SEQUENCE, STRUCTURE, AND FUNCTION OF TMPRSS2 COMMON MUTATIONS RELATING TO THE SEVERITY AND SUSCEPTIBILITY OF COVID-19 INFECTIONS

by

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Annotated Bibliography

Baughn, L. B., et al. (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 study states that ACE2 and TMPRSS2 are both important in the activation and entry of SARS-CoV. However, ACE2 as a drug target is not the best idea due to its fundamental role in the cardiovascular system. Rather, they recommend TMPRSS2 as a safer approach for therapies and treatments with evidence that supports this claim. The authors also provide two missense variants that are more than 5% allele frequency in world population, a beginning to our research question.

Bestle, D., et al. (2020). TMPRSS2 and furin are both essential for proteolytic activation and spread of SARS-CoV-2 in human airway epithelial cells and provide promising drug targets. *Life Science Alliance, 3*(9) e202000786; https://doi.org/10.26508/lsa.202000786

Cleavage of coronavirus spike proteins is not completely understood yet. Bestle et al.'s data suggests that both TMPRSS2 and furin are essential for SARS-CoV-2 activation. Furthermore, infecting TMPRSS2-KO epithelial cells lead to less viral replication, indicating a possible therapeutic role. Multiple sequence alignments of coronaviruses suggest that TMPRSS2 cleaves at single arginine residues located in the S2' site and furin cleaves at a motif located at the S1/S2 site.

David, A., et al. (2020). Structure, function and variants analysis of the androgen-regulated TMPRSS2, a drug target candidate for COVID-19 infection. bioRxiv. https://doi.org/10.1101/2020.05.26.116608

David et al. performed a bioinformatics search on TMPRSS2 SNPs that could be lethal and made 3D models of over 300 variants. The authors predicted the common variant, rs12329760, to be damaging since it is located in the conserved SRCS domain, which may have an important function.

Hoffmann, M., et al. (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. https://doi.org/10.1016/j.cell.2020.02.052

Hoffmann et al. presented one of the first pieces of evidence that ACE2 and TMPRSS2 are involved in SARS-CoV-2 activation and entry. It is also noted that a TMPRSS2 inhibitor, camostat mesylate, blocked SARS-CoV-2 entry and could also be a possible drug candidate.

Hussain, M., et al. (2020). Molecular docking between human TMPRSS2 and SARS-CoV-2 spike protein: conformation and intermolecular interactions. *AIMS microbiology*, *6*(3), 350. https://doi.org/10.3934/microbiol.2020021

This study contains the first TMPRSS2-SARS-CoV-2 complex peer-reviewed to date. It presents interactions present between the protease and the spike protein, as well as important residues such as the active sites and substrate binding sites.

Klaassen, K., et al. (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). ISSN 1567-1348, https://doi.org/10.1016/j.meegid.2020.104498

Klaassen et al. studied genetic variants in proteins and immunity relating to SARS-CoV-2. Even though the authors did not declare any significance for TMPRSS2, the idea that changes in host genes can affect infection severity and susceptibility still holds.

Paniri, A., et al. (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*:1-18 https://doi.org/10.1080/07391102.2020.1767690

This research group complied over 11,000 TMPRSS2 SNPs from the NCBI database to determine lethal effects/ population differences. 21 SNPS were found to lead to functional changes in the protease. This study was one of the first papers we found that complied TMPRSS2 SNPs.

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

These authors created a TMPRSS2-SARS-CoV-2 complex similar to Hussain et al. (2020). However, Ravikanth et al. (2020) also studied the interactions between the catalytic pocket of TMPRSS2 and protease inhibitors. All four inhibitors used were shown to bind strongly to the active site.

Russo, R., et al. (2020). Genetic analysis of the coronavirus SARS-CoV-2 host protease TMPRSS2 in different populations. *Frontiers in genetics*, 11, 872.

This study performed a bioinformatics search of TMPRSS2 variants to determine if certain populations are more at risk to being infected with COVID-19. Several SNPs have been shown to lead to increase of susceptibility in influenza A and could also possibly increase the risk of COVID-19.

Shen, L.W., et al. (2017). TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections, *Biochimie*, 142, 1-10. https://doi.org/10.1016/j.biochi.2017.07.016.

This review article briefly summarizes TMPRSS2 background and its role in coronavirus infections and flu infections. It also discusses different types of approved as well as non-approved drugs that could be used as TMPRSS2 inhibitors.

Strope, J. D., & Chau, C. H. (2020). TMPRSS2: Potential Biomarker for COVID-19 Outcomes. *Journal of clinical pharmacology*, 1-7.

This commentary discusses TMPRSS2 SNPs that have been relevant for various diseases such as breast cancer, prostate cancer, and H1N1 infection. Further research includes collecting DNA samples from COVID-19 patents to determine more SNPs that may be relevant to infection risk and/or severity.

Yamamoto, N., et al. (2020). SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. *Gene*, *758*, 144944. https://doi.org/10.1016/j.gene.2020.144944

This study presented how different genotypes of ACEI can possibly predict severity of COVID-19 infection. This paper reflected our curiosity on how different genetic variations could affect COVID-19 infection. Unfortunately, the paper had a lot of limitations that prevented us from using the paper as a guide for our research project.

Zang, R., et al. (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

Zang et al. suggests that the well-known TMPRSS2, as well as another protease in the same family, TMPRSS4, both play a part in activating SARS-CoV-2. This has led us to integrate TMPRSS4 into our research project.