Journal of Research in Pharmacy

Research Article

www.jrespharm.com

Evaluation of gene interaction and similarity in 17 different cancer pathways

Ertugrul Osman BURSALIOGLU [1,2*], Saban KALAY [3], Sefa METIN [4]

[1] Department of Medical Services and Techniques, Vocational School of Health Services, Sinop University, Sinop, Turkey
[2] Department of Nursing, Faculty of Health Science, Sakarya University, Sakarya, Turkey
[3] Division of Biochemistry, Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, University of Health Sciences, 34668 Istanbul, Türkiye
[4] Turkish Medicines and Medical Devices Agency, Republic of Türkiye Ministry of Health
* Corresponding Author. E-mail: ebursalioglu@sinop.edu.tr

Received: 28 October 2024/ Revised: 20 January 2025 / Accepted: 22 January 2025

ABSTRACT: This study investigates similarities and gene interactions in 17 different cancer types using Kyoto University's KEGG cancer pathways. Using Python software and the Google Colab platform, gene similarities and interactions within cancer pathways were calculated through Jaccard similarity indices and interaction analyses. The results reveal important genes and pathways shared between cancer types, providing insights into common molecular mechanisms underlying cancer development and progression. These findings may contribute to the identification of potential therapeutic targets by understanding the biological processes shared between cancers. In comparisons between different cancer types, gene similarities ranged between 43% and 47% and pathway similarities ranged between 25% and 46%. These results reveal that while some cancer types are genetically similar, they show differences in biochemical processes. In the gene interaction study among 17 different cancer pathways, the highest interaction rates were observed in colorectal cancer between entries '43-40' with ('activation'), in pancreatic cancer between entries '113-6' with ('activation'), and in hepatocellular carcinoma between entries '122-224' with ('activation'), showing nearly 100% interaction. On the other hand, the lowest interaction rates were found in colorectal cancer between entries '39-135' with ('missing interaction') and in melanoma between entries '95-106' with ('missing interaction'), showing 0% interaction.

KEYWORDS: Cancer pathways; Python; Jaccard similarity; gene interactions

1. INTRODUCTION

Colorectal cancer (CRC) is a prevalent malignancy, characterized by diverse genetic alterations that contribute to tumor development and progression [1]. The chromosomal instability (CIN) pathway, microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) are main molecular mechanisms driving CRC. Mutations in APC, TP53, and KRAS are frequently observed in sporadic CRC, leading to deregulated cell proliferation and tumor formation [2]. Hereditary syndromes account for a significant proportion of CRC cases, primarily due to germline mutations in mismatch repair (MMR) genes such as MLH1 and MSH2, which elevate lifetime CRC risk to nearly 80% [1,2]. Recent advances in next-generation sequencing have improved our understanding of the genetic landscape of CRC by identifying additional genetic predispositions, including mutations in POLE, POLD1 and MUTYH. This information is crucial for developing targeted therapeutic strategies and improving surveillance for at-risk populations [1-3]. These mutations are central to the processes of cell proliferation, apoptosis and DNA damage repair that are crucial for the development and progression of pancreatic tumours. For example, KRAS mutations are present in more than 90% of PDAC cases and play a critical role in oncogenic signalling pathways that promote uncontrolled cell growth [5]. In addition, TP53 mutations are involved in tumour progression by contributing to impaired cell cycle control and apoptosis [6].

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and during its development is strongly influenced by genetic mutations and environmental factors such as chronic hepatitis B (HBV), hepatitis C (HCV) infections and cirrhosis [7]. Basic genetic alterations in HCC include mutations in TP53, CTNNB1, AXIN1 and TERT, which disrupt critical cellular processes like cell cycle regulation, apoptosis, and the Wnt/β-catenin signaling pathway [8]. TP53 and TERT mutations are particularly important as they drive the cancer development process by promoting genomic instability and uncontrolled cellular

How to cite this article: Bursalioglu EO, Kalay S, Metin S. Evaluation of gene interaction and similarity in 17 different cancer pathways. J Res Pharm. 2025; 29(2): 742-750.

ISSN: 2630-6344

https://doi.org/10.12991/jrespharm.1664926

proliferation [7,8]. Gastric cancer is a somewhat complex malignancy process characterised by various genetic mutations and epigenetic modifications that contribute to its development and progression. Key mutated genes include TP53, CDH1, APC, and KRAS, which are involved in pathways regulating DNA repair, cell cycle, and apoptosis [9]. Mutations in TP53 are occurring in more than 50% of cases, contributing to genomic instability and tumor progression. Furthermore, dysregulation of signalling pathways such as Wnt/β-catenin and PI3K/AKT further promotes tumour formation [10]. Epigenetic alterations, including abnormal DNA methylation and miRNA deregulation, facilitate malignancy by playing an important role in silencing tumour suppressor genes [9,10]. Gliomas, especially glioblastomas, are aggressive brain tumours with significant genetic heterogeneity. Common mutations include alterations in PTEN.TP53, and IDH1. The IDH1 mutation found in low-grade gliomas is associated with a distinct metabolic phenotype and better prognosis. In contrast, glioblastomas frequently exhibit mutations in the EGFR gene and amplification of MDM2, both of which contribute to rapid tumour growth and resistance to therapy. The genetic profile of gliomas also reveals alterations in the p53 and PI3K/AKT pathways, both of which are critical for cell survival and proliferation [11].

