

KSBi-BIML 2021

Bioinformatics & Machine Learning (BIML)
Workshop for Life Scientists

생물정보학 & 머신러닝 워크샵(온라인)

Multi-omics Driven Systematic Approaches to Understand Cancer Complexity

김권일

Bioinformatics & Machine Learning for Life Scientists

BIML-2021

안녕하십니까?

한국생명정보학회의 동계 워크샵인 BIML-2021을 2월 15부터 2월 19일까지 개최합니다. 생명정보학 분야의 융합이론 보급과 실무역량 강화를 위해 도입한 전문 교육 프로그램인 BIML 워크샵은 2015년에 시작하였으며 올해로 7차를 맞이하게 되었습니다. 유례가 없는 코로나 대유행으로 인해 올해의 BIML 워크숍은 온라인으로 준비했습니다. 생생한 현장 강의에서만 느낄 수 있는 강의자와 수강생 사이의 상호교감을 가질 수 없다는 단점이 있지만, 온라인 강의의 여러 장점을 살려서 최근 생명정보학에서 주목받고 있는 거의 모든 분야를 망라한 강의를 준비했습니다. 또한 온라인 강의의 한계를 극복하기 위해서 실시간 Q&A 세션 또한 마련했습니다.

BIML 워크샵은 전통적으로 크게 생명정보학과 AI, 두 개의 분야로 구성되어오고 있으며 올해 역시 유사한 방식을 채택했습니다. AI 분야는 Probabilistic Modeling, Dimensionality Reduction, SVM 등과 같은 전통적인 Machine Learning부터 Deep Learning을 이용한 신약개발 및 유전체 연구까지 다양한 내용을 다루고 있습니다. 생명정보학 분야로는, Proteomics, Chemoinformatics, Single Cell Genomics, Cancer Genomics, Network Biology, 3D Epigenomics, RNA Biology, Microbiome 등 거의 모든 분야가 포함되어 있습니다. 연사들은 각 분야 최고의 전문가들이라 자부합니다.

이번 BIML-2021을 준비하기까지 너무나 많은 수고를 해주신 BIML-2021 운영위원회의 김태민 교수님, 류성호 교수님, 남진우 교수님, 백대현 교수님께 커다란 감사를 드립니다. 또한 재정적 도움을 주신, 김선 교수님 (AI-based Drug Discovery), 류성호 교수님, 남진우 교수님께 감사를 표시하고 싶습니다. 마지막으로 부족한 시간에도 불구하고 강의 부탁을 흔쾌히 허락하시고 훌륭한 강의자료를 만드는데 노력하셨을 뿐만 아니라 실시간 온라인 Q&A 세션까지 참여해 수고해 주시는 모든 연사분들께 깊이 감사드립니다.

2021년 2월

한국생명정보학회 회장 김동섭

강의개요

Multi-omics driven systematic approaches to understand cancer complexity

생물정보 흐름의 핵심요소인 DNA, RNA, 그리고 단백질의 서열과 발현양에 대한 data는 관련 기술의 비약적인 발전에 힘입어 big data 수준으로 축적되고 있다. 이에 따라 각 요소의 전체(계) 수준의 양상을 연구하는 omics 분야가 태동하게 되고, 나아가 각 계 사이의 상호작용을 통합 연구하는 multi-omics 분야가 현대 생물학에 자리잡게 되었다. 최근 이러한 상호작용을 강조하는 trans-omics 라는 개념도 등장하였고, multi-omics 연구에는 다양한 접근과 해석이 공존하고 있는 상태이다.

본 강의에서는 multi-omics 분야의 태동에서부터 최근 발표된 주요한 multi-omics 연구 사례를 대표적인 복잡 질병(complex disease)인 암을 대상으로 하여 소개하고자 한다. 특히, 각 계 내의 복잡계가 중첩된 양상을 나타내는 multi-omics 복합 층계를 이해하기 위해서는 시스템 생물학적 이해가 필수적인데, 이와 관련된 시스템 생물학 기반의 multi-omics 융합 연구 내용을 공유할 것이다. 연계된 실습에서는 암 multi-omics 공개 데이터를 대상으로 clustering 및 해석을 통합적으로 수행하고, 생물학 네트워크 기반의 multi-omics data 분석을 배울 것이다. 이를 통하여 multi-omics data에 내포된 생물학적 상호작용을 해석하고 이해하는 핵심 역량을 갖추는 것을 목표로 한다.

강의는 다음의 내용을 포함한다:

- Multi-omics 개요 및 암 생물학에서의 대표적인 multi-omics 연구
- 시스템 생물학 기반의 multi-omics data 해석
- Multi-omics data clustering 및 해석
- 생물학 network 기반 multi-omics data 분석

*실습 교육생 준비물 및 필요조건:

네트워크 사용이 가능한 노트북 또는 데스크탑

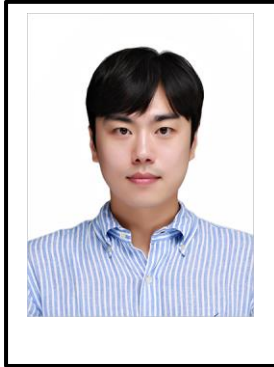
실습은 파이썬(python)으로 진행하므로 기본적인 파이썬 문법 숙지가 필요함

구글 코랩(google colab)이 세팅 되어 있으면 수월하게 진행 가능함(필수 아님)

* 강의: 김권일 교수 (경희대학교 생물학과)

Curriculum Vitae

Speaker Name: Kwoneel Kim, Ph.D.



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Research interest : Translational bioinformatics, Machine learning and computational genomics, Cancer genomics

Educational Experience

2009 B.S. Dept. Applied Bioscience, Konkuk University, Korea
2011 M.S. Dept. Functional Genomics, UST, Korea
2015 Ph.D. Dept. Bio and Brain Engineering, KAIST, Korea

Professional Experience

2015-2017 Post-Doctoral Researcher, Dept. Bio and Brain Engineering, KAIST
2017-2018 Senior Research Scientist, Asan Institute for Life Sciences, Asan Medical Center
2018- Assistant Professor, Department of Biology, Kyung Hee University

Selected Publications (5 maximum)

1. **Kim K**, Kim HS, Jeong YK, Jung H, Sun J-M, Ahn JS, Ahn M-J, Park K, Lee S-H, Choi JK. Predicting clinical benefit of immunotherapy by antigenic or functional mutations affecting tumour immunogenicity. *Nature Communications*. 11. 951 (2020).
2. Jang K*, **Kim K***, Cho A, Lee I, Choi JK. Network perturbation by recurrent regulatory variants in cancer. *PLoS Computational Biology*. 13. e1005449 (2017). *Co-first
3. **Kim K***, Jang K*, Yang W*, Choi EY, Park SM, Bae M, Kim YJ, Choi JK. Chromatin structure-based prediction of recurring noncoding mutations in cancer. *Nature Genetics*. 48.1321-1326 (2016). *Co-first
4. **Kim K**, Yang W, Lee KS, Bang H, Jang K, Kim SC, Yang JO, Park S, Park K, Choi JK. Global transcription network incorporating distal regulator binding reveals selective cooperation of cancer drivers and risk genes. *Nucleic Acids Research*. 43, 5716-5729 (2015).

KSBi-BIML 2021

Multi-omics driven systematic approaches to
understand cancer complexity

Department of Biology, Kyung Hee University

Kwoneel Kim, PhD

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본 강의 자료는 한국생명정보학회가 주관하는 KSBi-BIML 2021 워크숍 온라인 수업을 목적으로 제작된것으로 해당 목적 이외의 다른 용도로 사용할 수 없음을 분명하게 알립니다. 수업 목적으로 배포 및 전송 받은 경우에도 이를 다른 사람과 공유하거나 복제, 배포, 전송할 수 없습니다.

만약 이러한 사항을 위반할 경우 발생하는 모든 법적 책임은 전적으로 불법 행위자 본인에게 있음을 경고합니다.

2

DNA 염기서열분석기술은 인간 게놈 프로젝트 이후 꾸준히 발달해왔다.

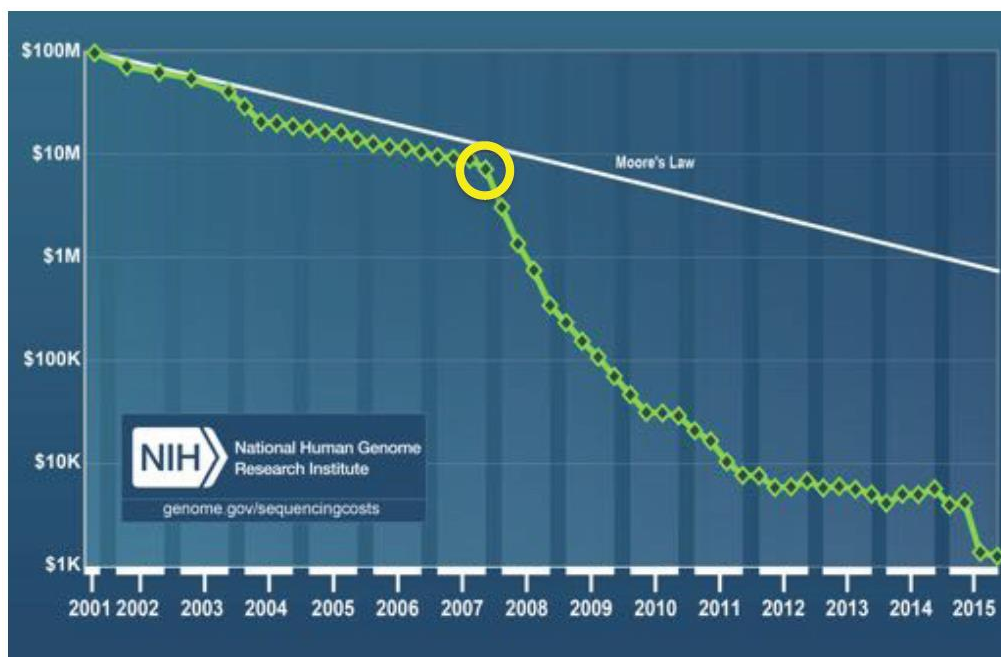
#2시간 30 분의 분량으로 준비가 되었기 때문에, 기초 오믹스 배경에 대한 설명은 skip 하거나 빠르게 듣기를 권장 (3~9p 까지)

#본격적인 내용은 슬라이드 제목 "-omics: -ome 을 연구하는 학문 (10p)" 에서부터 시작



3

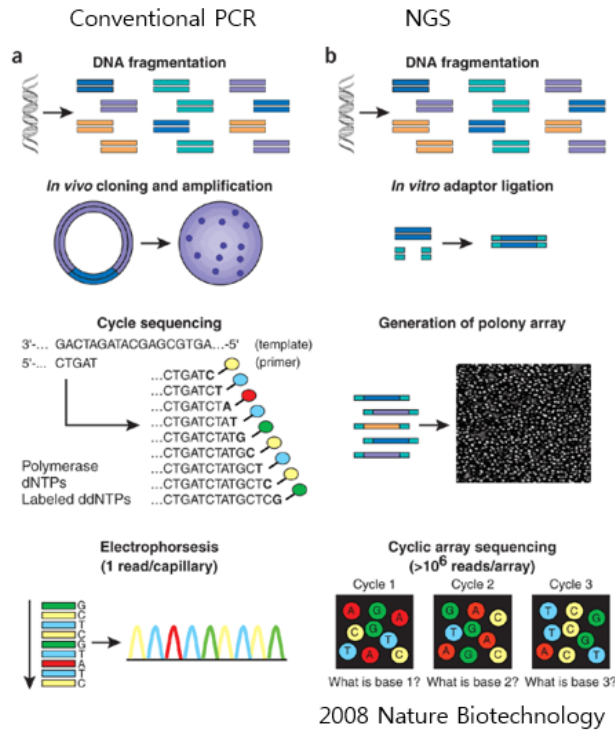
DNA sequencing 기술의 발전



4

차세대 염기서열 분석법 (Next-generation sequencing, NGS)

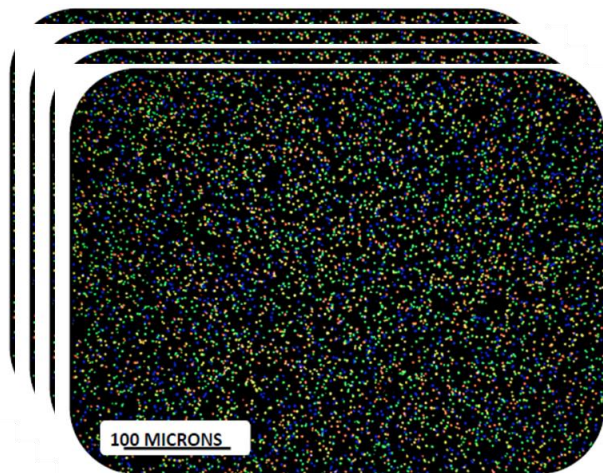
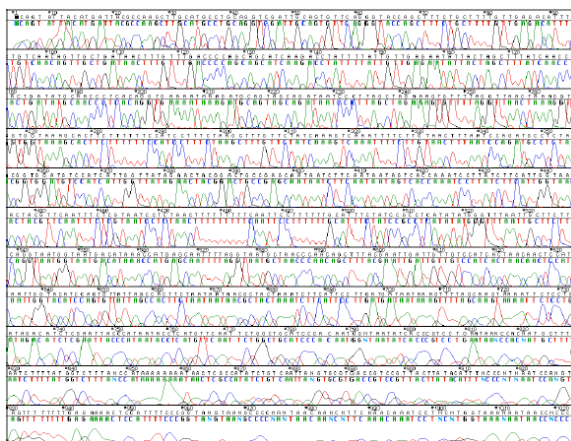
< 기존의 PCR법 VS NGS 법 >



NextSeq 550 Series +

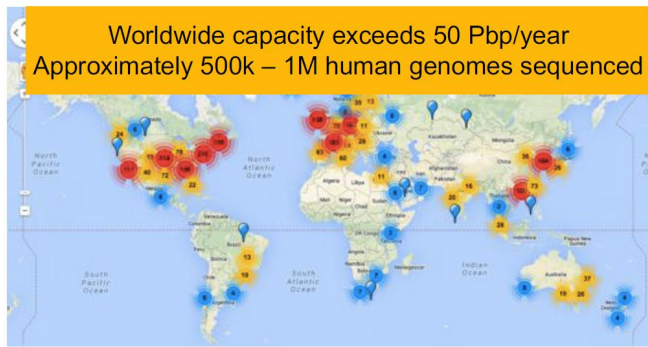
5

차세대 염기서열 분석법: “parallel” and “high throughput”



6

전세계 염기서열 분석센터 (2014)



Next Generation Genomics: World Map of High-throughput Sequencers
http://omicsmaps.com



100 GB / Genome
4.7GB / DVD
~20 DVDs / Genome

X

10,000 Genomes

=

1PB Data
200,000 DVDs



787 feet of DVDs
~1/6 of a mile tall

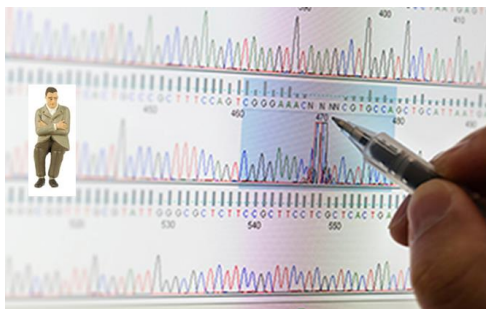


500 2 TB drives
\$100k

#염청 크기가 크다는 것만 이해하면
되겠습니다.

