JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

Open Access

REVIEW ARTICLE

Variation in COVID-19 mortality rate across populations, polymorphism in genes, and gender-associated genetic patterns

Kousain Kausar[1], Hafiz Muhammad Imran Aziz[2], Tahir Ahmad[3], Rameesha Abid[4]

[1] Research Assistant, Department of Industrial Biotechnology, Atta ur Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan

[2] Assistant Professor, Department of Pharmacology, Abwa Medical College, Faisalabad, Pakistan

[3] Associate Professor, Department of Industrial Biotechnology, Atta ur Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan

[4] PhD Scholar, Department of Microbiology, Quaid-i-Azam University, Islamabad, Pakistan

Author`s Contribution

[1] Conceptualization of study, analysis, and interpretation of data

[2-4] Drafting the article or revising it critically for important intellectual content. final approval of the version to be published

Article Info.

Conflict of interest: Nil

Funding Sources: Nil

Correspondence

Kousain Kausar

kousain777@outlook.com

Cite this article as *Kousar K, Aziz I, Ahmad T, Abid R. Variation in COVID-19 mortality rate across populations, polymorphism in genes and gender-associated genetic patterns. JSTMU. 2022; 5(2):114-120.*

A B S T R A C T

A severe onset of COVID-19 leads to death due to respiratory failure and ARDS is the common finding of lung histopathology in different people with different comorbidities. It can invade the nervous system leading to the manifestation of neurological symptoms and brain damage including encephalitis and stroke. Genetic polymorphism, comorbidities, and gender differences is playing a pivotal role in conferring resistance and susceptibility to COVID-19. Despite almost the same ACE2 expression profile in males and females, males have shown a high mortality rate due to higher expression of TMPRSS2 (pivotal for S protein binding) as these genes are androgen responsive. While women have shown higher expression of ADAM17, ADAM10 genes are associated with the shedding of ACE2 receptors and are estrogen-responsive, leading to low levels of membrane-bound ACE2 which is indispensable for SARS-Cov2 entry into the cell. People with blood Groups A, and AB are comparatively more susceptible to COVID-19 than people with blood group O, the reason for the O group is attributed to the presence of Anti A antibodies.

Keywords: *COVID-19, TMPRSS2, ACE2, Gene polymorphism, Blood group susceptibility, Gender*

Epidemiology

Since the onset of the COVID-19 pandemic, it has been observed that its infection and severity is varying across different geographical regions. Epidemiological studies confirm that populations carry different variants of ACE2, ABO, and TMPRSS2 genes at respective loci, making people susceptible or resistant to infection depending on their gene variant. In addition to variation in these genes, differences in immunity, sex, age, and comorbidities, and comorbidities are contributing factors in COVID-19-associated fatalities across various ethnic backgrounds.[1]

Up till now, Italy has seen the highest rate of Covid-19 disease and fatalities globally in a specific time duration. The overall death toll shows the USA being the top in fatalities followed by Brazil, the UK, and Italy In Europe and America. South Asia has reported less number of infections and mortality rates as compared to Europe and North America. Data on the number of confirmed cases and deaths, percent fatality rate, and deaths per 100,000

people in European and American populations as of June 25, 2020, when the pandemic was at its peak (Table 1).[2]

Table 1: Data on COVID-19 infection and death Statistics across various European and American countries

Country	Confirmed cases	Deaths	Deaths/ 100,000 people	Fatality %
Italy	239,410	34,644	57.33	14.5
USA	2,381,361	121,979	37.28	5.1
Germany	192,871	8,928	10.77	4.6
UK	308,337	43,165	64.92	14.0
Canada	104,087	8,544	23.06	8.2
Belgium	60,898	9,722	85.12	16.0
Spain	247,086	28,327	60.63	11.5
France	197,885	29,7334	44.39	15.0

In Asian countries, the lower instance of the disease may be attributed to lower testing capacity, genetic variations comorbidities, and previous infection with malarial disease (Table 2).[3] Testing done on people per 1000 till June 23, 2020, were 5.10 for Pakistan, 3.73 for Bangladesh, and 5.17 for India, compared to 82.92 and 186.49 in Italy and Iceland. Testing done per confirmed cases also show lower stats in South Asian Countries with 5.65 tests in Pakistan, 12.53 in India, and 4.54 In Bangladesh. Data on several confirmed cases and deaths, percent fatality rate, and deaths per 100,000 people in the Asian population as of June 25, 2020, is given in table 04 below (Our World In Data, 2020) (Figure 1).