Thyroid cancer is mainly caused by BRAF, RAS and RET/PTC mutations. The BRAF V600E mutation found in papillary thyroid carcinoma is the hallmark of this cancer and leads to constitutive activation of the MAPK signalling pathway, promoting uncontrolled cell division [12]. Alterations in the PI3K/AKT pathway are frequently seen in follicular thyroid cancers. Genetic mutations in TP53 are rare but are associated with more aggressive forms such as anaplastic thyroid carcinoma [13]. Promoter hypermethylation and other alterations in tumour suppressor genes are also involved in thyroid carcinogenesis [12,13]. Acute myeloid leukaemia (AML) is a type of cancer characterised by a series of genetic mutations that affect haematopoietic stem cell differentiation. [14]. Key mutations include alterations in NPM1,FLT3, IDH1/2, and DNMT3A, which disrupt normal hematopoiesis [15]. Mutations in FLT3, especially FLT3-ITD, are associated with a poor prognosis due to their role in activating cell survival pathways such as PI3K/AKT. In addition, NPM1 mutations are often seen in patients with favourable outcomes. Epigenetic changes, especially in DNA methylation and histone modification, further contribute to disease progression by silencing genes critical for cell differentiation [14,15]. Chronic myeloid leukaemia (CML) is mainly driven by the BCR-ABL1 fusion gene, which results from a translocation between chromosomes 9 and 22 [16,17].This fusion gene leads to constitutive activation of ABL1 tyrosine kinase, promoting uncontrolled cell proliferation and resistance to apoptosis [17]. However, resistance to TKIs can arise through mutations in the ABL1 kinase domain, amplification of the Philadelphia chromosome or alternative signalling pathways [18].

Basal cell carcinoma (BCC) is the most common type of skin cancer, largely caused by mutations in the Hedgehog (Hh) signalling pathway, especially alterations in the PTCH1 or SMO genes [19,20]. Mutations in PTCH1 abolish its inhibitory effect on SMO, leading to uncontrolled cellular proliferation [19]. Melanoma is primarily driven by mutations in the BRAF gene, particularly the BRAF V600E mutation, which leads to hyperactivation of the MAPK/ERK signaling pathway. BRAF inhibitors such as dabrafenib and vemurafenib have shown significant efficacy in the treatment of BRAF mutant melanoma. In addition, combination therapies with MEK inhibitors such as Trametinib have further improved outcomes by reducing resistance to BRAF inhibitors [21,22]. Renal cell carcinoma is largerly associated with mutations in the VHL gene, which regulates hypoxia-inducible factors (HIFs) [23]. Loss of VHL function leads to increased expression of HIF, driving angiogenesis and tumor growth. Targeted therapies such as mTOR inhibitors (e.g. everolimus) and VEGF inhibitors (e.g. pazopanib and sunitinib) are used to manage advanced RCC by inhibiting tumor angiogenesis and proliferation [24]. Bladder cancer is characterized as frequent mutations in TP53, FGFR3 and RB1. FGFR3 mutations are particularly common in non-muscle invasive bladder cancer and FGFR inhibitors such as erdafitinib could be seen as a promising therapeutic approach. PD-1/PD-L1 inhibitörleri (nivolumab ve atezolizumab) ile immünoterapi, kas invaziv mesane kanseri için standart bir tedavi haline gelmiştir [25,26].

Prostate cancer often involves mutations in the AR (androgen receptor) gene. Enzalutamid ve abirateron gibi AR-hedefli tedaviler kastrasyona dirençli prostat kanserinde yaygın olarak kullanılmaktadır [27]. Genetic mutations in BRCA1/2 are also important in advanced prostate cancer and PARP inhibitors such as olaparib are used in patients with these mutations [27,28].

Endometrial cancer often exhibits mutations in the PI3K/AKT/mTOR pathway, particularly in the PTEN gene, a tumor suppressor [29] and loss of PTEN gene function leads to uncontrolled cell proliferation. In advanced cases, targeted therapies that inhibit mTOR, such as everolimus, are used. Furthermore, microsatellite instability (MSI), a sign of DNA mismatch repair deficiency, is observed in a subset of endometrial cancers, making immune checkpoint inhibitors a viable treatment [30]. Breast cancer is a common

Journal of Research in Pharmacy
Research Article

disease involving key mutations in genes such as BRCA1/2, PIK3CA and TP53 [31]. Hormone receptor-positive breast cancer is typically treated with endocrine therapies such as tamoxifen or aromatase inhibitors, while HER2-positive breast cancer is managed with HER2-targeted therapies such as trastuzumab and PARP inhibitors are also effective in BRCA-mutant breast cancers [32]. Small cell lung cancer (SCLC) is highly aggressive and often leads to uncontrolled proliferation with mutations in the TP53 and RB1 genes [33]. Traditional chemotherapy remains the mainstay of treatment for this type of lung cancer, but recent advances in immune checkpoint inhibitors such as durvalumab and atezolizumab have improved outcomes in advanced disease [34]. Non-small cell lung cancer (NSCLC) is usually driven by mutations in the EGFR, ALK and KRAS genes [35]. EGFR mutations are usually targeted with tyrosine kinase inhibitors such as osimertinib and erlotinib while ALK disruptions are treated with ALK inhibitors such as crizotinib [36]. The use of PD-1/PD-L1 inhibitors, e.g. pembrolizumab, has also shown significant efficacy in the treatment of NSCLC with high PD-L1 expression [36, 37].

