

A network-based phenotype mapping approach to identify genes that modulate drug response phenotypes

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Supplementary Figure Legends

Supplementary Figure 1. Plots for distribution of EC50 values for LCL cell lines of African, Caucasian, and Chinese origin in response to anthracyclines (doxorubicin and epirubicin) and taxanes (docetaxel and paclitaxel). The 15 cell lines that are defined as sensitive (lower end of plots) and resistant (upper end) indicated in red and used for subsequent analyses.

Supplementary Figure 2. Number of overlapped PDEGs between LCL-derived taxane sensitive and resistant phenotypes with paclitaxel sensitive and resistant phenotypes for breast cancer cell lines from Cancer Cell Line Encyclopedia (CCLE).

Supplementary Figure 3. PDEG- and PDEG-interacting gene-enriched biological pathways in DRNs that confer taxane sensitivity and resistance. (A) Enriched pathways for PDEGs in taxane sensitive response network; (B) Enriched pathways for PDEGs in taxane resistant response network; (C) Enriched pathways in Gene Set Enrichment Analysis (GSEA) using pre-ranked option for PDEG-interacting genes in taxane sensitive and resistant response networks, ranked with phenotypic frequency (PF) scores. Red: enriched pathways in taxane sensitive network (positive PF scores); blue: enriched pathways in taxane resistant network (negative PF score). Four selected GSEA-enriched pathways for PDEG-interacting genes in taxane sensitive network are indicated at right panel.

Supplementary Figure 4. Response curves of MTS assays before and after knockdown of selected PDEG-interacting genes in BT549 and MDA-MB-231 triple-negative breast cancer

(TNBC) cell lines treated with taxanes (docetaxel and paclitaxel). (A) siRNA knockdown followed by docetaxel treatment in BT549 cells; (B) siRNA knockdown followed by paclitaxel treatment in BT549 cells; (C) siRNA knockdown followed by docetaxel treatment in MDA-MB-231 cells; (D) siRNA knockdown followed by paclitaxel treatment in MDA-MB-231 cells. Red: candidate siRNA; blue: negative control siRNA. X-axis: drug concentrations in logarithm scale of nM; Y-axis: fraction of surviving cells.

Supplementary Figure 5. Network for taxane-sensitive N1 PDEG-interacting genes. A portion of the taxane-sensitive drug response network showing N1 PDEG-interacting genes (green nodes) exhibiting high PF scores and their corresponding interacting PDEGs (red nodes).

Supplementary Figure 6. Computed distributions for the degree of connectedness for anthracycline resistant and taxane sensitive networks.

SUPPLEMENTARY DATA

Supplementary Data 1. Cytotoxicity data for corresponding cell lines.

Supplementary Data 2. Heatmaps of upregulated genes in all 24 drug response conditions.

Supplementary Data 3. Lists of PDEGs and the number of their occurrences with respect to the same drug response phenotype. The nominal p-value for a gene as PDEG is defined as the probability (approximated by the frequency from permutations via permuting EC50 labels) of picking this gene by chance.

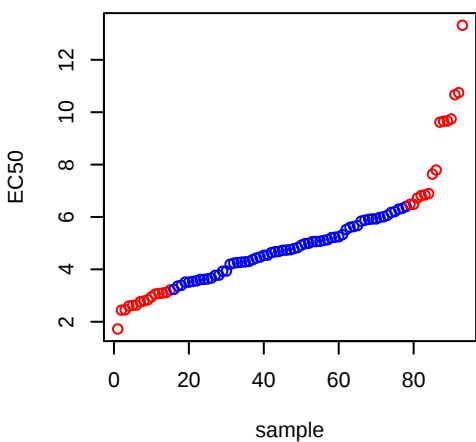
Supplementary Data 4. PDEG-interacting genes and their respective computed frequencies and PF scores in both anthracycline and taxane response networks. The nominal p-value for a gene as N1 for sensitive is defined as the frequency of picking this gene as N1 sensitive and having a larger frequency_sensitive by chance. The same criterion also applied to N1 for resistant, and for N2 sensitive, and N2 resistant genes. Since each gene has both frequency_sensitive and frequency_resistant, the smaller nominal p-value of the 2 should be used to describe the significance. The nominal p-value (1000 permutations for EC50 labels) for a gene as N1 or N2 is defined for sensitive and resistant separately, e.g. nominal p-value for an N1 gene as related to sensitive:

Nominal-P = Number of (frequency_sensitive as N1 scores from permutation $\geq$ frequency_sensitive as N1 scores in the results) / number of permutations.