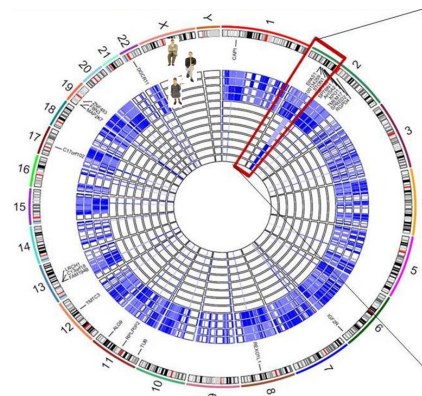
7

염기서열 분석기술의 발전은 한 명의 하나의 유전자를 분석하는 것에서 **여러 명의 여러 유전자**의 **서열과 발현** 분석을 가능하게 하였다: 유전체학 (genomics) and 전사체학 (transcriptomics)



#1-gene sequencing study 가 이미 연구가 너무
많이 되었다고 보면 좋겠습니다

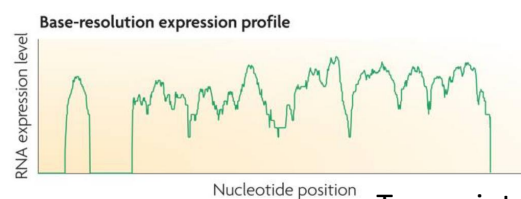
Gene



Genome

AAAAAAA mRNA

Transcript



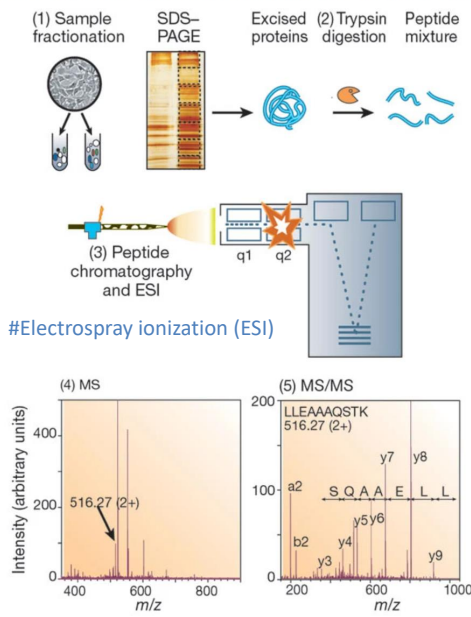
Transcriptome

8

Mass spectrometry (MS) for proteomics

#이 슬라이드에서 말하는 원소, 분자, 물질은 모두 amino acid 를 칭함

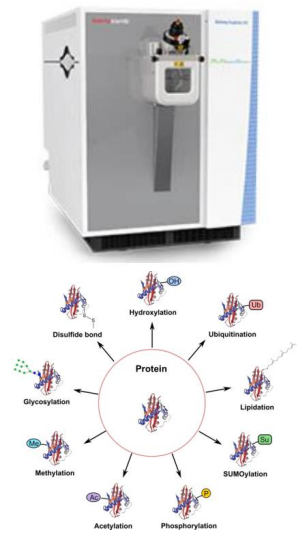
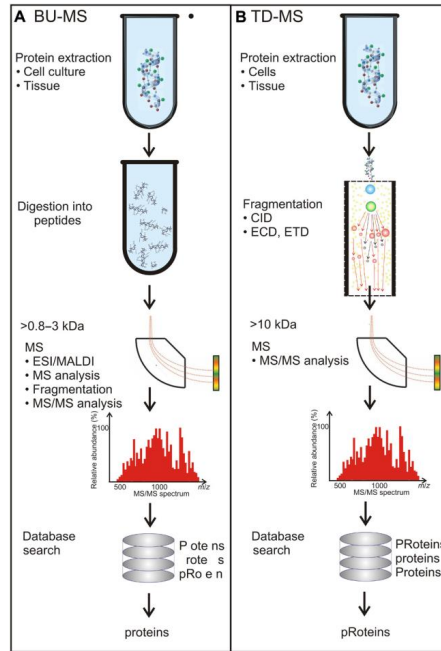
Figure 1: Generic mass spectrometry (MS)-based proteomics experiment.



#여러 원소로 구성된 화합물은 각자의 질량에 따라 구별될 수 있음; 구별하기가 쉬운 일은 아님..

#Bottom-up (BU-MS) approach that is used prevalently: 단백질을 짧게 조각낸 peptide를 분석

#Top-down (TD-MS) approach that analyzes intact protein <70 kDa: 온전한 형태의 단백질 (intact protein)을 분해없이 직접 분석. Post-translational modification (PTM) 을 동정할 수 있음



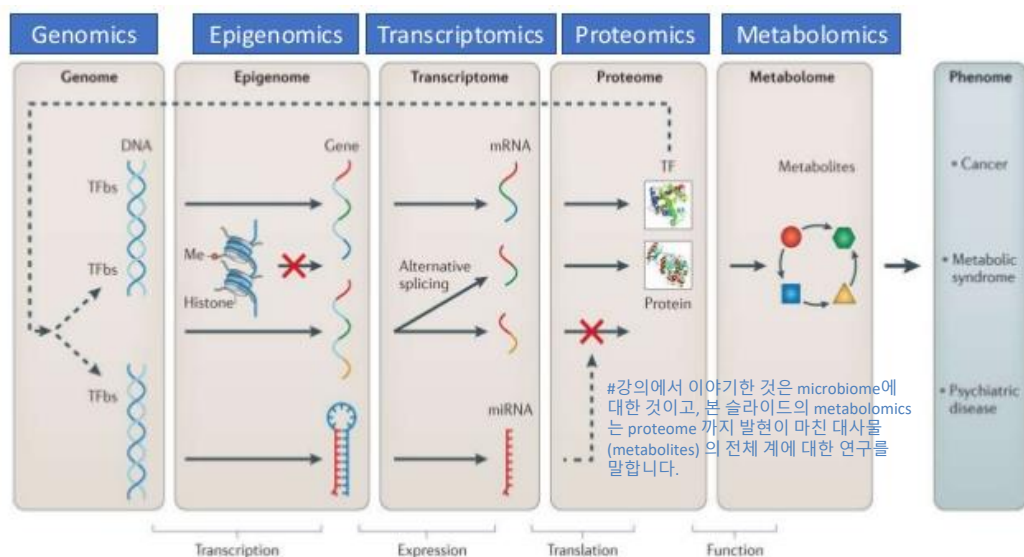
Nature. 422, 198–207 (2003)

Science Advances. 6, eaax8978 (2020)

9

-omics: -ome 을 연구하는 학문

“The suffix -ome as used in molecular biology refers to a **totality** of some sort”
“분자생물학에서 접미사 -ome 은 어떤 종류의 전체를 의미한다”



Nature Reviews | Genetics

10

Large-scale research efforts for omics study

Table 1 | Data types for integrative omics

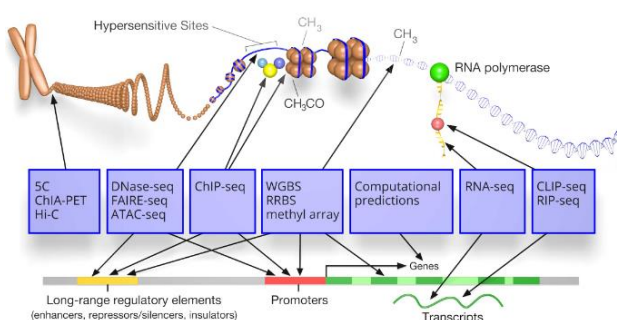
Data type	Large-scale research efforts	Utility and advantages	Major caveats
Genetic variation	Many GWAS consortia, 1000 Genomes, gnomAD and UK Biobank	Unbiased source of genetic basis of disease and direct inference of causality	At least one step removed from the phenotype
Epigenetics	ENCODE and Roadmap Epigenomics Project	Functional impact and typically easy to infer causality	Not applicable for all phenotypes
Gene expression	GTEx and GEUVADIS	Inexpensive assay for an intermediate step towards the phenotype	Not applicable for all phenotypes
Proteomics and metabolomics	CPTAC, EDNR and Common Fund	Likely to be very close to the phenotype	Expensive and difficult to scale (proteomics)
Microbiome	Human Microbiome Project	Likely to be very close to the phenotype and measures a combination of genetic and environmental influences	Combination of genetic and environmental influences makes it difficult to infer the direction of causality

In this table, 'phenotype' refers to an organismal phenotype. CPTAC, Clinical Proteomic Tumour Analysis Consortium; EDNR, Early Detection Research Network; ENCODE, Encyclopedia of DNA Elements; GEUVADIS, Genetic European Variation in Health and Disease; gnomAD, Genome Aggregation Database; GTEx, Genotype-Tissue Expression; GWAS, genome-wide association study.

Nature Reviews Genetics. 19, 299–310 (2018)

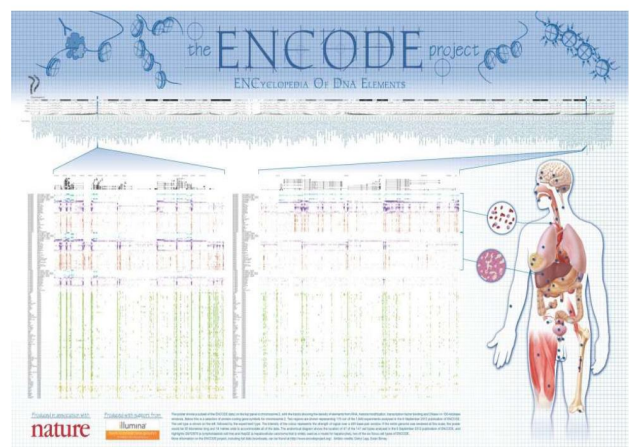
11

ENCyclopedia Of DNA Elements (ENCODE) project



#Experiments to analyze the function of DNA elements; coupled with NGS

#이후 소개하는 모든 consortium 의 데이터가 오믹스 연구가 가능한 수준의 big data 로 생산이 가능하게 된 것에는 NGS 와 MS technology 의 발전이 있었기 때문



#Epigenome map

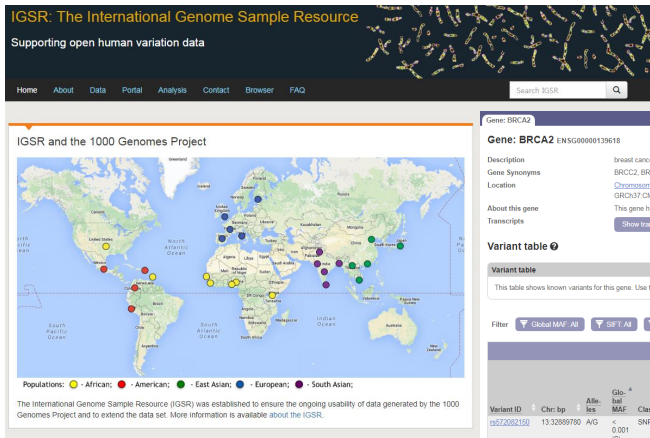
~ 9,000 experiments

~ 1,000 Consortium publications

~3,500 community publications using ENCODE data

12

1000 genome project



Gene: **BRCA2** ENSG00000139518

Gene Synonyms: BRCC2, BROVCA2, FACD, FAD, FAD1, FANCB, FANCD, FANCD1, GLM3, PNCA2

Location: Chromosome 13: 32,886,611-32,923,800 forward strand

About this gene: This gene has 8 transcripts (splice variants), 61 orthologues, is a member of 2 Ensembl protein families and is associated with 352 phenotypes

Transcript: [Show transcript table](#)

Variant table

This table shows known variants for this gene. Use the 'Consequence Type' filter to view a subset of these.

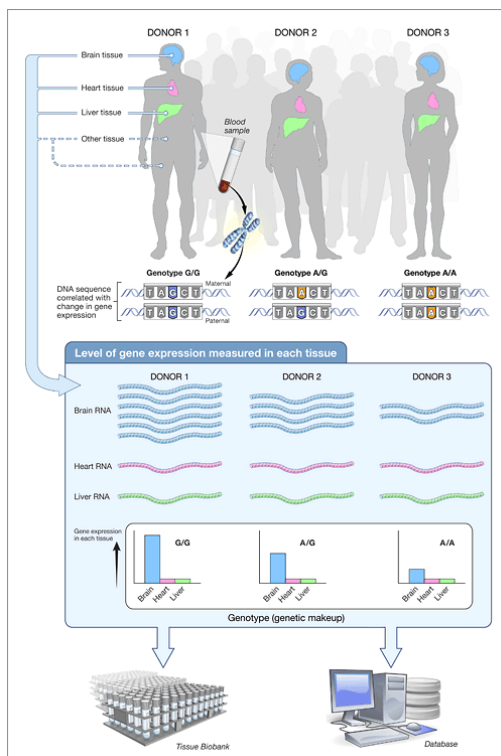
Filter: Global MAF: All DF: All Path: All Consequences: All Filter Other Columns

Show/hide columns

Variant ID	Chr: bp	Alleles	MAF	Class	Source	Evidence	Clin. Sig.	Contig	AA	AA coord	SIFT	Pol. Ph. n	CAD	REV	EL	Met. pLR	Mit. rlo	Ass. or	Transcript
rs172002150	13:32889700	A/G	< 0.001 (G)	SNP	dbSNP	● ● ● ●	-	Exon	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3
rs176543548	13:32889898	G/C	< 0.001 (G)	SNP	dbSNP	● ● ● ●	-	Intron	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3
rs156166551	13:32889898	G/A	< 0.001 (A)	SNP	dbSNP	● ● ● ●	-	Intron	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3
rs133407363	13:32890034	C/T	< 0.001 (T)	SNP	dbSNP	● ● ● ●	-	Intron	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3
rs18264531	13:32890059	G/A/C	< 0.001 (A)	SNP	dbSNP	● ● ● ●	-	Intron	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3
rs18264531	13:32890059	G/A/C	< 0.001 (A)	SNP	dbSNP	● ● ● ●	-	Intron	-	-	-	-	-	-	-	-	-	-	ENST0000030152.3

13

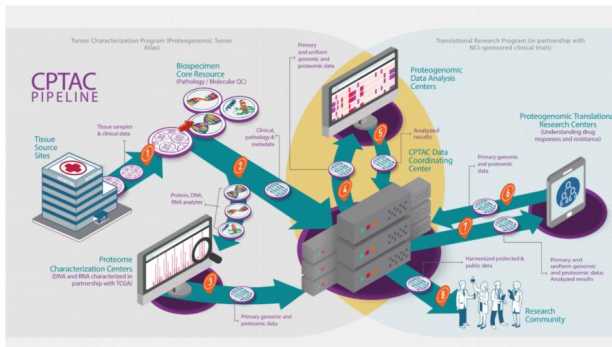
Genotype-tissue expression (GTEx) project



14

Clinical Proteomic Technology Assessment for Cancer (CPTAC)

CPTAC



The screenshot shows the CPTAC Assay Portal website. The header includes the NIH National Cancer Institute logo and the text 'Center for Strategic Scientific Initiatives'. The main navigation bar includes links for 'ASSAY PORTAL HOME', 'ANTIBODY PORTAL', 'DATA PORTAL', 'ABOUT', and 'SUBMIT ASSAYS'. The 'Assay Portal' section is highlighted. Below the header, there is a search bar and a table of assay data. The table has columns for 'Proteins and peptides with assays', 'Submitting Laboratory', 'Modification', 'Assay Type', 'Matrix', 'CPTAC ID', and 'Protein Name'. The table lists several assays, including those from the UIC-Genome BC Proteomics Centre.

