

Integrative Genomic and Transcriptomic Analysis Associated with Neoadjuvant Chemotherapy Response in HER2-Positive Breast Cancer

Team member:

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Date: 2024-6-11

01

Introduction



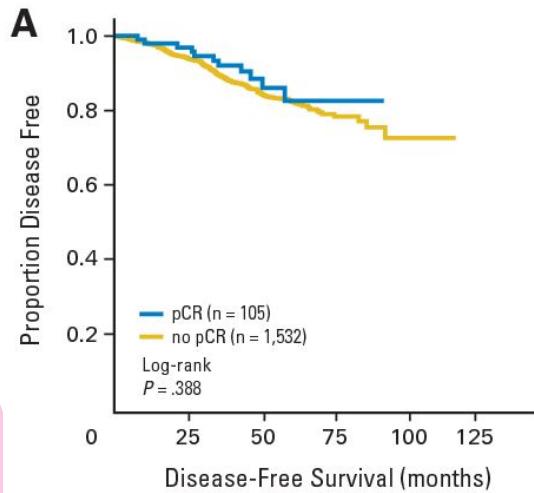
Treatment for breast cancer

Neoadjuvant chemotherapy

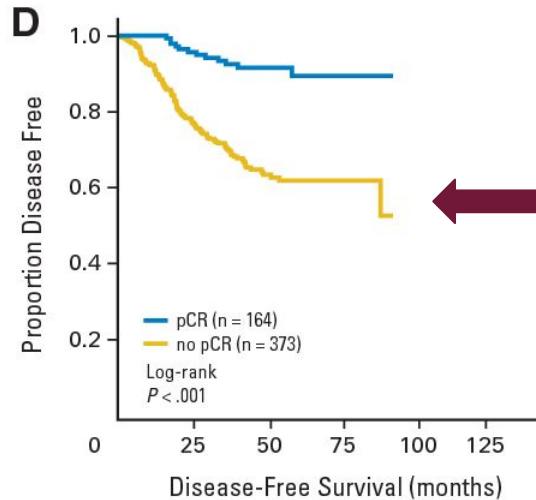
1. Before surgery
2. Reducing tumor size
3. Improving overall survival by treating undetected micrometastasis
4. Accelerating the development and application of new combination therapy drugs for breast cancer.
5. Resistance occurring

Treatment for breast cancer

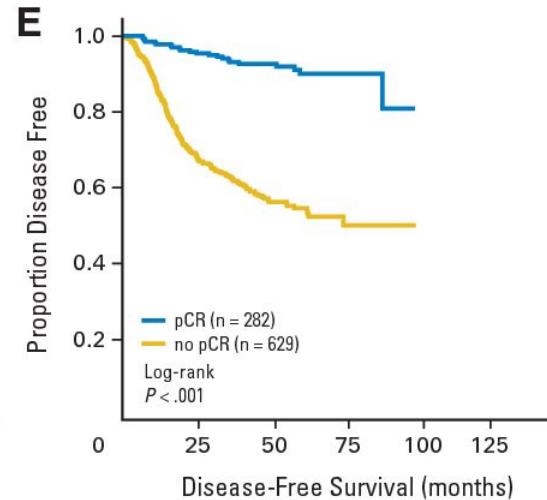
Luminal A (HER2-Low)



HER2+ (non luminal)



Triple-negative



Pathologic complete response (pCR) :
absence of invasive/ in situ cancer in the breast and/or axillary lymph node.

Von Minckwitz, et. al., *J Clin oncol*, 2012.

Specific aims

01

To analyze **differential gene expression** between the two patient groups using RNA-seq data, and validate the findings with an independent dataset.

02

To identify **drug resistance-associated gene variants** from two RNA-seq datasets, and integrate with DNA-level mutation data for comparative analysis.

03

To compare and discuss the results with previous studies.

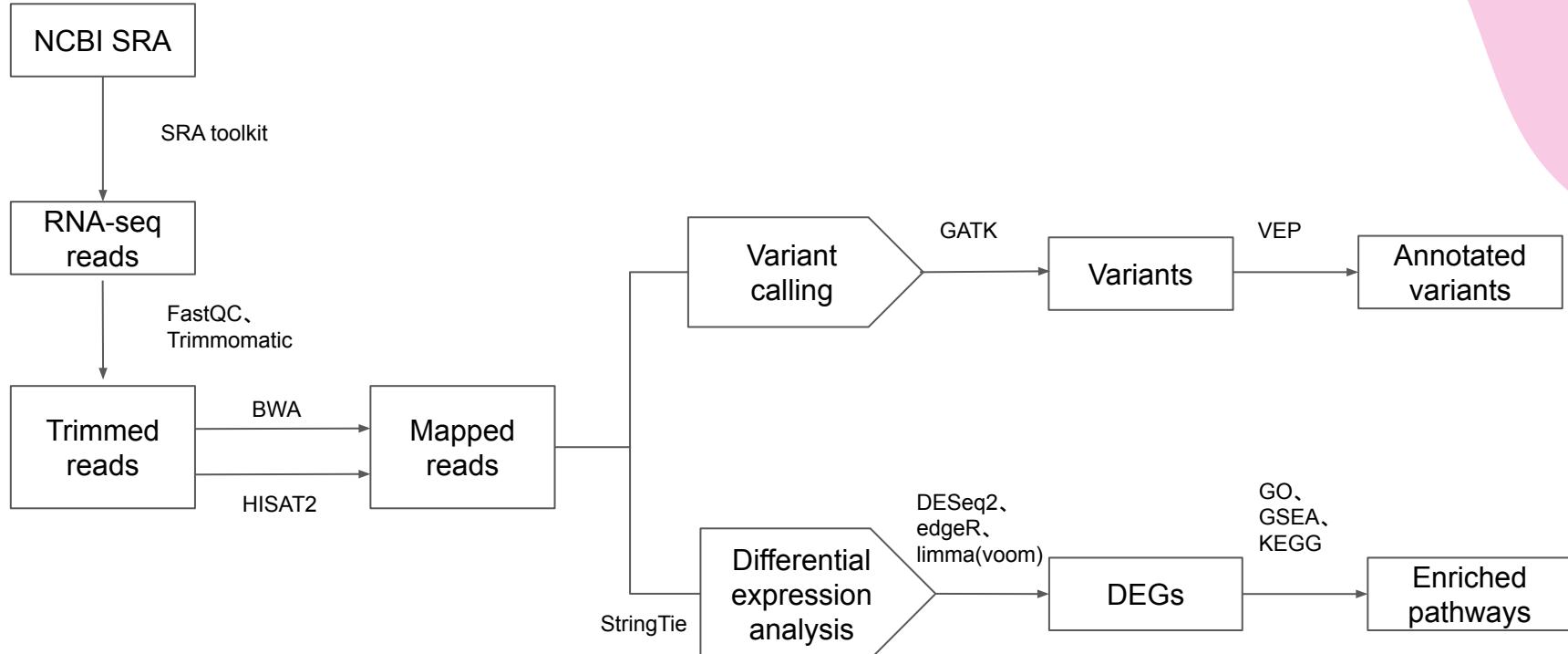


02

Methods



Pipeline

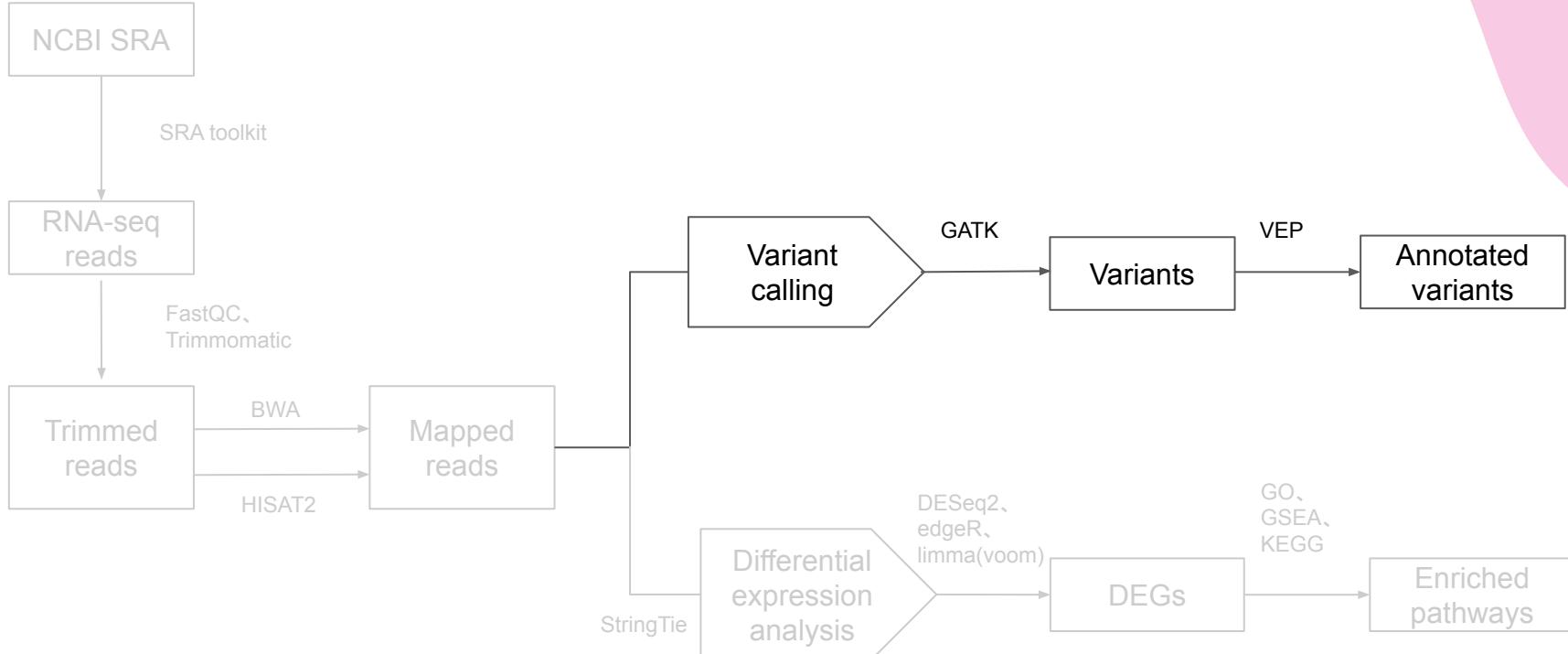




03

Results

Pipeline



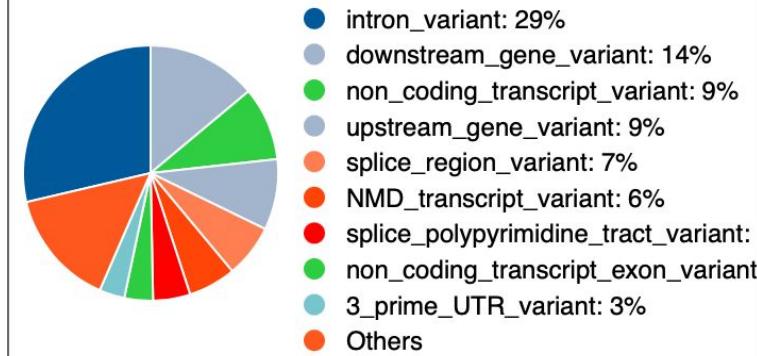
Variant Effect Predictor results

Dataset 1 (8 patients)

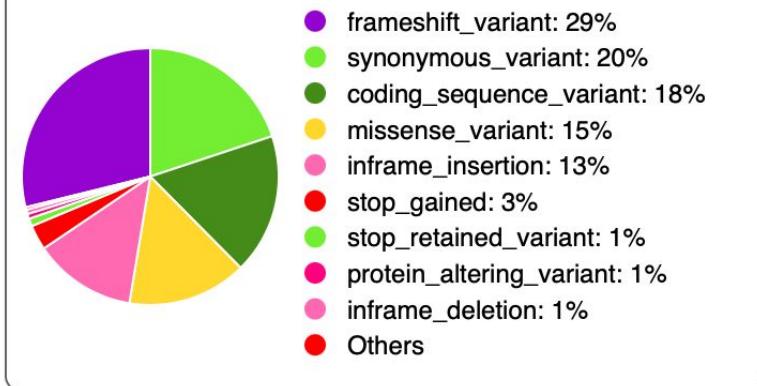
Therapy Sensitive Datasets (3 patients data)

