Hackathon P1RCC

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Research topic: Analyze the gene expression signature and come up with a treatment regimen

Background

P1RCC

Hereditary papillary renal carcinoma (HPRC) is a hereditary condition that increases the risk of the papillary type of renal cell carcinoma (kidney cancer). The tumors in HPRC are a specific type of papillary cancer called type 1 papillary renal cell cancer. Individuals with HPRC have an increased risk of multiple kidney tumors and an increased risk of developing tumors on both kidneys, called bilateral tumors Currently, no other types of cancer or noncancerous health problems are known to be related to HPRC. (www.cancer.net)

CMAP

The Connectivity Map, or CMap, is a resource that uses transcriptional expression data to probe relationships between diseases, cell physiology, and therapeutics. The changes in gene expression, or "signatures," that arise from a disease, genetic perturbation (knockdown or overexpression of a gene) or treatment with a small molecule are compared for similarity to all perturbational signatures in the database. Perturbations that elicit highly similar, or highly dissimilar, expression signatures are termed "connected"; their related transcriptional effects suggest they confer related physiological effects on the cell. The goal of CMAP is to use these connections to uncover novel treatments for a variety of diseases, including cancers, neurological diseases, and infectious diseases. (CMAP)

Goal

We will first identify gene expression signatures in P1RCC, then feed the genes into CMAP to check if there's any potential drug for the disease.

Data preprocessing

- Download data from TCGA
- 321 samples
- 288 tumors tissues
- 32 normal tissues
- 1 "additional primary tissues" was removed
- Used FPKM data to represent gene expression value

