Bölüm
13

# KOLOREKTAL KANSER GENETİĞİ, SPESİFİK GENLER VE MUTASYONLAR

**Osman CİVİL**[1]

## GİRİŞ

Kolorektal kanser (KRK) dünya genelinde olduğu gibi ülkemizde de kadın ve erkeklerde 3. en sık kanser türüdür [(1)]. Bu kanser türünün gelişmesinde çevresel ve kalıtsal faktörler önemli rol oynar. Ortaya çıkış şekli açısından sporadik, kalıtsal ya da familyal paternde olabilmektedir. Sporadik patern tüm KRK olgularının %70'ini oluşturmaktadır. Hiçbir aile hikayesi olmayan genellikle 50 yaş üzeri kişilerde çevresel ve beslenme faktörlerine bağlı olarak gelişir. Kalıtsal patern KRK olgularının %10'undan az bir kısmını oluşturur. Bu grup hastalar kanserin gelişiminin polip zemininde olup olmamasına göre sınıflandırılır. Polipozis zemininde gelişen hastalıklar familyal adenomatöz polipozis (FAP), MUTYH ilişkili polipozis (MAP), hamartomatöz polipozis sendromları (Peutz-Jeghers, Jüvenil Polipozis, PTEN Hamartom Tümör Sendromu) olarak adlandırılırken, polipozis zemininde gelişmeyen hastalıklar ise herediter non-polipozis kolorektal kanser (HNPCC; Lynch Sendromu) olarak adlandırılır. Familyal patern ise en az anlaşılan grup olup olguların %25'e yakın kısmından sorumludur. Bu gruptaki hastaların ailesinde KRK hikayesi olmasına rağmen herediter paternin özelliklerini taşımamaktadır [(2)]. Kalıtsal paternde spesifik mutasyonlar ile hastalık başlıyorken, sporadik olgularda somatik mutasyonların birikimi söz konusudur. Bir başka deyişle, sporadik olgularda genetik mutasyonlar sadece tümör dokusunda bulunurken kalıtsal olgularda bireyin tüm hücrelerinde mutasyon bulunur [(2)]. Familyal olgularda ise genetik anomaliler tam olarak anlaşılamamıştır [(2)].

Bu bölümde özellikle sporadik KRK olgularının moleküler genetik özelliklerine yer verilecektir.

[1] Genel Cerrahi Uzmanı, Medipol Üniversitesi Nisa Hastanesi, dr.ocivil@hotmail.com

Genel popülasyonda gelişen kolorektal kanserlere kıyasla MAP zemininde gelişenlerde prognoz daha iyi olabilir [66]. Retrospektif Avrupa kohort çalışmasında 147 MAP ilişkili kolorektal kanser olgusunun 272 eşleştirilmiş kontrol hastasına kıyasla yaş, evre, cinsiyet, tümör yerleşimi, ülke ve tanı yaşının dahil edildiği çok değişkenli analizde dahi anlamlı şekilde daha iyi sağkalıma sahip olduğu görülmüştür.

## KOLOREKTAL KANSERLERLE İLİŞKİLİ YENİ GENLER

### CHEK2 Mutasyonu

Hücre siklusu kontrol noktası kinaz 2 (cell cycle checkpoint kinase 2- CHEK2) geni germ hattı mutasyonu artmış meme ve KRK ile ilişkili bulunmuştur. Popülasyon tabanlı bir çalışmada 1934 kolon kanseri olgusunun 533'ünde CHEK2 mutasyonu saptanmıştır. Bu olguların ailesinde de kolon kanseri riskinin yüksek olduğu görülmüştür [67].

### GREM1 Mutasyonu

Gremlin 1 geni (GREM1) mutasyonu sonucu otozomal dominant kalıtılan herediter mixed polipozis sendromu gelişir. Bu sendrom Aşkenazi Yahudilerinde görülür ve adölesan dönemde başlayan çok sayıda kolorektal polip ve ekstrakolonik tümörlerle karakterizedir [68,69].

Bu mutasyonlara ek olarak AXIN2 mutasyonu, NTHL1 mutasyonu, POLD1 ve POLE mutasyonları da düşük oranlarda KRK ile ilişkili bulunmuştur [70].