Category	Count
Variants processed	405108
Variants filtered out	0
Novel / existing variants	199128 (49.2) / 205980 (50.8)
Overlapped genes	34393
Overlapped transcripts	189452
Overlapped regulatory features	45644

Consequences (all)



Coding consequences

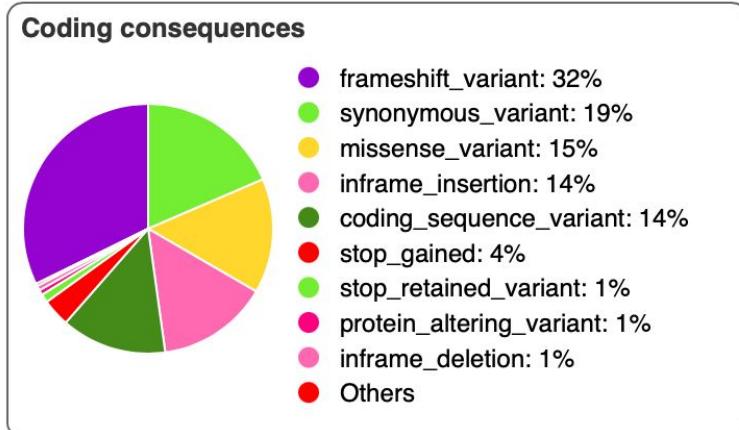
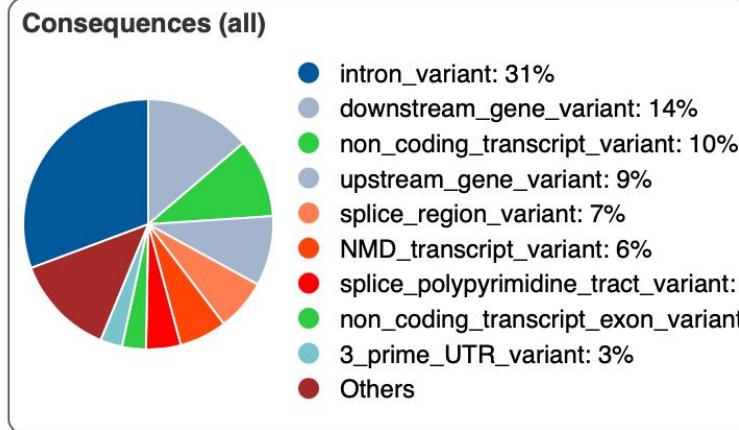


Variant Effect Predictor results

Dataset 1 (8 patients)

Therapy Resistant Datasets (5 patients data)

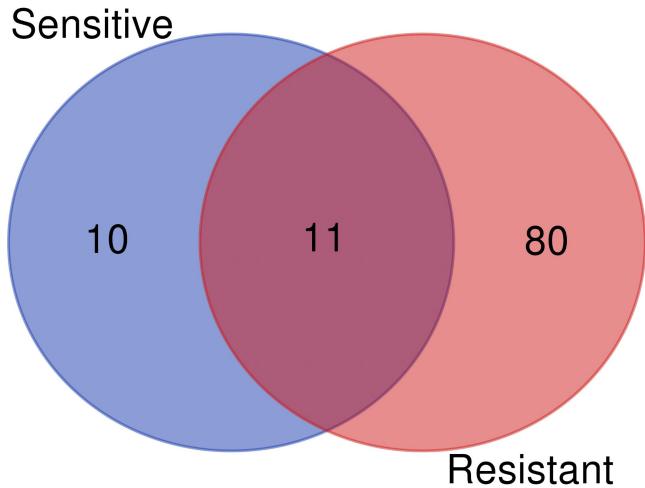
Category	Count
Variants processed	632679
Variants filtered out	0
Novel / existing variants	309203 (48.9) / 323476 (51.1)
Overlapped genes	38595
Overlapped transcripts	202842
Overlapped regulatory features	64279



Variant Effect Predictor results

Dataset 1 (8 patients)

Venn diagrams



Names	total	Elements
Resistant Sensitive	10	AGT PERM1 KMT2A BCL10 HMBS SDHB BRCA2 PLEKHN1 ZMPSTE24 OAT ATM
Sensitive	11	CCDC34 SLCO2B1 KRT1 ADRB1 POLR3A CENPF DPAGT1 SPART H2AX LGR4
Resistant	80	VDR ARNT OPTN PCSK9 N4BP2L2 BSCL2 ERCC5 HSPG2 SMOC1 LAMB3 CTSF ACTN3 BBS10 RPL35AP26 CEP290 TNFRSF1A PTPRJ ELP4 TBCE ARV1 AHDC1 COL11A1 KIF11 AGL EPHA2 PPP1R15B CZIB MTHFD1 MUTYH CEP55 ITPKB SMC3 PYGM CENPJ C11orf65 PTEN TOR1AIP1 GNPTAB MTHFR RET KLLN CLN5 PAX6 KAT6B FMO3 MRE11 CPT2 RPS21P1 LYST KCNJ11 C11orf167 KCNQ1 SAA1 POGZ MTPAP HBB CD4 EFEMP2 LRRN4CL FBXL3 OSBPL8 FOXRED1 CTSK RERE ERCC6 TTC36-AS1 MIR4260 MED13L RASGRP2 DPYD FCGR3B NFIA LAMC2 CFH WNT10B CSF3R CHIT1 PPP1R15B-AS1 PLEKHG6 FANCM

Variant Effect Predictor results

Dataset 1 (8 patients)

Specific gene variants in resistant samples

MAPK/PI3K-Akt pathway	ARNT, PTEN, RASGRP2, EPHA2, PTPRJ
Nucleotide excision repair	ERCC5, MRE11, MUTYH
Cell adhesion	LAMB3 , EPHA2
Cell cycle	KIF11 , KLLN

Article | [Open access](#) | Published: 28 May 2024

Targeting ARNT attenuates chemoresistance through destabilizing p38 α -MAPK signaling in glioblastoma

Wahafu Alafate , Gen Lv, Jiantao Zheng, Haiping Cai, Wei Wu, Yong Yang, Shichao Du, Dong Zhou & Peng Wang 

Cell Death & Disease 15, Article number: 366 (2024) | [Cite this article](#)

352 Accesses | [Metrics](#)



biomedicines



Review

DNA Damage Repair: Predictor of Platinum Efficacy in Ovarian Cancer?

Dimitra T. Stefanou ^{1,2}, Vassilis L. Souliotis ² , Roubini Zakopoulou ³ , Michalis Liantos ⁴  and Aristotelis Bamiatis ^{3,*} 

Article | [Open access](#) | Published: 08 March 2019

LAMB3 mediates apoptotic, proliferative, invasive, and metastatic behaviors in pancreatic cancer by regulating the PI3K/Akt signaling pathway

Hong Zhang, Yao-zhen Pan, May Cheung, Mary Cao, Chao Yu, Ling Chen, Lei Zhan, Zhi-wei He & Cheng-yi Sun 

Cell Death & Disease 10, Article number: 230 (2019) | [Cite this article](#)

Oncotarget, 2017 Nov 3; 8(54): 92106–92118.

Published online 2017 Sep 8. doi: [10.1863/oncotarget.20785](https://doi.org/10.1863/oncotarget.20785)

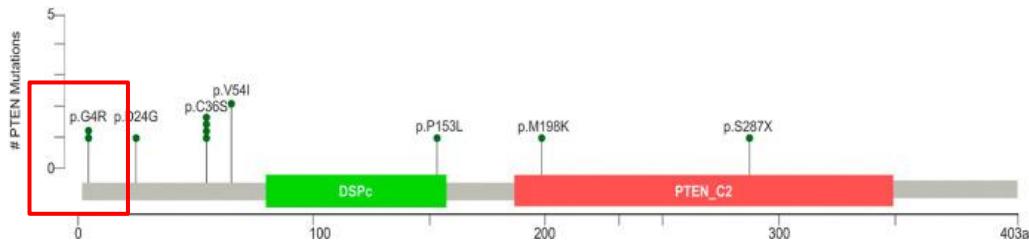
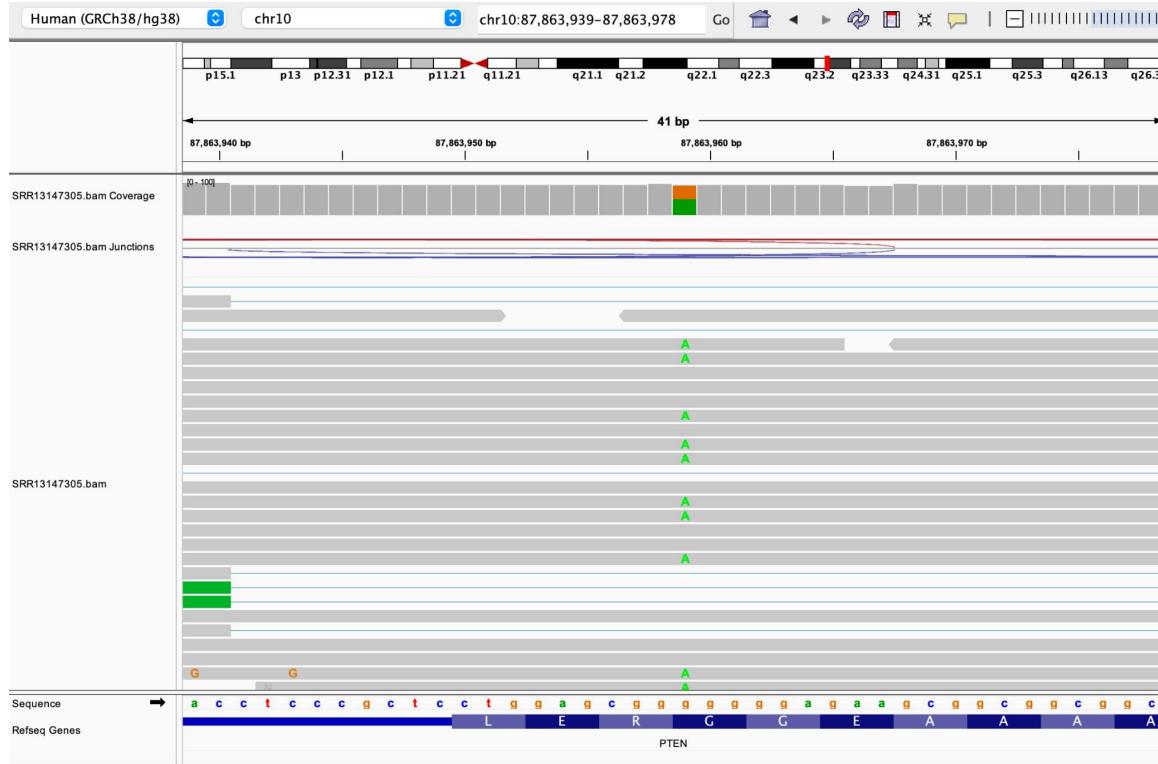
PMCID: PMC5696167

PMID: 29190901

KIF11 is required for proliferation and self-renewal of docetaxel resistant triple negative breast cancer cells

Meng Jiang, ^{#1,2} Huiru Zhuang, ^{#3} Rui Xia, ^{1,2} Lei Gan, ^{1,2} Yuantao Wu, ^{1,2} Junzhe Ma, ^{1,2} Yihui Sun, ⁴ and Zhixiang Zhuang ^{1,2}