Perform differential expression analysis

Top 200 differential expressed genes in P1RCC (all up-regulated in P1RCC)
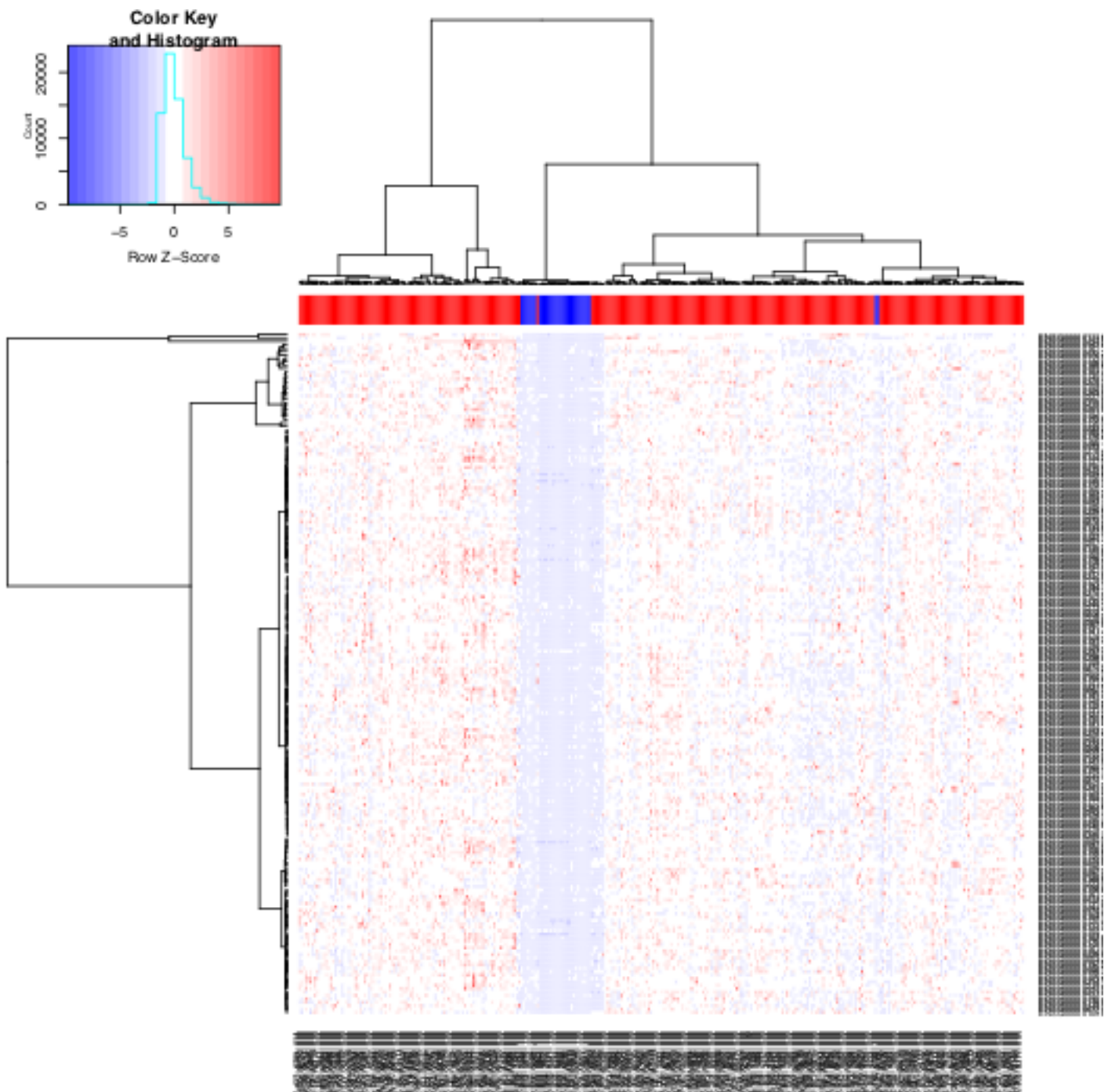
Top 200 down-regulated genes in P1RCC
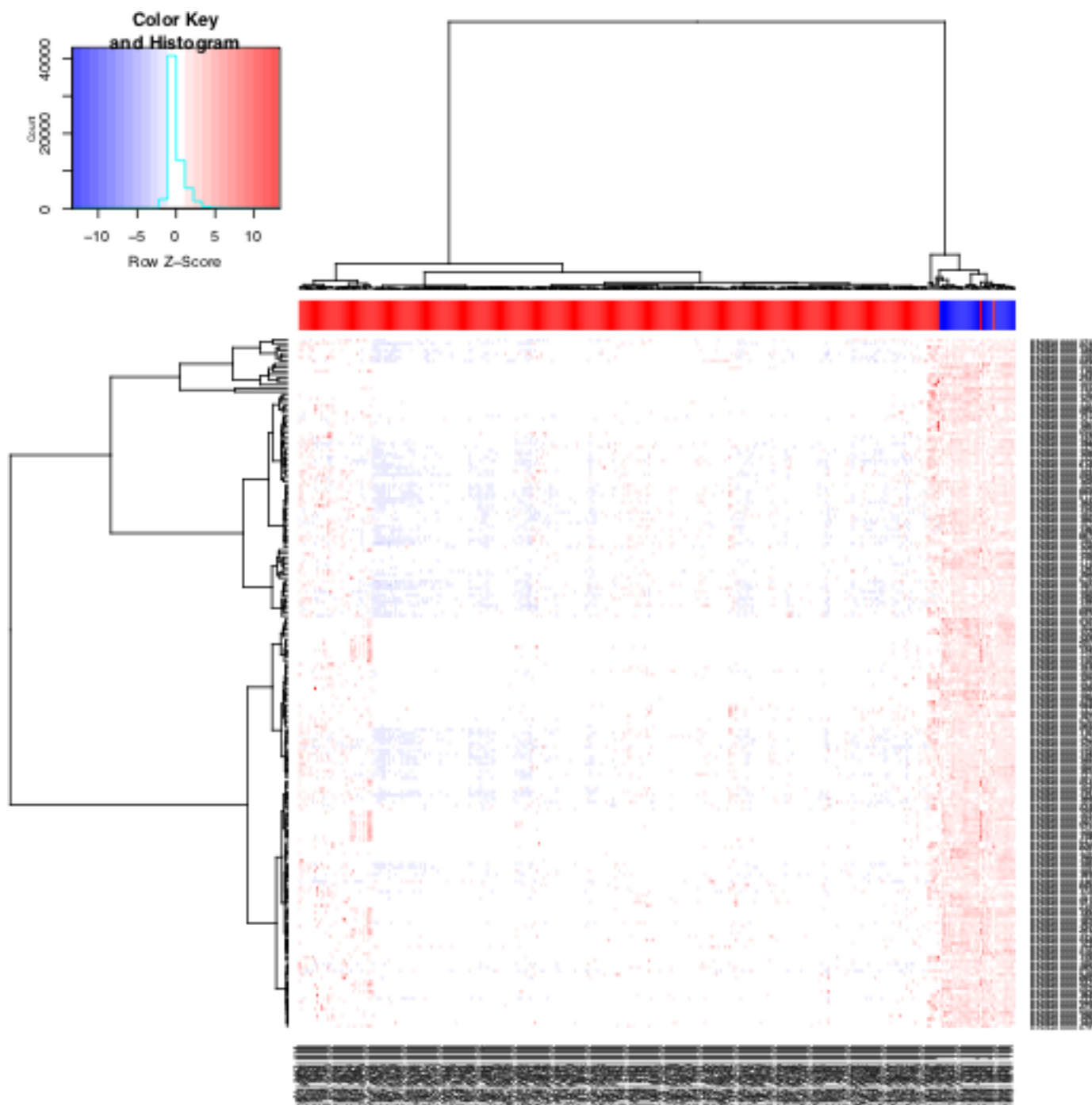
Top up-regulated genes in P1RCC

```
  hgnc_symbol entrezgene                                                        description
1      DBNDD1      79007      dysbindin domain containing 1 [Source:HGNC Symbol;Acc:HGNC:28455]
2      TMEM98      26022         transmembrane protein 98 [Source:HGNC Symbol;Acc:HGNC:24529]
3       ELAC2      60528          elaC ribonuclease Z 2 [Source:HGNC Symbol;Acc:HGNC:14198]
4      LRRC23      10233 leucine rich repeat containing 23 [Source:HGNC Symbol;Acc:HGNC:19138]
5         MVP       9961             major vault protein [Source:HGNC Symbol;Acc:HGNC:7531]
6         VIM       7431                       vimentin [Source:HGNC Symbol;Acc:HGNC:12692]
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Top down-regulated genes in P1RCC

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  hgnc_symbol entrezgene
1       FBXL3      26224                               F-box and leucine rich repeat protein
2       CSDE1       7812                                     cold shock domain containing
3      SEMA3G      56920                                                     semaphorin
4      PIK3C2A      5286 phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 al
5      SLC30A9      10463                                      solute carrier family 30 member
6       CNTN1       1272                                                        contactin
```