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The cancer genome atlas (TCGA) International cancer genome consortium (ICGC) Pan-cancer analysis of whole genomes (PCWAG)

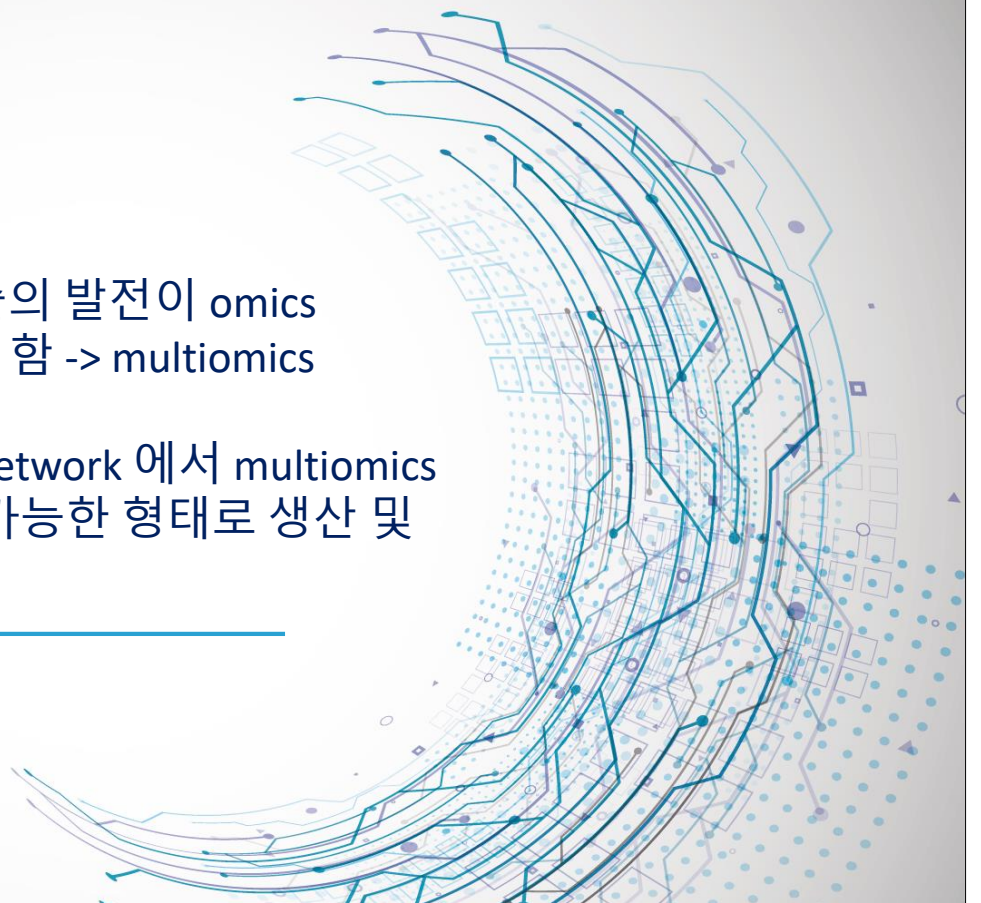
The image shows the cover of the journal 'Nature' from February 6, 2020, featuring the headline 'PAN-CANCER ANALYSIS OF WHOLE GENOMES PUBLISHED!' and 'CANCER CATALOGUED'. Below the cover, there is a text box that reads: 'Read about the ICGC/TCGA analysis of >2,600 whole cancer genomes across 38 tumour types in 23 papers published in Nature and other Nature journals. Photo credit: Nik Spencer/Nature.'

The screenshot shows the ICGC Data Portal Advanced Search interface. The top navigation bar includes the ICGC logo and a search bar. The main section is titled 'ADVANCED SEARCH' and features a sidebar with filters for 'Donors', 'Genes', and 'Mutations'. The main content area displays various charts and statistics, including 'Project', 'Primary Site', 'Gender', 'Tumour Stage', 'Vital Status', 'Disease Status', 'Relapse Type', 'Age', 'Data Types', and 'Analysis Types'. The bottom of the page includes a 'Donors' section and a 'Show Less' button.

16

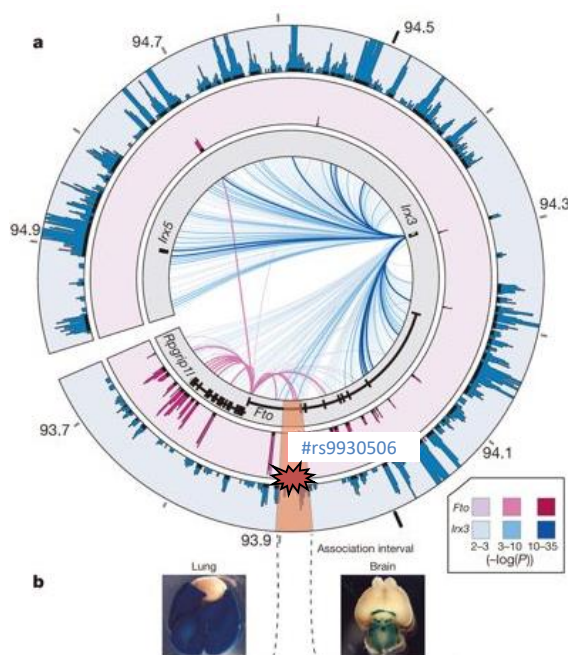
#Sequencing 기술의 발전이 omics 연구를 가능하게 함 -> multiomics

#Global science network 에서 multiomics big data 가 해석가능한 형태로 생산 및 제공되고 있음

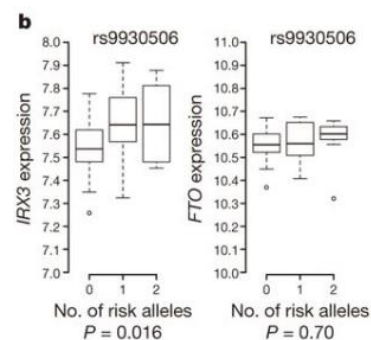


17/52

A case study of integration between epigenomics and genomics

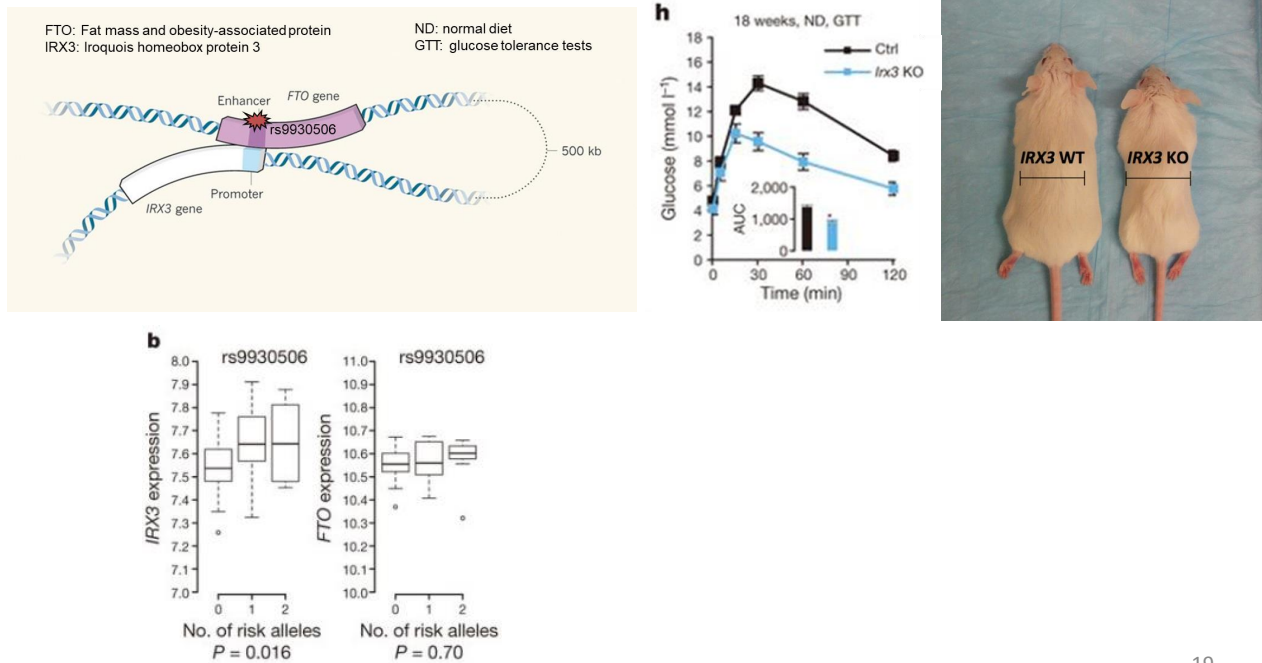


#FTO: Fat mass and obesity-associated protein
#IRX3: Iroquois homeobox protein 3



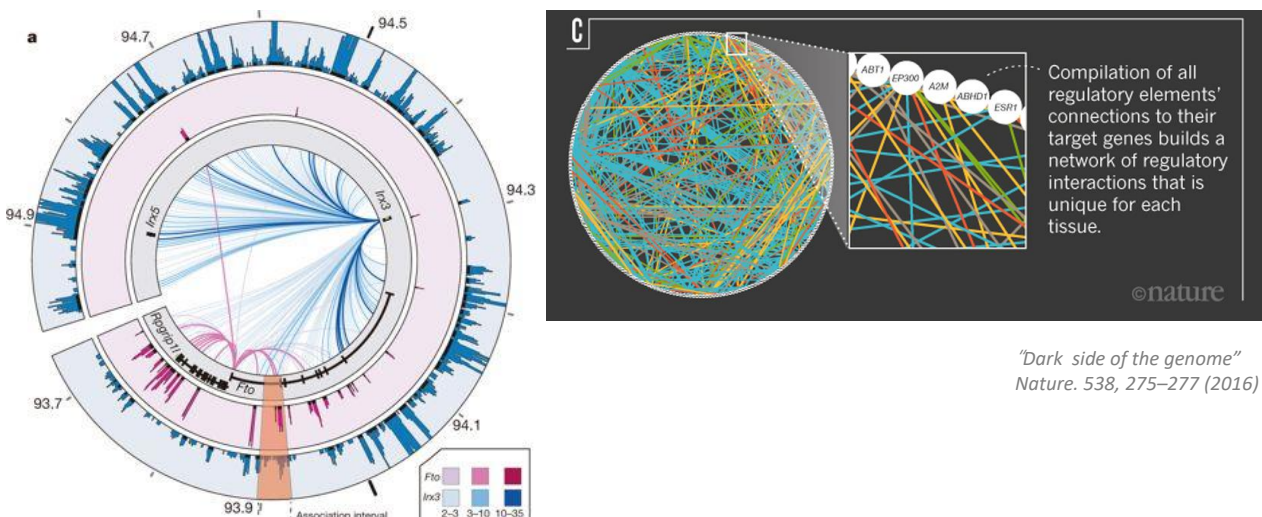
Unravel a hidden regulator

“IRX3 encodes a transcription factor — a type of protein involved in regulating the expression of other genes — and is highly expressed in the brain, consistent with a role in regulating **energy metabolism and eating behaviour.**”



19

“Systems” biology in transcriptional regulation



“Dark side of the genome”
Nature. 538, 275–277 (2016)

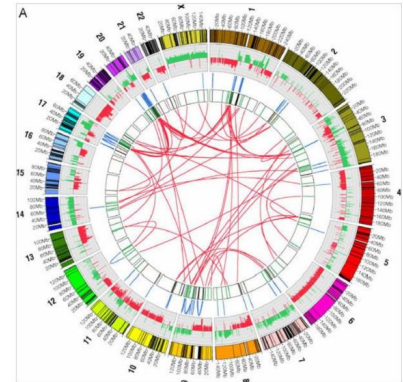
20

#Genomics 단독으로 해석하지 못하는 생물학적 양상을 epigenomics 와의 통합으로 해석 가능

#Epigenomics 조절은 복잡도가 매우 높아 system 수준의 이해가 필요

The Chaotic Complexity of Cancer

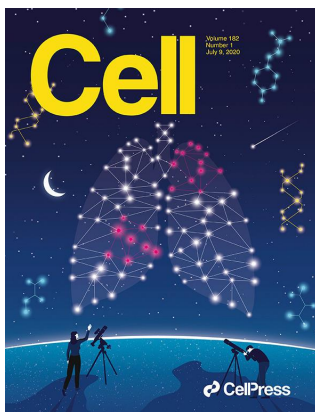
PUBLISHED ON October 28, 2014



(The Complicated Chaos Inside a Cancer Cell)

21

Milestone paper of multiomics study in lung cancer (2020)



CellPress
OPEN ACCESS

Resource Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma

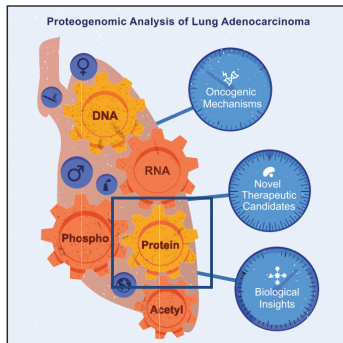
Michael A. Gillette,^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1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Cell

Resource

Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma

Graphical Abstract



Authors

Michael A. Gillette, Shankha Satpathy, Song Cao, ..., D.R. Mani, Steven A. Carr, Clinical Proteomic Tumor Analysis Consortium

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In Brief

Comprehensive proteogenomic characterization of lung adenocarcinomas and paired normal adjacent tissues from patients of diverse smoking status and country of origin yields insights into cancer taxonomy, oncogenesis, and immune response; offers novel candidate biomarkers and therapeutic targets; and provides a community resource for further discovery.