PTEN G4R mutation



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ACS
OMEGA

Article



<http://pubs.acs.org/journal/acsofd>

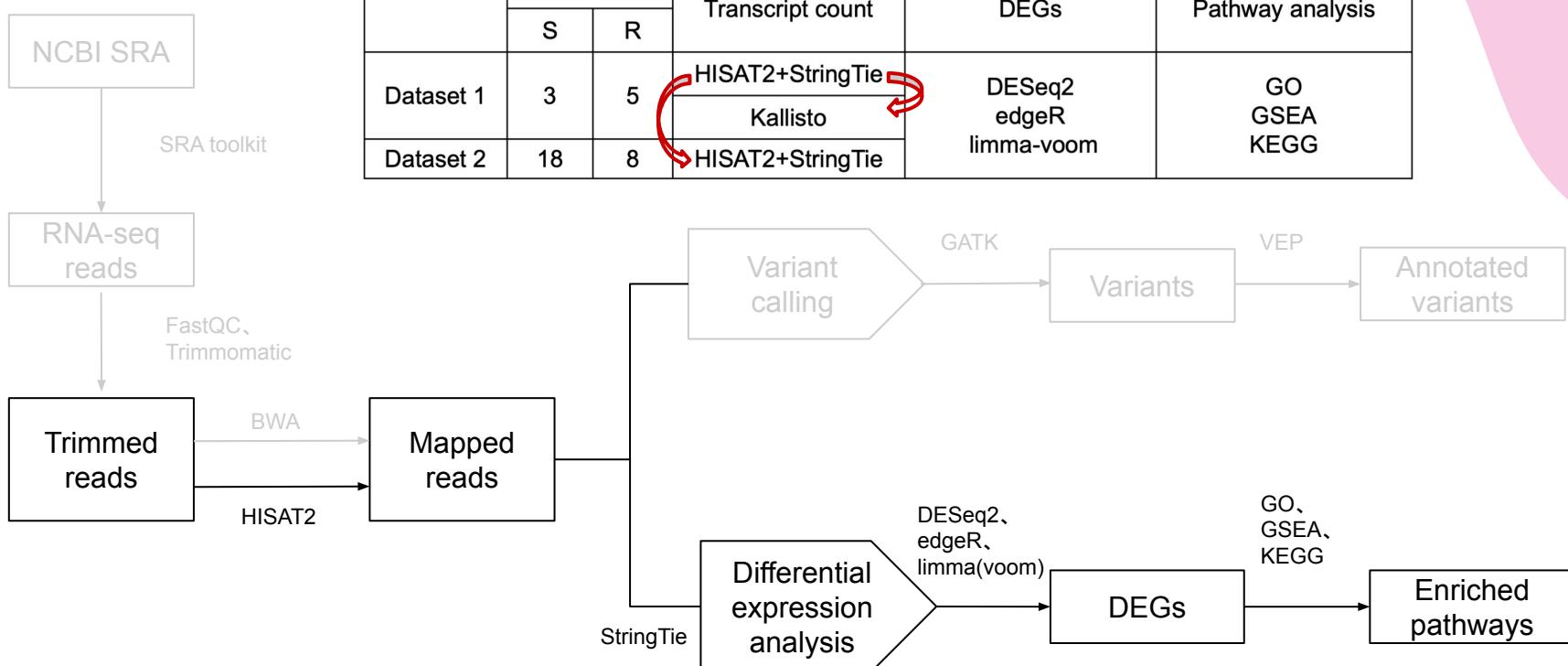
Mutational Landscape and In-Silico Analysis of *TP53*, *PIK3CA*, and *PTEN* in Patients with Breast Cancer from Khyber Pakhtunkhwa

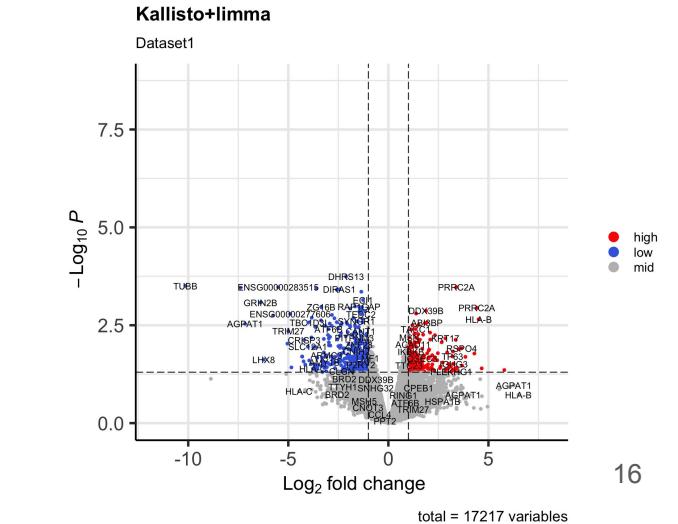
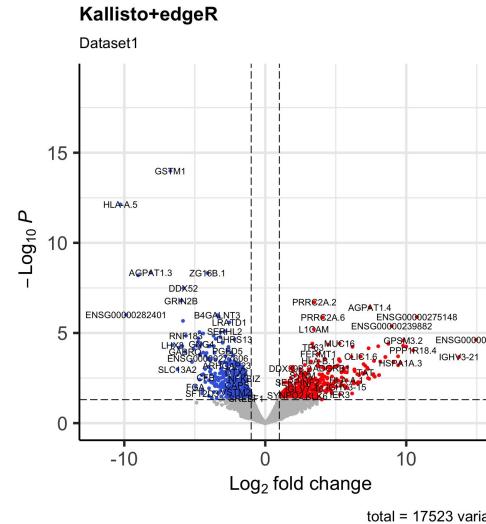
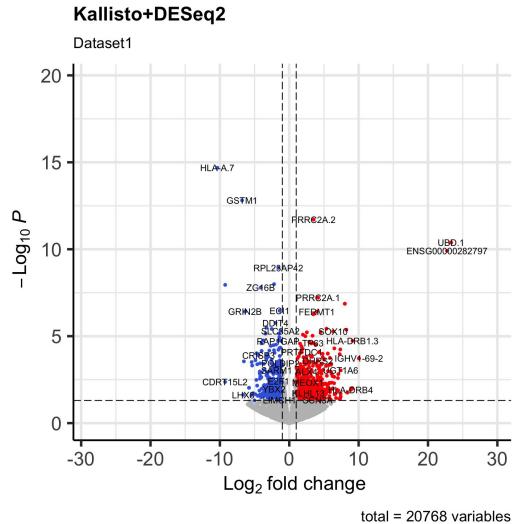
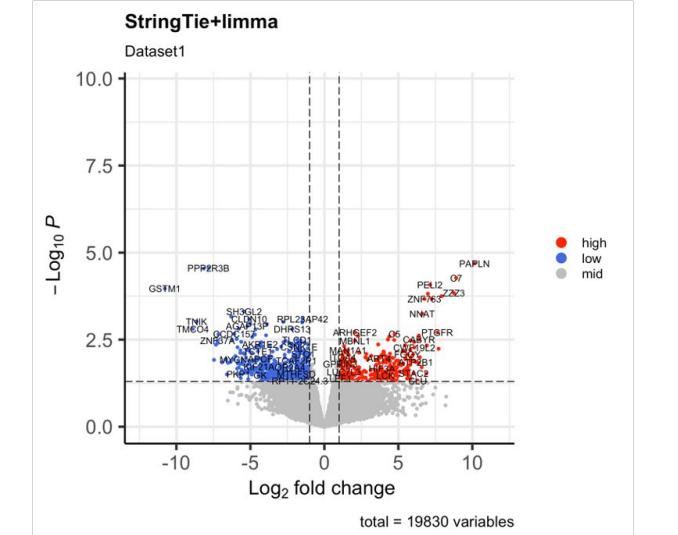
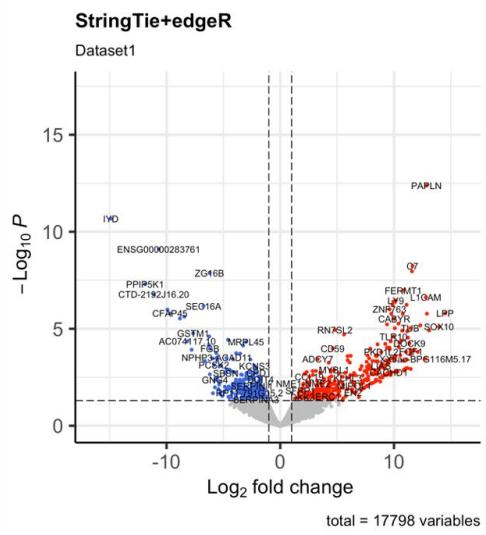
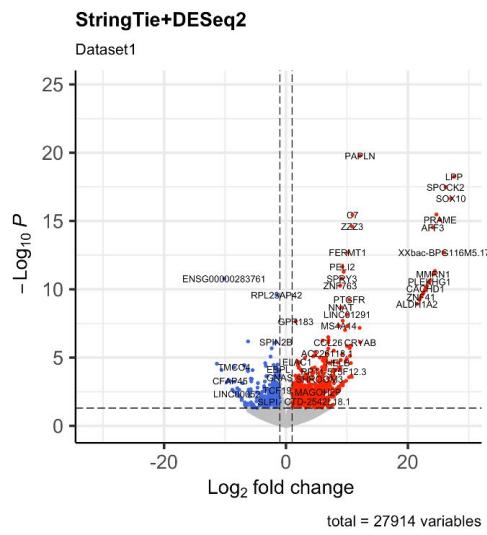
Hilal Ahmad, Asif Ali,* Roshan Ali, Ali 'Talha Khalil,* Ishaq Khan, Mah Muneer Khan, and Mohammed Alorini

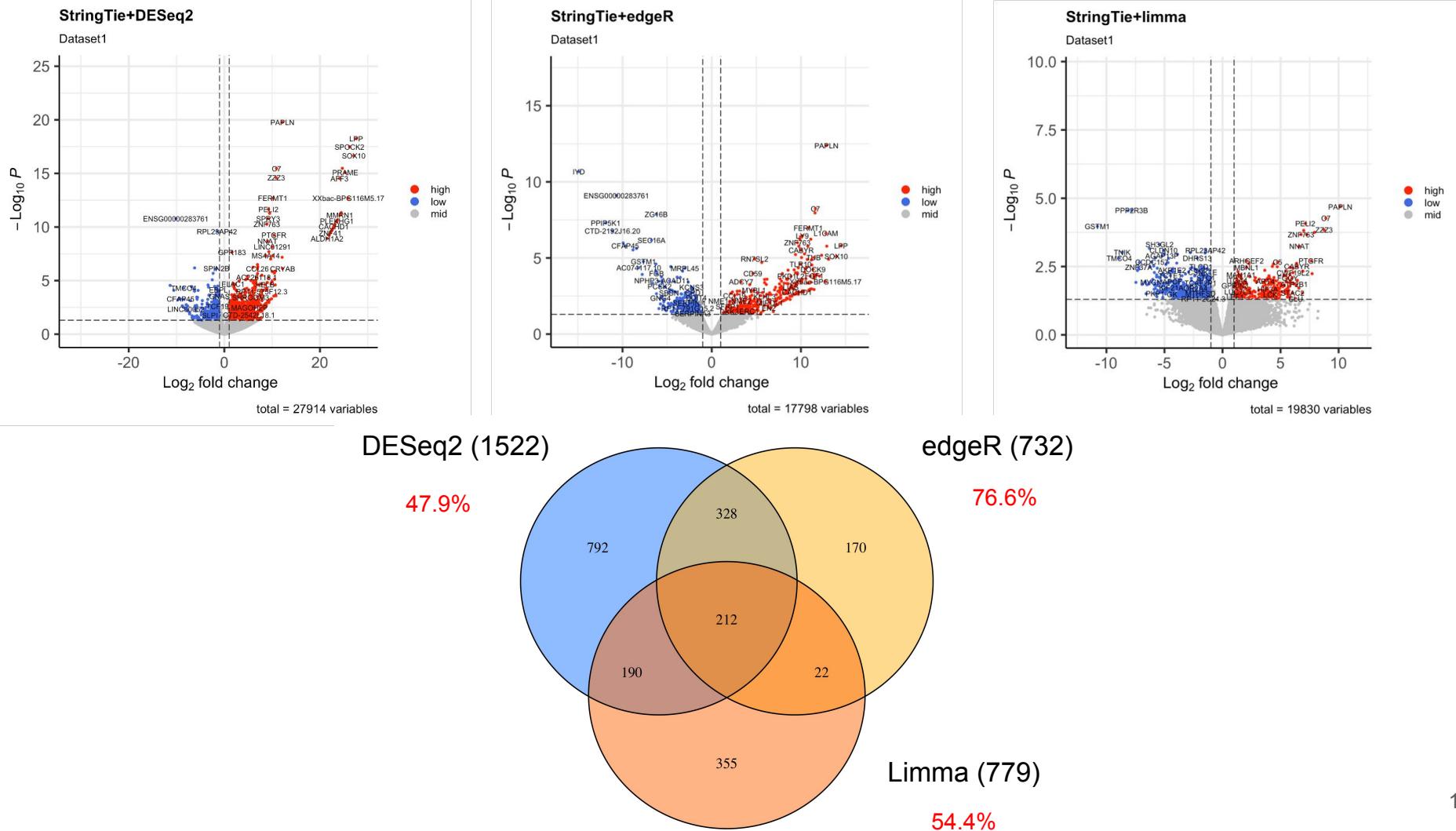
Cite This: *ACS Omega* 2023, 8, 43318–43331