## KAYNAKÇA


1. Türkiye Kanser İstatikleri (2015) 25.12.2019 tarihinde https://hsgm.saglik.gov.tr/depo/birimler/kanser- db/istatistik/Turkiye_Kanser_Istatistikleri_2015.pdf adresinden erişim sağlanmıştır
2. Frucht H, Lucas AL. Molecular genetics of colorectal cancer. Savarese DMF, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (02 Ocak 2020 tarihinde erişim sağlanmıştır)
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61:759.
4. Sherr CJ. Cancer cell cycles. Science 1996; 274:1672.
5. Cancer Genetics and Cancer Predisposition Testing. In: American Society of Clinical Oncology Curriculum, American Society of Clinical Oncology (Ed), Alexandria, VA 1998.
6. Takayama T, Ohi M, Hayashi T, et al. Analysis of K-ras, APC, and beta-catenin in aberrant crypt foci in sporadic adenoma, cancer, and familial adenomatous polyposis. Gastroenterology 2001; 121:599.
7. Shibata D, Schaeffer J, Li ZH, et al. Genetic heterogeneity of the c-K-ras locus in colorectal adenomas but not in adenocarcinomas. J Natl Cancer Inst 1993; 85:1058.
8. Tortola S, Marcuello E, González I, et al. p53 and K-ras gene mutations correlate with tumor aggressiveness but are not of routine prognostic value in colorectal cancer. J Clin Oncol 1999; 17:1375.

9. Bourne HR, Sanders DA, McCormick F. The GTPase superfamily: conserved structure and molecular mechanism. Nature 1991; 349:117.
10. Frattini M, Balestra D, Suardi S, et al. Different genetic features associated with colon and rectal carcinogenesis. Clin Cancer Res 2004; 10:4015.
11. Harada K, Hiraoka S, Kato J, et al. Genetic and epigenetic alterations of Ras signalling pathway in colorectal neoplasia: analysis based on tumour clinicopathological features. Br J Cancer 2007; 97:1425.
12. Giehl K. Oncogenic Ras in tumour progression and metastasis. Biol Chem 2005; 386:193.
13. Miranda E, Destro A, Malesci A, et al. Genetic and epigenetic changes in primary metastatic and nonmetastatic colorectal cancer. Br J Cancer 2006; 95:1101.
14. Tsang AH, Cheng KH, et al. Current and future molecular diagnostics in colorectal cancer and colorectal adenoma. World J Gastroenterol. 2014 Apr 14;20(14):3847-57. doi: 10.3748/wjg.v20.i14.3847.
15. Fransén K, Klintenäs M, Osterström A, et al. Mutation analysis of the BRAF, ARAF and Tsang AHF et al. Molecular diagnostics in colorectal cancer WJG|www.wjgnet.com 3856 April 14, 2014|Volume 20|Issue 14| RAF-1 genes in human colorectal adenocarcinomas. *Carcinogenesis* 2004; 25: 527-533
16. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 5705-5712. DOI:10.1200/jco.2008.18.0786
17. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 1971;68:820.
18. Knudson AG Jr. Hereditary cancer, oncogenes, and antioncogenes. Cancer Res 1985; 45:1437.
19. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988; 319:525.
20. Vogelstein B, Fearon ER, Kern SE, et al. Allelotype of colorectal carcinomas. Science 1989; 244:207.
21. Mahmoud NN, Bleier JIS, Aarons CB, Paulson EC, Shanmugan S, Fry RD (2017) . Colon and Rectum. Courtney M. Townsend JR., R. Daniel Beauchamp, B. Mark Evers, Kenneth L. Mattox (Ed.) Sabiston Textbook of Surgery (1360) Philadelphia, PA : Elsevier Saunders.
22. Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 1997; 17:79.
23. Drucker L, Shpilberg O, Neumann A, et al. Adenomatous polyposis coli I1307K mutation in Jewish patients with different ethnicity: prevalence and phenotype. Cancer 2000; 88:755.
24. Kirsch DG, Kastan MB. Tumor-suppressor p53: implications for tumor development and prognosis. J Clin Oncol 1998; 16:3158.
25. Russo A, Bazan V, Iacopetta B, et al. The TP53 colorectal cancer international collaborative study on the prognostic and predictive significance of p53 mutation: influence of tumor site, type of mutation, and adjuvant treatment. J Clin Oncol 2005; 23:7518.
26. Kastan MB, Onyekwere O, Sidransky D, et al. Participation of p53 protein in the cellular response to DNA damage. Cancer Res 1991; 51:6304.
27. Kuerbitz SJ, Plunkett BS, Walsh WV, et al. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. Proc Natl Acad Sci U S A 1992; 89:7491.
28. Woods DB, Vousden KH. Regulation of p53 function. Exp Cell Res 2001; 264:56.
29. Lane DP. Cancer. p53, guardian of the genome. Nature 1992; 358:15.
30. Yurgelun MB, Masciari S, Joshi VA, et al. Germline TP53 Mutations in Patients With Early-Onset Colorectal Cancer in the Colon Cancer Family Registry. JAMA Oncol 2015; 1:214.
31. Watanabe T, Sullenger BA. Induction of wild-type p53 activity in human cancer cells by ribozymes that repair mutant p53 transcripts. Proc Natl Acad Sci U S A 2000; 97:8490.
32. Hamid O, Varterasian ML, Wadler S, et al. Phase II trial of intravenous CI-1042 in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21:1498.

