

Bölüm

3

Hipertansiyon ve Gen Polimorfizmleri

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GİRİŞ

Tüm dünyada ve ülkemizde, beklenen yaşam süresinin uzaması ve sağıksız yaşam şartlarının artması ile birlikte kronik hastalıklarda da artış olduğu gözlelmektedir. Yaşlı nüfusun artışı, kronik hastalık görme sikliğinin artmasını da beraberinde getirmektedir. Artan kronik hastalıklar morbidite ve mortalite açısından önem arz etmektedir⁽¹⁾.

Hipertansiyon kronik bir hastalık olup, tekrarlanan ölçümlerde arteriyel kan basincının 140/90 mmHg'den daha yüksek olması olarak tanımlanan, ciddi komplikasyonlara neden olması ve toplumda sık olarak görülmesi sebebiyle önemli bir sağlık sorunudur⁽²⁾.

Dünya çapında 1 milyardan fazla kişiyi etkileyen hipertansiyonun tedavi edilmediği müddetçe, inme, koroner arter hastalığı, periferik arter hastalığı, kalp yetmezliğine sebep olduğu ve ölüm oranını artttığı ortaya konmuştur. Hipertansiyon, hem genetik hem de çevresel faktörleri içeren bir hastalık olduğundan, bu hastalığa dahil olan genetik ve çevresel faktörleri anlamak birçok ciddi durumu ve ölümü önlemeye yardımcı olabilir⁽³⁾.

Renin Anjiyotensin Aldosteron Sistemi, vücutun sodyum dengesi ve kan basincını düzenlemeye yönelik en güçlü sistemlerinden biridir⁽⁴⁾. Renin Anjiyotensin Aldosteron Sistemi'nin farklı genlerinin genotipik varyasyonları hipertansiyona yatkınlıkla ilişkilendirilmiştir. Buna göre, hipertansiyonun patogenezini ve ilgili komplikasyonlarını anlamak için Renin Anjiyotensin Aldosteron Sistemi'nin farklı bileşenleri ve yolları ile fizyolojik ve genetik yönlerinin derinlemesine kavranması gereklidir^(5, 6).

Hipertansiyonla ilgili genetik varyasyonların bilinmesi, hastalığın patofizyolojisini daha iyi anlaşılması ve yeni ortaya çıkan tedavi yöntemlerinin tasarımasına rehberlik etmesi açısından büyük önem taşımaktadır^(7, 8).

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KAYNAKÇA

1. Erkoç, Y., Yardım, N. (2011). Türkiye'de Bulaşıcı Olmayan Hastalıklar ve Risk Faktörleri ile Mücadele Politikaları. Ankara: Anıl Matbaası.
2. TEMD Obezite, Lipid Metabolizması ve Hipertansiyon Çalışma Grubu. (2018). *Hipertansiyon Tanı ve Tedavi Kılavuzu*. (1. Baskı). Ankara: Miki Matbaacılık.
3. Lin., H., J., Guo, X., Rotter, J., I. (2020). The Genetics of Blood Pressure Regulation. Reed E. Pyeritz (Ed.), *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics*. (pp.197-208). Academic Press.
4. Hall, M. E., Hall J. E. (2018). Section II. Pathophysiology Pathogenesis of Hypertension. *Hypertension: A Companion to Braunwald's Heart Disease* (Third Edition., 33-51).
5. El Shamieh S, Visvikis-Siest S. (2012). Genetic Biomarkers of Hypertension and Future Challenges Integrating Epigenomics. J. Delanghe, A.H. Wu (Eds). *Clinica Chimica Acta* (pp.259–265).
6. Ghafar, M. T. A. (2020). An overview of the classical and tissue-derived renin-angiotensin aldosterone system and its genetic polymorphisms in essential hypertension. *Steroids* (volume 163).
7. Antonarakis, S.E., Cooper, D. N. (2019). Human Genomic Variants and Inherited Disease: Molecular Mechanisms and Clinical Consequences. Reed E. Pyeritz, Wayne W. Grody, Bruce R. Korf (Eds.), *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics* (pp.125-200). Academic Press.
8. Kearney, P.M., Whelton, M., Reynolds, K. Worldwide prevalence of hypertension: a systematic review. *Journal of Hypertension*, 2004; 22 (1), 11-9. doi: 10.1097/00004872-200401000-00003.
9. Kumar P, Song Z. H. (2017). Chapter 61. Polymorphisms of the CB2 Cannabinoid Receptor. V.R. Preedy (Ed). *Andbook of Cannabis and Related Pathologies*. (pp.584-591). Academic Press.
10. Sukhumsirichart W. (2018). Polymorphisms. Yamin Liu (Ed). *Genetic Diversity and Disease Susceptibility* (pp. 1-22).
11. Matsuda K. (2017). PCR-Based Detection Methods for Single-Nucleotide Polymorphism or Mutation: Real-Time PCR and Its Substantial Contribution Toward Technological Refinement. Gregory S. Makowski (Ed.), *Advances in Clinical Chemistry* (pp. 45-72).
12. Rieder, M. J, Taylor, S. L, Clark, A. G. Sequence variation in the human angiotensin converting enzyme. *Nature Genetics*, 1999; 22, 59-62.
13. 1000 Genomes Project Consortium et al. A map of human genome variation from population-scale sequencing. *Nature*, 2010; 467 (7319), 1061–1073. doi:10.1038/nature09534.
14. Butler JM. (2012). Single Nucleotide Polymorphisms and Applications. Butler JM (Ed.), *Advanced Topics in Forensic DNA Typing: Methodology* (pp.347-369). Academic Press.
15. Rossi, G. P, Ceolotto, G, Caroccia, B. Genetic screening in arterial hypertension. *Nature Reviews Endocrinology*, 2017; 13 (5), 289-298. DOI: 10.1016/B978-0-12-374513-2.00012-9.
16. BMJ Best Practise Essential hypertension. (2018) <https://bestpractice.bmj.com/topics/en-gb/26/>; (accessed 10.09.18).
17. Pazoki, R, Dehghan, A, Evangelou, E. Genetic predisposition to high blood pressure and lifestyle factors. *Circulation*, 2018; 137 (7), 653-661.
18. Oparil, S, Acelajado, M. C, Bakris, G.L. Hypertension. *Nature reviews disease primers*, 2018; 2 (4), 18014.
19. Hottenga, J. J, Boomsma, D. I, Kupper, N. Heritability and stability of resting blood pressure. *Twin Res Hum Genet*, 2005; 8 (5), 499-508.
20. Kouremenos, N, Zacharopoulou, I. V, Triantafyllidi, H., Genes and genetic variations involved in the development of hypertension: Focusing on a Greek patient cohort. *Hellenic Journal of Cardiology*, 2014; 55 (1), (9–16).
21. Luft, F, C. (2004). Geneticism of essential hypertension. *Hypertension* (pp. 1155-1159).
22. Alejandro, M. A, Carlos, F. Genetics of hypertensive syndrome. *Hormone Research*, 2009; 71, 253-259.
23. Harrap, S. B. (2003). Where are all the blood-pressure genes? *Lancet* (361: pp. 2149-2151).