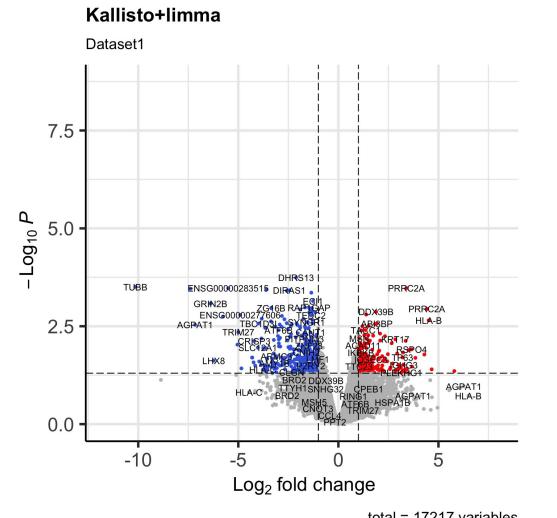
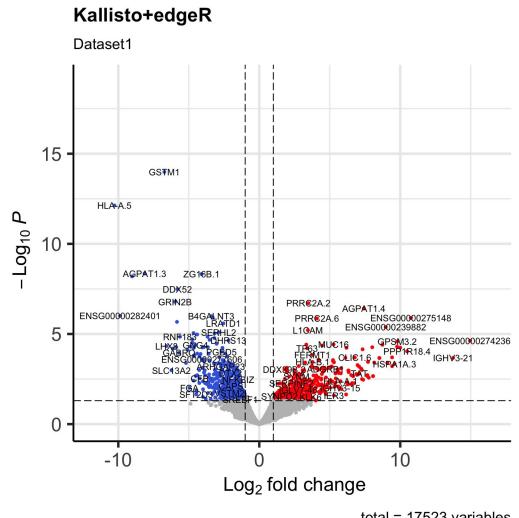
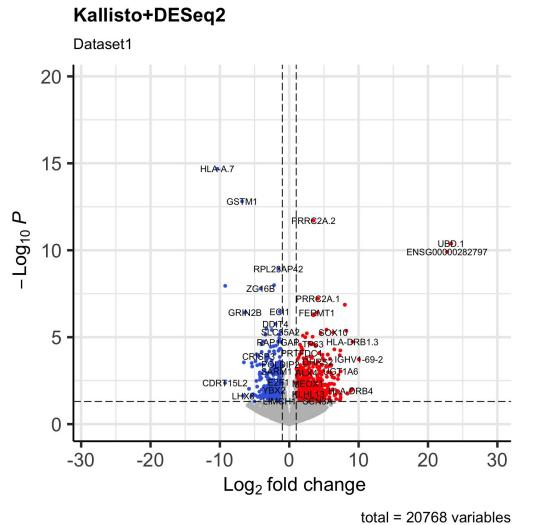
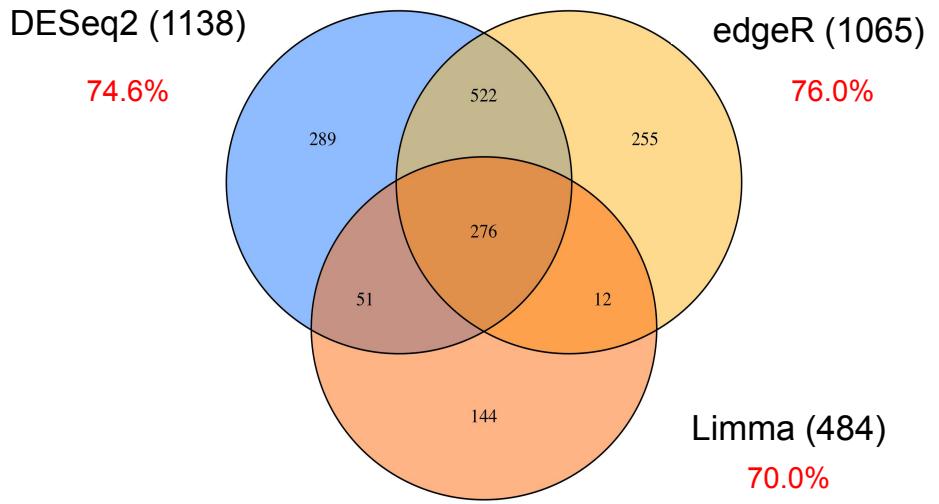
Read Online