Table 2: Data on COVID-19 infection and death Statistics across Asian countries

	Confirmed cases	Deaths	Deaths /100,000 people	Fatality %
Pakistan	192,970	3,903	1.84	0.8
Bangladesh	122,680	1,528	0.98	1.3
Nepal	10,099	24	0.09	0.2
Afghanistan	29,481	618	1.66	2.1
Sri Lanka	2,001	11	0.05	0.5
Thailand	3,158	58	0.08	1.8
Singapore	42,623	26	0.46	0.1
India	473,105	14,894	1.10	3.1

ACE2 Variation and Ethnicity

The 41.04 kb large ACE2 gene is located on chromosome Xp22.22. It has two variants with 18 or 19 exons each, with the larger variant having an additional exon at the 5' end. [4]

ACE2 Interaction inhibitor SNPs

18 variants of ACE2 18 SNPs including rs1348114695 [E35K], rs146676783 [E37K], rs1192192618 [Y50F], rs760159085 [N51D], rs1569243690 [N51S], rs1325542104 [M62V], rs755691167 [K68E], rs1256007252 [F72V], rs766996587 [M82I], rs759579097 [G326E], rs143936283 [E329G], rs370610075 [G352V], rs961360700 [D355N], rs751572714 [Q388L], rs762890235 [P389H], rs1016409802 [H505R], rs1352194082 [R514G/*], and rs1263424292 [Y515C] act as interaction-inhibitors, means that they bind less competently to SARS-CoV-2. Two of these variants M821 and Q388L have been found more commonly in Africans and Americans respectively. The impact of the Asian-specific variants on viral contagivity was still uncertain. [3]

TMPRSS Variation and Ethnicity

According to the generated information from Ensembl, TMPRSS2 is present on chromosome 21q22.3 and has 15 exons. The prevalence of TMPRSS2 variant kinds, including missense mutations, intronic variations, and frameshift mutations, were also identified by Ensembl. A total of 11,184 SNPs was found in TMPRSS2 according to the results of dbSNP, including 10,578 intronic, 187 synonymous, 392 missense, 21 frameshifts, 3 inframe insertions, 2 inframe deletions, and 1 initiator codon variants. Data from the analysis of 493 SNPs in 1000 genome browsers showed that only 92 SNPs had significantly changed frequency rates in Asian and non-Asian countries. In other words, just 21 out of 92 SNPs affected how the protein functioned. Nine SNPs (rs423596, rs8134203, rs464431, rs2298662, rs2094881, rs75603675, rs456142, rs462574, and rs456298) out of the 21 examined indicated a significant variation in incidence between the Asian population and other groups. Additionally, it was discovered that the frequency of 2 SNPs (rs402197 and rs456016) varied among other populations but was similar in American and Asian

groups. A considerable difference in frequency between Europeans and others was found for 8 SNPs (rs422761, rs8134203, rs2094881, rs75603675, rs456142, rs462574, rs456298, and rs12473206). One SNP (rs461194) reportedly showed a significantly different frequency in the African population compared to others. Five SNPs (rs402197, rs456016, rs461194, rs464431, and rs2298662) that were compared between populations in Europe and Africa exhibited nearly comparable frequencies. The table below shows important TMPRSS2 SNPs across various populations and their associated mutation in global (Glo), African (AFRN), Asian (ASN), European (EURO), South Asian(SASA), and American (AMRN) populations (Table 4).