Drug discovery at Connectivity Map (CMAP)

Input:

- 134 up-regulated genes
- 140 down-regulated genes

Output:

Top positively associated signatures

#	type	name	description	ts_pc
1		etodolac	cyclooxygenase inhibitor, TRPV agonist	
2		SB-216763	glycogen synthase kinase inhibitor	
3		alpha-estradiol	estrogen receptor agonist	
4		rucaparib	PARP inhibitor	
5		fulvestrant	estrogen receptor antagonist, DNA directed DNA polymerase inhibitor, soluble epoxide hydrolase inhibitor	
6		neurodazine	neurogenesis of non-pluripotent C2C12 myoblast inducer	
7		BRD-K39187410	antiamyloidogenic agent	
8		nikkomycin	chitinase inhibitor	
9		skatole	thrombin inhibitor	
10		lacidipine	calcium channel blocker, L-type calcium channel blocker	
11		desoxycortone	mineralocorticoid receptor agonist	
12		AT-9283	Aurora kinase inhibitor, JAK inhibitor, Abl kinase inhibitor, Bcr-Abl kinase inhibitor, FLT3 inhibitor, mitotic inhibitor, protein kinase inhibitor	
13		liquiritigenin	aromatase inhibitor	
14		parthenolide	NFkB pathway inhibitor, adiponectin receptor agonist	
15		BRD-K15107389	ribosomal protein inhibitor	
16		BMY-45778	IP1 prostacyclin receptor agonist	
17		tosyl-phenylalanyl-chlc	chymotrypsin inhibitor, serine protease inhibitor	
18		naftopidil	adrenergic receptor antagonist, calcium channel antagonist	
19		BRD-K87426499	caspase inhibitor	
20		indirubin	CDK inhibitor, glycogen synthase kinase inhibitor, cyclin-dependent kinase inhibitor, PKC inhibitor	
21		bisindolylmaleimide	CDK inhibitor, PKC inhibitor, leucine rich repeat kinase inhibitor	
22		alisertib	Aurora kinase inhibitor, mitotic inhibitor, protein kinase inhibitor	
23		tyrphostin-AG-1295	FLT3 inhibitor, PDGFR tyrosine kinase receptor inhibitor	
24		nomegestrol	progesterone receptor agonist	
25		nifedipine	calcium channel blocker, L-type calcium channel blocker	
26		GW-9662	PPAR receptor antagonist	
27		BRD-K59222562	CLK inhibitor, dual specificity tyrosine-(Y)-phosphorylation regulated kinase inhibitor, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1B inhibitor	
28		KUC103898N	G protein coupled receptor	
29		mupirocin	isoleucyl-tRNA synthetase inhibitor	
30		evodiamine	ATPase inhibitor, TRPV agonist	
31		zolpidem	benzodiazepine receptor agonist, GABA benzodiazepine site receptor agonist, non-benzodiazepine hypnotic	
32		fluticasone	glucocorticoid receptor agonist	
33		lisuride	dopamine receptor agonist, prolactin inhibitor, serotonin receptor antagonist, serotonin receptor ligand	
34		ALW-II-49-7	ephrin inhibitor	
35		BRL-50481	phosphodiesterase inhibitor	
36		huperzine-a	acetylcholinesterase inhibitor, glutamate receptor antagonist	
37		SAL-1	adenosine receptor antagonist	
38		flubendazole	acetylcholinesterase inhibitor, microtubule inhibitor, tubulin inhibitor	
39		acetyl-farnesyl-cystein	inhibitor of methylation of endogenous isoprenylated proteins	
40		fenbendazole	cytochrome P450 inhibitor, tubulin inhibitor	
41		irinotecan	topoisomerase inhibitor	
42		salubrinal	eukaryotic translation initiation factor inhibitor, GlyT-1 inhibitor	
43		parthenolide	NFkB pathway inhibitor, adiponectin receptor agonist	
44		rhodomyrtoxin	cytotoxic, DNA intercalator	
45		NSC-603868	CDK inhibitor, glycogen synthase kinase inhibitor	