Highlights

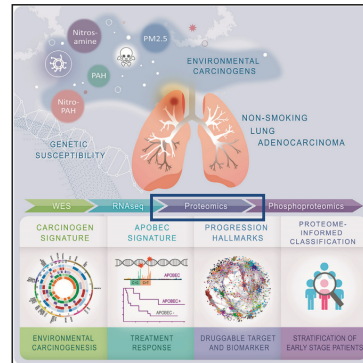
- Comprehensive LUAD proteogenomics exposes multi-omic clusters and immune subtypes
- Phosphoproteomics identifies candidate *ALK*-fusion diagnostic markers and targets
- Candidate drug targets: *PTPN11* (*EGFR*), *SOS1* (*KRAS*), neutrophil degranulation (*STK11*)
- Phospho and acetyl modifications denote tumor-specific markers and druggable proteins

Cell

Resource

Proteogenomics of Non-smoking Lung Cancer in East Asia Delineates Molecular Signatures of Pathogenesis and Progression

Graphical Abstract



Authors

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Correspondence

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In Brief

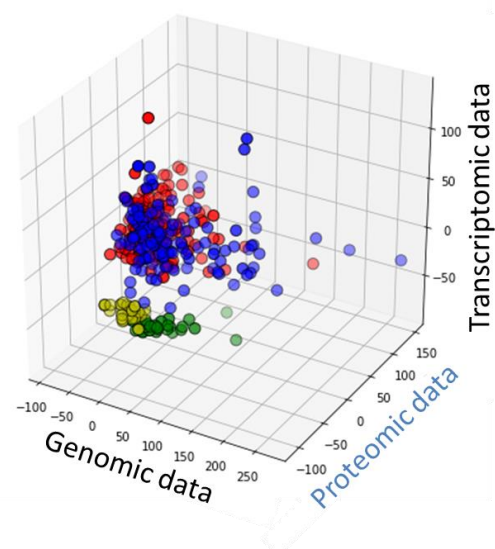
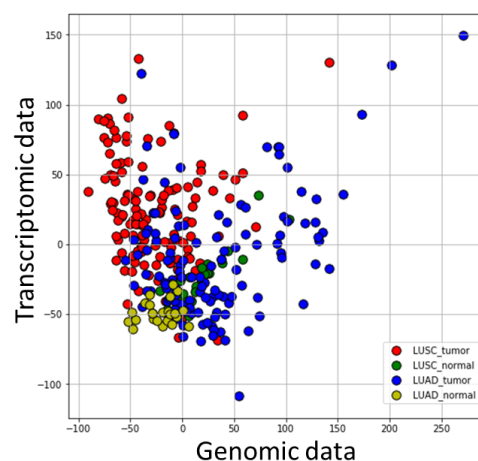
Deep proteogenomic landscape of early stage lung adenocarcinoma in a cohort of mostly non-smokers reveals unique drivers and biomarkers, as well as gender-associated mutagenesis.

Highlights

- First deep proteogenomic landscape of non-smoking lung adenocarcinoma in East Asia
- Identified age, sex-related endogenous, and environmental carcinogen mutagenic processes
- Proteome-informed classification distinguished clinical features within early stages
- Protein networks identified tumorigenesis hallmarks, biomarkers, and druggable targets

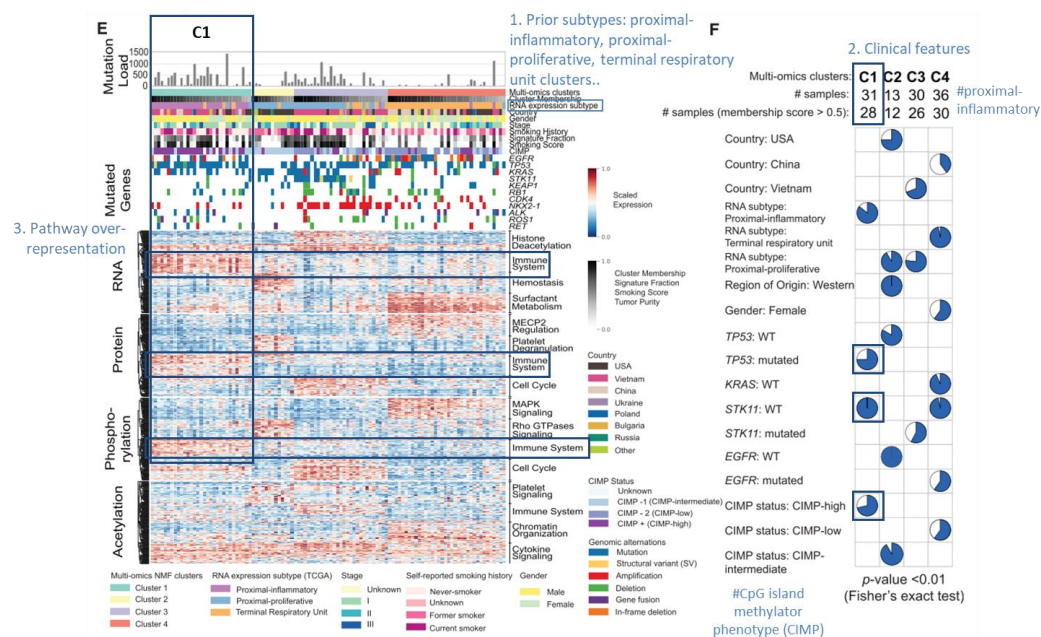
23

Multi-omics clustering



24

Non-negative matrix factorization (NMF)-based unsupervised “multi-omics clustering”: samples of the clusters were significantly associated with distinctive clinical and molecular features

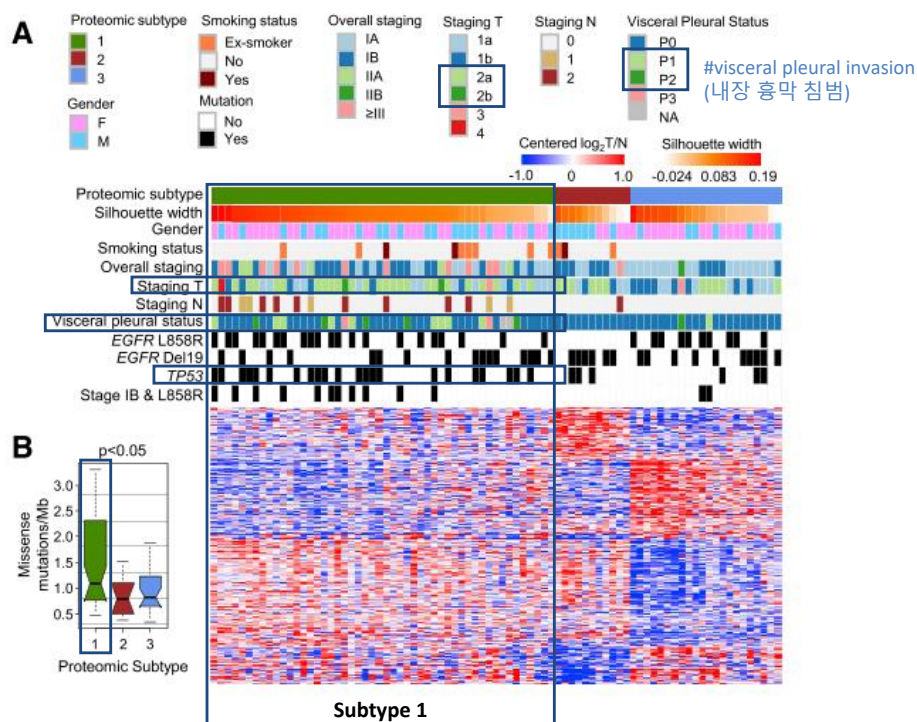


#3. 관련하여 다시한번 정리: multiomics clustering 을 통해 발굴한 sample cluster 가 독특한 clinical and molecular 특징을 나타내면서, 이미 알려진 유전자 구성 (pathway) 특성을 재현성 있게 나타냄

Cell. 182, 200–225 (2020)

25

Alignment of the proteomic subtypes with clinical features revealed a strong separation by tumor staging, as well as by driver mutations

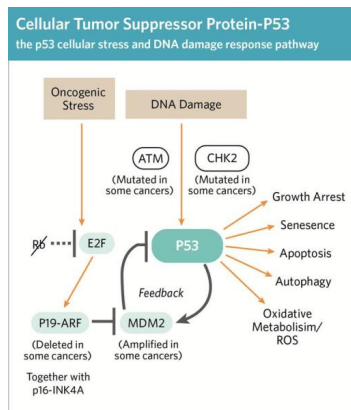
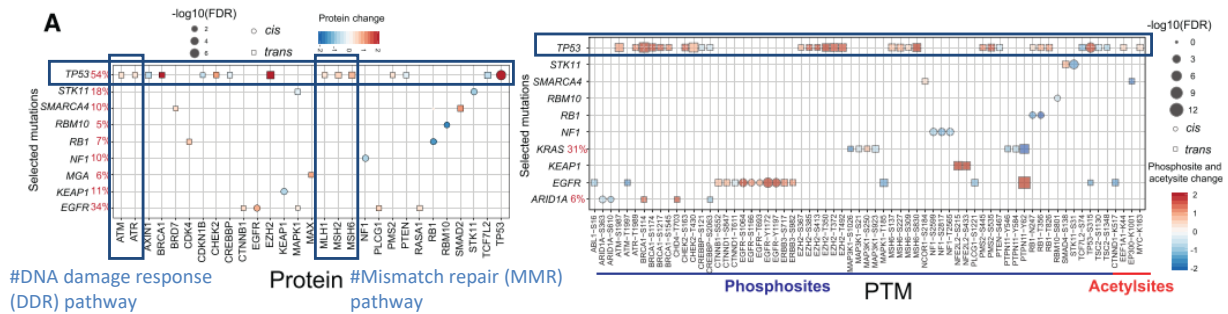


Cell. 182, 226–244 (2020)

26

Connecting driver mutations to proteome, phosphoproteome, and pathways

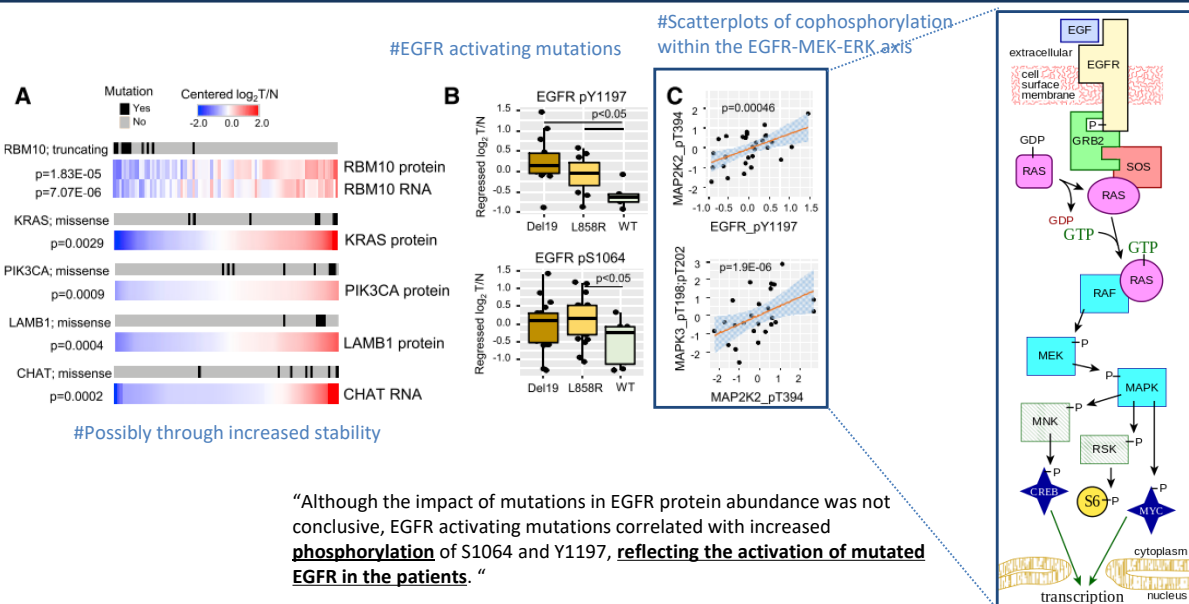
#SKT11 은 중요하지 않다고 하였지만 해당 논문에서는 의미 있게 다룸. 본 워크샵에서는 분량상 생략



Cell. 182, 200–225 (2020)

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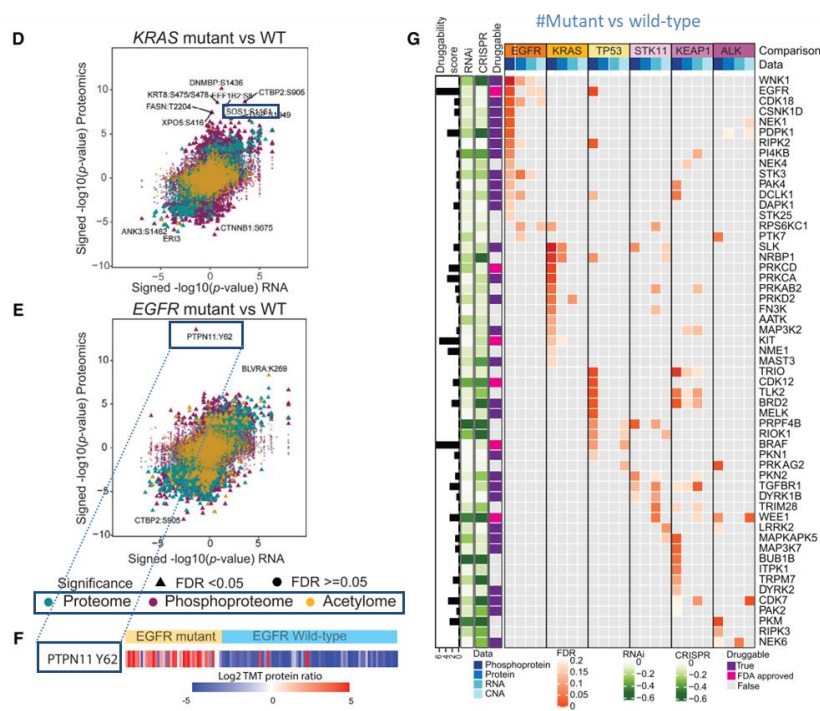
Direct and indirect consequences of genomic aberrations at the transcriptome and proteome levels



Cell. 182, 226–244 (2020)

28

Identification of therapeutic strategies from proteogenomics analyses



“SOS1 is a guanine exchange factor (GEF) that activates KRAS (Vigil et al., 2010), and inhibition of **SOS1 and KRAS is an emerging therapeutic strategy for KRAS mutant cancers** (Hillig et al., 2019; O’Bryan, 2019).”