Diverse population frequencies of TMPRSS2 SNPs have been found in the 1000 genome study.

Employing PolyPhen-2, the impact of SNPs on TMPRSS2 was assessed, and it was discovered that both missense SNPs had the greatest impact on the TMPRSS2 function. The occurrence of SNPrs1239760 is found to be highest in America, followed by South Asian, European, African, and Asian, whereas the occurrence of SNPrs75603675 was found to be highest in Asia, followed by South Asian, American, African, and then European (PolyPhen-2) Table 5.

Gender differences in ACE2, TMPRSS2, and ADAM17 expression in relation to COVID-19 vulnerability

It has been reported that males are lightly at a higher risk of getting infected with COVID-19 than females and make up the majority of the severely ill and fatality cases, especially those having chronic diseases like Type 2 Diabetes, and hypertension or are above 60 years of age.5 The two molecules are crucial for one another in terms of SARS-CoV2 entrance because SARS-CoV-2 enters human alveolar cells via the SARS-CoV receptor ACE2 and TMPRSS2 for activating spike protein. ACE1 and ACE2 antagonistic enzymes work in coordination in the renin–angiotensin system (RAS) to balance the proliferative/ local vasoconstrictor and antiproliferative vasodilator activity. [6, 7].

All organs revealed significant positive relationships with CD8+ T cell abundance levels exclusively in males (0.20 r 0.68) in a study examining tissue expression levels of ACE2. Female CD8+ T-cell enrichment levels were adversely linked with thyroid and lung ACE2 expression levels (r = -0.36). Similar to this, both males and females showed substantial positive correlations between the interferon reaction pattern and the levels of ACE2 expression in skin blood vessels (0.14 r 0.75). [8] Male's ACE2 expression levels displayed substantial positive relationships with the interferon reaction pattern in the lungs, kidneys, thyroid, adrenal gland, bladder, and colon (0.32 r 0.82). ACE2 expression levels, on the other hand, were inversely linked (-0.26 r -0.20) with the interferon response profile in the lungs, thyroid, and colon of females. The ACE2 tissue expression data extracted from GTEx.org shows that males and females exhibit the same expression of ACE2in lungs and arteries, while in kidneys and left heart ventricles the expression is high in females than males (Figure 2).

The androgen hormone is thought to have an impact on the mRNA levels of TMPRSS2, according to research. By attaching to the androgen response element (ARE) found in the TMPRSS2 promoter, androgen hormones control the amount of time that TMPRSS2 is expressed. [9] Therefore the expression of TMPRSS2 is slightly higher in males than in females (Figure 3). Metallopeptidase ADAM17 and ADAM10 that cleave the intracellular domain of ACE2 and are involved in ACE2 shedding are responsive to estrogen hormone, therefore estrogen lowers the susceptibility of infection in females as SARS-CoV2 can enter the cell only through membrane-bound ACE2 receptor. [10, 11] The expression profile of ADAM17 in both males and females reveal that females have higher expression of ADAM17 in the lungs than males and thus have higher expression of membrane-bound ACE2 receptor which makes them more susceptible to COVID-19 (Figure 4).

Table 3: Number of SNPs for the X-linked Ace2 locus with significant variations in occurrence across different ethnicities

Specific for a common population of the comparisons				
Comparisons	**Total**	**Specific SNPs in either of the comparisons**	**Specific SNPs in all of the comparisons (Frequency)**	**Population size (Avg-/Median)**
Asians vs Europeans, Americans or Africans	55	43	4 (0.00013-0.00030)	40,150/45,859
Europeans vs Asians, Americans or Africans	86	12	1 (0.000143)	122,845/147,472
Africans vs Asians, Americans, or Europeans	47	46	8 (0.00013- 0.00336)	20,482/21,424
Americans vs Asians, Europeans, or Africans	52	29	2 (0.00016-0.00018)	-