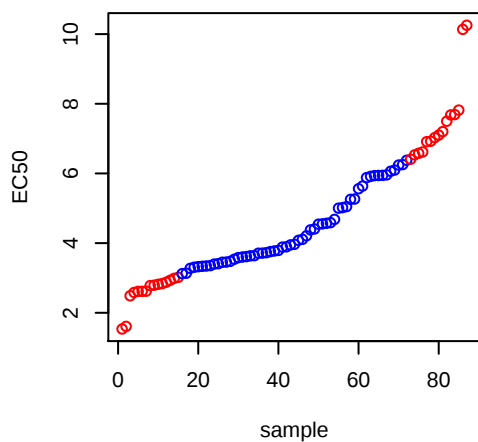
Supplementary Data 5. Results for statistical tests for PDEGs enriched pathways. The nominal p-value for a KEGG pathway is defined as finding this pathway as significant (adjusted pvalue $\geq$ 0.2) by chance. Over-representation test was performed for PDEGs in each permutation (total 1000 permutations for EC50 labels) and the nominal p-values for the KEGG pathways are defined as:

Number of finding a pathway as significant / number of permutations.

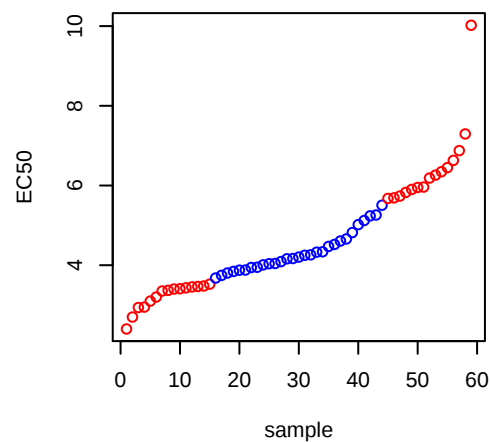
EC50.docetaxel African 95



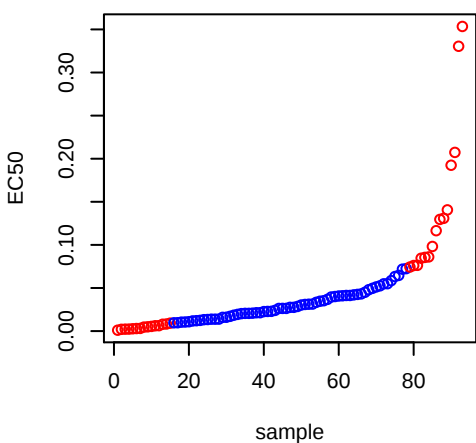