24. Dilek, M, Arik, N. Primer Hipertansiyon Patogenezi. *Türkiye Klinikleri J Nephrol-Special Topics*, 2017; 10 (1), 1-7.
25. O'Shaughnessy, K. M. The genetics of essential hypertension. *J Br Clin Pharmacol*, 2001; 51 (1), 5-11.
26. Cui, J, Hopper, J. L, Harrap, S. B. Genes and family environment explain correlations between blood pressure and body mass index. *Hypertension*. 2002; 40, 7-12.
27. Feinleib, M, Garrison, R. J, Fabsitz, R. The NHLBI twin study of cardiovascular disease risk factors: methodology and summary of results. *Am J Epidemiol*. 1977; 106, 284-285.
28. Rapp, J.P. (2000). Genetic analysis of inherited hypertension in the rat. *Physiol Rev* (pp. 135-172).
29. Levy, D, DeStefano, A. L, Larson, M.G. Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham heart study. *Hypertension*, 2000; 36, 477-483.
30. Samani N.J. Genome scans for hypertension and blood pressure regulation. *J Am Hypertens* 2003; 16, 167-171.
31. Kwon, J. M, Goate, A. M. The candidate gene approach. *Alcohol Research & Health*. 2000; 24 (3), 164 -168.
32. Zhu, M, Zhao, S. Candidate Gene Identification Approach: Progress and Challenges. *Int J Biol Sci*, 2007; 3 (7), 420-427.
33. Frossard, P. M, Obineche, E. N, Lestringant, G. G. Association of an apolipoprotein B gene marker with essential hypertension. *Hypertension* 1999; 33, 1052-1056.
34. Oparil, S, Zaman, M. A, Calhoun, D. A. Pathogenesis of hypertension. *Ann Intern Med*, 2003; 139, 761-776.
35. Ndiaye, N. C, Azimi, N. M, El Shamieh, S, Stathopoulou MG, Visvikis-Siest S. Cardiovascular diseases and genome-wide association studies. *Clinica Chimica Acta*, 2011; 412, 1697-701.
36. Sayed-Tabatabaei, F. A, Oostra, B. A, Isaacs, A. ACE polymorphisms. *Witteman Circ Res*, 2006; 98, 1123-1133.
37. Jalil, J. E, Córdova, S, Ocaranza, M, Angiotensin I-converting enzyme insertion/deletion polymorphism and adrenergic response to exercise in hypertensive patients. *Med Sci Monit*, 2002; 8, 566-571.
38. Higaki, J, Baba, S, Katsuya, T. Deletion allele of Angiotensin-Converting Enzyme gene increases risk of essential hypertension in Japanese men: The SUITA study. *Circulation*, 2000; 101, 2060-2065.
39. Di Pasquale, P, Cannizzaro, S, Paterna, S. Does ACE gene polymorphism affect blood pressure? Findings after 6 years follow of healthy subjects. *Eur J Heart Fail*, 2004; 6, 11-16.
40. Özdemir, Ş.Ö. Çocukluk Çağı Primer Hipertansiyon Patogenezinde Renin, Aldosteron, Angiotensin Ve Lipid Metabolizma Genlerinin Araştırılması ve Genotip-Fenotip İlişkisi. İzmir: Ege Üniversitesi, Tıp Fakültesi, Tıpta Uzmanlık Tezi, 2016.
41. Padma, G, Charita, B, Swapna, N, Mamata, M, & Padma, T. (2014). Novel variants detected in AGT gene among patients with essential hypertension. *J Renin Angiotensin Aldosterone Syst*. 2015 ;16 (3), 642-646. doi:10.1177/1470320313513483.
42. Jeunemaitre, X, Inoue, I, Williams, C. Haplotypes of angiotensinogen in essential hypertension. *Am J Hum Genet*, 1997; 60, 1448-1460.
43. Gopi Chand, M, Srinath, J, Rao, R. S, Lakkakula, B. V, Kumar, S, Rao, V. R. Association between the M268T polymorphism in the angiotensinogen gene and essential hypertension in a South Indian population. (2011). *Biochem. Genet.* (49), 474-482.
44. Fang, Y. J, Deng, H. B, Thomas, G. N. Linkage of angiotensinogen gene polymorphisms with hypertension in a sibling study of Hong Kong Chinese. *J. Hypertens*, 2010 (28), 1203-1209.
45. Heidari, F, Vasudevan, R, Mohd Ali S. Z. RAS Genetic Variants in Interaction with ACE Inhibitors Drugs Influences Essential Hypertension Control. *Arch Med Re*,. 2017; 48 (1), 88-95.