2. RESULTS

I. Phyton code to find jaccard similarity in these 17 different KEGG cancer pathways (Suppl.1)
II. Phyton code to find gene interactions in these 17 different KEGG cancer pathways

This script is used to extract gene interactions from the specified 17 pathway files and convert them into a pandas DataFrame. This DataFrame contains information such as pathway name, genes in the interaction, interaction type and subtypes. When you run the script, a table with gene interactions in all pathways is created (Suppl. 2).

Phyton software was used to compare KEGG pathways between 17 different cancer types and gene similarities ranged from 43% to 47% and pathway similarities ranged from 25% to 46%. These results reveal that while some cancer types are genetically similar, they show differences in biochemical processes (Supp. 1). Secondly, gene interaction between Kyoto University KEGG cancer metabolic pathways was examined using Phyton codes, and the highest interaction rates among 17 different cancer pathways were observed between ('activation') and entries '43-40' in colorectal cancer, between ('activation') and entries '113-6' in pancreatic cancer, and between ('activation') and entries '122-224' in hepatocellular carcinoma, showing almost 100% interaction. On the other hand, the lowest interaction rates were found between ('missing interaction') and entries '39-135' in colorectal cancer and between ('missing interaction') and entries '95-106' in melanoma, showing 0% interaction (table 1)(Supp.2).

Table 1. Jaccard similarity in these 17 different KEGG cancer pathways

Comparison between cancer16.xml and cancer17.xml: Gene similarity: 0.47 Common genes: hsa*:5925, 6654, 6655, 25759, 399694, 53358, 6464, 4040, 4041, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 581, 2932, 1026, 1855, 1856, 1857, 7048, 4609, 6198, 6199, 11211, 2535, 7855, 7976, 8321, 8322, 8323, 8324, 8325, 8326, 5604, 5605, 1869, 1870, 1871, 3082, 51426, 5594, 5595, 2549, 8312, 8313, 1499, 7012, 7040, 7042, 7043, 3265, 3845, 4893, 10912, 1647, 4616, 7046, 7015, 10000 207 208, 10297, 324, 4087, 4088, 122011, 1452, 4089, 369, 5894, 673, 578, 2475, 10023,23401, 1643, 4233, 2885, 51384, 54361, 7471, 7472, 7473, 7474, 7475, 7476, 7477, 7478, 7479, 7480, 7481, 7482, 7483, 7484, 80326, 81029, 89780, 595, 7157, 1956 Pathway similarity: 0.40 Common pathways: path:hsa04151, path:hsa04350, path:hsa04310, path:hsa04010, path:hsa04110, path:hsa04115
Comparison between cancer17.xml and cancer16.xml: Gene similarity: 0.47 Common genes: hsa*:5925, 6654, 6655, 25759, 399694, 53358, 6464, 4040, 4041, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 581, 2932, 1026, 1855, 1856, 1857, 7048, 4609, 6198, 6199, 11211, 2535, 7855, 7976, 8321, 8322, 8323, 8324, 8325, 8326, 5604, 5605, 1869, 1870, 1871, 3082, 51426, 5594, 5595, 2549, 8312, 8313, 1499, 7012, 7040, 7042, 7043, 3265, 3845, 4893, 10912, 1647, 4616, 7046, 7015, 10000, 207, 208, 10297, 324, 4087, 4088, 122011, 1452, 4089, 369, 5894, 673, 578, 2475, 10023, 23401, 1643, 4233, 2885, 51384, 54361, 7471, 7472, 7473, 7474, 7475, 7476, 7477, 7478, 7479, 7480, 7481, 7482, 7483, 7484, 80326, 81029, 89780, 595, 7157, 1956, Pathway similarity: 0.40 Common pathways: path:hsa04151, path:hsa04350, path:hsa04310, path:hsa04010, path:hsa04110, path:hsa04115
Comparison between cancer5.xml and cancer9.xml: Gene similarity: 0.47