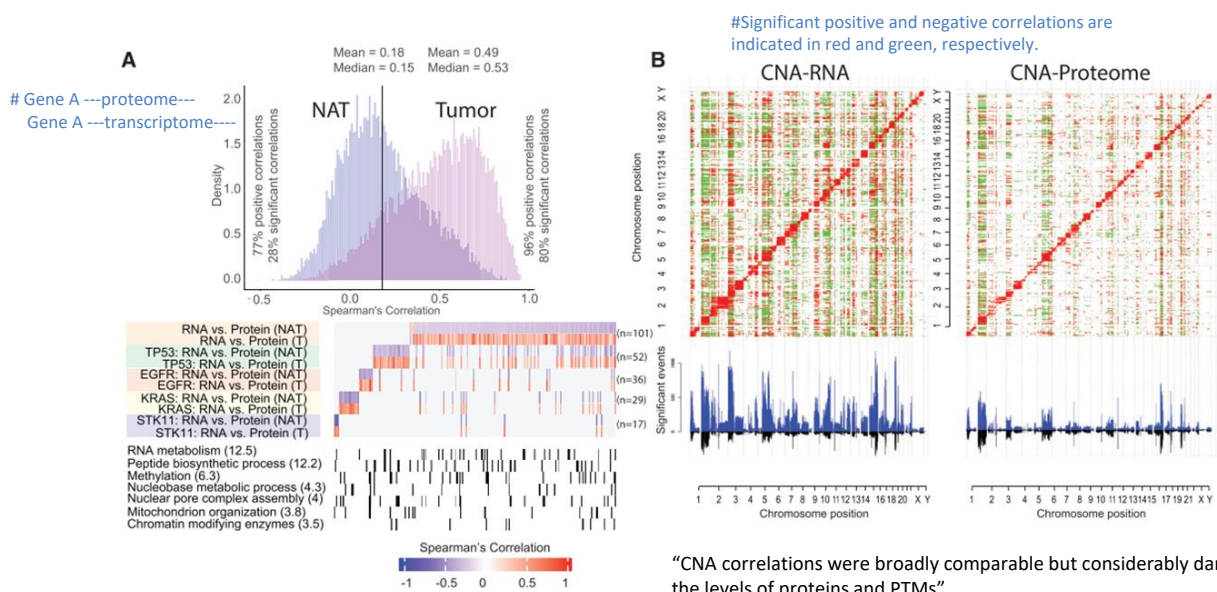
“**EGFR mutant** tumors showed highly significant and remarkably consistent **tyrosine phosphorylation of PTPN11/Shp2 at Y62**.

Although prior studies have associated PTPN11/Shp2 phosphorylation with important biological consequences in NSCLC cell lines and xenograft models, this is, to our knowledge, **the first report of such phosphorylation in a large set of primary treatment-naïve LUADs.**”

Cell. 182, 200–225 (2020)

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Gene-wise CNA-mRNA-protein correlations displayed striking differences



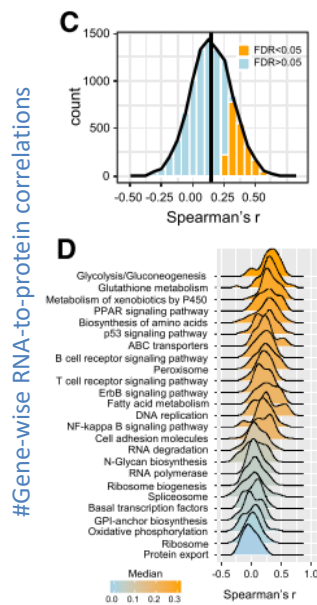
“Although sample-wise mRNA-protein correlations were fairly consistent between tumors and NATs, **gene-wise correlations displayed striking differences**”

“CNA correlations were broadly comparable but considerably dampened at the levels of proteins and PTMs”

Cell. 182, 200–225 (2020)

30

Gene-wise mRNA-protein correlations displayed striking differences



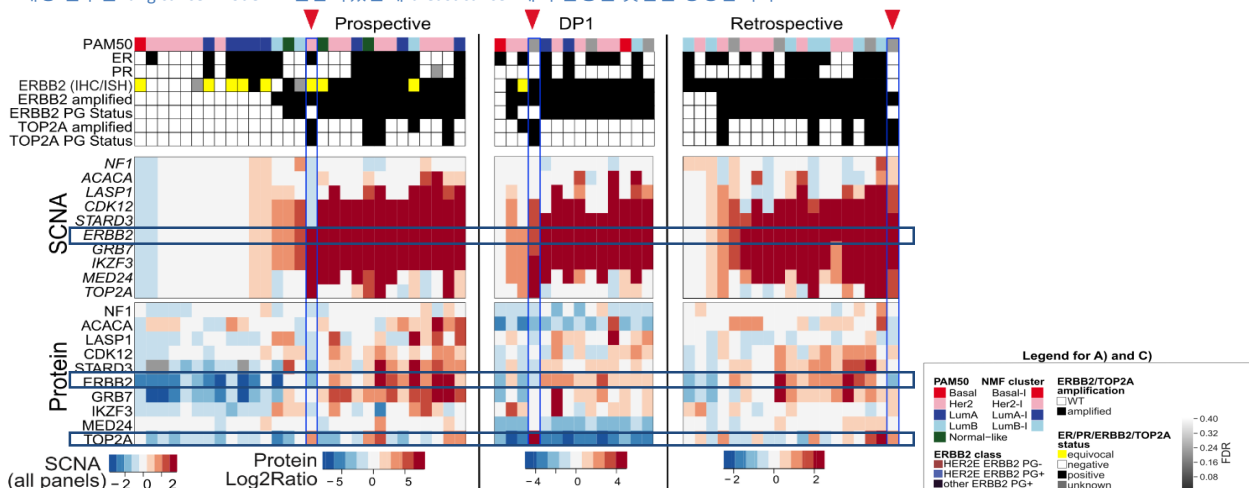
"Only 22% proteins displayed significant positive correlations with the cognate RNA. Enrichment analysis showed a pathway-dependent RNA-to-protein correlation, with **basic cellular functions poorly corresponding to RNA**. Taken together, these analyses indicate transcriptionally modulated upregulation of DNA replication, glycolysis, glutathione metabolism, and immune-related pathways, while upregulation of DNA repair, protein processing and transport pathways, and downregulation of cell-adhesion-related pathways were more apparent at protein level (전사체와 단백질이 pathway 별 변화 양상이 다르다)."

Cell. 182, 226–244 (2020)

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"Pseudo-ERBB2+" status in resistance for anti-ERBB2 antibody therapy

#해당 연구를 lung cancer model 로 언급하였는데 breast cancer 에서 진행된 것임을 정정합니다.



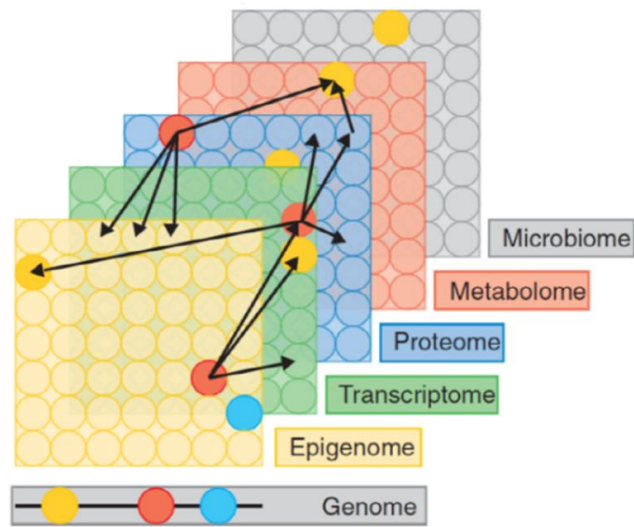
"Because these **pseudo-ERBB2+** samples are examples where anti-ERBB2 treatment may not have **been effective** because of lack of drug target expression, proteogenomics approaches were used to assess ERBB2 driver status in the current dataset and our earlier cohort.

"..amplification and overexpression of TOP2A, suggesting an **alternative chromosome 17 amplicon driver in some cases (Harris et al., 2009).**"

Cell. 183, 1436–1456 (2020)

32

Changes of a layer of one omics do not always transfer into other layer

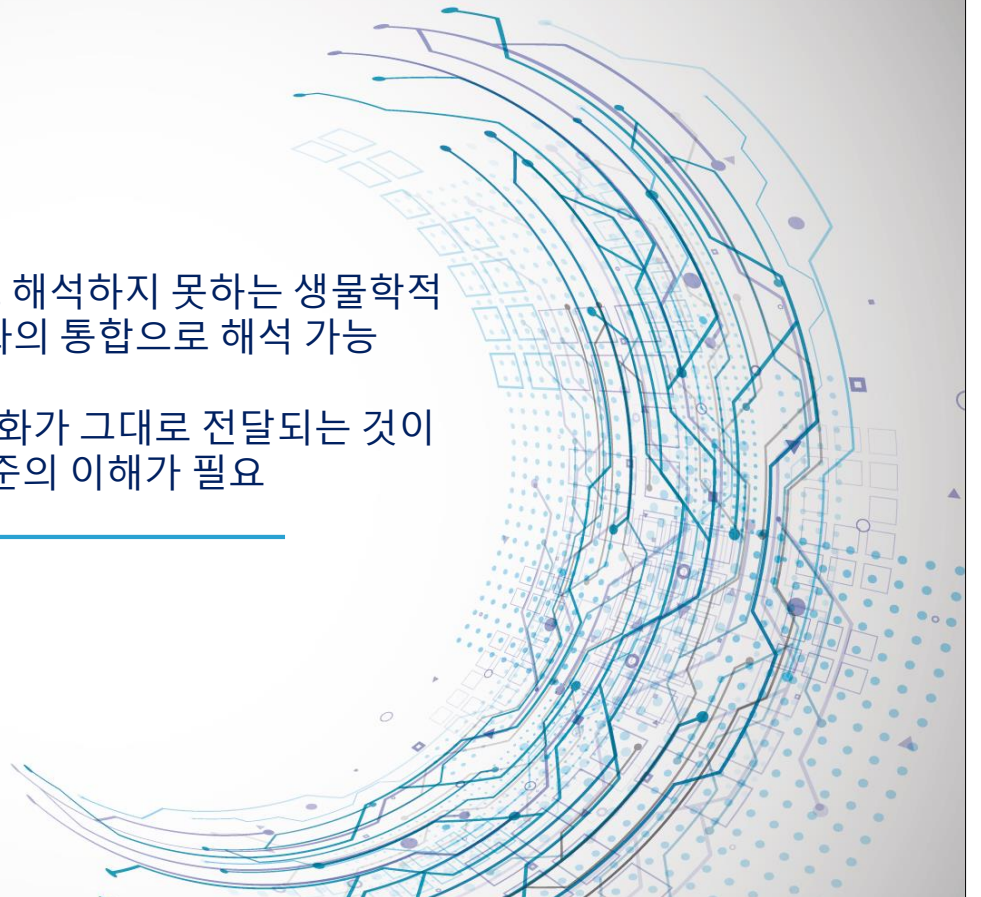


Genome Biology. 18, 83 (2017)

33

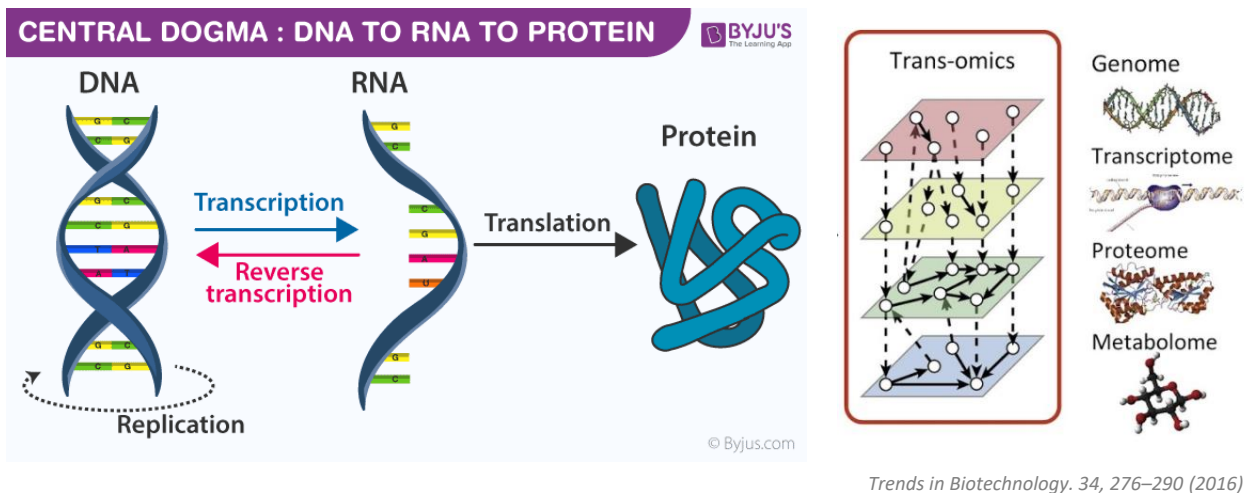
#Genomics 단독으로 해석하지 못하는 생물학적 양상을 proteomics 와의 통합으로 해석 가능

