

18.

Bölüm

COVID-19 GENETİK İLİŞKİSİ

Özlem SEZER¹

1. COVID-19 enfeksiyonuna genetik yatkınlık var mıdır?
2. SARS-CoV-2 ile karşılaşan herkes enfekte olur mu?
3. SARS-CoV-2 neden tüm vücutta bulgu ve semptomlara neden olur?
4. SARS-CoV-2 enfeksiyonu neden farklı yaşlarda ve cinsiyetlerde farklı klinik semptom ve bulgularla gözlenir?
5. COVID-19 ve doku grubu genleri arasında ilişki var mı?
6. COVID-19 ve immün mekanizma arasında ilişki var mı?
7. COVID-19 ve Vitamin D arasında nasıl bir ilişki var?

GİRİŞ

SARS-CoV-2 enfeksiyonunun geniş kitleleri kısa sürede etkilemesinde yaygın coğrafik değişimler göstermesinde, hastalar arasında gözlenen bulgular, semptomlar ve klinik şiddetin değişkenliğinde, ülkeler ve kıtalar arasında mortalite oranlarının farklı olmasında ve her bireyin **tedaviye değişken yanıtında**; gerek enfeksiyon ajanının gerekse konağın genetik **farklılıklarından kaynaklanabileceği** düşünülmektedir (1,2-35).

SARS-COV-2’NİN GENETİK ÖZELLİKLERİ

SARS-CoV-2’nin de dahil olduğu Koronavirüsler, zoonotik virüslerdir. Ana kaynağı, yarasalar, domuzlar, keçi, koyun, tavşan, köpek ve yırtıcı yabani hayvanlardır (3).

¹ Uzm. Dr. Özlem SEZER, Sağlık Bilimleri Üniversitesi Samsun Eğitim ve Araştırma Hastanesi, Genetik Bölümü ozlemturkeli@yahoo.com

rına karşı duyarlıdır. Antijenler vücudumuza girdikleri zaman MyD88 ve NF-kB etkilenir; transkripsiyon faktörü olan NF-kB proinflamatuvar sitokinlerin salınmasına neden olarak inflamasyonu başlatır. TLR7’de defekt, IFNRF7 yi aktive eder bunun sonucu olarak tip1 IFN baskılanır, aynı zamanda IFN ile stimüle edilen genlerin aktivasyonu da baskılanmış olur. IFN ve IFN ile stimüle edilen genler, virüsle mücadelede rol oynar ve virüsün daha ağır enfeksiyona neden olmasını engeller (34). TLR7 defekti olanlarda TLR7 aktivasyonunu sağlayan ve HPV enfeksiyonunda verrülerin tedavisinde kullanılan imiquimod (IQ) tedavisinin de etkili olabileceği düşünülmektedir (35).

SONUÇ

COVID-19 enfeksiyonuna yatkınlık ve dirençten kompleks genetik mekanizmalar sorumludur. Hastaların COVID-19 enfeksiyonuna verdiği klinik ve tedavi yanıtı da kişiye özgüdür. Konak genotipinin ve konakçı genotip-fenotip korelasyonunun araştırılması COVID-19 enfeksiyonunun etiopatogenezini aydınlatmada ve kişiye özgü yeni tedavi stratejilerinin geliştirilmesinde önemlidir.

KAYNAKLAR

1. World Health Organization Naming the Coronavirus Disease (COVID-19 and the Virus That Causes it. (2020). Available online at: [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(COVID-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(COVID-2019)-and-the-virus-that-causes-it) (accessed March 14, 2020).
2. WHO Director-General’s opening remarks at the media briefing on COVID19 -March 2020
3. Lu R, Zhao X, Li J et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020 Feb 22;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8. Epub 2020 Jan 30. PMID: 32007145; PMCID: PMC7159086.
4. Liu DX, Liang JQ, Fung TS. Human Coronavirus-229E, -OC43, -NL63, and -HKU1. *Reference Module in Life Sciences*. 2020;B978-0-12-809633-8.21501-X. doi: 10.1016/B978-0-12-809633-8.21501-X. Epub 2020 May 7. PMCID: PMC7204879.
5. Ceraolo C, Giorgi FM. Genomic variance of the 2019-nCoV coronavirus. *J Med Virol*. 2020 May;92(5):522-528. doi: 10.1002/jmv.25700. Epub 2020 Feb 19. PMID: 32027036; PMCID: PMC7166773.
6. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. *J Microbiol Immunol Infect*. 2020 Mar 31. doi: 10.1016/j.jmii.2020.03.022. Epub ahead of print. PMID: 32265180; PMCID: PMC7138183.
7. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Front Immunol*. 2020 Jun 16;11:1441. doi: 10.3389/fimmu.2020.01441. PMID: 32612615; PMCID: PMC7308593.
8. Gregersen PK, Olsson LM. Recent advances in the genetics of autoimmune disease. *Annu Rev Immunol*. 2009;27:363-91. doi: 10.1146/annurev.immunol.021908.132653. PMID: 19302045; PMCID: PMC2992886.
9. Matusiak, M., Schürch, C.M. Expression of SARS-CoV-2 entry receptors in the respiratory tract of healthy individuals, smokers and asthmatics. *Respir Res* 21, 252 (2020). <https://doi.org/10.1186/s12931-020-01441-1>