46. Mohana, V. U, Swapna, N, Surender, R. S. Gender-related association of AGT gene variants (M235T and T174M) with essential hypertension--a case-control study. *Clin. Exp. Hypertens.*, 2012; 34 (1), 38–44.
47. Pereira, T. V, Nunes A. C, Rudnicki, M. Meta-analysis of the association of 4 angiotensinogen polymorphisms with essential hypertension: a role beyond M235T? *Hypertensio.*, 2008; 51 (3), 778-783.
48. Barley, J, Blackwood, A, Sagnella, G. Angiotensinogen Met235-->Thr polymorphism in a London normotensive and hypertensive black and white population. *J. Hum. Hypertens.*, 1994; 8 (8), 639–640.
49. Ying, C. Q, Wang, Y. H, Wu, Z. L. Association of the Renin Gene Polymorphism, Three Angiotensinogen Gene Polymorphisms and the Haplotypes with Essential Hypertension in the Mongolian Population. *Clinical and Experimental Hypertension*, 2010; 32 (5), 293–300.
50. Ong, F. S, Bernstein, K. E, Rotter J. I. (2013). The Genetics of Blood Pressure Regulation. *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics* (p:1-22).
51. Bonnardeaux, A, Davies, E, Jeunemaitre, X. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. *Hypertension*, 1994; 24, 63-69.
52. Wang, W., Y., S, Zee, R., Y., L, Morris, B., J. Association of angiotensin II type I receptor gene polymorphism with esentiel hypertension. *Clin Genet*, 1997; 51, 31–34.
53. Zhang, X., Erdmann, J., Regitz-Zagrosek, V. Evaluation of three polymorphisms in the promoter region of the angiotensin II type I receptor gene. *J Hypertens.*, 2000; 18, 267–272.
54. Jiang, Z., Zhao, W., Yu, F. Association of angiotensin II type 1 receptor gene polymorphism with essential hypertension. *Chin Med J* 2001; 114, 1249-1251.
55. Wang, J., G., Staessen, J., A. Genetic polymorphisms in the renin-angiotensin system: relevance for susceptibility to cardiovascular disease. *Eur J Pharmacol*, 2000; 410, 289-302.
56. Amrani-Midoun, A., Kiando, S., R., Treard, C. Genetic association study between T-786C NOS3 polymorphism and essential hypertension in an Algerian population of the Oran city. *Diabetes Metab Syndr.*, 2019; 13 (2), 1317-1320.
57. Markus, H., S., Ruigrok, Y., Ali, N. Endothelial nitric oxide synthase exon 7 polymorphism, ischemic cerebrovascular disease, and carotid atheroma. *Stroke*, 1998; 29, 1908–1911.
58. Sladowska-Kozłowska, J., Litwin, M., Niemirska, A. Associations of the eNOS G894T gene polymorphism with target organ damage in children with newly diagnosed primary hypertension. *Pediatr Nephrol*. 2015; 30 (12), 2189-2197.
59. Li, J., Cun, Y., Tang, W., R. Association of eNOS gene polymorphisms with essential hypertension in the Han population in southwestern China. *Genet Mol Res*, 2011; 10 (3), 2202-2212.
60. Sun, H., Yang, Z. Q., Liu, S. Y. Correlation between natriuretic peptide receptor C (NPR3) gene polymorphisms and hypertension in the Dai people of China. *Genetics and molecular research*, 2015; 14 (3), 8786-8795