Top negatively associated signatures

#	type	name	description	ts_pc
1		varenicline	acetylcholine receptor partial agonist	
2		BX-912	AKT inhibitor, phosphoinositide dependent kinase inhibitor, pyruvate dehydrogenase kinase inhibitor	
3		ISOX	HDAC inhibitor	
4		linifanib	PDGFR tyrosine kinase receptor inhibitor, VEGFR inhibitor, angiogenesis inhibitor, colony stimulating factor receptor antagonist, colony stimulating factor receptor inhibitor, FLT3 inhibitor, macrophage colony stimulating factor antagonist,	
5		calyculin	protein phosphatase inhibitor	
6		genipin	aglycone, nitric oxide production inhibitor	
7		RO-90-7501	amyloid precursor protein inhibitor, beta amyloid aggregation inhibitor	
8		NVP-AUY922	HSP inhibitor	
9		ZSTK-474	PI3K inhibitor	
10		piperacillin	cell wall synthesis inhibitor	
11		XMD-1150	leucine rich repeat kinase inhibitor	
12		TG-101348	JAK inhibitor, FLT3 inhibitor, RET tyrosine kinase inhibitor	
13		PHA-793887	CDK inhibitor	
14		BIIB021	HSP inhibitor	
15		staurosporine	PKC inhibitor, AKT inhibitor, BMX inhibitor, CDK inhibitor, CHK inhibitor, G protein coupled receptor agonist, glycogen synthase kinase inhibitor, leucine rich repeat kinase inhibitor, ribosomal protein inhibitor, sodium/hydrogen exchanger	
16		CS-110266	dopamine receptor agonist	
17		XMD-892	MAP kinase inhibitor, BMK inhibitor, leucine rich repeat kinase inhibitor	
18		lestaurtinib	FLT3 inhibitor, growth factor receptor inhibitor, JAK inhibitor, apoptosis stimulant	
19		NU-7441	DNA dependent protein kinase, DNA dependent protein kinase inhibitor, P glycoprotein inhibitor	
20		helveticoside	ATPase inhibitor	
21		nisoxetine	dopamine transporter inhibitor, norepinephrine transporter inhibitor, serotonin transporter (SERT) inhibitor	
22		geldanamycin	HSP inhibitor	
23		purvalanol-a	CDK inhibitor, dual specificity tyrosine-(Y)-phosphorylation regulated kinase inhibitor	
24		KU-0060648	DNA dependent protein kinase, DNA dependent protein kinase inhibitor, PI3K inhibitor	
25		nicardipine	calcium channel blocker, L-type calcium channel blocker	
26		entinostat	HDAC inhibitor, cell cycle inhibitor	
27		isradipine	calcium channel blocker, L-type calcium channel blocker	
28		NVP-TAE684	ALK tyrosine kinase receptor inhibitor, ALK tyrosine kinase receptor mutant inhibitor, leucine rich repeat kinase inhibitor	
29		thiothixene	dopamine receptor, dopamine receptor antagonist	
30		BI-2536	PLK inhibitor, apoptosis stimulant, cell cycle inhibitor, protein kinase inhibitor	
31		ranitidine	histamine receptor antagonist	
32		THM-I-94	HDAC inhibitor, apoptosis stimulant, cell cycle inhibitor	
33		vorinostat	HDAC inhibitor, cell cycle inhibitor	
34		H-9	cAMP dependent protein kinase inhibitor, PKA inhibitor	
35		manumycin-a	farnesyltransferase inhibitor, NFkB pathway inhibitor, ras farnesyltransferase inhibitor	
36		bisacodyl	stimulant laxative	
37		scriptaid	HDAC inhibitor	
38		erlotinib	EGFR inhibitor, epidermal growth factor receptor (EGFR) inhibitor, tyrosine kinase inhibitor	
39		triptolide	RNA polymerase inhibitor	
40		chloramphenicol	30S ribosomal protein inhibitor, 50S ribosomal subunit inhibitor, antibacterial agent	
41		nicotinamide	oxidoreductase stimulant, protein synthesis stimulant	
42		thiazolidinecarboxylic-	glutathione synthase stimulant, reducing agent	
43		ascorbic-acid	vitamin C, antioxidant	
44		ochratoxin-a	phenylalanyl tRNA synthetase inhibitor	
45		HSP990 inhibitor	HSP inhibitor, HSP antagonist	

Potential drugs

According to the top negatively associated signatures, here's the potential drug list

- AKT inhibitor

- HDAC inhibitor
- PI3K inhibitor ...