https://doi.org/10.12991/jrespharm.1664926
J Res Pharm 2025; 29(2): 742-750

Journal of Research in Pharmacy
Research Article

Common genes: hsa*:4193, 5925, 1019, 1021, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 1026, 5728, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 3265, 3845, 4893, 10912, 1647, 4616, 1029, 10000, 207, 208, 369, 5894, 673, 578, 1643, 595, 7157, Pathway similarity: 0.25 Common pathways: path:hsa04110, path:hsa04010, path:hsa04115
Comparison between cancer9.xml and cancer5.xml: Gene similarity: 0.47 Common genes: hsa*:4193, 5925, 1019, 1021, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 1026, 5728, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 3265, 3845, 4893, 10912, 1647, 4616, 1029, 10000, 207, 208, 369, 5894, 673, 578, 1643, 595, 7157, Pathway similarity: 0.25 Common pathways: path:hsa04110, path:hsa04010, path:hsa04115
Comparison between cancer5.xml and cancer14.xml: Gene similarity: 0.46 Common genes: hsa*:7039, 5925, 6654, 6655, 1019, 1021, 1950, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 1026, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 3265, 3845, 4893, 10912, 1647, 4616, 1029, 10000, 207, 208, 5335, 5336, 369, 5894, 673, 578, 5578, 5579, 5582, 1643, 2885, 595, 1956, 7157 Pathway similarity: 0.45 Common pathways: path:hsa04020, path:hsa04010, path:hsa04012, path:hsa04110, path:hsa04115
Comparison between cancer14.xml and cancer5.xml: Gene similarity: 0.46 Common genes: hsa*:7039, 5925, 6654, 6655, 1019, 1021, 1950, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 1026, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 3265, 3845, 4893, 10912, 1647, 4616, 1029, 10000, 207, 208, 5335, 5336, 369, 5894, 673, 578, 5578, 5579, 5582, 1643, 2885, 595, 1956, 7157 Pathway similarity: 0.45 Common pathways: path:hsa04020, path:hsa04010, path:hsa04012, path:hsa04110, path:hsa04115
Comparison between cancer1.xml and cancer4.xml: Gene similarity: 0.44 Common genes: hsa*:6654, 6655, 1950, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 2932, 1026, 4609, 5604, 5605, 572, 51426, 5594, 5595, 8312, 8313, 1499, 3265, 3845, 4893, 3845, 10912, 1647, 4616, 842, 10000, 207, 208, 10297, 324, 4292, 369, 5894, 673, 578, 1643, 2885, 595, 1956, 7157 Pathway similarity: 0.46 Common pathways: path:hsa04151, path:hsa04310, path:hsa04010, path:hsa04012, path:hsa04110, path:hsa04115
Comparison between cancer4.xml and cancer1.xml: Gene similarity: 0.44 Common genes: hsa*:6654, 6655, 1950, 581, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 2932, 1026, 4609, 5604, 5605, 572, 51426, 5594, 5595, 8312, 8313, 1499, 3265, 3845, 4893, 3845, 10912, 1647, 4616, 842, 10000, 207, 208, 10297, 324, 4292, 369, 5894, 673, 578, 1643, 2885, 595, 1956, 7157 Pathway similarity: 0.46 Common pathways: path:hsa04151, path:hsa04310, path:hsa04010, path:hsa04012, path:hsa04110, path:hsa04115
Comparison between cancer15.xml and cancer17.xml: Gene similarity: 0.43 Common genes: hsa*:5925, 6654, 6655, 25759, 399694, 53358, 6464, 1950, 4040, 4041, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 581, 2932, 1026, 1855, 1856, 1857, 4609, 6198, 6199, 11211, 2535, 7855, 7976, 8321, 8322, 8323, 8324, 8325, 8326, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 8312, 8313, 1499, 3265, 3845, 4893, 10912, 1647, 4616, 2064, 10000, 207, 208, 10297, 324, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 26281, 26291, 27006, 8074, 8817, 8822, 8823, 9965, 122011, 1452, 369, 5894, 673, 578, 2475, 10023, 23401, 1643, 2885, 51384, 54361, 7471, 7472, 7473, 7474, 7475, 7476, 7477, 7478, 7479, 7480, 7481, 7482, 7483, 7484, 80326, 81029, 89780, 595, 1956, 7157 Pathway similarity: 0.38 Common pathways: path:hsa04151, path:hsa04310, path:hsa04010, path:hsa04110, path:hsa04115
Comparison between cancer17.xml and cancer15.xml: Gene similarity: 0.43 Common genes: hsa*:5925, 6654, 6655, 25759, 399694, 53358, 6464, 1950, 4040, 4041, 110117499, 5290, 5291, 5293, 5295, 5296, 8503, 51176, 6932, 6934, 83439, 581, 2932, 1026, 1855, 1856, 1857, 4609, 6198, 6199, 11211, 2535, 7855, 7976, 8321, 8322, 8323, 8324, 8325, 8326, 5604, 5605, 1869, 1870, 1871, 51426, 5594, 5595, 8312, 8313, 1499, 3265, 3845, 4893, 10912, 1647, 4616, 2064, 10000, 207, 208, 10297, 324, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 26281, 26291, 27006, 8074, 8817, 8822, 8823, 9965, 122011, 1452, 369, 5894, 673, 578, 2475, 10023, 23401, 1643,

https://doi.org/10.12991/jrespharm.1664926
J Res Pharm 2025; 29(2): 742-750

2885, 51384, 54361, 7471, 7472, 7473, 7474, 7475, 7476, 7477, 7478, 7479, 7480, 7481, 7482, 7483, 7484, 80326, 81029, 89780, 595, 1956, 7157 Pathway similarity: 0.38 Common pathways: path:hsa04151, path:hsa04310, path:hsa04010, path:hsa04110, path:hsa04115
hsa*: refers to hsa codes