Pipeline

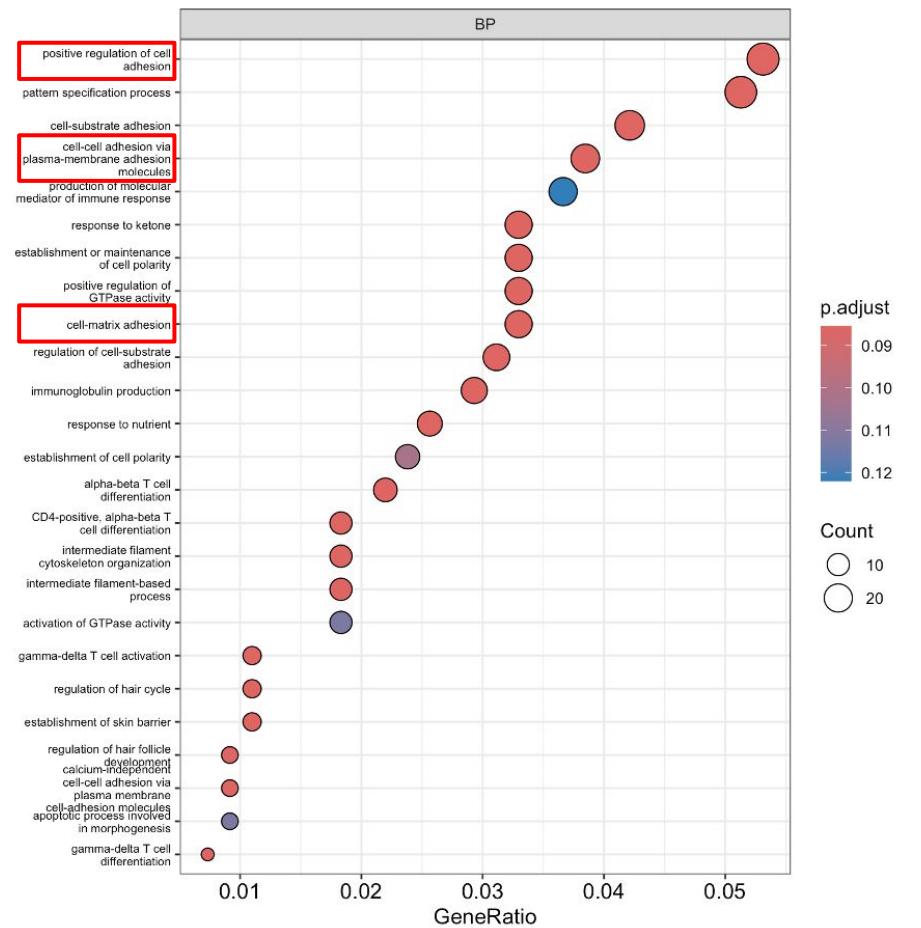




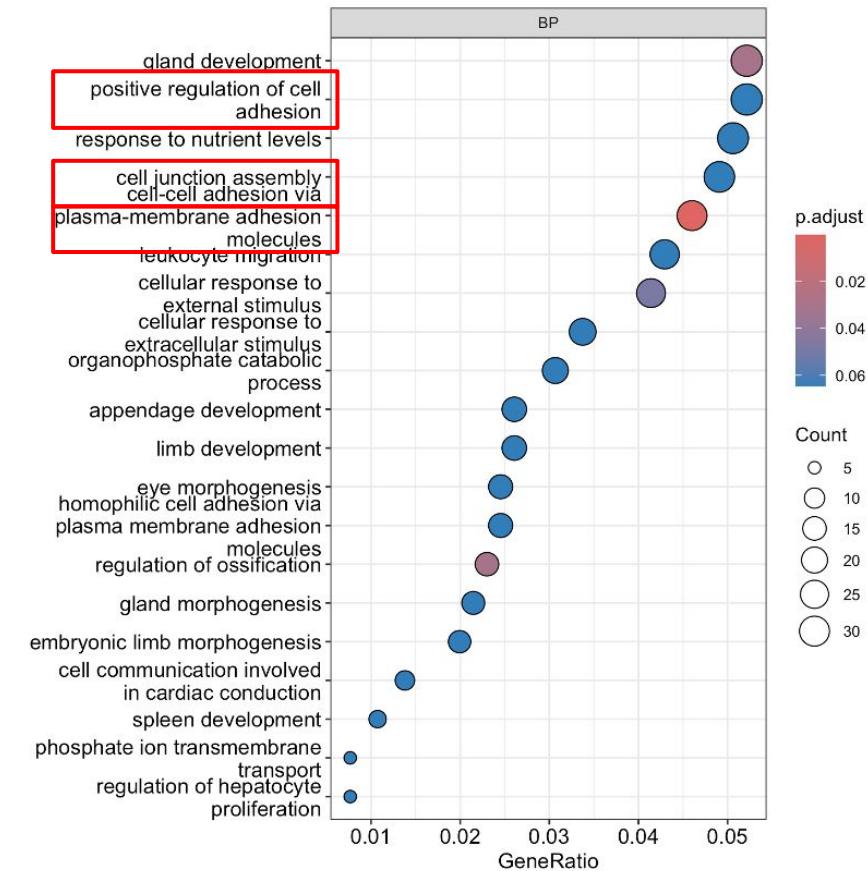




StringTie+DEG analysis+GO

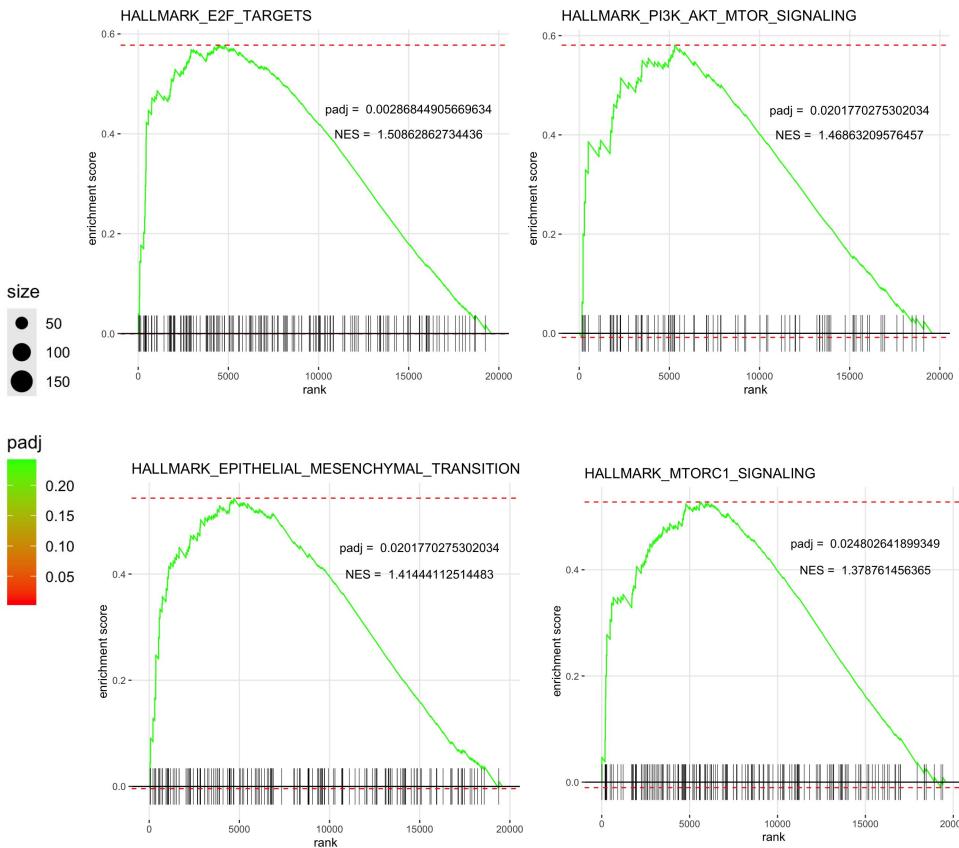


Kallisto+DEG analysis+GO

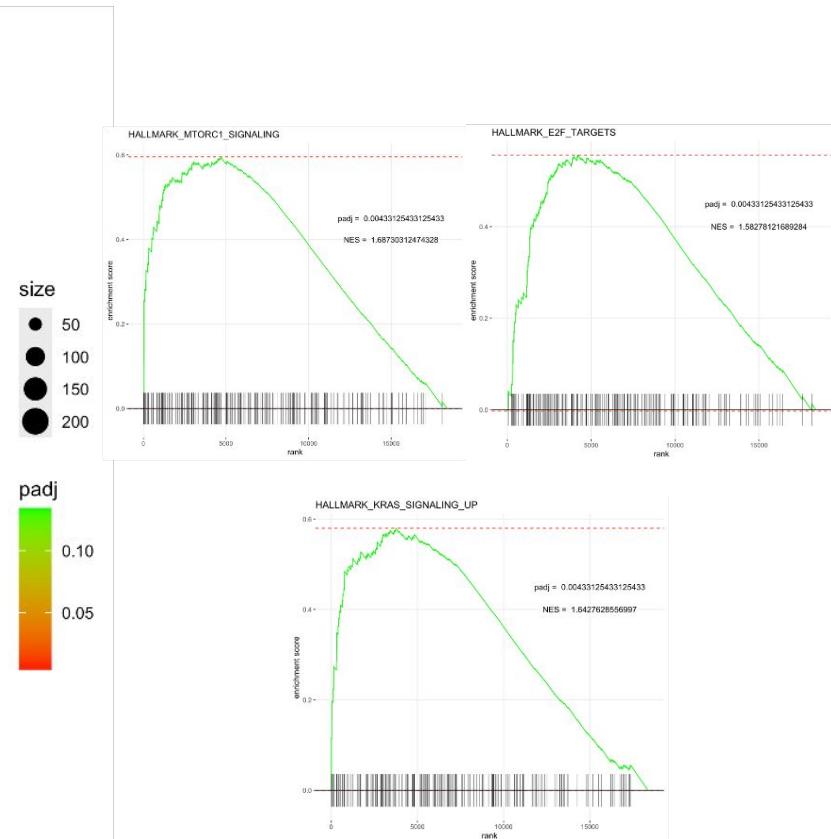
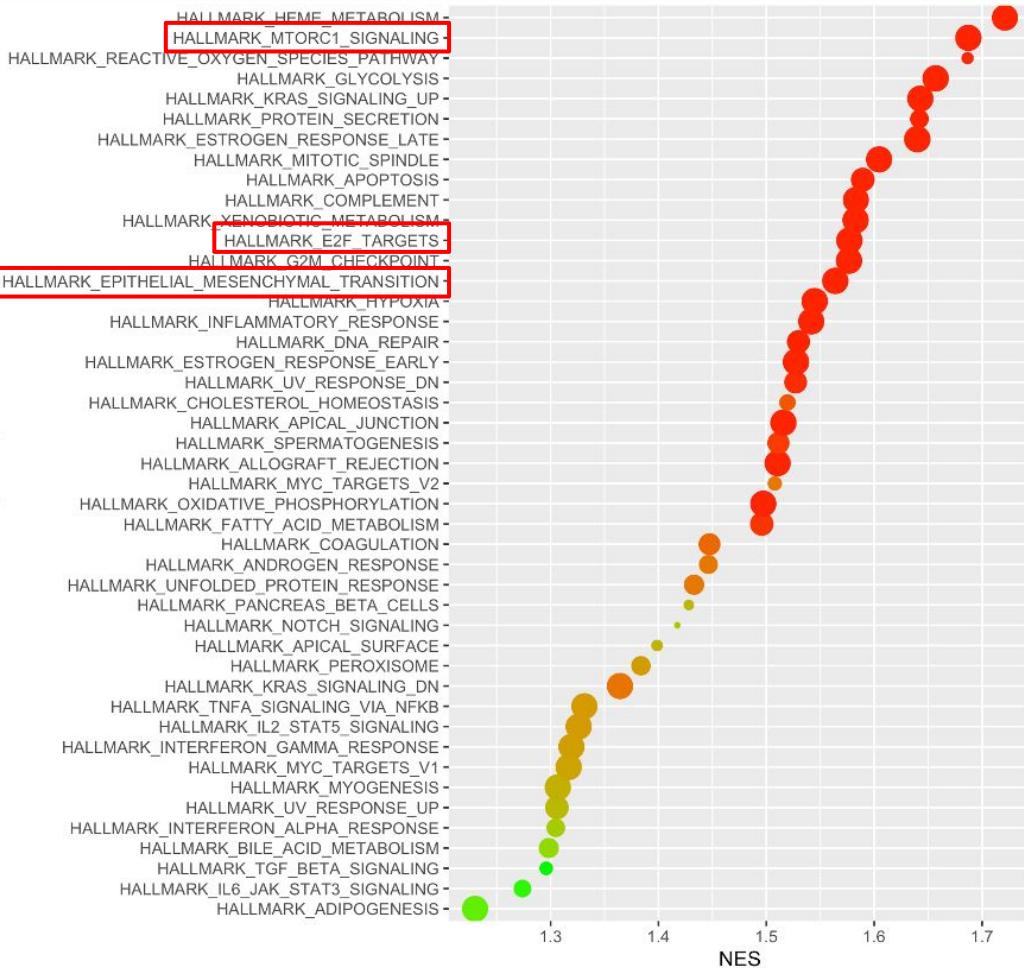