EC50.docetaxel Caucasian 96



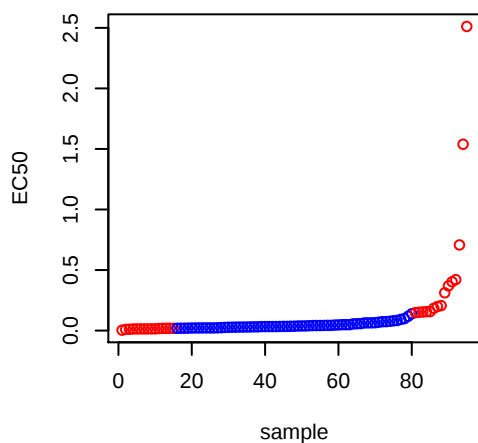
EC50.docetaxel Chinese 59



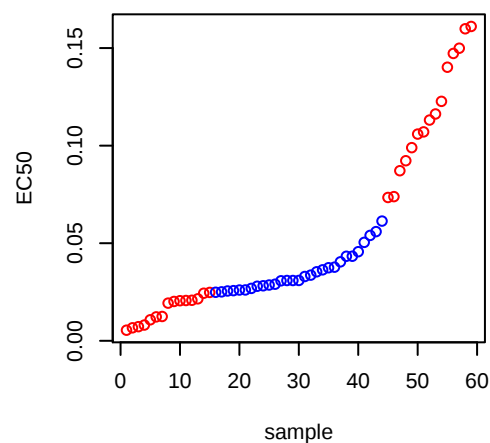
EC50.doxorubicin African 95



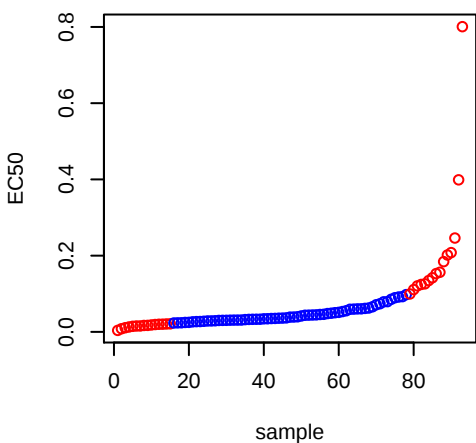
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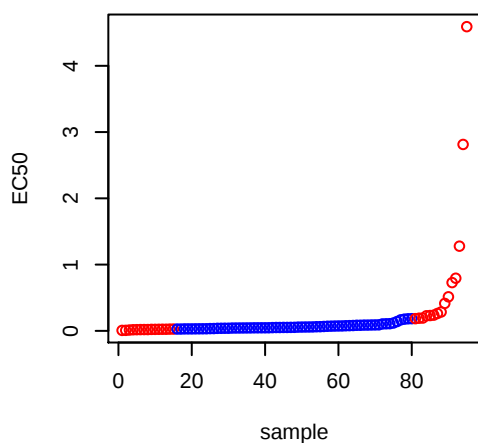
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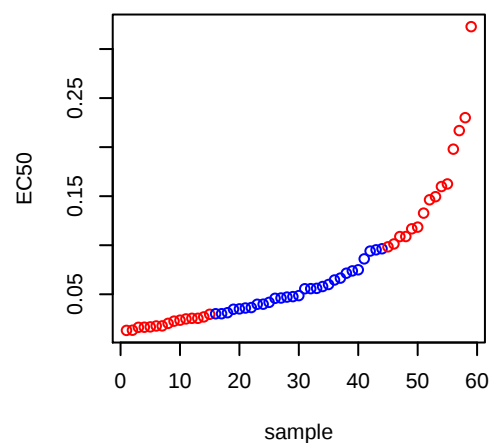
EC50.epirubicin African 95



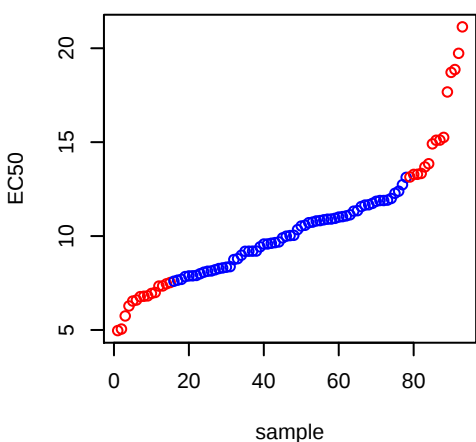
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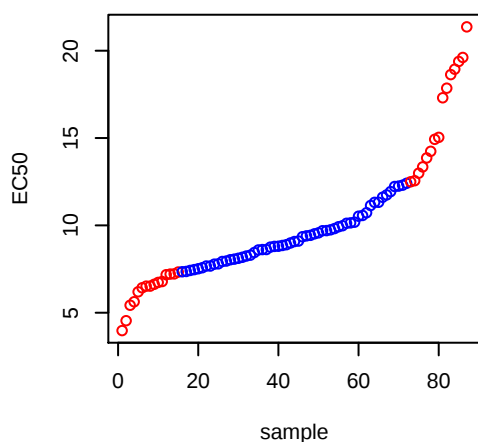
EC50.epirubicin Chinese 59