The application of Jaccard similarity in this study allowed for a comparative analysis of gene content across 17 different cancer pathways. Jaccard similarity measures the overlap between gene sets in different cancer types, providing insights into the degree of shared genetic features across various cancers. High Jaccard similarity values indicate significant overlap and point to potential common molecular mechanisms leading to these cancers [38-40]. For instance, in our study, colorectal and pancreatic cancers exhibited a Jaccard similarity of 0.47, revealing substantial shared genetic components. This could reflect similarities in pathways associated with tumorigenesis, such as mutations in KRAS and TP53, which are commonly implicated in both cancers [41].

The gene interaction analysis further elucidated the complexity of these pathways. It was possible to highlight critical regulatory nodes that may play a central role in cancer progression, by identifying key interactions between genes in the pathways [42,43]. For example, interactions between genes such as BRAF and TP53 have been frequently observed in many types of cancer, taking important roles in cell cycle regulation and apoptosis [44]. As disruptions in these pathways are often associated with aggressive tumor behavior, these interactions may provide potential drug targets [45,46].

Comparing gene interaction networks in pathways using both Jaccard similarity and gene interaction mapping can provide a comprehensive view of cancer biology (table 1; table 2). Integration of these methodologies can help identify not only common features in genes, but also cancer-specific deviations in pathway architecture [47,48]. For example, while pancreatic and colorectal cancers share many genetic mutations, the patterns of interaction between these genes may differ to reflect the tumor microenvironments and different tissue environments in which these cancers develop [49].

Table 2. Pathway Gene Interactions. **

Pathway	Entry1	Entry2	Type	Subtypes
Colorectal cancer	43.0	40.0	PPrel	activation
Colorectal cancer	44.0	40.0	PPrel	activation
Renal cell carcinoma	40.0	41.0	PPrel	binding/association
Renal cell carcinoma	39.0	41.0	PPrel	binding/association
Pancreatic cancer	51.0	4.0	PPrel	binding/association
Pancreatic cancer	35.0	52.0	PPrel	binding/association
Endometrial cancer	37.0	24.0	PPrel	compound
Endometrial cancer	37.0	18.0	PPrel	compound
Glioma	6.0	10.0	PPrel	activation
Glioma	7.0	10.0	PPrel	activation
Prostate cancer	52	42	PPrel	comact
Prostate cancer	52	51	PPrel	comact
Thyroid cancer	29.0	28.0	PPrel	indirect effect
Thyroid cancer	30.0	28.0	PPrel	indirect effect
Basal cell carcinoma	9.0	16.0	PPrel	activation
Basal cell carcinoma	16.0	15.0	PPrel	activation
Melanoma	28	27	PPrel	comact
Melanoma	15.0	14.0	PPrel	activation
Bladder cancer	25.0	38.0	PPrel	indirect effect
Bladder cancer	5.0	37.0	PPrel	activation
Chronic myeloid leukemia	48.0	47.0	PPrel	compound
Chronic myeloid leukemia	156.0	48.0	PPrel	activation
Acute myeloid leukemia	42.0	41.0	PPrel	compound
Acute myeloid leukemia	37.0	42.0	PPrel	activation
Small cell lung cancer	27.0	20.0	PPrel	compound
Small cell lung cancer	21.0	48.0	PPrel	activation
Non-small cell lung cancer	49.0	38.0	PPrel	activation
Non-small cell lung cancer	49.0	16.0	PPrel	activation
Breast cancer	53.0	6.0	PCrel	binding/association
Breast cancer	14.0	7.0	PCrel	binding/association

Hepatocellular carcinoma	113.0	9.0	PPrel	activation
Hepatocellular carcinoma	29.0	30.0	PPrel	activation
Gastric cancer	15.0	16.0	PPrel	activation
Gastric cancer	16.0	17.0	PPrel	activation

** PCrel: An interaction type used in the KEGG database and PCrel represents the relationships between proteins and chemical compounds and refers to states such as activation, inhibition or binding depending on the type of interaction. GErel: defines how one gene affects another in the KEGG database and is used in calculations of gene interaction between pathways, to understand the biological consequences of genetic edits. PPrel: (Protein-Protein relation) refers to the interactions between proteins. Entry1: will be the first component or protein/gene to interact. The first gene or protein (the initiator of the interaction), Entry2: The second gene or protein that interacts (the receiving or regulating side of the interaction). Abbreviation: Acphos : Acphos, Activation, indirect effect: Acineff, inhphos : inhphos, dismisint: dismisint, comact: comact, inhibition, dephosphorylation: inhdephos, inhibition phosphorylation: inhphos, binding/association,missing interaction: binass misibt, expression, missing interaction: exp misint, activation, missing interaction: act misint, inhibition, missing interaction: inh misint.
- The full data of the pathway gene interaction table are given in Suppl. 3.

