CBW Module 4 Lab Answers (2014 data)

Example 1

1. 2014: EGFR, PTEN, PI3KCA, BRAF, FGFR1, PDGFRA – PI3K/AKT, EGFR, ERBB signalling, etc.

Example 2

The overall sub-network consists of 272 nodes and 712 edges. The largest component of the subnetwork consists of 225 nodes and 584 edges, with the remainder of nodes and edges distributed amongst 13 other small subnetworks and interactions.

1. The driver gnes are probably the frequently mutated gene in the samples. The node size is proportional to the number of samples where the gene is mutated. The largest node is TP53, ie. mutations in the TP53 gene are highly prevalent, occurring in 100 samples. Other driver mutations include EGFR (95) and PTEN (93). Additional mutations of interest include NF1, PIK3R1, PIK3CA, PIK3R1, RYR2, RB1.
2. Annotated Functional Interaction based upon data from the TRED database. This targeted interaction describes an interaction between TP53 (regulator) and PEG3 (target). An immunoprecipitation experiment demonstrates the interaction, and the supporting evidence has been published in the paper with a PubMed ID: 11679586.
3. Predicted Functional Interaction based upon data (2/9 sources are true) from a human interaction database and GO (GO BP sharing). FI score: 0.64
4. 22 modules, with 10 modules of 10 ≥ genes.
5. 6 or 7 modules, depending on the results of the enrichment analysis. Some pathways gene sets at the cutoff threshold may come or go but those highly significant gene sets are always there.
6. 0: RTK signalling, 1: ECM and Integrin signalling, 2: TP53 signaling.
7. Yes.

Cancer type: human breast cancer
Primary NCI role code: Gene_Has_Expression_Measurement
Other roles: Gene_Product_Decreased_in_Disease, Gene_Expression_Downregulated_in_Disease
Evidence code: EV-AS-NAS
Negation indicator: no
Cellline indicator: yes
Status: finished
PubMedID: 11566491

Human breast cancer MDA-MB-231 cells fail to express the neurofibromin protein, lack its type I mRNA isoform and show accumulation of P-MAPK and activated Ras.

Cancer type: human breast cancer
Primary NCI role code: Gene_Product_Expressed_In_Tissue, Gene_Has_Expression_Measurement
Other roles: Gene_Product_Increased_in_Disease, Gene_Product_Decreased_in_Disease
Evidence code: EV-EXP, EV-AS-TAS
Negation indicator: no
Cellline indicator: yes
Status: finished
PubMedID: 11566491

Strikingly, neurofibromin was nearly absent in MB-231 human breast cancer cells and present in the remaining four

cell lines studied, with higher levels in BT-474 and MB-453 than in MCF-7 and BT-20 cells, as tested with polyclonal antibodies to both the N-terminal as well as the C-terminal peptides.

Cancer type: breast cancer
Primary NCI role code: Gene_Product_Expressed_In_Tissue, Gene_Expressed_In_Tissue
Other roles: Gene_Product_Expressed_in_Disease, Gene_Expression_Changed_in_Disease
Evidence code: EV-EXP-IDA
Negation indicator: no
Cellline indicator: yes
Status: finished
PubMedID: 11566491

This result documents for the first time an altered NF1 expression at the protein and mRNA levels in MDA-MB-231 breast cancer cells.