Table.4: Important TMPRSS2 SNPs across various populations

SNP	Function class	Allele	GLO	AFRN	ASN	EURO	SASA	AMRN
rs386416	Intron	G>C	G = 0.444	G = 0.431	G = 0.698	G = 0.300	G = 0.354	G = 0.439
rs402197	Intron	T>C	T = 0.126	T = 0.018	T = 0.349	T = 0.021	T = 0.072	T = 0.236
rs112467088	Intron	A>T	A = 0.814	A = 0.743	A = 0.981	A = 0.7187	A = 0.867	A = 0.771
rs422761	Intron	G>A	G = 0.775	G = 0.707	G = 0.682	G = 0.981	G = 0.759	G = 0.764
rs423596	Intron	C>T	C = 0.904	C = 0.994	C = 0.750	C = 0.961	C = 0.833	C = 0.977
rs456016	Intron	T>C	T = 0.125	T = 0.019	T = 0.349	T = 0.018	T = 0.075	T = 0.231
rs461194	Intron	C >G	C = 0.131	C = 0.004	C = 0.347	C = 0.030	C = 0.113	C = 0.228
rs8134203	Intron	C >T	C = 0.464	C = 0.506	C = 0.741	C = 0.256	C = 0.326	C = 0.477
rs464431	Intron	A >G	A = 0.126	A = 0.019	A = 0.349	A = 0.019	A = 0.075	A = 0.232
rs2298662	Intron	G>C	G = 0.123	G = 0.006	G = 0.346	G = 0.020	G = 0.082	G = 0.231
rs7364088	Intron	G>A	G = 0.695	G = 0.675	G = 0.604	G = 0.736	G = 0.736	G = 0.751
rs875393	Intron	G>A	G = 0.944	G = 0.998	G = 0.822	G = 0.942	G = 0.970	G = 0.986
rs2094881	Intron	T>C	T = 0.470	T = 0.524	T = 0.744	T = 0.252	T = 0.324	T = 0.491
rs75603675	Exon G>D	C >A	C = 0.756	C = 0.705	C = 0.983	C = 0.595	C = 0.777	C = 0.728
rs12329760	Exon V>M	C >T	C = 0.738	C = 0.738	C = 0.637	C = 0.764	C = 0.774	C = 0.846
rs456142	3'UTR	T >A	T = 0.370	T = 0.372	T = 0.634	T = 0.1690	T = 0.317	T = 0.352
rs462574	3'UTR	A >G	A = 0.257	A = 0.177	A = 0.590	A = 0.0338	A = 0.254	A = 0.252
rs456298	3'UTR	T >A	T = 0.372	T = 0.372	T = 0.636	T = 0.1690	T = 0.321	T = 0.353
rs12627374	3'UTR	C >T	C = 0.940	C = 0.995	C = 0.850	C = 0.998	C = 0.863	C = 0.996
rs12473206	3'UTR	C >G	C = 0.861	C = 0.959	C = 0.955	C = 0.740	C = 0.800	C = 0.800
rs75036690	3'UTR	G>A	G = 0.989	G = 1.000	G = 0.955	G = 1.000	G = 0.993	G = 1.000

