5.3713E-09	3.8931	44	0.00683	48	0.00745
		SAS	3.7924E-06	2.9601	44	0.00683	45	0.00699
		CAR	8.4692E-11	12.4070	76	0.00448	4	0.00024
		FVG	2.7623E-24	18.8715	76	0.00448	8	0.00047
		VBI	3.2118E-30	42.4223	76	0.00448	4	0.00024
ENST00000621226	MUC5AC	QGP	1.2101E-64	23.1499	76	0.00448	250	0.01474
		EUR	4.0071E-08	2.6675	76	0.00448	92	0.00542
		AFR	1.0241E-10	3.1351	76	0.00448	103	0.00607
		SAS	9.9471E-05	1.9678	76	0.00448	117	0.00690

Table S10: Multinomial analysis results, comparing classes of disease severity, considering the burden of singletons in the whole gene. Class 1: Asymptomatic/Paucisymptomatic; Class 2: Severe; Class 3: Critical/life-threatening. Only significant predictors are reported.

IC 95%								
Severity Class	Predictor	Estimate	Std. Error	P-value	OR	Lower bound	Upper bound	Std. Error (OR)
Class 2 vs Class 1	Age	6.72E-02	1.36E-02	8.35E-07	1.0695029	1.0412933	1.0984768	0.0145859
	Gender (Male)	9.25E-01	4.63E-01	0.05	2.5208194	1.0173269	6.2463014	1.1670436
Class 3 vs Class 1	Age	1.01E-01	1.63E-02	4.92E-10	1.1064869	1.0717711	1.1423270	0.0179959
	Gender (Male)	1.10E+00	5.09E-01	0.03	2.9987634	1.1061065	8.1299424	1.5259327
Class 3 vs Class 2	Age	3.40E-02	1.17E-02	0	1.0345794	1.0111462	1.0585557	0.0120932

Table S11: Multinomial analysis results, comparing classes of disease severity, considering the burden of singletons in the coding regions of each gene. Class 1: Asymptomatic/Paucisymptomatic; Class 2: Severe; Class 3: Critical/life-threatening. Only significant predictors are reported.

IC 95%								
Severity Class	Predictor	Estimate	Std. Error	P-value	OR	Lower bound	Upper bound	Std. Error (OR)
Class 2 vs Class 1	Age	6.87E-02	1.38E-02	6.09E-07	1.0711545	1.0426111	1.1004793	0.0147605
	Gender (Male)	9.39E-01	4.68E-01	0.04	2.5573716	1.0227587	6.3946161	1.1958014
	FLNA	-1.04E+01	7.39E-05	< 2.2e-16	0.0000296	0.0000296	0.0000296	0.0000000022
Class 3 vs Class 1	Age	9.86E-02	1.60E-02	6.42E-10	1.1036457	1.0696605	1.1387107	0.0176120
	Gender (Male)	1.18E+00	5.08E-01	0.02	3.2520969	1.2007352	8.8080493	1.6532035
Class 3 vs Class 2	Age	2.99E-02	1.14E-02	0.01	1.0303340	1.0076149	1.0535653	0.0117211
	FLNA	7.98E+00	5.18E-01	< 2.2e-16	2933.6216596	1063.3832398	8093.1650220	1518.8708798

Table S12: Logistic analysis results for disease outcome classification. Only significant predictors are reported.

IC 95%								
Outcome	Predictor	Estimate	Std. Error	P-value	OR	Lower bound	Upper bound	Std. Error (OR)
Survied vs Deceased	Age	1.07E-01	1.67E-02	1.50E-10	1.1129343	1.0770954	1.1499656	0.0185860
	ABCA7	4.20E-01	1.85E-01	0.0228	1.5225705	1.0603341	2.1863118	0.2810665

Table S13: Logistic analysis results for disease outcome classification considering the burden of singletons in the coding regions of each gene. Only significant predictors are reported.

IC 95%								
Outcome	Predictor	Estimate	Std. Error	P-value	OR	Lower bound	Upper bound	Std. Error (OR)
Survied vs Deceased	Age	1.05E-01	1.66E-02	2.33E-10	1.1110439	1.0754556	1.1478098	0.0184544