

A Bioinformatic Analysis of the Structural and Functional Consequences of TMPRSS2 SNPs on
Binding Interactions Critical for SARS-CoV-2 Infection.

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Annotated Bibliography

Baughn, L. B., Sharma, N., Elhaik, E., Sekulic, A., Bryce, A. H., & Fonseca, R. (2020).

Targeting TMPRSS2 in SARS-CoV-2 Infection. *Mayo Clinic proceedings*, 95(9), 1989–1999. <https://doi.org/10.1016/j.mayocp.2020.06.018>

This research article provides insight from researchers and physicians on two critical components of the SARS-CoV-2 infection mechanism, ACE2 and TMPRSS2. Following expression analysis of ACE2 and TMPRSS2, the authors importantly distinguish TMPRSS2 as a more reasonable therapeutic target. They cite the critical role that ACE2 plays in human heart regulation through the renin-angiotensin system (RAS) and note that previous studies involving mice with ACE2 expression knocked out resulted in lethal effects, whereas TMPRSS2 knockout mice survived with less viral transmission. The potential dangers cited of reducing ACE2 expression led to the focus of the current research revolving around TMPRSS2 expression rather than ACE2 expression. TMPRSS2 is of critical importance in facilitating viral entry, yet is not as critical as ACE2 for normal life function, therefore analyzing its expression levels are important to develop safe and effective therapeutics.

David, A., Khanna, T., Beykou, M., Hanna, G., & Sternberg, M. J. (2020). Structure, function and variants analysis of the androgen-regulated TMPRSS2, a drug target candidate for COVID-19 infection. bioRxiv.

Bioinformatic researchers developed structural models of TMPRSS2 and relevant SNPs in this work, finding many variants that could potentially damage the structure of TMPRSS2. This paper still provided valuable SNPs that are further analyzed in current research. A notable limitation of this study is that many of these variants were rare in the population, which

showcases the importance of analyzing the population frequencies of SNPs to determine the most prevalent variants of interest.

Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time.

Lancet Infect Dis; published online Feb 19.

[https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1).

This data report offers a valuable, comprehensive understanding of the current number of SARS-CoV-2 cases and deaths around the world. Because this dashboard is constantly updated in real time, it offers an accurate depiction of the severity of this disease. Understanding the current global spread of this coronavirus is essential to appreciating the importance of scientific studies regarding this pandemic.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S.,

Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., &

Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2

and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, *181*(2),

271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>

This academic study details the specific mechanisms SARS-CoV-2 utilizes to facilitate viral entry into the cell. The authors found that TMPRSS2 primes the spike protein of SARS-CoV-2 to facilitate viral entry, making it crucial to SARS-CoV-2 infection. They also explored ways to prevent infection by blocking this mechanism, finding that inhibition of TMPRSS2 disrupts viral entry into the cell. These findings offer necessary background knowledge on how SARS-CoV-2 initiates infection, inspiring interest in TMPRSS2 due to its necessary role in the beginning stages of infection. The mentioned success of TMPRSS2 inhibitors suggest TMPRSS2

expression may be related to disease severity, demonstrating its significance in the current research.

Hussain, M., Jabeen, N., Amanullah, A., Baig, A. A., Aziz, B., Shabbir, S., ... & Uddin, N.

(2020). Molecular docking between human TMPRSS2 and SARS-CoV-2 spike protein: conformation and intermolecular interactions. *AIMS microbiology*, 6(3), 350.

In this study, researchers utilized bioinformatic software to model the structure of TMPRSS2 and observe the potential docking interactions between TMPRSS2 and the SARS-CoV-2 spike protein that initiate viral cell entry. The structure of TMPRSS2 generated was a useful guide to understanding how changes to specific residues alter the specific binding interactions between TMPRSS2 and SARS-CoV-2 to alter disease development. The significance of docking interactions in disrupting binding necessary for infection lead the current study to analyze docking interactions between chosen SNPs of interest and the spike protein.

Klaassen, K., Stankovic, B., Zukic, B., Kotur, N., Gasic, V., Pavlovic, S., & Stojiljkovic, M.

(2020). Functional prediction and comparative population analysis of variants in genes for proteases and innate immunity related to SARS-CoV-2 infection. *Infection, Genetics and Evolution*, 84, 104498.

The aim of this academic study was to analyze SNPs of genes that play a role in cellular infection of SARS-CoV-2 in order to discover if variants can offer a harmful or protective function. This study presented useful softwares to predict the effect of SNPs of interest, specifically PolyPhen-2 and SIFT. This research also thoroughly explained how to compare the frequencies of genetic variants across different populations, which was utilized in the current study.

Mollica, V., Rizzo, A., & Massari, F. (2020). The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer. *Future Medicine*, 16(27), 2029–2033.

<https://doi.org/10.2217/fon-2020-0571>

This review paper highlights the limited knowledge regarding TMPRSS2's physiological function. The authors share their well-informed understanding of heightened TMPRSS2 expression in prostate cancer and hypothesize that this knowledge may be translatable to the relationship between TMPRSS2 and SARS-CoV-2 infection. This hypothesis helped inspire the question of the ability of SNPs to alter TMPRSS2's expression, and subsequently, SARS-CoV-2 cell entry. The limited general knowledge available on TMPRSS showcases the importance in studying this protein, as there is an opportunity to contribute significant knowledge to the scientific community.