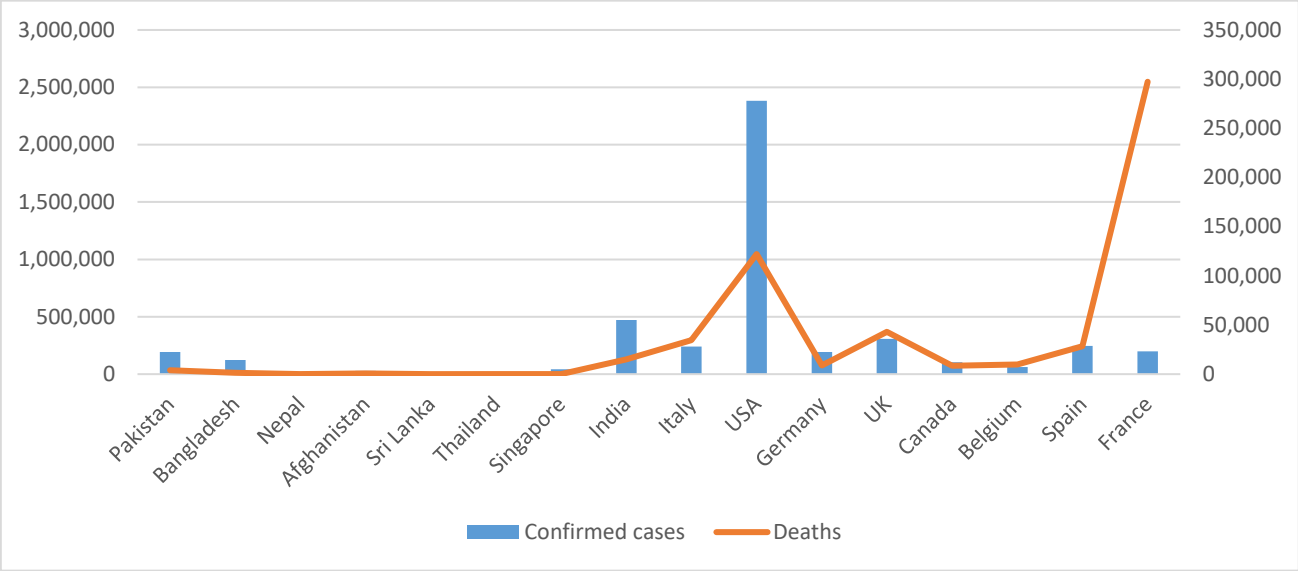

Figure 1: COVID-19 confirmed cases and death stats across some American, European and Asian countries