#각 omics 에서의 변화가 그대로 전달되는 것이 아니므로 system 수준의 이해가 필요



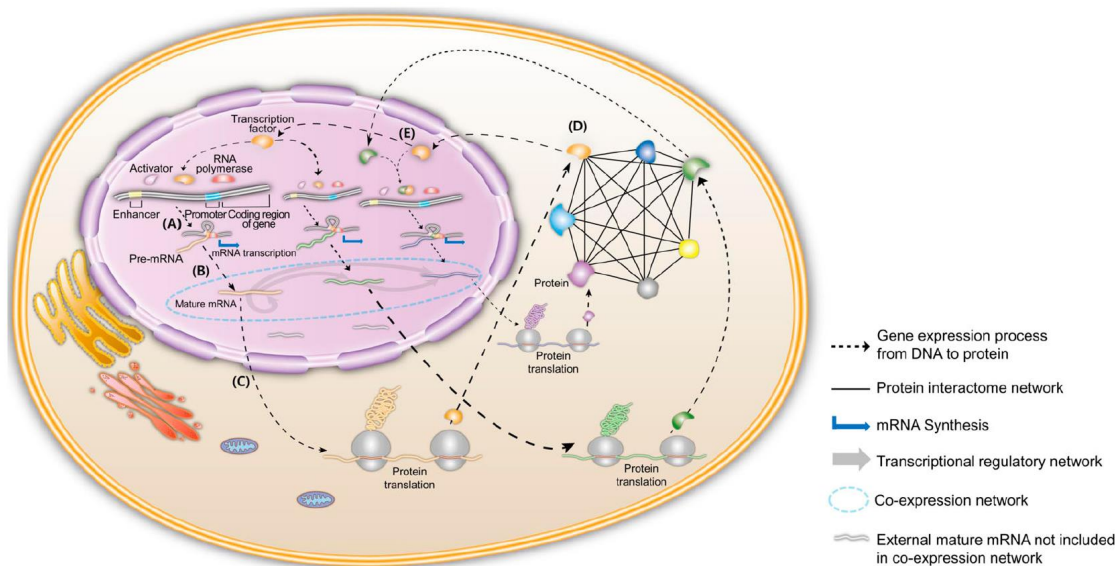
34

Complexity of controlling quantity in central dogma

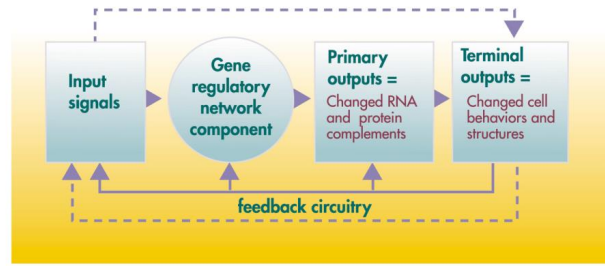
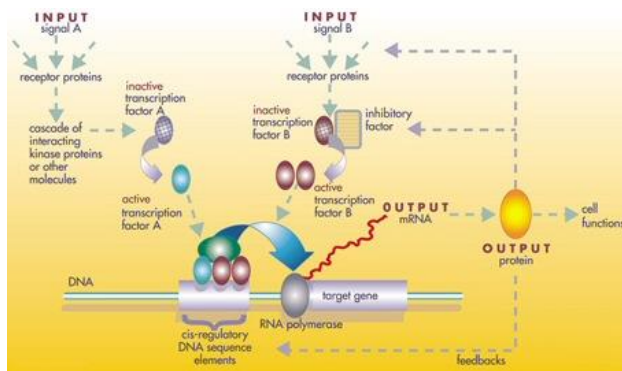


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Multi-omics data for systems biology in cell systems



Gene regulatory network



YGG 01-0086

RegNetwork: Regulatory Network Repository
of Transcription Factor and microRNA Mediated Gene Regulation

HOME SEARCH ABOUT SOURCE DOWNLOAD CONTRIBUTION LINKS

Welcome to RegNetwork! RegNetwork is a data repository of the type transcriptional and posttranscriptional regulatory relationships for human and mouse.

Legend:
 - TF=TF
 - TF=TF
 - TF=miRNA
 - miRNA=TF

“..the potential regulations inferred based on the **transcription factor binding sites (TFBSs).**”

Updated with new regulatory (Releases - [using log/next Download 50mb](#))

Reference:
 Zhi Peng Liu, Guang Wu, Mingyue Xiao and Huihui Wu (2013). RegNetwork: an integrated database of transcriptional and posttranscriptional regulatory networks in human and mouse. Database.org. doi: 10.1093/database/bat001

TRRUST version 2
Transcriptional Regulatory Relationships
Unraveled by Sentence-based Text mining

About TRRUST Search Download

TRRUST (version 2) is a manually curated database of human and mouse transcriptional regulatory networks.

Current version of TRRUST contains 8,444 and 6,552 TF-target regulatory relationships of 800 human TFs and 828 mouse TFs, respectively. They have been derived from 11,237 PubMed articles, which describe small-scale experimental studies of transcriptional regulations. To efficiently search for regulatory relationships from over 20 million PubMed articles, we used sentence-based text mining approach.

TRRUST database also provides information of mode of regulation (activation or repression). Currently 6,972 (59.8%) regulatory relationships are known for mode of regulation.

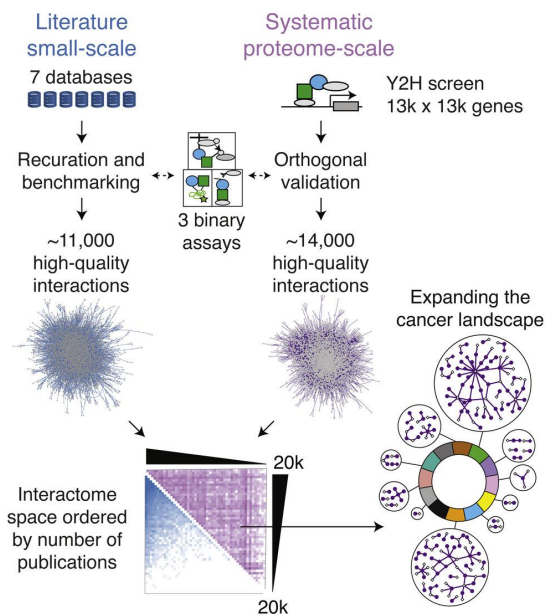
Tables for human genes and mouse genes included in TRRUST.

TRRUST network edge information is freely available for non-commercial research at Download page.

* TRRUST version 1 website can be found [HERE](#).

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Interactome network



The Human Reference Protein Interactome Mapping Project

Home Search Download Downloads About FAQ Contact Register Login

HuRI
The Human Reference Interactome and Literature Benchmark
PROTEINS 11600 INTERACTIONS 76563

Mission
At the Center for Cancer Systems Biology at Dana-Farber Cancer Institute all pairwise combinations of human protein-coding genes are systematically being interrogated to identify which are involved in binary protein-protein interactions. In our most recent effort 17,500 proteins have been tested and a first human reference interactome (HuRI) map has been generated. The entirety of all interactions identified in systematic screens at CCSB forms H5-unions.

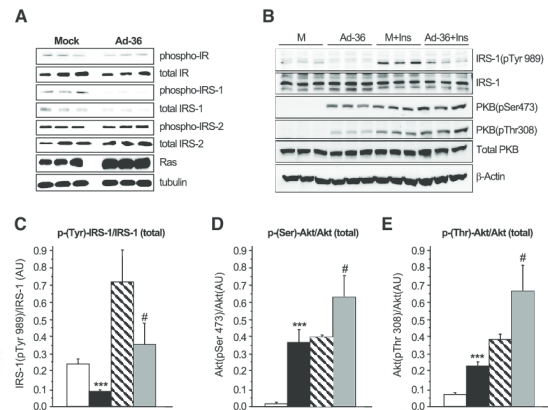
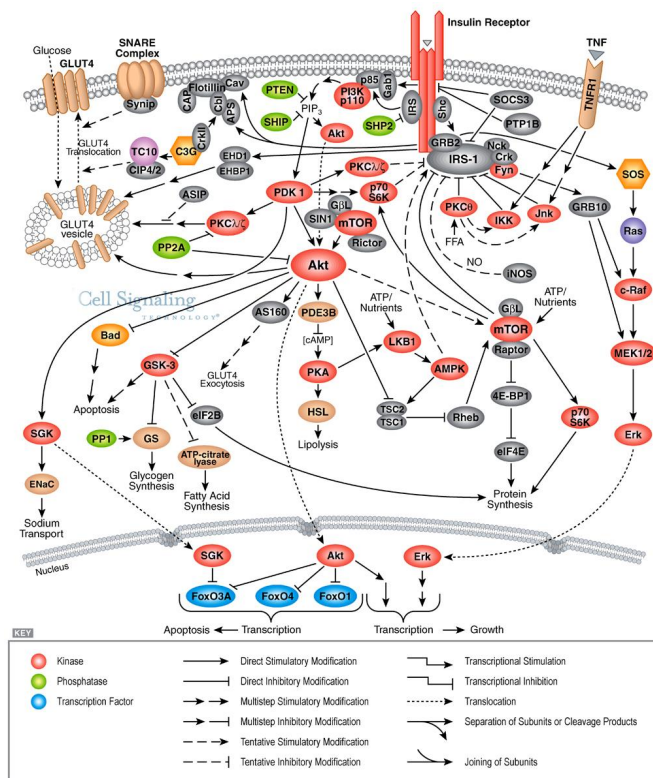
Search, Information, Download icons

Network diagram showing interactions between proteins like GPC1, GPC2, GPC3, GPC4, GPC5, GPC6, GPC7, GPC8, GPC9, GPC10, GPC11, GPC12, GPC13, GPC14, GPC15, GPC16, GPC17, GPC18, GPC19, GPC20, GPC21, GPC22, GPC23, GPC24, GPC25, GPC26, GPC27, GPC28, GPC29, GPC30, GPC31, GPC32, GPC33, GPC34, GPC35, GPC36, GPC37, GPC38, GPC39, GPC40, GPC41, GPC42, GPC43, GPC44, GPC45, GPC46, GPC47, GPC48, GPC49, GPC50, GPC51, GPC52, GPC53, GPC54, GPC55, GPC56, GPC57, GPC58, GPC59, GPC60, GPC61, GPC62, GPC63, GPC64, GPC65, GPC66, GPC67, GPC68, GPC69, GPC70, GPC71, GPC72, GPC73, GPC74, GPC75, GPC76, GPC77, GPC78, GPC79, GPC80, GPC81, GPC82, GPC83, GPC84, GPC85, GPC86, GPC87, GPC88, GPC89, GPC90, GPC91, GPC92, GPC93, GPC94, GPC95, GPC96, GPC97, GPC98, GPC99, GPC100.

Cell. 159, 1212-1226 (2014)
Nature. 580, 402-408 (2020)

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Signaling network



39

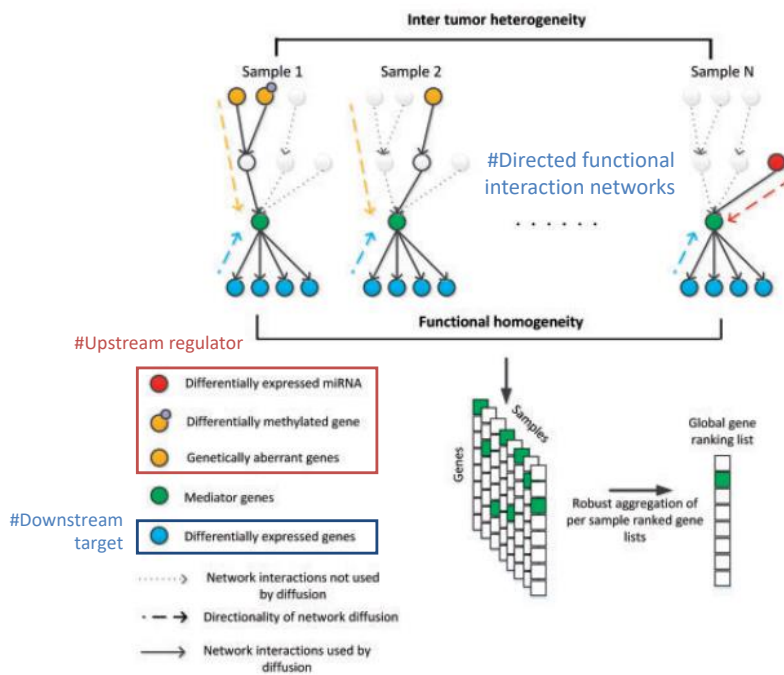
#Multiomics system 에는 다양한 층위 및 network 가 존재

#이것을 multiomics 해석에 어떻게 적용할지는 case-dependent



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Network-based integration of multi-omics data for prioritizing cancer genes



#원론, 청사진 등으로 언급한 대상은 생명현상의 정보를 담고 있는 DNA

Bioinformatics. 34, 2441-2448 (2018)

The final scores for all genes are computed as the Hadamard product

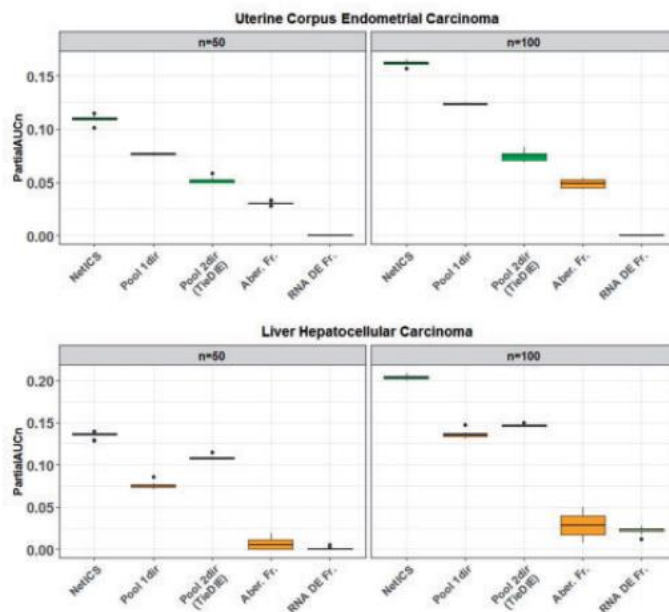
$$E = E_M \circ E_D. \quad (7)$$

"The vector E determines the **mediator effect** for each gene.

A large entry in E_M at position i means that gene i is **proximal to many upstream-located aberrant genes or miRNA**, and a large entry in E_D at position i means that gene i is **proximal to many downstream-located differentially expressed genes**."