StringTie+DEG analysis+**GSEA**

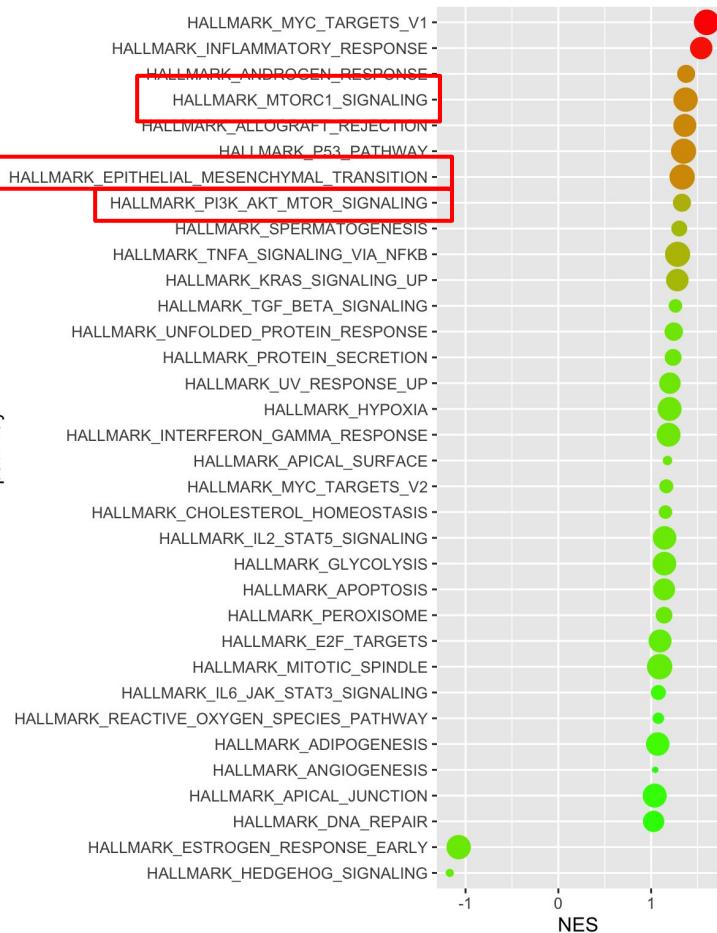
pathway



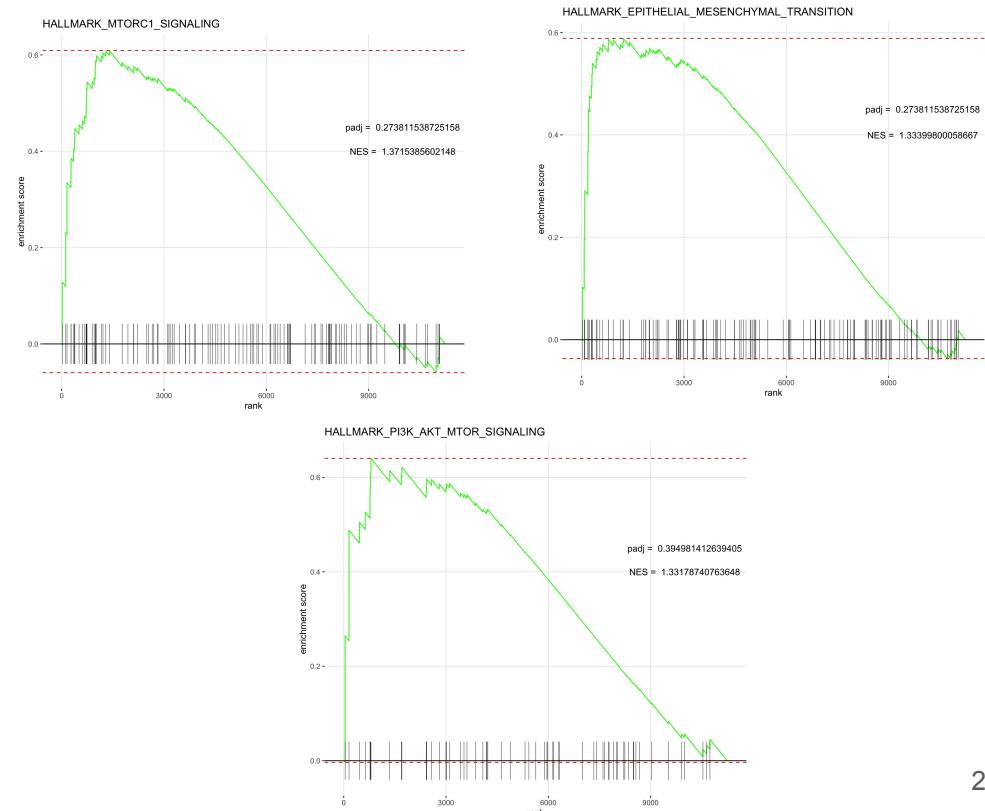
Kallisto+DEG analysis+GSEA

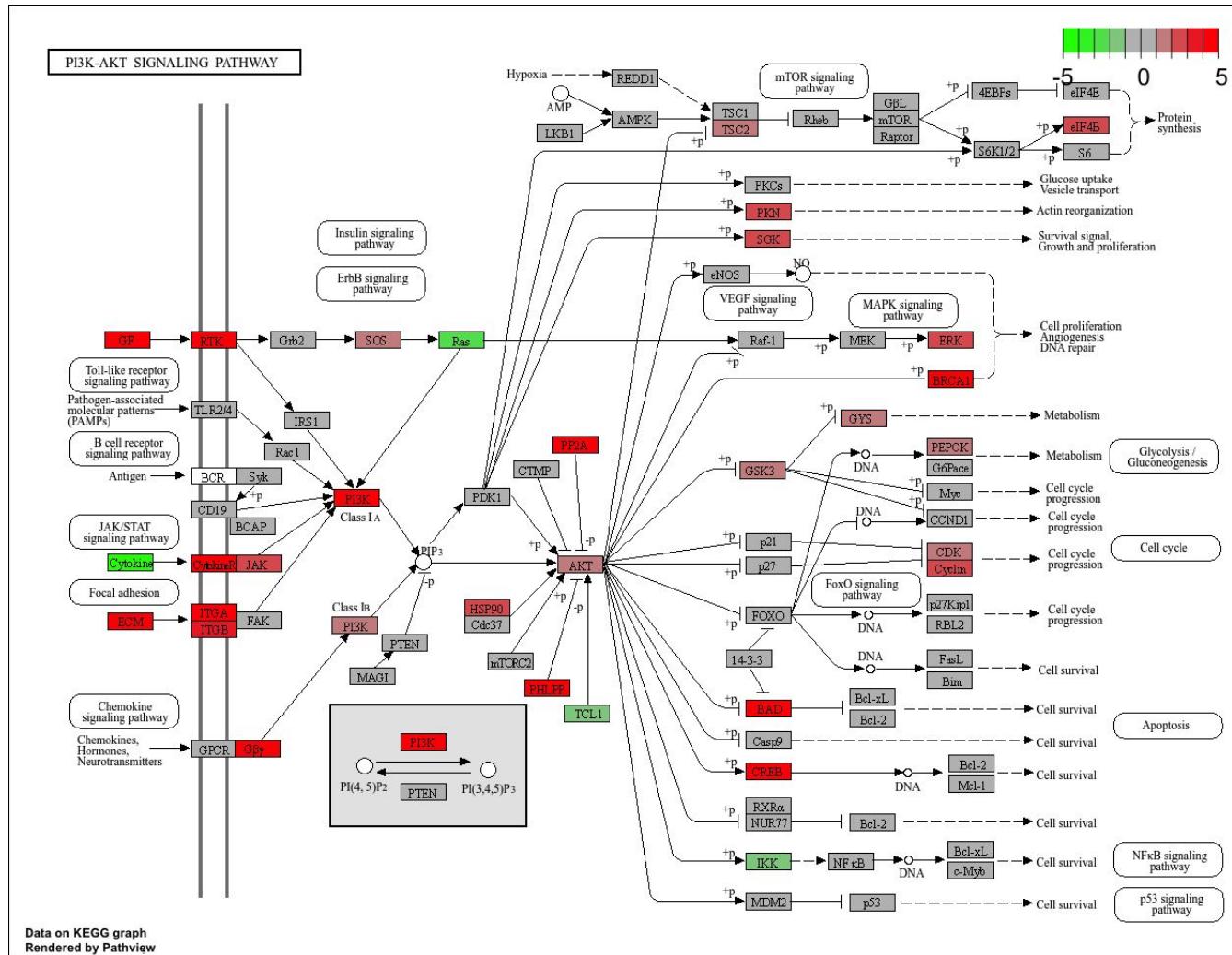


(Dataset 2)StringTie+DEG analysis+GSEA



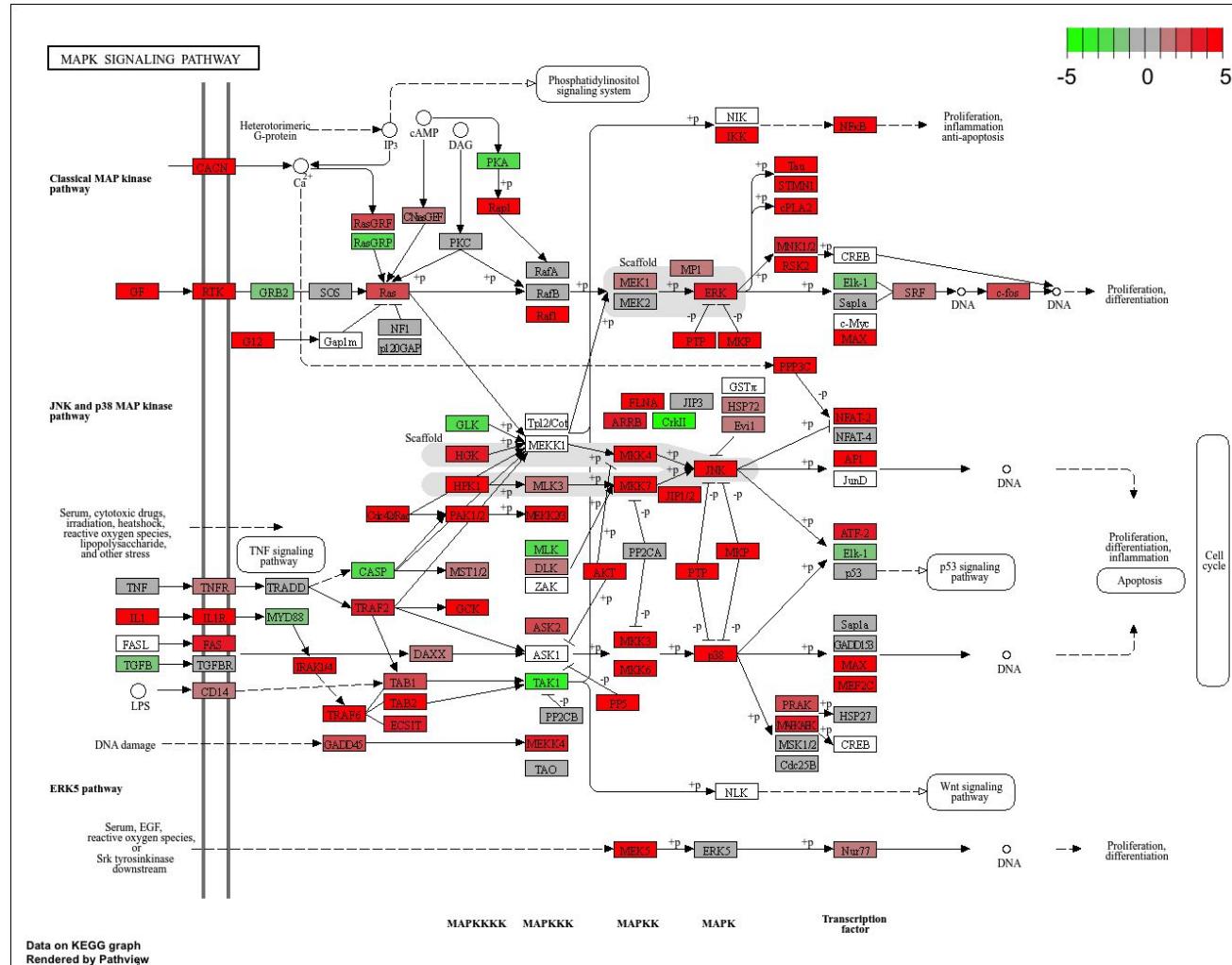
	Patients		Transcript count	DEGs	Pathway analysis
	S	R			
Dataset 1	3	5	HISAT2+StringTie	DESeq2 edgeR	GO GSEA
			Kallisto		
	18	8	HISAT2+StringTie	limma-voom	KEGG





Cell survival,
Proliferation,
Actin
reorganization





Proliferation,
differentiation,
inflammation,
anti-apoptosis



04

Discussion

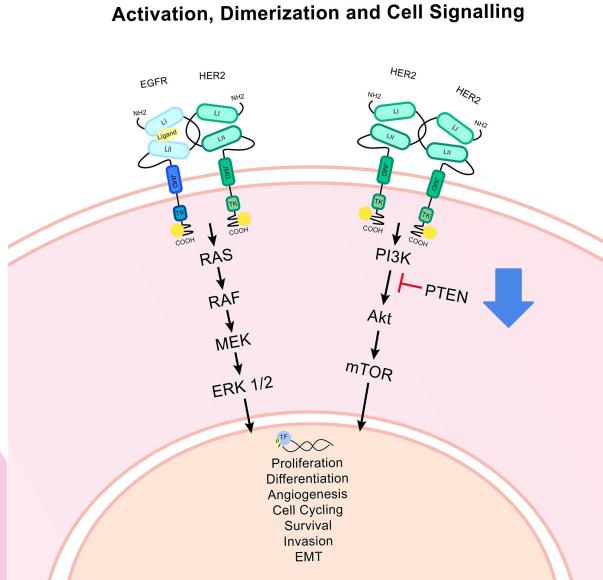


Discussion

1. Chemoresistance in HER2+ breast cancer is associated with:

PI3K/akt/mTOR signalling, Cell cycle, DNA repair,

Epithelial mesenchymal transition (EMT)

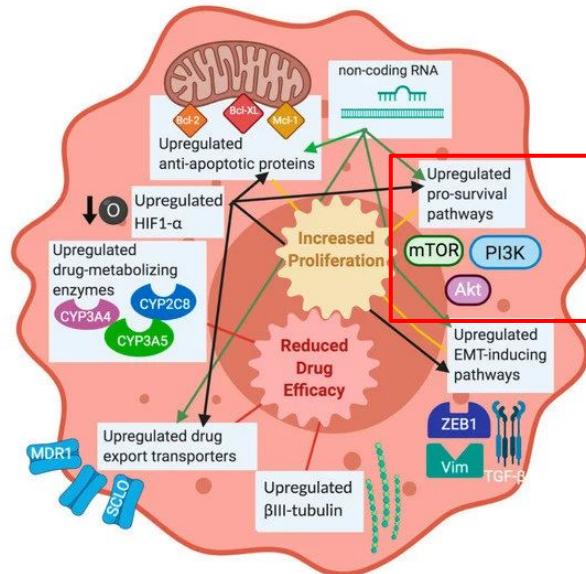


Review Article | Published: 11 April 2017

EMT, CSCs, and drug resistance: the mechanistic link and clinical implications

Tsukasa Shibue & Robert A. Weinberg [✉](#)

Nature Reviews Clinical Oncology 14, 611–629 (2017) | [Cite this article](#)

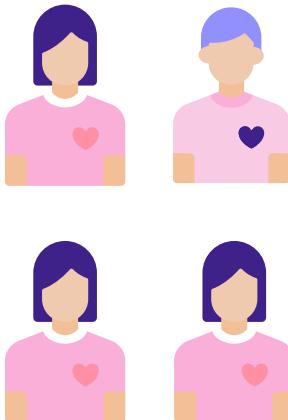


Discussion: tools

1. StringTie finds more genes than Kallisto
2. DEG analysis: DESeq2 finds the most DEGs
3. Pathway analysis:

In two datasets of HER2+ breast cancer patients, the results of GSEA & KEGG are more consistent compared to GO.