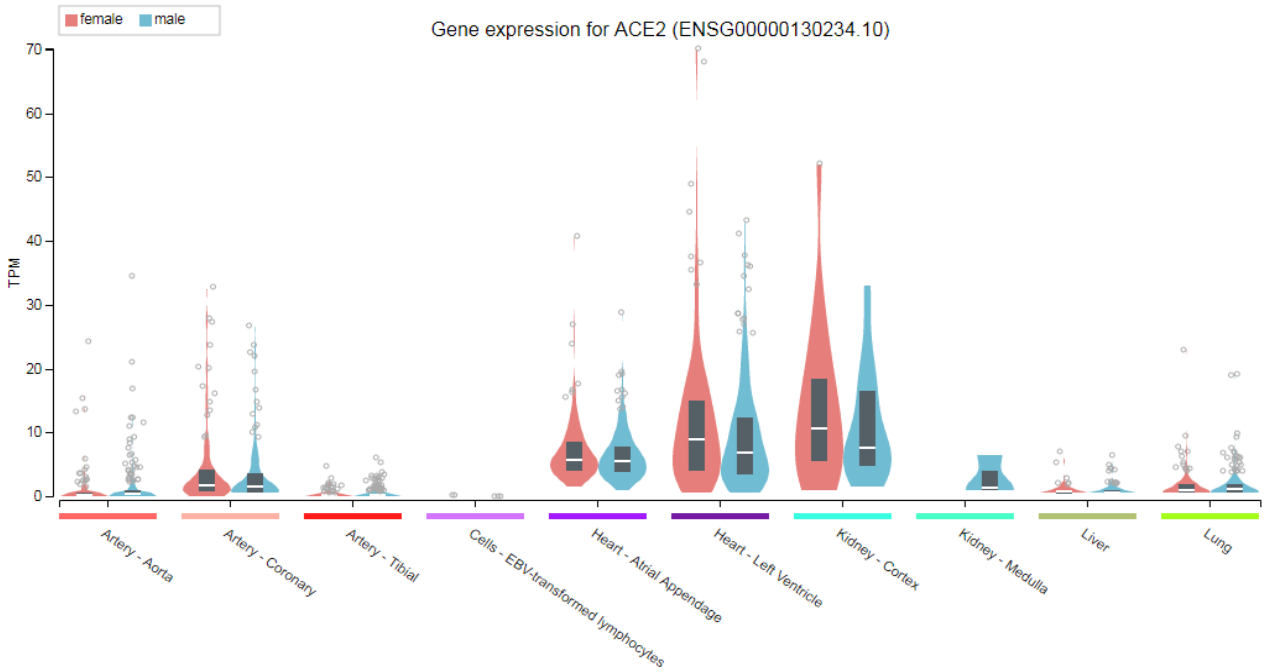

Figure 2: ACE2 Expression in major tissues associated with COVID-19 mediated damage

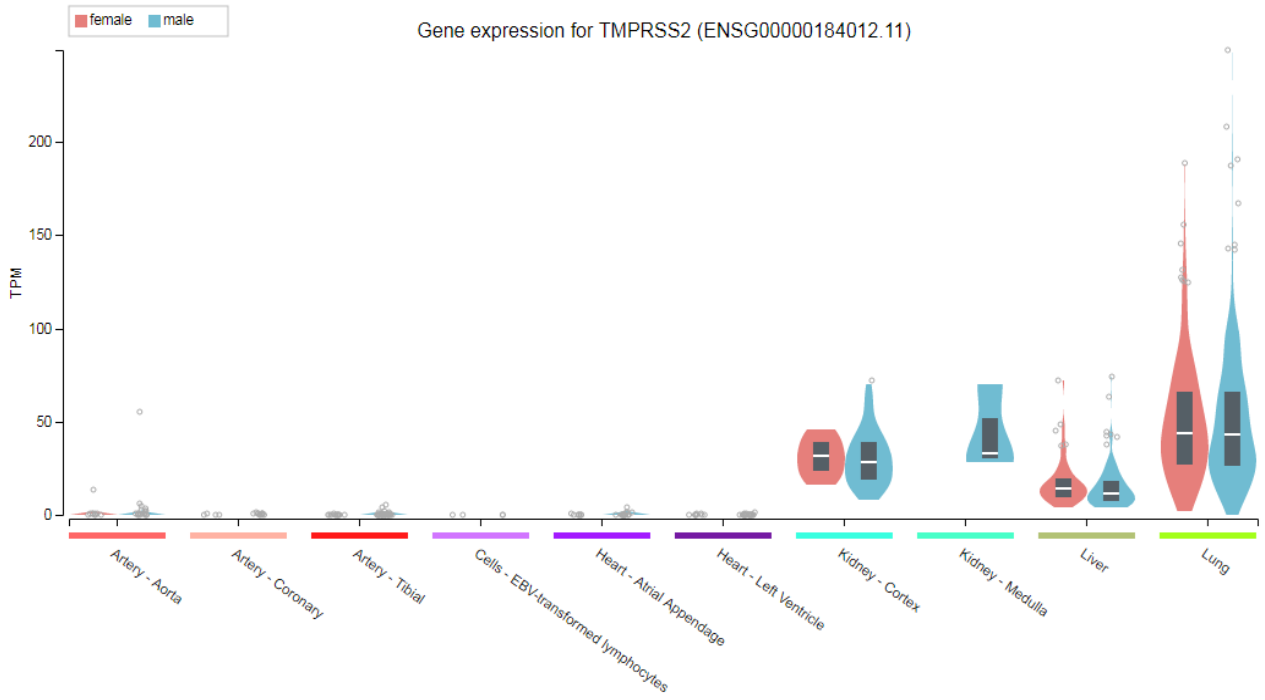

Figure 3: ACE2 Expression in males and females in major tissues associated with COVID-19-mediated damage