Paniri, A., Hosseini, M. M., & Akhavan-Niaki, H. (2020). First comprehensive computational analysis of functional consequences of TMPRSS2 SNPs in susceptibility to SARS-CoV-2 among different populations. *Journal of Biomolecular Structure and Dynamics*, (just-accepted), 1-18.

In this academic study, researchers performed a thorough investigation into the potential structural and functional changes of TMPRSS2 due to different SNPs. They found various SNPs that were observed to alter the function of TMPRSS2 in different ways, including altering the protein's folding, miRNA function, and splicing. This study provided multiple SNPs that were chosen as SNPs of interest for the current research. Their findings highlight the relevance of analyzing SNP effects on TMPRSS2 in relation to susceptibility of SARS-CoV-2.

Ravikanth V. et al. (2020) Genetic variants in TMPRSS2 and Structure of SARS-CoV-2 spike glycoprotein and TMPRSS2 complex. bioRxiv. doi:10.1101/2020.06.30.179663

This primary research paper investigated a specific SNP, rs12329760, that had been previously identified to alter TMPRSS2 activity and may ultimately disrupt cellular infection by SARS-CoV-2. Researchers modelled native TMPRSS2 along with rs12329760 and observed the specific differences in their structures, finding that the mutant residue resulted in deformation of the protein that ultimately hindered its stability. The significant disruption this genetic variant caused to TMPRSS2 led it to be studied as one of the SNPs of interest in the current research project. Furthermore, this paper provided softwares that could be used to analyze structural models (I-Tasser, HADDOCK) and docking interactions (ClusPro, SWISSMODEL) of rs12329760 and other SNPs of interest.

Russo, R., Andolfo, I., Lasorsa, V. A., Iolascon, A., & Capasso, M. (2020). Genetic analysis of the coronavirus SARS-CoV-2 host protease TMPRSS2 in different populations. *Frontiers in genetics*, 11, 872.

In this scholarly research article, the authors highlight key epidemiologic trends observed throughout the SARS-CoV-2 pandemic. Specifically, the researchers note that certain populations experience severe sickness while others are asymptomatic. They analyzed different genetic variants of TMPRSS2 and found that some SNPs associated with lowered expression of TMPRSS2 may confer a protective role from viral infection. These findings helped form the hypothesis of the current research that genetic variants of TMPRSS2 may underlie differences in clinical symptoms. This study also provided various SNPs of interest and detailed methodology on how to analyze population frequencies of SNPs.

Shen, L. W., Mao, H. J., Wu, Y. L., Tanaka, Y., & Zhang, W. (2017). TMPRSS2: A potential

target for treatment of influenza virus and coronavirus infections. *Biochimie*, 142, 1-10.

This scholarly article was of great significance to the background knowledge necessary for this research project, as it details why TMPRSS2 has potential to be a significant target to prevent SARS-CoV-2 infection. Published in a reputable journal, this research details both the physiological role of TMPRSS2 as well as the mechanistic role it plays in activating viral entry of coronaviruses and influenza viruses into the cell. These findings established an understanding of what is currently known about TMPRSS2 and aided in formulating further questions about what is left to be discovered about the function of TMPRSS2 and its expression in relation to the novel SARS-CoV-2.

Zang, R., Gomez Castro, M. F., McCune, B. T., Zeng, Q., Rothlauf, P. W., Sonnek, N. M., Liu, Z., Brulois, K. F., Wang, X., Greenberg, H. B., Diamond, M. S., Ciorba, M. A., Whelan, S., & Ding, S. (2020). TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. *Science Immunology*, 5(47), eabc3582.

<https://doi.org/10.1126/sciimmunol.abc3582>

This research paper highlights TMPRSS4, a serine protease very similar to TMPRSS2, as being linked to greater RNA levels of SARS-CoV-2 and subsequent infection by the virus when its levels of expression are high. They discovered that knocking out TMPRSS4 expression leads to a great decrease in viral infection, which aligns with previous findings surrounding TMPRSS2 expression. These findings led to TMPRSS4 and potential relevant SNPs being further explored in the current research. TMPRSS4 is relatively under studied in terms of SNPs related to SARS-CoV-2, allowing an opportunity to provide significant contribution in this arena by comparing TMPRSS4 to what has been found about TMPRSS2.

Zhou, L., Niu, Z., Jiang, X., Zhang, Z., Zheng, Y., Wang, Z., ... & Sun, Q. (2020). Systemic analysis of tissue cells potentially vulnerable to SARS-CoV-2 infection by the protein-validated single-cell RNA profiling of ACE2, TMPRSS2 and Furin proteases.

doi: <https://doi.org/10.1101/2020.04.06.028522>

This scholarly research analyzed the co-expression of TMPRSS2, FURIN, and ACE2 in various cellular tissues. While ACE2 is understood to be the necessary receptor for SARS-CoV-2 cellular entry, this study found that cells containing co-expression of TMPRSS2 and ACE2 may be more susceptible to infection. Such findings explain why investigating TMPRSS2 expression levels in relation to disease infection is important.