3. CONCLUSION

The combination of Jaccard similarity and gene interaction analysis offers a robust approach to understanding the system of cancer biology. Despite the diversity in cancer types, these findings suggest that common genetic and molecular features can be exploited for targeted therapies. Future studies could focus on integrating other omics data such as proteomics and metabolomics to build a more detailed picture of cancer pathway dynamics.

4. MATERIALS AND METHODS

Kyoto University KEGG pathways and phyton program and google colab application were used to analyze these pathways. Phyton code was created and run on google colab, an online page to jaccard similarity and gene interactions in 17 different cancer pathways. Jaccard similarity is a widely used method for measuring the similarity between two data sets and has been used in various applications such as genome skimming [50], and in new methods to compare whole genomes and study taxonomic diversity in the microbiome [51,52].

Gene interactions are an important method used to understand the interactions between genes that form different biochemical pathways. These interactions between genes reveal how they work together to regulate biological processes and influence cellular functions [42]. The analysis of gene interaction networks plays a critical role in understanding the molecular mechanisms of cancer and other complex diseases [43]. By comparing the interactions of genes in different pathways, it may be possible to determine which genes play a central role in disease processes [53].

The Python program includes a set of bioinformatics tools and libraries developed to analyse gene interactions and biochemical pathways. In this study, the Google Colab platform was preferred because it enables the processing of large data sets and offers cloud-based computing power. The KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway library provided by Kyoto University was used in this study to study the roles of genes in biochemical networks by providing a large data set on biochemical pathways and gene functions. Detailed analyses of genetic interactions were performed by accessing the KEGG database through Python software. In this way, the roles of genes involved in different cancer types in biochemical processes were analysed and study results were obtained.

Acknowlegements:

Author contributions: All authors have participated in conceptualization, design, and analysis and interpretation of the data; drafting or editing the article, meaning fully contributing to intellectual content; and approval of the final version.

Conflict of interest statement: No conflict of interest was declared by the authors.

REFERENCES

[1] Makohon-Moore A, Brosnan JA, Iacobuzio-Donahue CA. Pancreatic cancer genomics: insights and opportunities for clinical translation. Genome Med. 2013; 28(3):26. https://doi.org/10.1186/gm430.

[2] Lu W, Li N, Liao F. Identification of key genes and pathways in pancreatic cancer gene expression profile by ıntegrative analysis. Genes (Basel). 2019;10(8):612. https://doi.org/10.3390/genes10080612.

[3] Montalvo-Javé EE, Nuño-Lámbarri N, López-Sánchez GN, Ayala-Moreno EA, Gutierrez-Reyes G, Beane J, Pawlik TM. Pancreatic Cancer: Genetic conditions and epigenetic alterations. J Gastrointest Surg. 2023;27(5):1001-1010. https://doi.org/10.1007/s11605-022-05553-0.

[4] Fischer J, Walker LC, Robinson BA, Frizelle FA, Church JM, Eglinton TW. Clinical implications of the genetics of sporadic colorectal cancer. ANZ J Surg. 2019;89(10):1224-1229. https://doi.org/10.1111/ans.15074.

[5] Gonzalez RS, Washington K, Shi C. Current applications of molecular pathology in colorectal carcinoma. Appl Cancer Res. 2017;37:13. https://doi.org/10.1186/s41241-017-0020-1.

[6] Rebuzzi F, Ulivi P, Tedaldi G. Genetic Predisposition to Colorectal Cancer: How Many and Which Genes to Test? Int J Mol Sci. 2023;24(3):2137. https://doi.org/10.3390/ijms24032137.

[7] Khemlina G, Ikeda S, Kurzrock R. The biology of Hepatocellular carcinoma: implications for genomic and immune therapies. Mol Cancer. 2017;16(1):149. https://doi.org/10.1186/s12943-017-0712-x.

[8] Wang Y, Deng B. Hepatocellular carcinoma: molecular mechanism, targeted therapy, and biomarkers. Cancer Metastasis Rev. 2023;42:629-652. https://doi.org/10.1007/s10555-023-10084-4.

[9] Guo J, Yu W, Su H, Pang X. Genomic landscape of gastric cancer: molecular classification and potential targets. Sci China Life Sci. 2017;60(2):126-137. https://doi.org/10.1007/s11427-016-0034-1.

[10] Abdolahi F, Shahraki A, Sheervalilou R, Mortazavi SS. Identification of differentially expressed genes associated with the pathogenesis of gastric cancer by bioinformatics analysis. BMC Med Genomics. 2023;16(1):311. https://doi.org/10.1186/s12920-023-01720-7.

[11] Cai H, Jing C, Chang X, Ding D, Han T, Yang J, Lu Z, Hu X, Liu Z, Wang J, Shang L, Wu S, Meng P, Lin L, Zhao J, Nie M, Yin K. Mutational landscape of gastric cancer and clinical application of genomic profiling based on target next-generation sequencing. J Transl Med. 2019;17(1):189. https://doi.org/10.1186/s12967-019-1941-0.