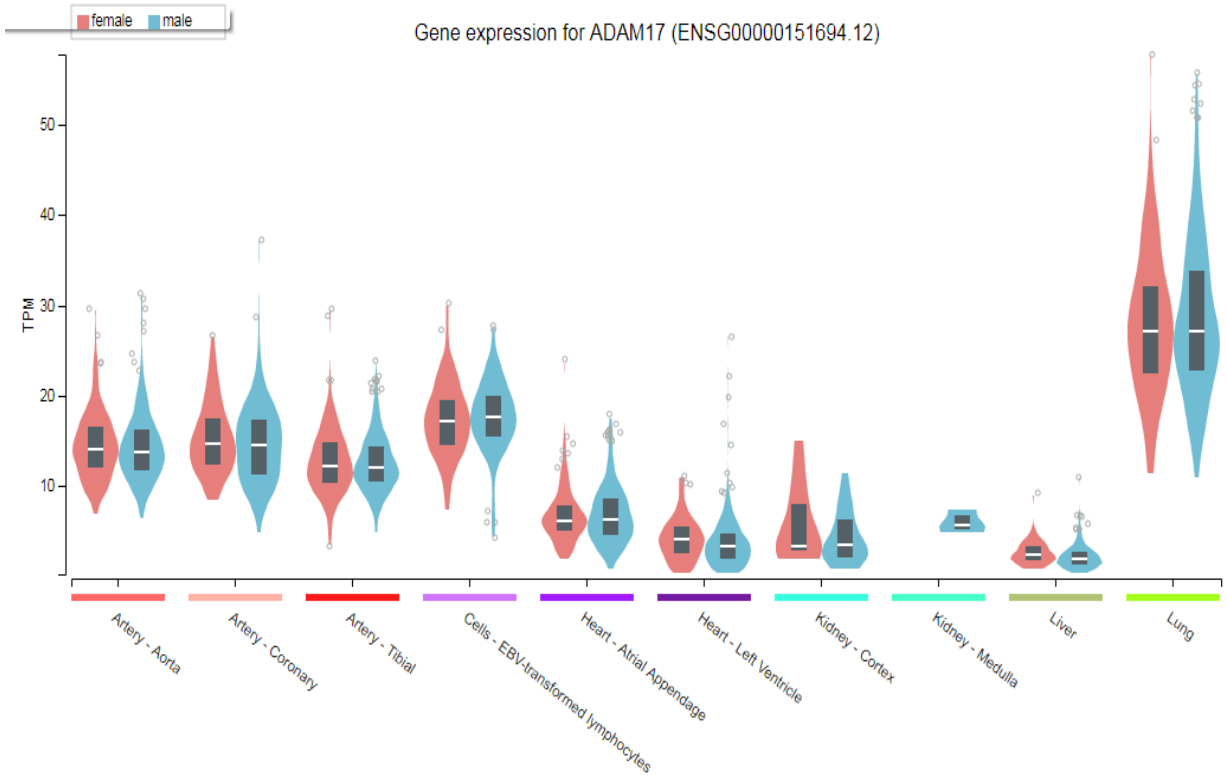

Figure 4: ADAM17 Expression in males and females in major tissues associated with COVID-19 mediated damage.

ABO Blood group variation across ethnicities and susceptibility to COVID-19

The ABO blood types proposed by Landsteiner are built on glucose residues found on the outer surfaces of human cells. Trisaccharide moieties Gal1-3-(Fuc1,2)-Gal and GalNAc1-3-(Fuc1,2)-Gal identifies the nature of A or type B blood group, whereas Fuc1,2-Gal determines the type O blood group. Even though blood group types are biologically transmitted, external conditions also have an impact on the type of blood group that will be passed on to offspring. 11 The ABO blood group has already been shown to be linked to virus proneness. Hepatitis B and the Norwalk virus, for instance, clearly have a blood group susceptibility. 12 Additionally, it was noted that people with the O blood group had a lower risk of contracting Covid-19. ABO blood type is an indicator for differential proneness to COVID-19, as it has been shown that blood group A is connected with an increased likelihood of becoming infected with COVID-19 while blood group O was related to reduced risk. These results are in line with prior research that identified similar ABO blood group probability trends for other coronavirus diseases. [13]