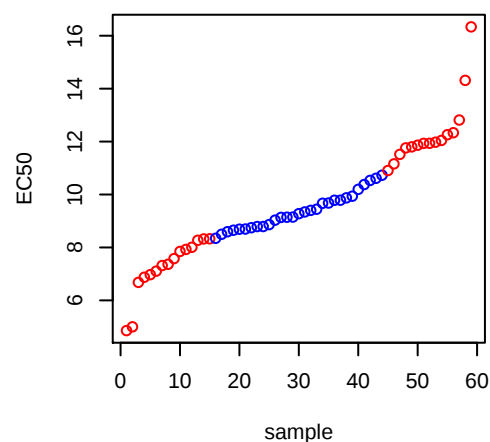
EC50.pactilatxel African 95



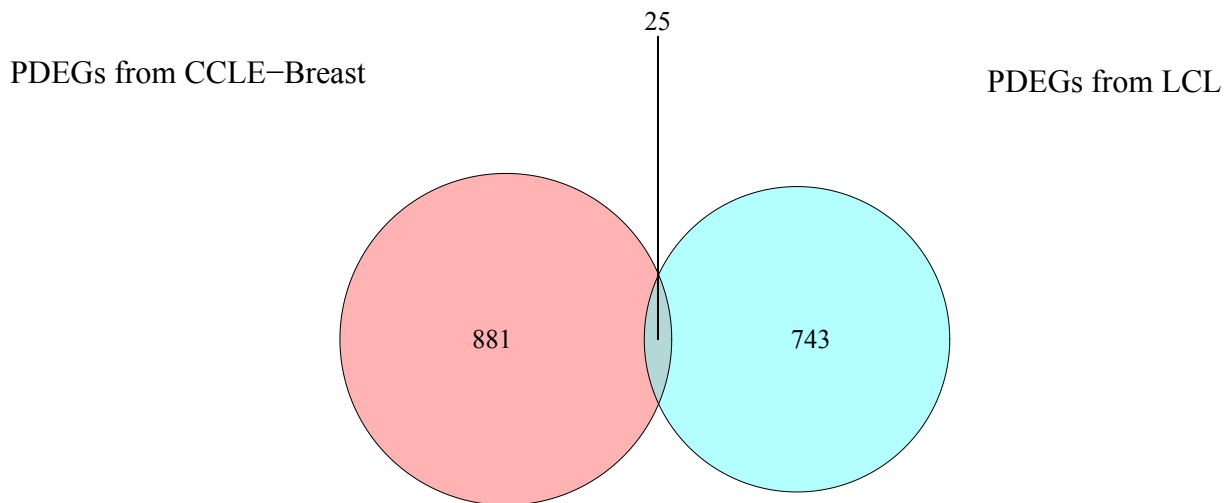
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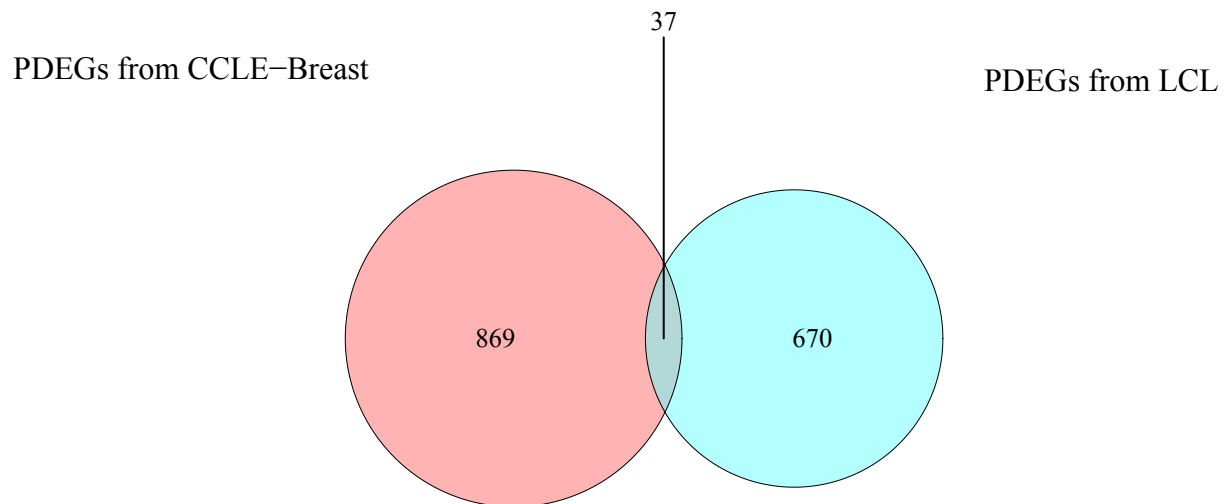
EC50.pactilatxel Chinese 59