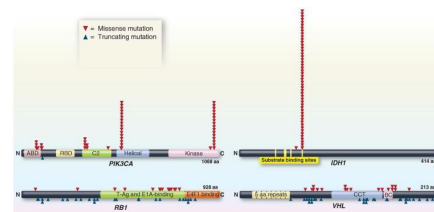
41

Prediction of known cancer genes



#Aberr Fr.: ranking by **frequency of aberrant genes** across all samples

#RNA DE Fr.: ranking by **frequency of differentially expressed genes** across all samples

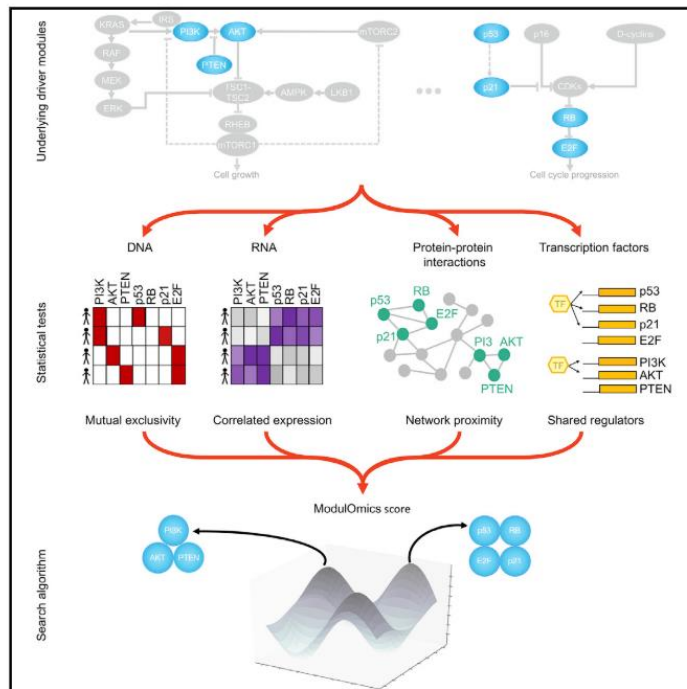


Science. 339, 1546-1558 (2013)

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Simultaneous integration of multi-omics data improves the identification of cancer driver modules

Graphical Abstract

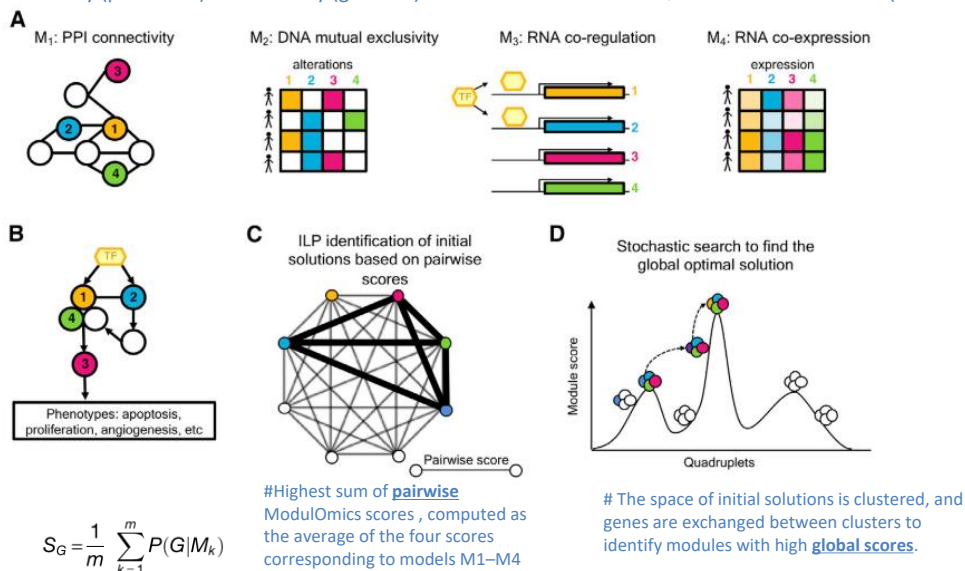


Cell Systems. 8, 456-466 (2019)

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Modulomics

#M1 = frequency of connectivity (proteome) #M2 = DNA mutual exclusivity (genome) #M3 = co-regulation for common TF (transcriptome) #M4 = co-expression correlation (transcriptome)

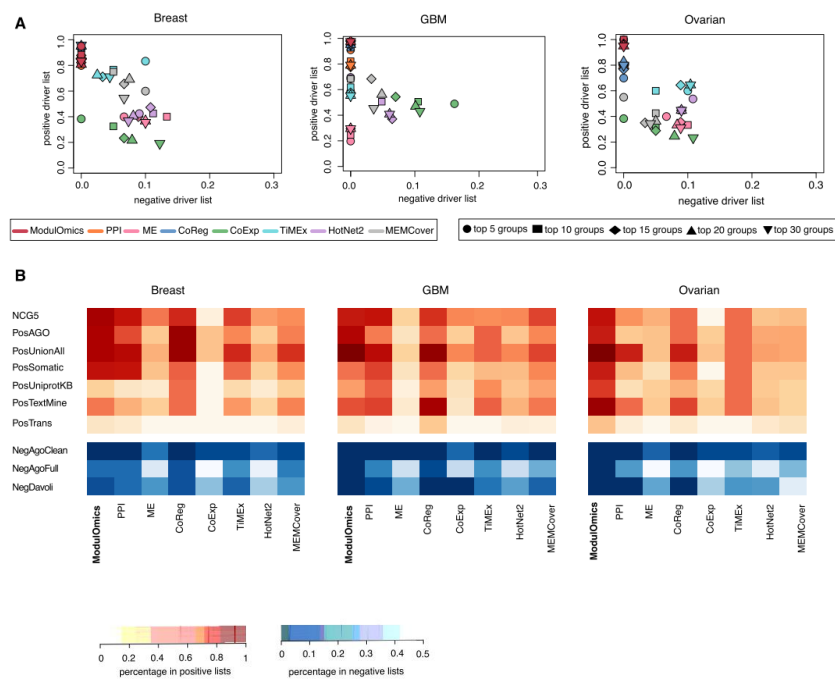


"Given a set $G=\{G_1, \dots, G_n\}$ of genes and a collection $M=\{M_1, \dots, M_m\}$ of models for different data types, we are interested in computing S_G reflecting **how likely are the genes in G to be functionally connected**.

S_G is the genes in G are, under different models: computed as the mean of m probabilistic scores $P(G|M_k)$. Each of these m scores represents how strongly functionally connected the genes in G are, under different models."

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The driver module inferred by ModulOmics are enriched with cancer driver genes:
no single omics data type dominated the ModulOmics score



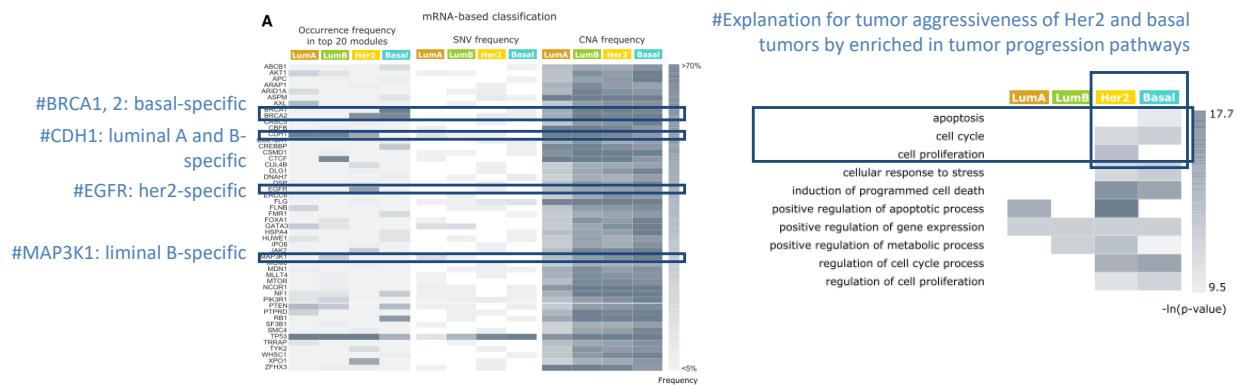
45

The driver modules inferred by ModulOmics are enriched with cancer driver pathways



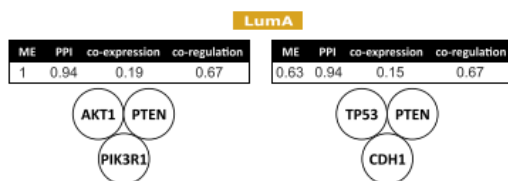
46

Driver modules in breast cancer subtypes recapitulate known mechanisms



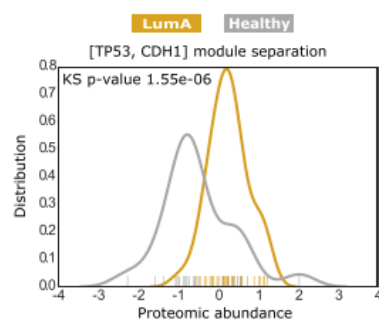
47

Driver modules in breast cancer subtypes suggest unexplored functionalities

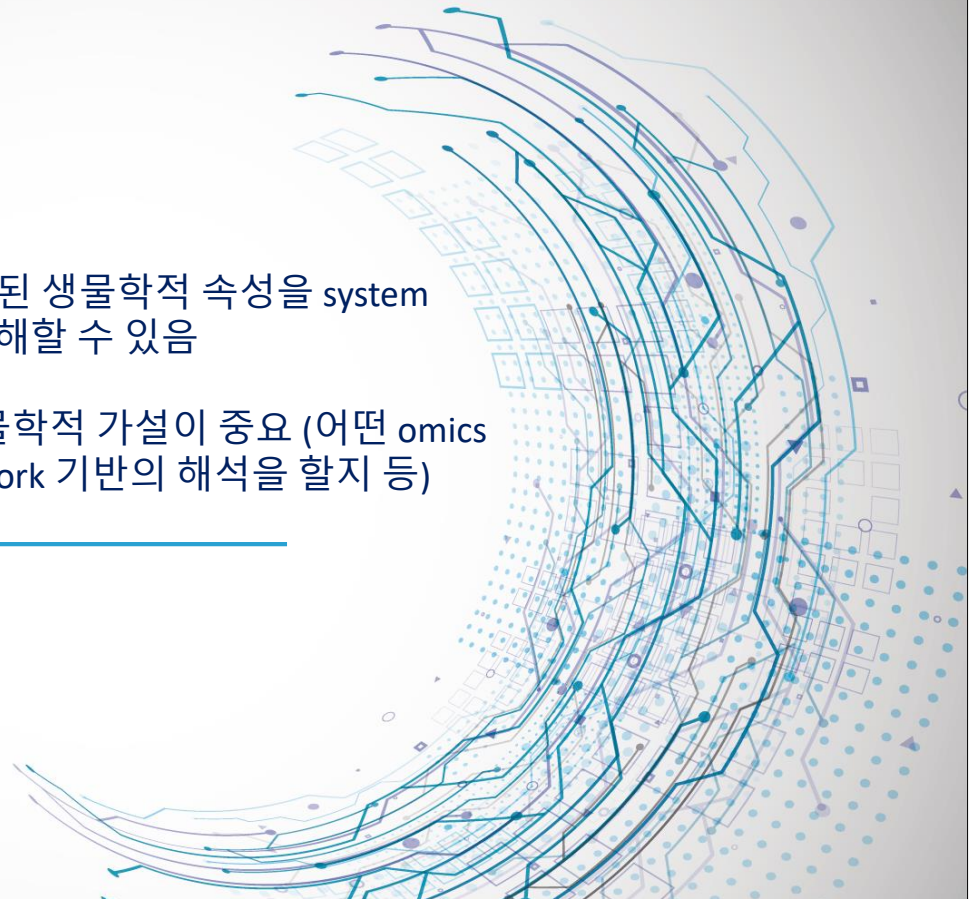


“The canonical module PTEN, AKT1, PIK3R1 recapitulates the known mutual exclusivity pattern of mutations within the PI3K pathway.”

“In contrast, the module suggesting the **noncanonical role (PTEN, CDH1, TP53)** supports the hypothesis that PTEN regulates cell proliferation by increasing the binding of CDH1 to APC/C, a complex known for its tumor-suppressive function, and by increasing TP53 acetylation following DNA damage.”



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#Multiomics 에 내재된 생물학적 속성을 system
기반의 분석으로 이해할 수 있음

#알맞게 고안된 생물학적 가설이 중요 (어떤 omics
데이터에 어떤 network 기반의 해석을 할지 등)

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#Sequencing 기술의 발전이 omics 연구를 가능하게 함 -> multiomics

#Global science network 에서 multiomics big data 가 해석가능한
형태로 생산 및 제공되고 있음

#Omics 단독으로 해석하지 못하는 생물학적 양상을 multiomics 로
해석 가능

#Multiomics 간 조절은 매우 복잡도가 매우 높고, 각 omics 에서의
변화가 그대로 전달되는 것이 아니므로 system 수준의 이해가 필요

#생물학적 system 에는 다양한 층위가 존재하므로, 이것을
multiomics 해석에 어떻게 적용할지는 case-dependent

#알맞게 고안된 생물학적 가설이 중요 (어떤 omics 데이터에 어떤
network 기반의 해석을 할지 등)

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Thank you

실습: NMF clustering of multiomics data and network analysis

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Kwoneel Kim, PhD

Kwoneelkim@gmail.com

KSBi-BIML 2021

NMF clustering of LUAD multi-omics data
and network analysis

Kyung Hee University

Jiyeon Kim

본 강의 자료는 한국생명정보학회가 주관하는 KSBi-BIML 2021 워크숍 온라인 수업을 목적으로 제작된것으로 해당 목적 이외의 다른 용도로 사용할 수 없음을 분명하게 알립니다. 수업 목적으로 배포 및 전송 받은 경우에도 이를 다른 사람과 공유하거나 복제, 배포, 전송할 수 없습니다.

만약 이러한 사항을 위반할 경우 발생하는 모든 법적 책임은 전적으로 불법 행위자 본인에게 있음을 경고합니다.

실습 목표

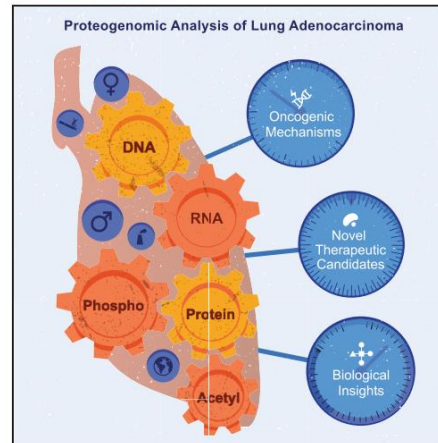
- Multi-omics data를 NMF method를 이용하여 clustering
- Analysis of network-based mechanism

Cell

Resource

Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma

Graphical Abstract



Authors

Michael A. Gillette, Shankha Satpathy, Song Cao, ..., D.R. Mani, Steven A. Carr, Clinical Proteomic Tumor Analysis Consortium

Correspondence

gillette@broadinstitute.org (M.A.G.), shankha@broadinstitute.org (S.S.), scarr@broad.mit.edu (S.A.C.)

In Brief

Comprehensive proteogenomic characterization of lung adenocarcinomas and paired normal adjacent tissues from patients of diverse smoking status and country of origin yields insights into cancer taxonomy, oncogenesis, and immune response; offers novel candidate biomarkers and therapeutic targets; and provides a community resource for further discovery.

Data preparing

Data Download

#Data는 논문에서 제공하는 supplementary data 사용
#제공된 multiomics 데이터를 사용하여 NMF clustering 수행

- RNA expression
- Protein expression
- Copy number variation

Data pre-processing

- 전체 샘플의 30% 이상 NA값을 가진 feature 제거
- Feature name filtering
- Sample filtering
- Feature 별 std < 0.5인 feature 제거

RNA	9259
Protein	7107
CNV	19

Google Colaboratory

Colaboratory에 오신 것을 환영합니다의 사본 ☆

파일 수정 보기 삽입 런타임 도구 도움말 2019년 11월 5일에 마지막으로 수정됨

Colaboratory에 오신 것을 환영합니다

Colaboratory는 설치가 필요 없으며 완전히 클라우드에서 실행되는 무료 Jupyter 노트북 환경입니다. Colaboratory를 사용하면 브라우저를 통해 무료로 코드를 작성 및 실행하고, 분석을 저장 및 공유하며, 강력한 컴퓨팅 리소스를 이용할 수 있습니다.

