

KANSER BİYOİNFORMATIĞI

36.

BÖLÜM

Gonca ALTINIŞIK İNAN ¹
Mustafa ALTAN ²

GİRİŞ

Biyoinformatik özellikle DNA, RNA gibi büyük makromoleküllerden edinilen biyolojik bilginin bilgisayar desteği ile toplanması, işlenmesi ve analiz edilmesidir. Disiplinler arası bir bilim olan biyoinformatik sayesinde elde edilen yüksek veri yükü depolanabilmekte, oluşturulan veri tabanları sayesinde kurulan bazı hipotezlerin yanıtları laboratuvar çalışmalarına gerek duymadan elde edilebilmektedir. Kullanılan biyoinformatik yöntemlerin uygunluğu ve güvenilirliği elde edilen verilerin kalitesini de belirlemektedir. Özellikle sağlık bilimlerinde önemi ortaya çıkan biyoinformatik kanser araştırmalarında da gün geçtikçe önem kazanmaktadır. Son dönemde onkolojide klinik ve translaşyonel çalışmalarla elde edilen oldukça büyük veri havuzu biyoinformatik sayesinde farklı araştırmacılar tarafından değerlendirilebilmekte, farklı hipotezler için veriler tekrar kullanılabilir.

Bu veriler sayesinde sentezlenebilecek olan proteinler, bunların alacağı şekil, hangi genetik anomaliliğin hangi kanserin etyopatogenezinde yer aldığı gibi birçok onkolojide çığır açacak veriye ulaşılabilir. Daha da önemlisi yeni nesil sekanslama tekniklerinin dünya genelinde ulaşılabilir hale gelmesi ile kişiselleştirilmiş onkolojik tedaviler ortaya çıkmaya başlayacaktır (1).

Tüm bu sayılan faydalar için elde edilen verilerin bilimsel kalitesi oldukça önemlidir ve bunda en büyük belirleyici uygun biyoinformatik yöntemlerin ve veri tabanlarının kullanılmasıdır.

1. KANSER İLİŞKİLİ VERİ TABANLARI

Kanser biyoinformatik çalışmalarında kullanılan farklı veri tabanları mevcuttur. (Tablo 1)

Bunların çoğuna çok az kısıtlama ile erişim mümkündür. Tablo 1 de örnekleri verilen genel

Tablo 1. Kanser çalışmalarında kullanılan bazı genomik veri tabanları

The Cancer Genome Atlas /TCGA (2)	TCGA konsorsiyumu tarafından elde edilen verilerin incelenebileceği veri tabanı
Cancer Cell Line Encyclopedia (CCLE)(3)	İnsan kanser modellerinin hem genetik hem de farmakolojik karakterizasyonlarının yürütüldüğü platform
Therapeutically Applicable Research to Generate Effective Treatments (TARGET) (4)	Çocukluk çağı kanserine neden olan moleküler değişikliklere odaklanan kapsamlı kaynak
International Cancer Genome Consortium (ICGC) (5)	50 farklı tümör tipine veya alt tipine bakmakla ilgilenen ve bunların genomik, transkriptomik ve epigenetik değişikliklerini kapsamlı bir şekilde tanımlayan bir konsorsiyumdur.

¹ Dr. Öğr Üyesi, Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi ABD- Ankara Şehir Hastanesi Radyasyon Onkolojisi Kliniği, goncaaltinisikin@gmail.com ORCID iD: 0000-0002-7385-3480

² Uzm. Dr., Ankara Şehir Hastanesi Tıbbi Genetik Bölümü, mustafaltan@gmail.com ORCID iD: 0000-0002-8998-3087