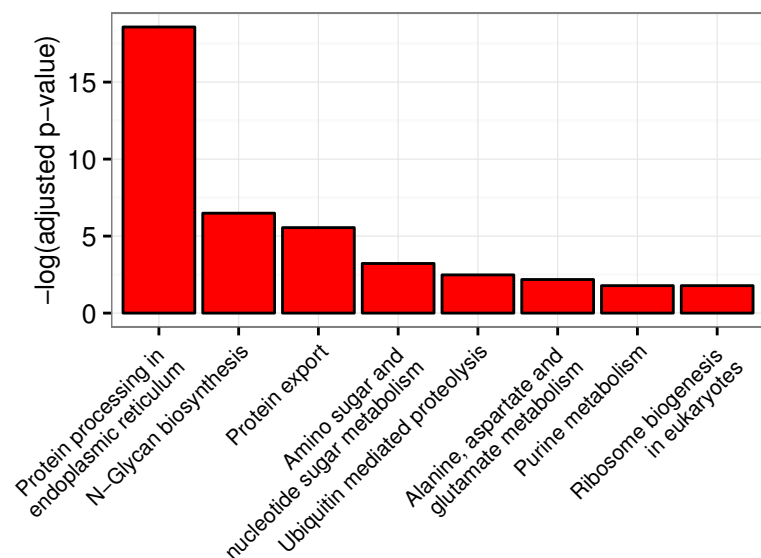
Taxane - sensitive



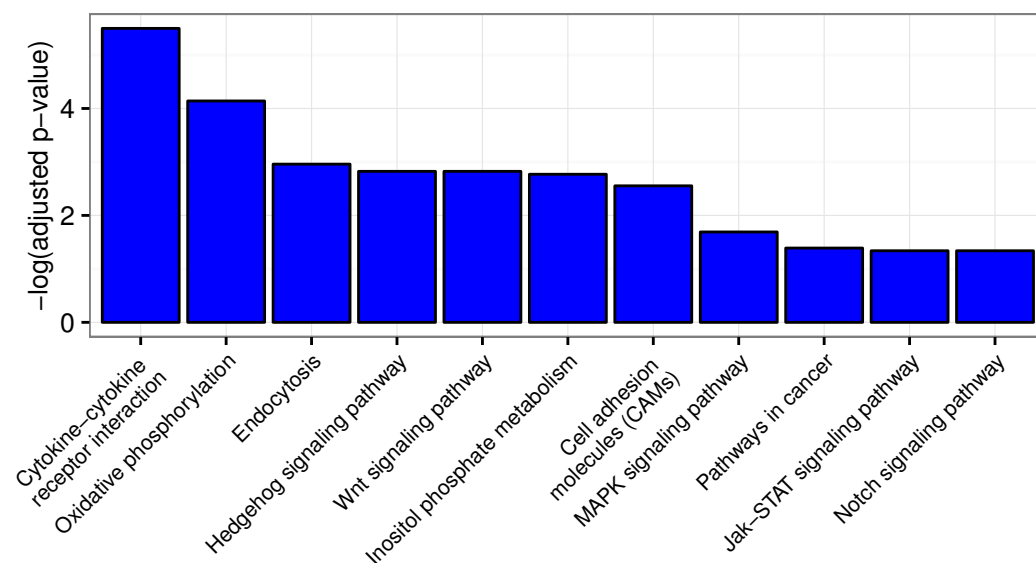
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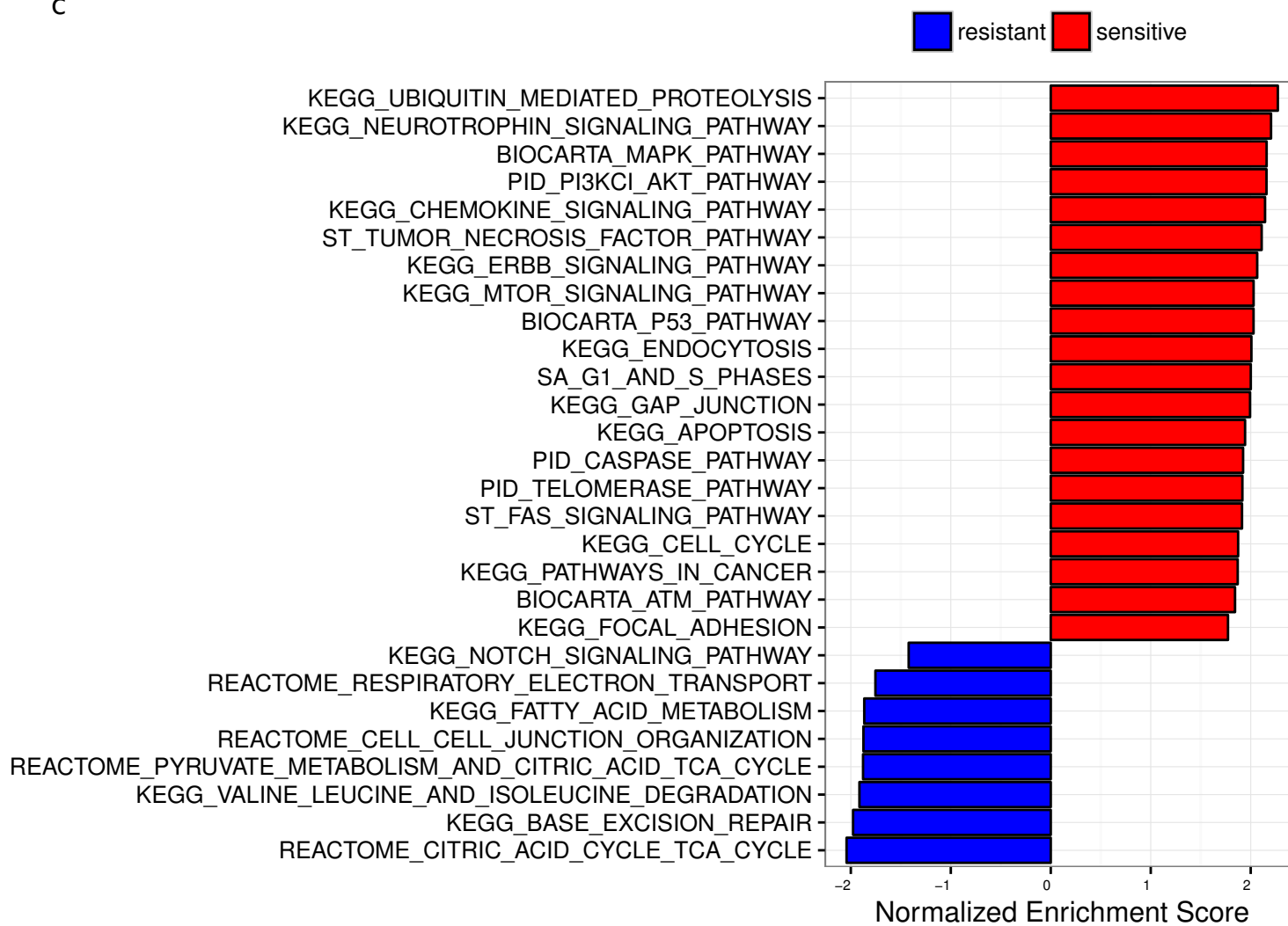
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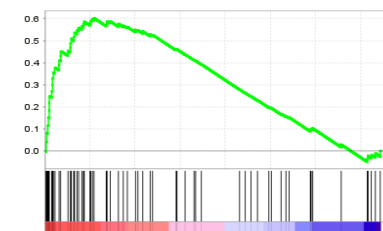
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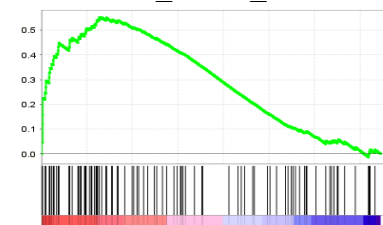
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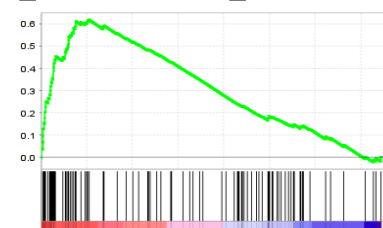
KEGG_APOPTOSIS