33. Warren RS, Kirn DH. Liver-directed viral therapy for cancer p53-targeted adenoviruses and beyond. Surg Oncol Clin N Am 2002; 11:571.
34. Raj K, Ogston P, Beard P. Virus-mediated killing of cells that lack p53 activity. Nature 2001; 412:914.
35. Fearon ER, Cho KR, Nigro JM, et al. Identification of a chromosome 18q gene that is altered in colorectal cancers. Science 1990; 247:49.
36. Hedrick L, Cho KR, Fearon ER, et al. The DCC gene product in cellular differentiation and colorectal tumorigenesis. Genes Dev 1994; 8:1174.
37. Chan SS, Zheng H, Su MW, et al. UNC-40, a C. elegans homolog of DCC (Deleted in Colorectal Cancer), is required in motile cells responding to UNC-6 netrin cues. Cell 1996; 87:187.
38. Thiagalingam S, Lengauer C, Leach FS, et al. Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. Nat Genet 1996; 13:343.
39. Cho KR, Oliner JD, Simons JW, et al. The DCC gene: structural analysis and mutations in colorectalcarcinomas. Genomics 1994; 19:525.
40. Popat S, Houlston RS. A systematic review and meta-analysis of the relationship between chromosome 18q genotype, DCC status and colorectal cancer prognosis. Eur J Cancer 2005; 41:2060.
41. Sun XF, Rütten S, Zhang H, Nordenskjöld B. Expression of the deleted in colorectal cancer gene is related to prognosis in DNA diploid and low proliferative colorectal adenocarcinoma. J Clin Oncol 1999;17:1745.
42. Goyette MC, Cho K, Fasching CL, et al. Progression of colorectal cancer is associated with multiple tumor suppressor gene defects but inhibition of tumorigenicity is accomplished by correction of any single defect via chromosome transfer. Mol Cell Biol 1992; 12:1387.
43. Reiss M, Santoro V, de Jonge RR, et al. Transfer of chromosome 18 into human head and neck squamous carcinoma cells: evidence for tumor suppression by Smad4/DPC4. Cell Growth Differ 1997;8:407.
44. MacGrogan D, Pegram M, Slamon D, et al. Comparative mutational analysis of DPC4 (Smad4) in prostatic and colorectal carcinomas. Oncogene 1997; 15:1111.
45. Riggins GJ, Thiagalingam S, Rozenblum E, et al. Mad-related genes in the human. Nat Genet 1996;13:347.
46. Eppert K, Scherer SW, Ozcelik H, et al. MADR2 maps to 18q21 and encodes a TGFbeta-regulated MADrelated protein that is functionally mutated in colorectal carcinoma. Cell 1996; 86:543.
47. Xie W, Rimm DL, Lin Y, et al. Loss of Smad signaling in human colorectal cancer is associated with advanced disease and poor prognosis. Cancer J 2003; 9:302.
48. Moynahan ME, Chiu JW, Koller BH, et al. Brca1 controls homology-directed DNA repair. Mol Cell 1999; 4:511.
49. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell 2001; 7:263.
50. Phelan CM, Iqbal J, Lynch HT, et al. Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: results from a follow-up study. Br J Cancer 2014; 110:530.
51. Oh M, McBride A, Yun S, et al. BRCA1 and BRCA2 Gene Mutations and Colorectal Cancer Risk: Systematic Review and Meta-analysis. J Natl Cancer Inst 2018; 110:1178.
52. Chung DC, Rustgi AK. DNA mismatch repair and cancer. Gastroenterology 1995; 109:1685.
53. Papadopoulos N, Nicolaides NC, Liu B, et al. Mutations of GTBP in genetically unstable cells. Science 1995; 268:1915.
54. Baker SM, Bronner CE, Zhang L, et al. Male mice defective in the DNA mismatch repair gene PMS2 exhibit abnormal chromosome synapsis in meiosis. Cell 1995; 82:309.
55. Papadopoulos N, Nicolaides NC, Wei YF, et al. Mutation of a mutL homolog in hereditary colon cancer. Science 1994; 263:1625.
56. Al-Sohaily S, Biankin A, Leong R, et al. Molecular pathways in colorectal cancer. *J Gastroenterol Hepatol* 2012; 27: 1423-1431 [PMID: 22694276 DOI: 10.1111/j.1440-1746.2012.07200.x]

57. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003; 348:791.
58. Sampson JR, Dolwani S, Jones S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet 2003; 362:39.
59. Wang L, Baudhuin LM, Boardman LA, et al. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. Gastroenterology 2004; 127:9.
60. Ricciardiello L, Goel A, Mantovani V, et al. Frequent loss of hMLH1 by promoter hypermethylation leads to microsatellite instability in adenomatous polyps of patients with a single first-degree member affected by colon cancer. Cancer Res 2003; 63:787.
61. Croitoru ME, Cleary SP, Di Nicola N, et al. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J Natl Cancer Inst 2004; 96:1631.
62. Enholm S, Hienonen T, Suomalainen A, et al. Proportion and phenotype of MYH-associated colorectal neoplasia in a population-based series of Finnish colorectal cancer patients. Am J Pathol 2003; 163:827.
63. Kambara T, Whitehall VL, Spring KJ, et al. Role of inherited defects of MYH in the development of sporadic colorectal cancer. Genes Chromosomes Cancer 2004; 40:1.
64. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet 2002; 30:227.
65. Mahmoud NN, Bleier JIS, Aarons CB, Paulson EC, Shanmugan S, Fry RD (2017) . Colon and Rectum. Courtney M. Townsend JR., R. Daniel Beauchamp, B. Mark Evers, Kenneth L. Mattox (Ed.) Sabiston Textbook of Surgery (1362) Philadelphia, PA : Elsevier Saunders.
66. Nielsen M, van Steenbergen LN, Jones N, et al. Survival of MUTYH-associated polyposis patients with colorectal cancer and matched control colorectal cancer patients. J Natl Cancer Inst 2010; 102:1724.
67. Gronwald J, Cybulski C, Piesiak W, et al. Cancer risks in first-degree relatives of CHEK2 mutation carriers: effects of mutation type and cancer site in proband. Br J Cancer 2009;100:1508–1512.
68. Jaeger E, Leedham S, Lewis A, et al. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Nat Genet 2012;44:699–703.
69. Lieberman S, Walsh T, Schechter M, et al. Features of patients with hereditary mixed polyposis syndrome caused by duplication of GREM1 and implications for screening and surveillance. Gastroenterology 2017;152:1876–1880.e1.
70. Gupta S, Provenzale D, Regenbogen SE, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017. J Natl Compr Canc Netw. 2017 Dec;15(12):1465-1475. doi: 10.6004/jnccn.2017.0176.