KAYNAKÇA

1. Singer J, Irmisch A, Ruscheweyh HJ, et al. Bioinformatics for precision oncology. *Brief Bioinform* 2019 May 21;20(3):778-788.
2. The Cancer Genome Atlas. <http://cancergenome.nih.gov>
3. Cancer Cell Line Encyclopedia (CCLE). <https://www.broadinstitute.org/software/>
4. Therapeutically applicable research to generate effective treatments. <https://ocg.cancer.gov/programs/target>
5. ICGC Cancer Genome Projects. <https://icgc.org/icgc>
6. Landi MT, Consonni D, Rotunno M, Bergen AW, Goldstein AM, Lubin JH, Goldin L, Alavanja M, Morgan G, Subar AF (2008) Environment And Genetics in Lung cancer Etiology (EAGLE) study: an integrative populationbased case-control study of lung cancer. *BMC Public Health* 8:203
7. Baker M. Structural variation: the genome's hidden architecture. *Nat Methods*. 2012; 9 (2):133-137.
8. Tuzun E, Sharp AJ, Bailey JA, et al. Fine-scale structural variation of the human genome. *Nat Genet*. 2005;37(7):727-732.
9. Human Genome Structural Variation Working Group, Eichler EE, Nickerson DA, Altshuler D, et al. Completing the map of human genetic variation. *Nature*. 2007; 447 (7141):161-165.
10. Mills RE, Walter K, Stewart C, et al. Mapping copy number variation by population-scale genome sequencing. *Nature*. 2011; 470(7332):59-65.
11. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007; 448(7153):561-566.
12. Nowell PC. The minute chromosome (Ph1) in chronic granulocytic leukemia. *Blut*. 1962; 8:65-66
13. Liu L, Li Y, Li S, et al. Comparison of nextgeneration sequencing systems. *J Biomed Biotechnol*. 2012; 25:1364.
14. Navin N, Kendall J, Troge J, et al. Tumour evolution inferred by single-cell sequencing. *Nature*. 2011; 472 (7341):90-94.
15. Sun G, Krasnitz A. CORE: cores of recurrent events. 2014. <https://cran.r-project.org/package=CORE>
16. Roychowdhury S, Iyer MK, Robinson DR, et al. Personalized oncology through integrative high-throughput sequencing: a pilot study. *Sci Transl Med*. 2011; 3:111ra121.
17. Roychowdhury S, Chinnaiyan AM. Translating cancer genomes and transcriptomes for precision oncology. *CA Cancer J Clin*. 2016; 66:75-88.
18. Meyerson M, Gabriel S, Getz G. Advances in understanding cancer genomes through second-generation sequencing. *Nat Rev Genet*. 2010; 11:685-696.
19. Wilkerson MD, Cabanski CR, Sun W, et al. Integrated RNA and DNA sequencing improves mutation detection in low purity tumors. *Nucleic Acids Res*. 2014; 42: e107.
20. Gimelbrant A, Hutchinson JN, Thompson BR, et al. Widespread monoallelic expression on human autosomes. *Science*. 2007; 318 (5853):1136-1140
21. Lee MP. Allele-specific gene expression and epigenetic modifications and their application to understanding inheritance and cancer. *Biochim Biophys Acta*. 2012; 1819(7):739-742
22. Ha G, Roth A, Lai D, et al. Integrative analysis of genome-wide loss of heterozygosity and monoallelic expression at nucleotide resolution reveals disrupted pathways in triple-negative breast cancer. *Genome Res*. 2012; 22(10):1995-2007
23. Tuch BB, Laborde RR, Xu X, et al. Tumor transcriptome sequencing reveals allelic expression imbalances associated with copy number alterations. 2010; *PLoS One* 5(2):e9317.
24. Su X, Zhang L, Zhang J, et al. PurityEst: estimating purity of human tumor samples using nextgeneration sequencing data. *Bioinformatics*. 2012; 28(17):2265-2266
25. Yoshihara K, Shahmoradgoli M, Martinez E, et al. Inferring tumour purity and stromal and immune cell admixture from expression data. *Nat Commun*. 2013; 4:2612
26. Consortium EP, Birney E, Stamatoyannopoulos JA, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature*. 2007; 447(7146):799-816.
27. Cech TR, Steitz JA. The noncoding RNA revolution-trashing old rules to forge new ones. *Cell*. 2014; 157(1):77-94.
28. Kapranov P, Cheng J, Dike S, et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. *Science*. 2007;316(5830):1484-148.
29. Ulitsky I, Bartel DP. lncRNAs: genomics, evolution, and mechanisms. *Cell*. 2013; 154 (1):26-46
30. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov*. 2011; 1(5):391-407.
31. Liu Q, Huang J, Zhou N, et al. lncRNA loc285194 is a p53-regulated tumor suppressor. *Nucleic Acids Res*. 2013; 41(9):4976-4987.
32. Zhang Z, Zhu Z, Watabe K, et al. Negative regulation of lncRNA GAS5 by miR-21. *Cell Death Differ*. 2013; 20(11):1558-1568.
33. Zhang A, Zhou N, Huang J, et al. The human long non-coding RNA-RoR is a p53 repressor in response to DNA damage. *Cell Res*. 2012;23(3):340-35
34. Huang J, Zhou N, Watabe K, et al. Long non-coding RNA UCA1 promotes breast tumor growth by suppression of p27 (Kip1). *Cell Death Dis*. 2014; 5: e1008
35. Singh R, Gupta SC, Peng WX, et al. Regulation of alternative splicing of Bcl-x by BC200 contributes to breast cancer pathogenesis. *Cell Death Dis*. 2016; 7(6): e2262.
36. Zhang Z, Zhou N, Huang J, et al. Regulation of androgen receptor splice variant AR3 by PCGEM1. *Oncotarget*. 2016; 7 (13):15481-15491.
37. Lee GL, Dobi A, Srivastava S. Prostate cancer: diagnostic performance of the PCA3 urine test. *Nat Rev Urol*. 2013; 8(3):123-124
38. Prensner JR, Iyer MK, Balbin OA, et al. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lncRNA implicated in disease progression. *Nat Biotechnol*. 2011; 29(8):742-749
39. Lennerz V, Fatho M, Gentilini C, et al. The response of autologous T cells to a human melanoma is dominated by mutated neoantigens. *Proc Natl Acad Sci U S A*. 2005; 102:16013-16018.
40. Zhou J, Dudley ME, Rosenberg SA, et al. Persistence of