[12] Zhang Y, Lyu Y, Chen L, Cao K, Chen J, He C, Lyu X, Jiang Y, Xiang J, Liu B, Wu C. Exploring the Prognosis-Related Genetic Variation in Gastric Cancer Based on mGWAS. Int J Mol Sci. 2023;24(20):15259. https://doi.org/10.3390/ijms242015259.

[13] Lu XQ, Zhang JQ, Zhang SX, Qiao J, Qiu MT, Liu XR, Chen XX, Gao C, Zhang HH. Identification of novel hub genes associated with gastric cancer using integrated bioinformatics analysis. BMC Cancer. 2021;21(1):697. https://doi.org/10.1186/s12885-021-08358-7.

[14] Grimwade D, Ivey A, Huntly BJ. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood. 2016;127(1):29-41. https://doi.org/10.1182/blood-2015-07-604496.

[15] Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. https://doi.org/10.1182/blood-2016-08-733196

[16] Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031-1037. https://doi.org/10.1056/nejm200104053441401.

[17] O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348(11):994-1004. https://doi.org/10.1056/NEJMoa022457.

[18] Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ, Breccia M, Goh YT, Talpaz M, Hochhaus A, le Coutre P, Ottmann O, Heinrich MC, Steegmann JL, Deininger MWN, Janssen JJWM, Mahon FX, Minami Y, Yeung D, Ross DM, Tallman MS, Park JH, Druker BJ, Hynds D, Duan Y, Meille C, Hourcade-Potelleret F, Vanasse KG, Lang F, Kim DW. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019;381(24):2315-2326. https://doi.org/10.1056/NEJMoa1902328.

[19] Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, Coppola C, Chanana AM, Marji J, Bickers DR, Epstein EH Jr. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366(23):2180-2188. https://doi.org/10.1056/NEJMoa1113538.

[20] Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, Solomon JA, Yoo S, Arron ST, Friedlander PA, Marmur E, Rudin CM, Chang AL, Low JA, Mackey HM, Yauch RL, Graham RA, Reddy JC, Hauschild A. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012;366(23):2171-2179. https://doi.org/10.1056/nejmoa1113713.

[21] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-2516. https://doi.org/10.1056/NEJMoa1103782.

[22] Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S,

Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(18):1694-1703. https://doi.org/10.1056/NEJMoa1210093.

[23] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-124. https://doi.org/10.1056/NEJMoa065044.

[24] Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-1068. https://doi.org/10.1200/jco.2009.23.9764.

[25] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-1920. https://doi.org/10.1016/S0140-6736(16)00561-4.

[26] O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, Tahover E, Lowery MA, Chou JF, Sahai V, Brenner R, Kindler HL, Yu KH, Zervoudakis A, Vemuri S, Stadler ZK, Do RKG, Dhani N, Chen AP, Kelsen DP. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. J Clin Oncol. 2020;38(13):1378-1388. https://doi.org/10.1200/JCO.19.02931.

[27] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005. https://doi.org/10.1056/NEJMoa1014618.

[28] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, Nava Rodrigues D, Robinson D, Omlin A, Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G, Jain S, Ralph C, Protheroe A, Hussain S, Jones R, Elliott T, McGovern U, Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM, Cao X, Brough R, Pemberton H, A'Hern R, Swain A, Kunju LP, Eeles R, Attard G, Lord CJ, Ashworth A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, Hall E, de Bono JS. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015;373(18):1697-1708. https://doi.org/10.1056/NEJMoa1506859.

[29] Slomovitz BM, Filiaci VL, Walker JL, Taub MC, Finkelstein KA, Moroney JW, Fleury AC, Muller CY, Holman LL, Copeland LJ, Miller DS, Coleman RL. A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study. Gynecol Oncol. 2022;164(3):481-491. https://doi.org/10.1016/j.ygyno.2021.12.031.

[30] Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-413. Science. 2017; 357(6349): 409-413. https://doi.org/10.1126/science.aan6733.

[31] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-792. https://doi.org/10.1056/nejm200103153441101.

[32] Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533. doi: 10.1056/NEJMoa1706450. Erratum in: N Engl J Med. 2017;377(17):1700. https://doi.org/10.1056/nejmoa1706450.

[33] George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, Leenders F, Lu X, Fernández-Cuesta L, Bosco G, Müller C, Dahmen I, Jahchan NS, Park KS, Yang D, Karnezis AN, Vaka D, Torres A, Wang MS, Korbel JO, Menon R, Chun SM, Kim D, Wilkerson M, Hayes N, Engelmann D, Pützer B, Bos M, Michels S, Vlasic I, Seidel D, Pinther B, Schaub P, Becker C, Altmüller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel PA, Petersen I, Chen Y, Soltermann A, Tischler V, Choi CM, Kim YH, Massion PP, Zou Y, Jovanovic D, Kontic M, Wright GM, Russell PA, Solomon B, Koch I, Lindner M, Muscarella LA, la Torre A, Field JK, Jakopovic M, Knezevic J, Castaños-Vélez E, Roz L, Pastorino U, Brustugun OT, Lund-Iversen M, Thunnissen E, Köhler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen HB, Achter V, Lang U, Bogus M, Schneider PM, Zander T, Ansén S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis WD, Nürnberg P, Reinhardt C, Perner S, Heukamp L, Büttner R, Haas SA, Brambilla E, Peifer M, Sage J, Thomas RK. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015;524(7563):47-53. https://doi.org/10.1038/nature14664.