Example 3

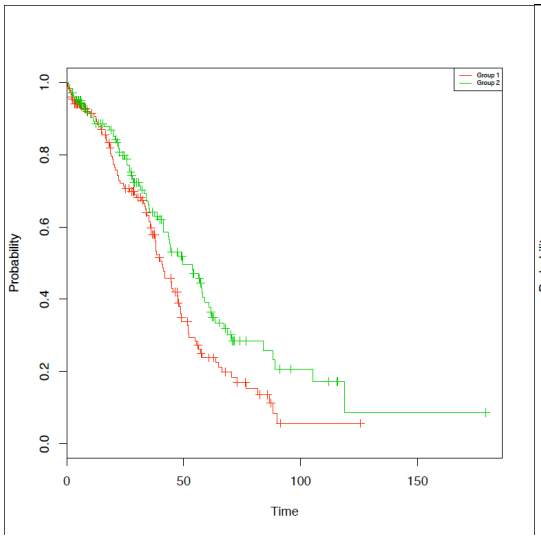
1. The overall sub-network consists of 243 nodes and 472 edges. The largest component of the subnetwork consists of 189 nodes and 405 edges, with the remainder of nodes and edges distributed amongst 16 other small subnetworks and interactions.
2. The largest sub-network and smaller networks contain 201 nodes and 400 edges.
3. The driver gene is probably the frequently mutated gene in the samples. The node size is proportional to the number of samples where the gene is mutated. The largest node is TP53, ie. mutations in the TP53 gene are highly prevalent, occurring in at least 96% of HGS-OvCa samples.
4. After clustering, there are 23 modules with 10 modules of 10 ≥ genes.
5. 17 modules, depending on the results of the enrichment analysis. Some pathways gene sets at the cutoff threshold may come or go but those highly significant gene sets are always there.
6. 0: DNA Repair, Cell Cycle and TP53 Signalling, 1: ECM and Integrin signalling and PI3K Signaling, 2: Calcium Signalling.
7. Yes, DNA Repair.
8. Extracellular region, ECM, Extracellular space.
9. Modules 0, 3 will be highlighted. Navigate through hierarchy. Neoplasm > Neoplasm_by_Site > Breast Neoplasm > Maligant_Breast_Neoplasm > Breast Carcinoma > Stage_IV_Breast_Cancer. Go back to the Network Module Browser. Genes in the modules that have 'Stage IV Breast Cancer' annotations will be yellow-highlighted: BRCA1, BRCA2, TP53, etc.
10. 2 modules: 1, 2

Analysis: Coxph (all modules)

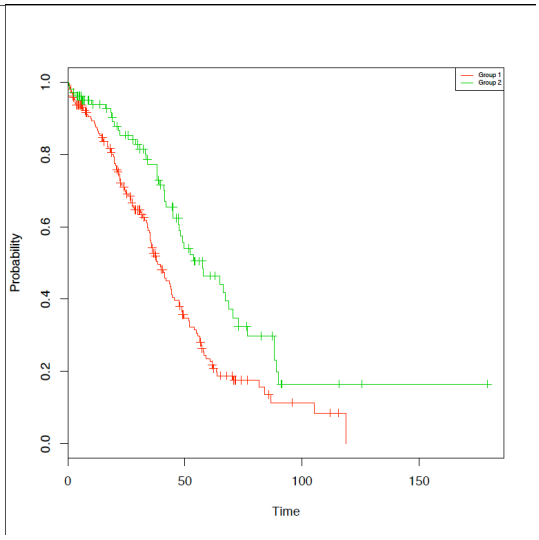
----Output----
Note: Click underlined modules in blue for single module-based analysis. You may not see any underlined module if all p-values > 0.05.

Module	Coefficient	P-value
0	-0.4214759	0.354021
1	-0.3596989	0.01981377
2	-0.5825354	0.0006015822
3	-0.1820369	0.2837648
4	0.03250961	0.853349
5	-0.3148655	0.05547871
6	-0.1778184	0.3644498
7	-0.01888722	0.9204951
8	0.128442	0.5230743
9	-0.300684	0.1456164
10	-0.1751839	0.530286

11. In Modules 1 (KM: p= 0.0192) and 2 (KM: p= 0.000507), patient with genes mutated (green line) have a better prognosis than patients with no gene mutations (red line). Module 1 and 2 are the most statistically significant modules from the CoxPH analysis. The ReactomeFIViz app splits samples into two groups: samples having genes mutated in a module (red line), and samples having no genes mutated in the module (green line). The plugin uses the log-rank test to compare the two survival curves, and estimates p-values.



Module 1 KM plot



Module 2 KM plot

12. In Module 2, the Calcium signaling, Chemical Synapse/Neurotransmission and Muscle Contraction annotations reflect a shared set of genes. These genes represent voltage-gated ion channels, which are a group of transmembrane ion channels that activated by changes in electrical potential difference. Even though ion channels are especially critical in neurons and muscle tissue, they are common in many types of cells, controlling the influx and outflux of ions. There are a number of genetic disorders, which disrupt normal functioning of ion channels. Calcium homeostasis is essential for cell migration, and tumor metastasis in particular. It may be that mutations in Module 2 genes disrupt calcium homeostasis, thereby impairing the tumour's ability to metastasize, and extending patient's overall survival.