- multiple tumorspecific T-cell clones is associated with complete tumor regression in a melanoma patient receiving adoptive cell transfer therapy. *J Immunother.* 2005; 28:53–62.
41. van Rooij N, van Buuren MM, Philips D, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. *J Clin Oncol.* 2013; 31:e439–e442.
 42. Rajasagi M, Shukla SA, Fritsch EF, et al. Systematic identification of personal tumorspecific neoantigens in chronic lymphocytic leukemia. *Blood.* 2014; 124:453–462.
 43. Rooney MS, Shukla SA, Wu CJ, et al. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell.* 2015; 160:48–61.
 44. Olsen LR, Campos B, Winther O, et al. Tumor antigens as proteogenomic biomarkers in invasive ductal carcinomas. *BMC Med Genet.* 2014; 15:1–10.
 45. Reuter JA, Spacek DV, Snyder MP. High-throughput sequencing technologies. *Mol Cell.* 2015; 58:586–597.
 46. Sandoval J, Esteller M. Cancer epigenomics: beyond genomics. *Curr Opin Genet Dev.* 2012; 22(1):50–55.
 47. Bibikova M, Le J, Barnes B, et al. Genome-wide DNA methylation profiling using Infinium (R) assay. *Epigenomics.* 2009; 1 (1):177–200.
 48. Parker JS, Mullins M, Cheang MCU, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol.* 2009;27:1160–1167.
 49. Murugaesu N, Wilson GA, Birkbak NJ, et al. Tracking the genomic evolution of esophageal adenocarcinoma through neoadjuvant chemotherapy. *Cancer Discov.* 2015; 5(8):821–831.
 50. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. *Cell.* 2011; 147:275–292.
 51. Bethge A, Schumacher U, Wree A, et al. Are metastases from metastases clinically relevant? Computer modelling of cancer spread in a case of hepatocellular carcinoma. *PLoS One.* 2012; 7:e35689.
 52. Brodbeck T, Nehmann N, Bethge A, et al. Perforin-dependent direct cytotoxicity in natural killer cells induces considerable knockdown of spontaneous lung metastases and computer modelling-proven tumor cell dormancy in a HT29 human colon cancer xenograft mouse model. *Mol Cancer.* 2014; 13:244.
 53. Bethge A, Schumacher U, Wedemann G. Simulation of metastatic progression using a computer model including chemotherapy and radiation therapy. *J Biomed Inform.* 2015; 57:74–87.
 54. Benzekry S, Tracz A, Mastro M, et al. Modeling spontaneous metastasis following surgery: an in vivo-in silico approach. *Cancer Res.* 2015;76:535–547.
 55. Newton PK, Mason J, Bethel K, et al. Spreaders and sponges define metastasis in lung cancer: a Markov chain mathematical model. *Cancer Res.* 2013; 73:2760–2769.
 56. Gazit Y, Baish JW, Safabakhsh N, et al. Fractal characteristics of tumor vascular architecture during tumor growth and regression, microcirculation, Informa healthcare. *Microcirculation.* 1997; 4:395–402.