- org/10.1186/s12931-020-01521-x
10. <https://www.biocompare.com/Editorial-Articles/563489-SARS-CoV-2-Molecular-Targets/>
 11. Gemmati D, Bramanti B, Serino ML et al., COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? *Int J Mol Sci.* 2020 May 14;21(10):3474. doi: 10.3390/ijms21103474. PMID: 32423094; PMCID: PMC7278991.
 12. Gheblawi M, Wang K, Viveiros A et al., Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res.* 2020 May 8;126(10):1456-1474. doi: 10.1161/CIRCRESA-HA.120.317015. Epub 2020 Apr 8. PMID: 32264791; PMCID: PMC7188049.
 13. Yan R, Zhang Y, Li Y et al., Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science.* 27 March 2020; 367 (6485): 1444-1448. doi: 10.1126 / science. abb2762. PMID: 32132184; PMCID: PMC7164635.
 14. Li W, Zhang C, Sui Jet al., Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. *EMBO J.* 2005 Apr 20; 24(8):1634-43.
 15. Shi Y, Wang Y, Shao C et al., COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* 2020 May; 27(5):1451-1454.
 16. <https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2>
 17. Hou, Y., Zhao, J., Martin, W. et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. *BMC Med* 18, 216 (2020). <https://doi.org/10.1186/s12916-020-01673-z>
 18. Jia Y., Shen G., Zhang Y. et al., Analysis of the mutation dynamics of SARS-CoV-2 reveals the spread history and emergence of RBD mutant with lower ACE2 binding affinity. *bioRxiv* 2020.04.09.034942; doi: <https://doi.org/10.1101/2020.04.09.034942>
 19. Ou J., Zhou Z., Dai R. Et al., Emergence of RBD mutations in circulating SARS-CoV-2 strains enhancing the structural stability and human ACE2 receptor affinity of the spike protein. *bioRxiv* 2020.03.15.991844; doi: <https://doi.org/10.1101/2020.03.15.991844>
 20. Lyon MF. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature.* 1961; 190:372–3. 10.1038/190372a0
 21. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature.* 2005; 434:400–4. 10.1038/nature03479
 22. Tukiainen T, Villani AC, Yen A. Et al., Landscape of X chromosome inactivation across human tissues. *Nature.* 2017; 550:244–48. 10.1038/nature24265
 23. Asselta R, Paraboschi EM, Mantovani A. Et al., ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. *Aging (Albany NY).* 2020 Jun 5;12(11):10087-10098. doi: 10.18632/aging.103415. Epub 2020 Jun 5. PMID: 32501810; PMCID: PMC7346072.
 24. Clinckemalie L, Spans L, Dubois ., et al., Androgen regulation of the TMPRSS2 gene and the effect of a SNP in an androgen response element. *Mol Endocrinol.* 2013 Dec;27(12):2028-40. doi: 10.1210/me.2013-1098. Epub 2013 Oct 9. PMID: 24109594; PMCID: PMC5426606.
 25. Van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA.* 2020;324(7):663–673. doi:10.1001/jama.2020.13719
 26. Azkur AK, Akdis M, Azkur D. et al., Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy.* 2020 Jul;75(7):1564-1581. doi: 10.1111/all.14364. PMID: 32396996; PMCID: PMC7272948.
 27. Severe COVID-19 GWAS Group, Ellinghaus D, Degenhardt F, et al., Genomewide Association Study of Severe COVID-19 with Respiratory Failure. *N Engl J Med.* 2020 Oct 15;383(16):1522-1534. doi: 10.1056/NEJMoa2020283. Epub 2020 Jun 17. PMID: 32558485; PMCID: PMC7315890.
 28. Chu H, Chan JE, Wang Y. et al., Comparative Replication and Immune Activation Profiles of

- SARS-CoV-2 and SARS-CoV in Human Lungs: An Ex Vivo Study With Implications for the Pathogenesis of COVID-19. *Clin Infect Dis*. 2020 Sep 12;71(6):1400-1409. doi: 10.1093/cid/ciaa410. PMID: 32270184; PMCID: PMC7184390.
29. Blanco-Melo D, Nilsson-Payant BE, Liu WC. et al., Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell*. 2020 May 28;181(5):1036-1045.e9. doi: 10.1016/j.cell.2020.04.026. Epub 2020 May 15. PMID: 32416070; PMCID: PMC7227586.
 30. Zhang Q, Bastard P, Liu Z, et al., Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020 Oct 23;370(6515):eabd4570. doi: 10.1126/science.abd4570. Epub 2020 Sep 24. PMID: 32972995.
 31. Gao T, Hu M, Zhang X., et al., Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. *medRxiv* 2020.03.29.20041962; doi: <https://doi.org/10.1101/2020.03.29.20041962>
 32. Grant WB, Lahore H, McDonnell SL, et al., Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*. 2020 Apr 2;12(4):988. doi: 10.3390/nu12040988. PMID: 32252338; PMCID: PMC7231123.
 33. Trindade GG, Caxito SMC, Xavier AREO, et al., COVID-19: therapeutic approaches description and discussion. *An Acad Bras Cienc*. 2020 Jun 15;92(2):e20200466. doi: 10.1590/0001-3765202020200466. PMID: 32556054.
 34. Patra R, Chandra Das N, Mukherjee S. Targeting human TLRs to combat COVID-19: A solution? *J Med Virol*. 2020 Aug 4:10.1002/jmv.26387. doi: 10.1002/jmv.26387. Epub ahead of print. PMID: 32749702; PMCID: PMC7436140.
 35. Poulas K, Farsalinos K, Zanidis C. Activation of TLR7 and Innate Immunity as an Efficient Method Against COVID-19 Pandemic: Imiquimod as a Potential Therapy. *Front Immunol*. 2020 Jun 11;11:1373. doi: 10.3389/fimmu.2020.01373. PMID: 32612613; PMCID: PMC7307572.