Colaboratory 소개

3분 길이의 동영상 통해 Colaboratory의 주요 기능을 간단하게 알아보세요.

Get started with Google Colaboratory (Code)

Intro to Google Colab

Coding TensorFlow

#Colab 기본 정보 참고 자료

https://drive.google.com/drive/folders/1jxOCihLdevxyBilt9IKidrb_x74PWSyl?usp=sharing

5

NMF clustering

• Nimfa library 사용

Nimfa

Star 437

Navigation

Models (models)

Methods (methods)

Utils (utils)

Examples (examples)

Datasets (datasets)

Quick search

Go

Welcome to Nimfa

Nimfa is a Python library for nonnegative matrix factorization. It includes implementations of several factorization methods, initialization approaches, and quality scoring. Both dense and sparse matrix representation are supported.

Nimfa is distributed under the BSD license.

The sample script using Nimfa on medulloblastoma gene expression data is given below. It uses alternating least squares nonnegative matrix factorization with projected gradient method for subproblems [Lin2007] and Random Vcol [Albright2006] initialization algorithm. The returned object is fitted factorization model through which user can access matrix factors and estimate quality measures.

#Rank = sample cluster

```
import nimfa

V = nimfa.examples.medulloblastoma.read(normalize=True)

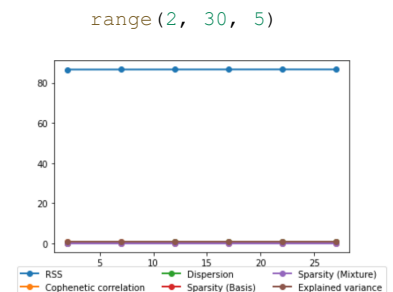
lsnmf = nimfa.Lsnmf(V, seed='random_vcol', rank=50, max_iter=100)
lsnmf_fit = lsnmf()

print('Rss: %5.4f' % lsnmf_fit.fit.rss())
print('Evar: %5.4f' % lsnmf_fit.fit.evar())
print('K-L divergence: %5.4f' % lsnmf_fit.distance(metric='kl'))
print('Sparseness, W: %5.4f, H: %5.4f' % lsnmf_fit.fit.sparseness())
```

Running this script produces the following output, where slight differences in reported scores across different runs can be attributed to randomness of the Random Vcol initialization method:

```
Rss: 0.2668
Evar: 0.9997
K-L divergence: 38.8744
Sparseness, W: 0.7297, H: 0.8796
```

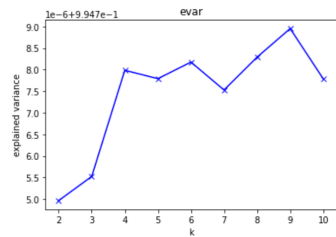
#Clustering score 에 기반하여 최적의 cluster number 를 찾으려 하는데, score 간 scale 이 상당히 차이가 나기 때문에 다양한 scoring 기법을 시도함



6

NMF clustering

#k = the number of sample clusters

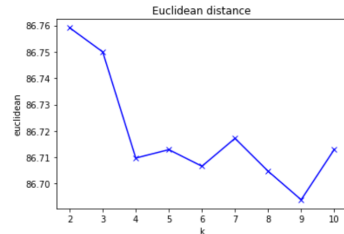


#Evaluated variance(evar) 가 증가하고 residual sum of squares와 euclidean distance 가 감소할수록 clustering 이 잘 되었다고 판단할 수 있음
#k 초기값의 설정에 따라 scoring이 달라질 수 있음

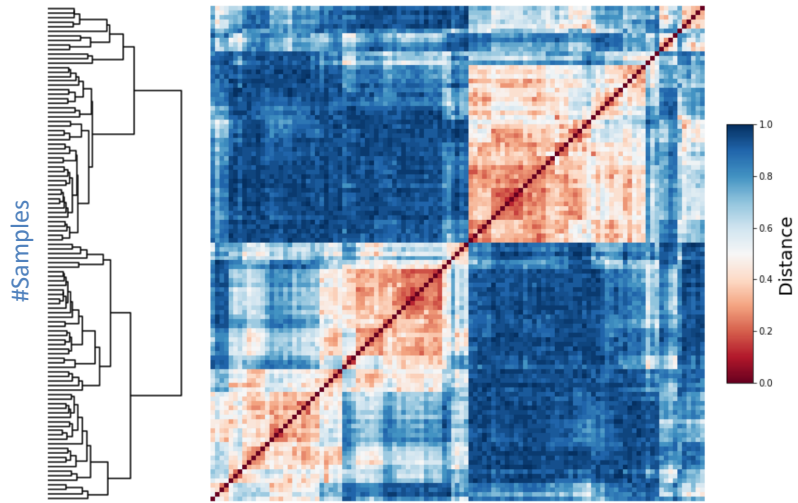
Determined k : 4



Determined k : 4



Determined k : 4



#유전자별 각 clustering에 대한 기여도를 알고리즘에서 산출해 줌

7

Protein-protein interaction

<https://string-db.org/cgi/download?sessionId=bnEQRR5VwVKB>

#본 실습에서는 가정을 매우 단순히 하여 protein interactome 만을 사용하여 clustering 결과에 대한 system 수준의 접근을 시도

	node1	node2	combined_score
0	ARF5	SPTBN2	909
1	ARF5	KIF13B	910
2	ARF5	KIF21A	910
3	ARF5	TMED7	906
4	ARF5	ARFGAP1	971
...	...	...	...
648299	OR6Q1	REEP1	900
648300	OR6Q1	REEP4	900
648301	OR6Q1	GNB1	900
648302	OR6Q1	RTP3	900
648303	OR6Q1	REEP2	900

648304 rows × 3 columns

#combined_score: 두 유전자가 interacting 할 확률 값. 확률x103 값으로 반환됨.

```

Features = [features_0, features_1, features_2, features_3]

def change_ID(features):
    #feature = gene
    """change proteinID to geneSymbol"""
    result_name = []
    for name in features:
        if (name.split('_')[-1] == 'RNA') or (name.split('_')[-1] == 'CNV'):
            result_name.append(name.split('_')[0])
        elif name.split('_')[-1] == 'Protein':
            result_name.append(proid2gene[name[:-8]])
    return result_name

def get_ppis(features, ppis):
    feature_rst = change_ID(features)
    feature_rst = list(set(feature_rst))
    print(len(features), '->', len(feature_rst))

    ppi_tmp = ppis[(ppi['node1'].isin(feature_rst)) & (ppi['node2'].isin(feature_rst))]
    ppi_list = list(set(ppi_tmp['node1']))
    print(len(ppi_list))
    return ppi_list

for c, features in enumerate(Features):
    setattr(mod, f'ppis_{c}', get_ppis(features, ppis))
    
```

1000 -> 903
324
1000 -> 889
537
1000 -> 873
456
1000 -> 894
265

#각 omics data 간의 gene symbol - gene id mapping
에 중복이 있을 수 있음

8

Pathway enrichment analysis

<https://maayanlab.cloud/Enrichr/#stats>

#NMF cluster 에서 protein interaction 을 하는 그룹들이 어떤 biological pathway 에 enrichment 되어 있는지 확인

- Gseapy library 사용



Enrichr

Login | Register

31,333,825 lists analyzed

339,127 terms

171 libraries

Analyze

What's new?

Libraries

Gene search

Term search

About

Help

```
len(gp.get_library_name())
```

171

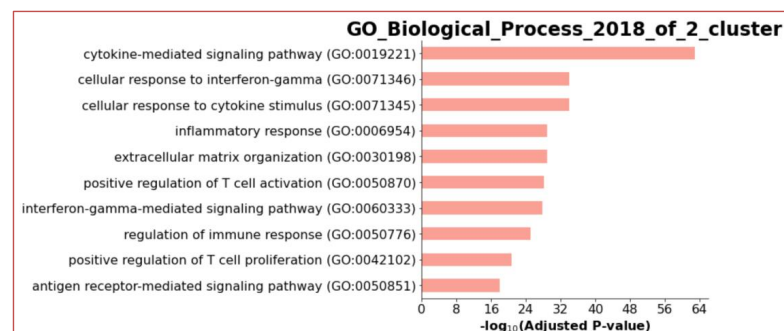
Gene-set Library	Terms	Gene Coverage	Genes per Term
Genes_Associated_with_NIH_Grants	32876	15886	9
Cancer_Cell_Line_Encyclopedia	967	15797	176
Achilles_fitness_decrease	216	4271	128
Achilles_fitness_increase	216	4320	129
Aging_Perturbations_from_GEO_down	286	16129	292
Aging_Perturbations_from_GEO_up	286	15309	308
Allen_Brain_Atlas_10x_scRNA_2021	766	12361	124
Allen_Brain_Atlas_down	2192	13877	304
Allen_Brain_Atlas_up	2192	13121	305
ARCHS4_Cell-lines	125	23601	2395
ARCHS4_IDG_Coexp	352	20883	299
ARCHS4_Kinases_Coexp	498	19612	299
ARCHS4_TFs_Coexp	1724	25983	299
ARCHS4_Tissues	108	21809	2316

GO Biological Process 2018

5103

14433

#실습에서는 immune-related pathway 에 enrichment 를 보인 2번째 cluster 에 집중

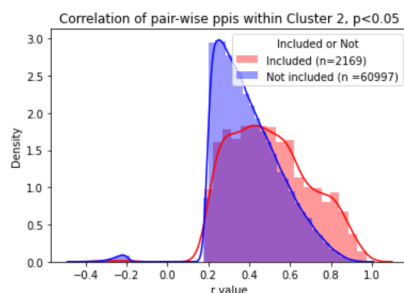


9

DEG correlation

#DEG(differentially expressed gene) correlation 분석을 통해 normal-tumor 사이에 유전자 발현 변화 양상이 cluster 2의 protein interacting group 내에서 유전자 간 연관성이 있는 지를 protein interacting 하지 않는 group 과의 비교를 수행, 이를 통해 cluster 2 내부의 protein interacting gene 들은 서로 간 normal-tumor 의 변화의 양상이 연관성을 갖고 있음을 간접적으로 증명

All pair-wise of PPIs



```
ranksums(list(pyr.values()),list(pnr.values()))
```

RanksumsResult(statistic=24.84229574295336, pvalue=3.13237299847862e-136)

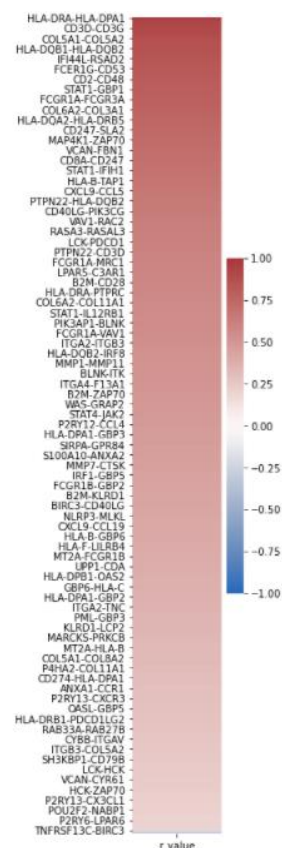
Degree of PPIs

B2M	61
HLA-DRB1	60
HLA-DRA	60
LCK	56
PTAFR	55

#feature = gene

CD226	1
AK4	1
CLEC7A	1
HAVCR2	1
NRK	1

Name: node1, Length: 456, dtype: int64



10

The screenshot shows the cBioPortal website interface. At the top, there is a navigation bar with links to Data Sets, Web API, R/MATLAB, Tutorials/Webinars, FAQ, News, Visualize Your Data, About, and cBioPortal Installations. Below the navigation bar, there is a search bar and a 'Quick Search Beta!' button. The main content area is titled 'Select Studies for Visualization & Analysis:'. On the left, there is a list of cancer types with their respective sample counts: PanCancer Studies (7), Pediatric Cancer Studies (13), Immunogenomic Studies (8), Cell lines (3), Adrenal Gland (3), Ampulla of Vater (1), Biliary Tract (9), Bladder/Urinary Tract (17), Bone (2), Bowel (10), Breast (18), CNS/Brain (20), Cervix (2), Esophagus/Stomach (18), and Eye (5). On the right, there is a list of studies under the 'PanCancer Studies' section. The studies listed are: MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017) with 10945 samples, Metastatic Solid Cancers (UMich, Nature 2017) with 500 samples, MSS Mixed Solid Tumors (Broad/Dana-Farber, Nat Genet 2018) with 249 samples, SUMMIT - Neratinib Basket Study (Multi-Institute, Nature 2018) with 141 samples, TMB and Immunotherapy (MSKCC, Nat Genet 2019) with 1661 samples, Tumors with TRK fusions (MSK, Clin Cancer Res 2020) with 106 samples, and Cancer Therapy and Clonal Hematopoiesis (MSK, Nat Genet 2020) with 24146 samples. Below the 'PanCancer Studies' section, there is a 'Pediatric Cancer Studies' section with a list of studies: Pediatric Preclinical Testing Consortium (CHOP, Cell Rep 2019) with 261 samples, Pediatric Acute Lymphoid Leukemia - Phase II (TARGET, 2018) with 1978 samples, Pediatric Rhabdoid Tumor (TARGET, 2018) with 72 samples, Pediatric Wilms' Tumor (TARGET, 2018) with 657 samples, Pediatric Acute Myeloid Leukemia (TARGET, 2018) with 1025 samples, Pediatric Neuroblastoma (TARGET, 2018) with 1089 samples, Pediatric Pan-Cancer (DKFZ, Nature 2017) with 961 samples, Pediatric Pan-cancer (Columbia U, Genome Med 2016) with 103 samples, Acute Lymphoblastic Leukemia (St Jude, Nat Genet 2016) with 73 samples, Acute Lymphoblastic Leukemia (St Jude, Nat Genet 2015) with 93 samples, Pediatric Ewing Sarcoma (DFCI, Cancer Discov 2014) with 107 samples, Ewing Sarcoma (Institut Curie, Cancer Discov 2014) with 112 samples, and Medulloblastoma (PCPG, Nature 2012) with 37 samples. On the right side of the interface, there is a 'What's New' section with a cBioPortal logo and a brief description of the new year's features. Below this, there is a 'Sign up for low-volume' button and a 'Subscribe' button. At the bottom right, there is an 'Example Queries' section with a list of queries: Primary vs. metastatic prosta, RAS/RAF alterations in color, BRCA1 and BRCA2 mutation, POLE hotspot mutations in ei, TP53 and MDM2/4 alteration, PTEN mutations in GBM in te, Patient view of an endometric, All TCGA Pan-Cancer, MSK-IMPACT clinical cohort, and Histone mutations across car. Below the 'Example Queries' section, there is a 'Local Installations' section with a map of the world showing the locations of various installations.

Thank you