According to research, those with the blood group O were less likely to contract an infection than those with other blood types. According to Patrice et al., anti-A antibodies particularly prevented SARS-CoV S protein-expressing cells from adhering to ACE2-expressing cell lines. Given the nucleic acid sequence homology and ACE2 binding homogeneity between SARS-CoV and SARS-CoV, it is possible that the presence of naturally occurring anti-blood group antibodies, especially anti-A antibodies, in the blood contributes to blood group O's lower proneness to COVID-19 and blood group A's higher susceptibility. [14]

Conclusion

This review summarizes the role of gene polymorphism in rendering susceptibility to COVID-19 infection. Expression of genes like TMPRSS2, ACE-2, ADAM 10, and ADAM7 across various populations and gender can help predict the susceptible genetic makeup. Greater insight into these and other COVID-19 genes can help researchers understand the infection pattern of this pandemic.

References

1. Daniel G, Paola AR, Nancy G, Fernando SO, Beatriz A, Zulema R, et al. Epigenetic mechanisms and host factors impact ACE2 gene expression: Implications in COVID-19 susceptibility. Infect Genet Evol. 2022; 104:105357. DOI: https://doi.org/10.1016/j.meegid.2022.105357.
2. Sargin G, Yavaşoğlu Sİ, Yavasoglu I. Is Coronavirus Disease 2019 (COVID-19) seen less in countries more exposed to Malaria? Med Hypotheses. 2020; 140:109756. DOI: https://doi.org/10.1016/j.mehy.2020.109756
3. Darbani B. The expression and polymorphism of entry machinery for COVID-19 in human: juxtaposing population groups, gender, and different tissues. Int J Environ Res. Public Health. 2020; 17(10):3433. DOI: https://doi.org/10.3390/ijerph17103433
4. Paniri A, Hosseini MM, Akhavan-Niaki H. First comprehensive computational analysis of functional consequences of TMPRSS2 SNPs in susceptibility to SARS-CoV-2 among different populations. J Biomol Struct Dyn. 2021; 39(10):3576-93. DOI: https://doi.org/10.1080/07391102.2020.1767690
5. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics. 2019; 13(1):1-2. DOI: https://doi.org/10.1186/s40246-018-0185-z
6. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271-80. DOI: https://doi.org/10.1016/j.cell.2020.02.052
7. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell. 2020; 19(7):e13168. DOI: https://doi.org/10.1111/acel.13168
8. Clinckemalie L, Spans L, Dubois V, Laurent M, Helsen C, Joniau S, Claessens F. Androgen regulation of the TMPRSS2 gene and the effect of a SNP in an androgen response element. Mol Endocrinol. 2013; 27(12):2028-40. DOI: https://doi.org/10.1210/me.2013-1098
9. Jia HP, Look DC, Tan P, Shi L, Hickey M, Gakhar L, et al. Ectodomain shedding of angiotensin converting enzyme 2 in human airway epithelia. Am J Physiol Lung Cell. 2009; 297(1):L84-96. DOI: https://doi.org/10.1152/ajplung.00071.2009
10. Golinelli D, Boetto E, Maietti E, Fantini MP. The association between ABO blood group and SARS-CoV-2 infection: A meta-analysis. PLoS One. 2020; 18;15(9):e0239508. DOI: https://doi.org/10.1371/journal.pone.0239508.
11. Sijjeel F, Khalid A, Khan MY, Khurshid R, Habiba UE, Majid H, et al. Prevalence of ABO and Rh Blood Groups and Their Association with Transfusion-Transmissible Infections (TTIs) among Blood Donors in Islamabad, Pakistan. BioScientific Rev. 2021; *3*(4),13-26. DOI: https://doi.org/10.32350/BSR.0304.02
12. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol. 2020; 190(1): 24-27 DOI: https://doi.org/10.1111/bjh.16797
13. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, Ng MH, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. J Am Med Assoc 2005; 293(12):1447-51. DOI: https://doi.org/10.1001/jama.293.12.1