Work distribution



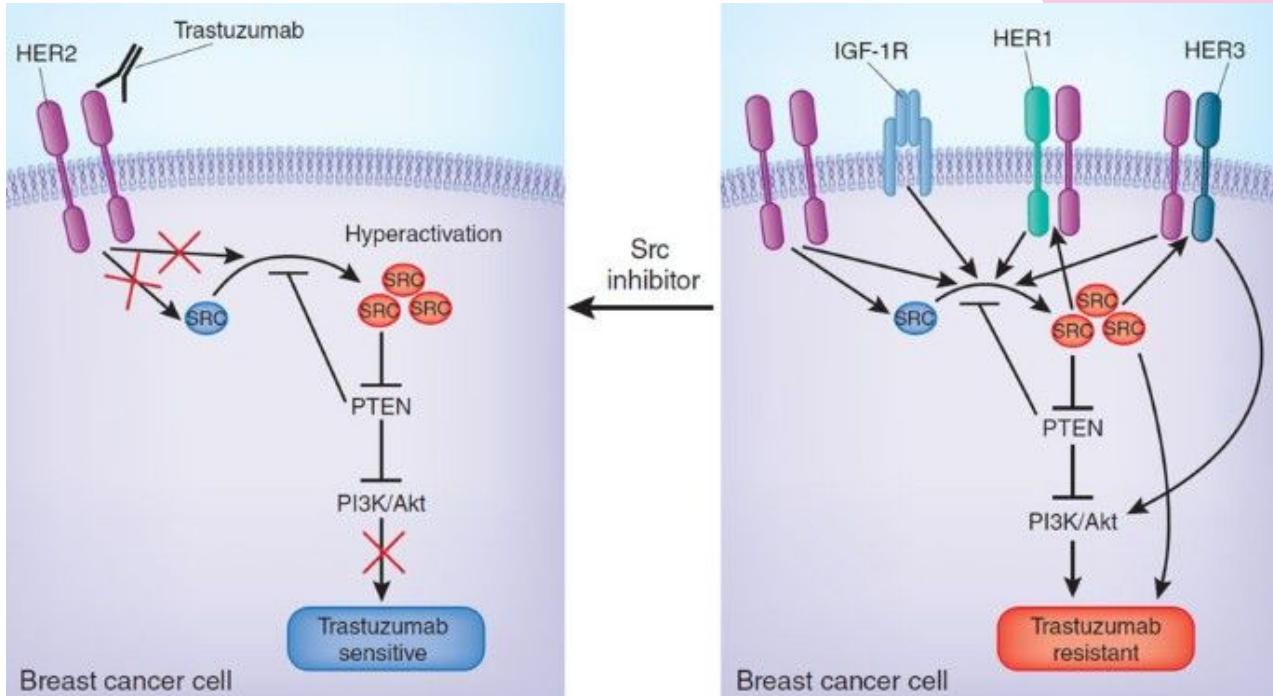
構思問題	黃以慧、黃宣瑜、王瀅茜
搜集資料	黃以慧、黃宣瑜、王瀅茜
設計方法	黃以慧
撰寫程式	林東甫
詮釋結果	黃以慧、黃宣瑜、王瀅茜
進行報告	黃以慧、黃宣瑜、王瀅茜、林東甫

Thank you for your listening!

Treatment for breast cancer

Trastuzumab

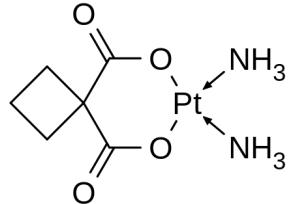
1. Monoclonal antibody
2. Mechanism of action :
Block HER2
3. FDA approval :
Breast, gastric cancer
4. Resistance :
SRC



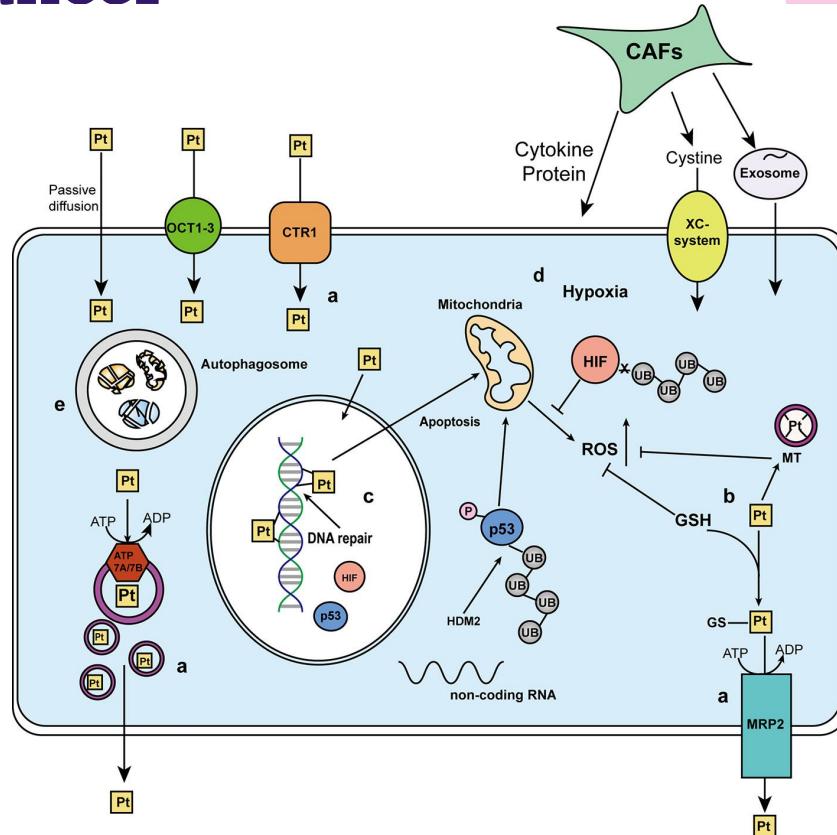
Muthuswamy SK. Trastuzumab resistance: all roads lead to SRC. Nat Med. 2011 Apr;17(4):416-8.

Treatment for breast cancer

Carboplatin



1. Chemotherapy
2. Mechanism of action :
Inhibits DNA synthesis
3. FDA approval :
Breast, ovarian, lung, brain
cancer, neuroblastoma ...
4. Resistance :
Efflux, Detoxification system,
DNA repair, Apoptosis



Hormone Receptor Status After breast cancer diagnosed...

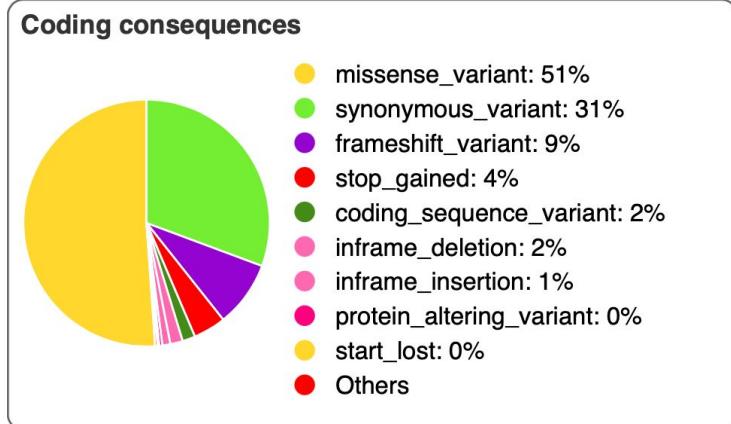
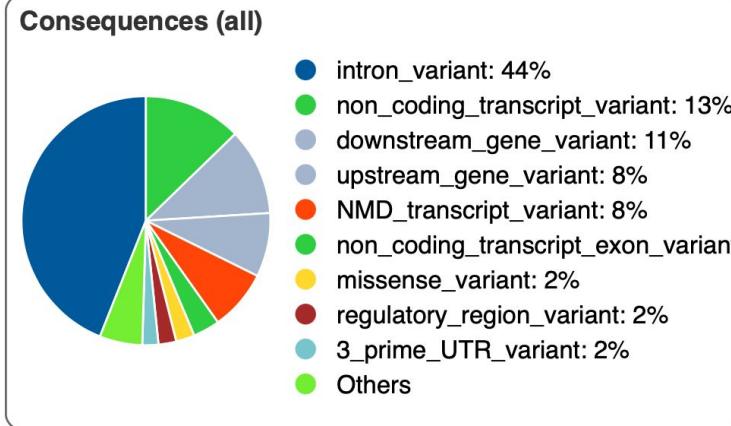
Status	Treatment	Frequency
ER and PR	Adjuvant endocrine therapy	80%
HER2	HER2-directed therapy	23% (32% HR-; 67% HR+)
Triple Negative (ER, PR, HER2-)	Chemotherapy, Immunotherapy, Target therapy	13%

Variant Effect Predictor results

Dataset 2 (26 patients)

Therapy Sensitive Datasets (18 patients data)

Category	Count
Variants processed	235671
Variants filtered out	0
Novel / existing variants	162881 (69.1) / 72790 (30.9)
Overlapped genes	31358
Overlapped transcripts	173608
Overlapped regulatory features	17442

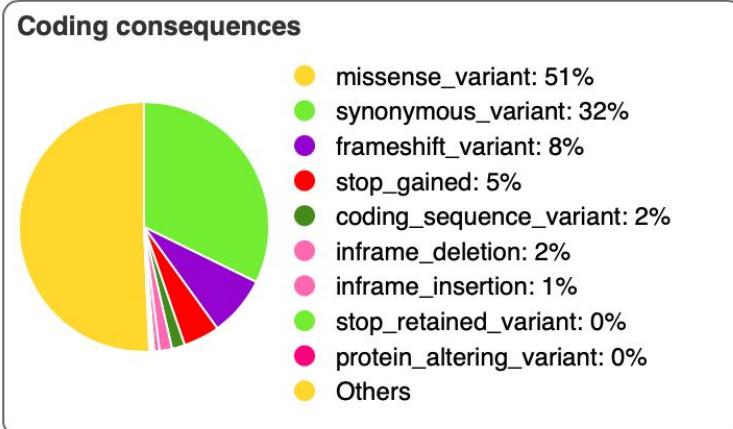
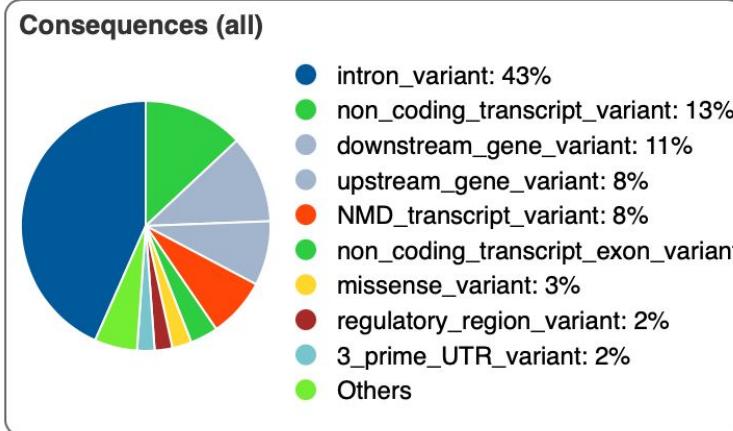


Variant Effect Predictor results

Dataset 2 (26 patients)

Therapy Resistant Datasets (8 patients data)

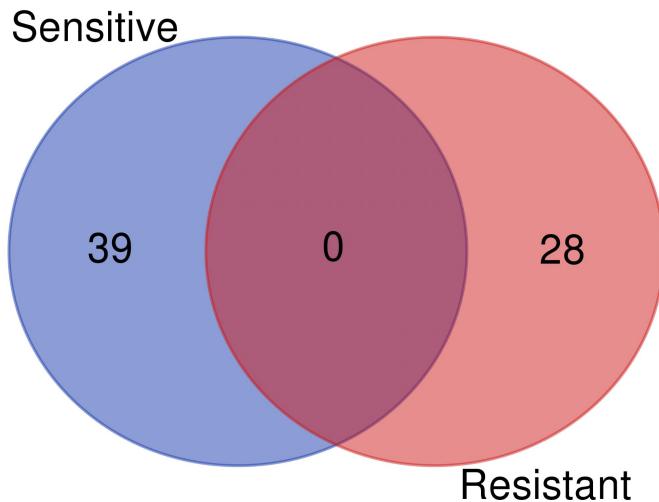
Category	Count
Variants processed	154095
Variants filtered out	0
Novel / existing variants	107317 (69.6) / 46778 (30.4)
Overlapped genes	27296
Overlapped transcripts	156400
Overlapped regulatory features	13558