[34] Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV; IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018; 379(23):2220-2229. https://doi.org/10.1056/NEJMoa1809064.

[35] Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-957. https://doi.org/10.1056/nejmoa0810699.

[36] Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-2177. doi: 10.1056/NEJMoa1408440. Erratum in: N Engl J Med. 2015;373(16):1582. https://doi.org/10.1056/nejmoa1408440.

[37] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-2028. https://doi.org/10.1056/nejmoa1501824.

[38] Wang X, Sun Z, Zimmermann MT, Bugrim A, Kocher JP. Predict drug sensitivity of cancer cells with pathway activity inference. BMC Med Genomics. 2019;12(Suppl 1):15. https://doi.org/10.1186/s12920-018-0449-4.

[39] Dannenfelser R, Clark NR, Ma'ayan A. Genes2FANs: connecting genes through functional association networks. BMC Bioinformatics. 2012;13:156. https://doi.org/10.1186/1471-2105-13-156.

[40] Teng YHF, Quah HS, Suteja L, Dias JML, Mupo A, Bashford-Rogers RJM, Vassiliou GS, Chua MLK, Tan DSW, Lim DWT, Iyer NG. Correction to: Analysis of T cell receptor clonotypes in tumor microenvironment identifies shared cancer-type-specific signatures. Cancer Immunol Immunother. 2022;71(4):999. doi: 10.1007/s00262-021-03086-0. Erratum for: Cancer Immunol Immunother. 2022;71(4):989-998. doi: 10.1007/s00262-021-03047-7. https://doi.org/10.1007/s00262-021-03086-0.

[41] Prior IA, Hood FE, Hartley JL. The Frequency of Ras Mutations in Cancer. Cancer Res. 2020;80(14):2969-2974. https://doi.org/10.1158/0008-5472.can-19-3682.

[42] Barabási AL, Gulbahce N, Loscalzo J. Network medicine: A network-based approach to human disease. Nat Rev Genet. 2011;12(1): 56-68. https://doi.org/10.1038/nrg2918.

[43] Vidal M, Cusick ME, Barabási AL. Interactome networks and human disease. Cell. 2011;144(6): 986-998. https://doi.org/10.1016/j.cell.2011.02.016.

[44] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-674. https://doi.org/10.1016/j.cell.2011.02.013.

[45] Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J. Cancer: A Systems Biology disease. Biosystems. 2006;83(2-3):81-90. https://doi.org/10.1016/j.biosystems.2005.05.014.

[46] Ideker T, Sharan R. Protein networks in disease. Genome Res. 2008;18(4):644-652. https://doi.org/10.1101/gr.071852.107.

[47] Bader GD, Hogue CW. An automated method for finding molecular complexes in large protein interaction networks. BMC Bioinformatics. 2003;4:2. https://doi.org/10.1186/1471-2105-4-2.

[48] Creixell P, Reimand J, Haider S, Wu G, Shibata T, Vazquez M, Mustonen V, Gonzalez-Perez A, Pearson J, Sander C, Raphael BJ, Marks DS, Ouellette BFF, Valencia A, Bader GD, Boutros PC, Stuart JM, Linding R, Lopez-Bigas N, Stein LD; Mutation Consequences and Pathway Analysis Working Group of the International Cancer Genome Consortium. Pathway and network analysis of cancer genomes. Nat Methods. 2015;12(7):615-621. https://doi.org/10.1038/nmeth.3440.

[49] Underhill ML, Germansky KA, Yurgelun MB. Advances in Hereditary Colorectal and Pancreatic Cancers. Clin Ther. 2016;38(7):1600-1621. https://doi.org/10.1016/j.clinthera.2016.03.017.

[50] Denver DR, Brown AM, Howe DK, Peetz AB, Zasada IA. Genome Skimming: A Rapid Approach to Gaining Diverse Biological Insights into Multicellular Pathogens. PLoS Pathog. 2016;12(8):e1005713. https://doi.org/10.1371/journal.ppat.1005713.

[51] Ondov BD, Treangen TJ, Melsted P, Mallonee AB, Bergman NH, Koren S, Phillippy AM. Mash: fast genome and metagenome distance estimation using MinHash. Genome Biol. 2016;17(1):132. https://doi.org/10.1186/s13059-016-0997-x.

[52] Sarmashghi S, Bohmann K, P Gilbert MT, Bafna V, Mirarab S. Skmer: assembly-free and alignment-free sample identification using genome skims. Genome Biol. 2019;20(1):34. https://doi.org/10.1186/s13059-019-1632-4.

[53] Lehner B. Molecular mechanisms of epistasis within and between genes. Trends Genet. 2011;27(8):323-331. https://doi.org/10.1016/j.tig.2011.05.007.