Variant Effect Predictor results

Dataset 2 (26 patients)

Venn diagrams

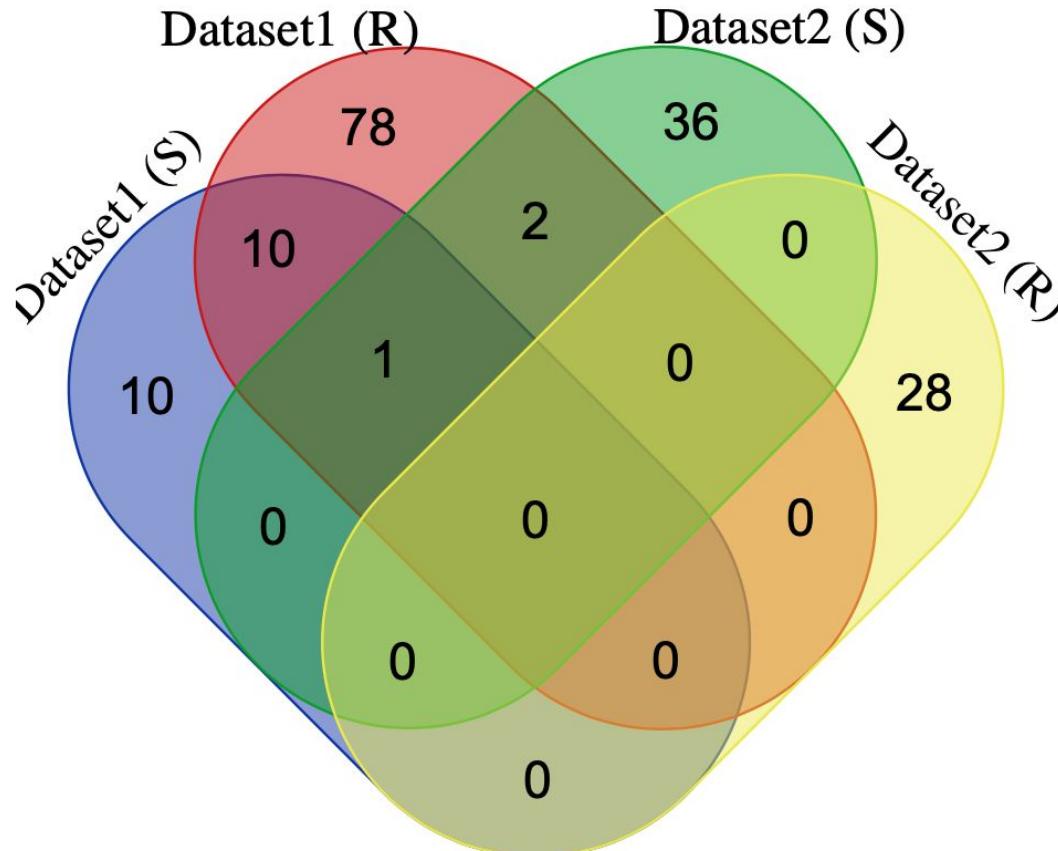


Names	total	Elements
Sensitive	39	VDR DNAAF4 PIEZO1 CDH1 PCBD1 CD3E APRT CDT1 FASLG STAT3 POC1B CYBA DCLRE1B F2 COL1A1 SRCAP TMEM126B SYT1 IL21R-AS1 UNG AP4B1 FMN2 SELENON GALNS SPG7 MECR IL21R HBB CREBBP SDHB PARK7 CHD2 CEP164 CENPCP1 AP4B1-AS1 ALG1 SGPL1 ABCA4 PSAP
Resistant	28	DPM2 UGT1A8 PIGO UGT1A7 UGT1A10 PQBP1 TUBB6 UGT1A4 CYP24A1 MIR6807 ARSB UGT1A3 UGT1A5 EEIG1 UGT1A6 SLC35A2 TRIM28 PALB2 DST MFSD8 LPL UGT1A1 TRIP12 CRBN PIGO-AS1 CHMP2A AFG3L2 UGT1A9

Variant Effect Predictor results

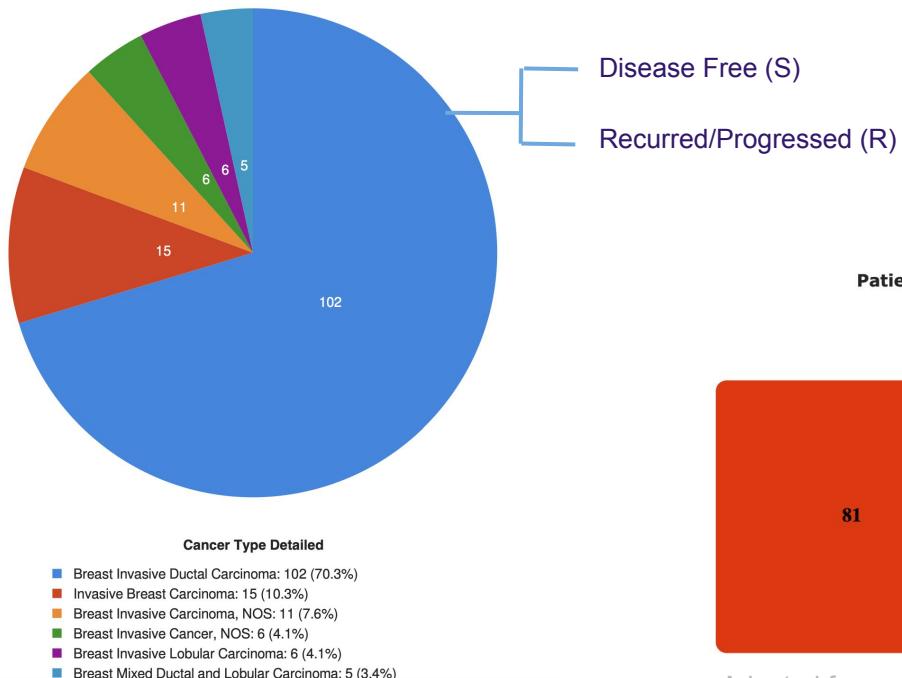
Dataset 1 & 2

Venn diagrams



Dataset 1

MAPK on resistance to anti-HER2 therapy for breast cancer
 (MSK, Nat Commun. 2022)

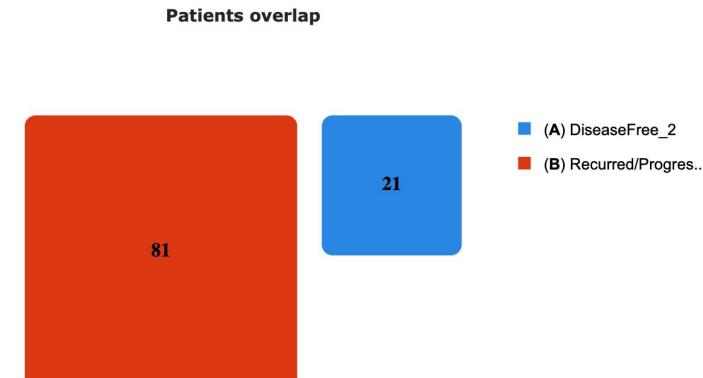


ARTICLE

<https://doi.org/10.1038/s41467-021-27093-y> OPEN

HER2 + breast cancers evade anti-HER2 therapy via a switch in driver pathway

Alison E. Smith^{1,2}, Emanuela Ferraro^{1,3}, Anton Safonov^{1,3}, Cristina Bernado Morales⁴, Enrique J. Arenas Lahuerta^{1,4}, Qing Li¹, Amanda Kulick⁵, Dara Ross⁶, David B. Solit^{1,2}, Elisa de Stanchina⁵, Jorge Reis-Filho^{1,6}, Neal Rosen^{1,7}, Joaquín Arribas⁴, Pedram Razavi^{1,2,3} & Sarat Chandarlapaty^{1,2,3,8}



Adapted from cBioPortal database

Dataset 2

Transcriptomic analysis of breast cancer patients sensitive and resistant to chemotherapy:
 Looking for overall survival and drug resistance biomarkers
 (GSE162187)

	Treatment	Response	Age	molecular subtype	histological type	histological grade
Breast_cancer_44R	Carboplatin-Docetaxel- Trastuzumab 6 cycles	R	58	HER 2	Invasive ductal carcinoma	SBRII
Breast_cancer_30S	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 3 cycles	S	NA	NA	Invasive ductal carcinoma	NA
Breast_cancer_9S	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles	S	31	Luminal B	Invasive ductal carcinoma	SBRII
Breast_cancer_41S	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles + Trastuzumab 6 concomitant cycles	S	52	Luminal B	Invasive ductal carcinoma	SBRII
Breast_cancer_24S	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles + Trastuzumab 6 concomitant cycles	S	67	HER 2	Invasive ductal carcinoma	SBRIII
Breast_cancer_28R	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles + Trastuzumab 8 concomitant cycles	R	33	HER 2	Invasive ductal carcinoma	SBRIII
Breast_cancer_21S	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles + Trastuzumab 8 concomitant cycles	S	48	Luminal B	Invasive ductal carcinoma	SBRIII
Breast_cancer_5R	Carboplatin-Paclitaxel weekly 4 cycles + Epirubicin-Cyclophosphamide 4 cycles	R	44	Triple Negative	Invasive ductal carcinoma	SBRIII
Breast_cancer_8R	Doxorubicin-Cyclophosphamide 2 cycles	R	53	Luminal B	Invasive ductal carcinoma	SBRII
Breast_cancer_32S	Doxorubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	S	55	HER 2	Invasive ductal carcinoma	SBRIII
Breast_cancer_7S	Doxorubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles + trastuzumab 3 concomitant cycles	S	64	HER 2	Invasive ductal carcinoma	SBRII
Breast_cancer_25R	Doxorubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	R	54	Luminal B	Invasive ductal carcinoma	SBRII
Breast_cancer_20S	Doxorubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	S	45	Luminal B	Invasive ductal carcinoma	SBRIII
Breast_cancer_22R	Epirubicina-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	R	62	LUMINAL A	Invasive ductal carcinoma	SBRII
Breast_cancer_40R	Epirubicin-Cyclophosphamide + Paclitaxel weekly 4 cycles	R	54	Triple Negative	Invasive ductal carcinoma	SBRIII
Breast_cancer_2R	Epirubicin-Cyclophosphamide 4 cycles + Docetaxel 1 cycle	R	29	LUMINAL A	Invasive ductal carcinoma	SBRII
Breast_cancer_3R	Epirubicin-Cyclophosphamide 4 cycles + Docetaxel 4 ciclo + Trastuzumab 3 concomitant cycles	R	49	HER 2	Invasive ductal carcinoma	SBRII
Breast_cancer_6R	Epirubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	R	55	LUMINAL A	Invasive ductal carcinoma	SBRI
Breast_cancer_39S	Epirubicin-Cyclophosphamide 4 cycles + Docetaxel 4 cycles	S	50	Triple Negative	Invasive ductal carcinoma	SBRIII
Breast_cancer_27R	Epirubicin-cyclophosphamide 4 cycles, docetaxel 4 ciclo and trastuzumab 3 cycles	R	56	HER 2	Invasive ductal carcinoma	NA
Breast_cancer_11R	Epirubicin-Cyclophosphamide 6 cycles	R	51	Triple Negative	Invasive ductal carcinoma	SBRIII
Breast_cancer_12R	Fluorouracil-Epirubicin-Cyclophosphamide 6 cycles	R	65	HER 2	Invasive ductal carcinoma	SBRII



Dataset 3

Multi-center retrospective evaluation of a RNA expression classifier to predict pathological complete response to neoadjuvant chemotherapy in breast cancer biopsies
(GSE163882)