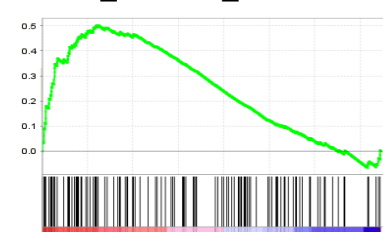
KEGG_CELL_CYCLE

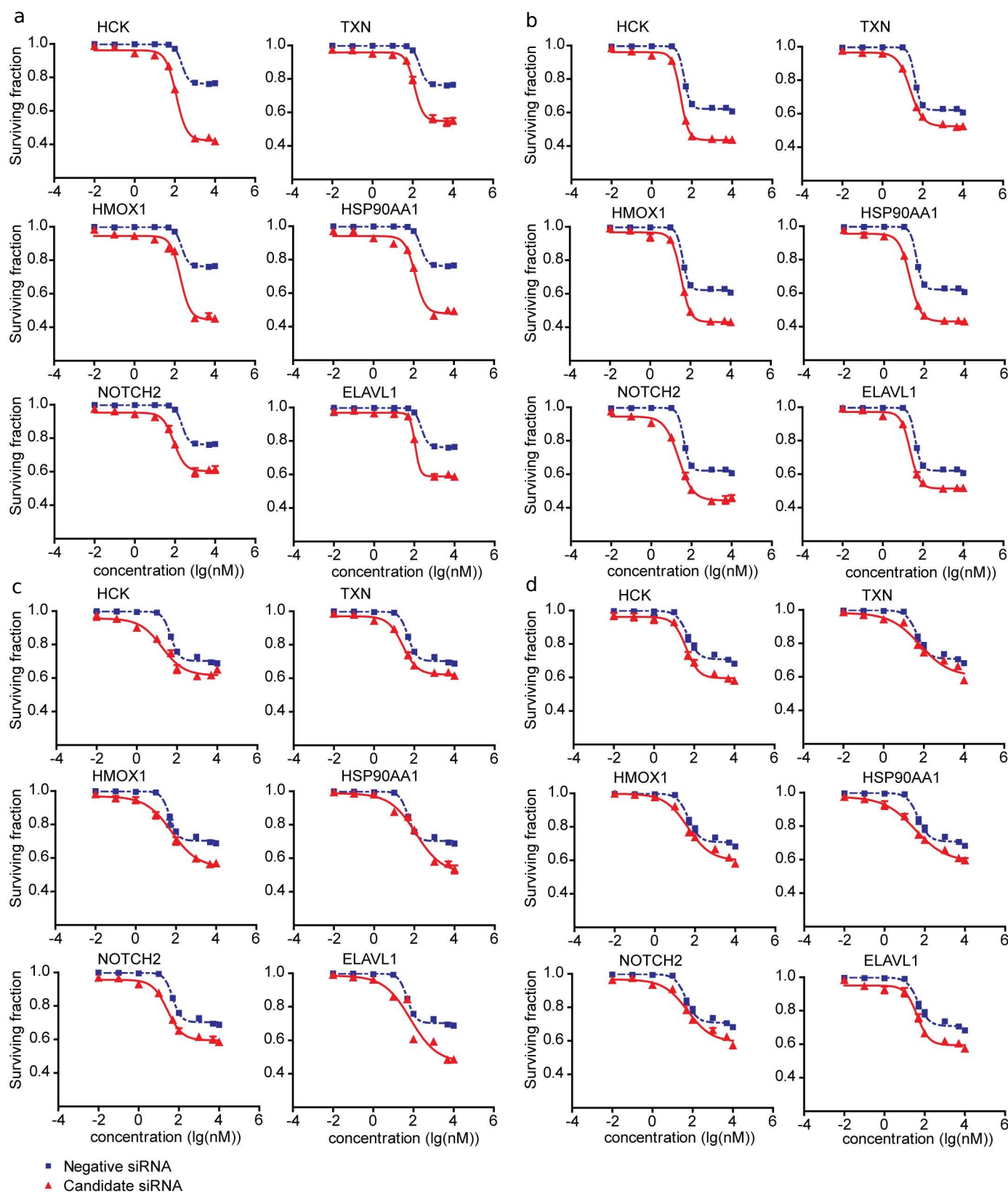


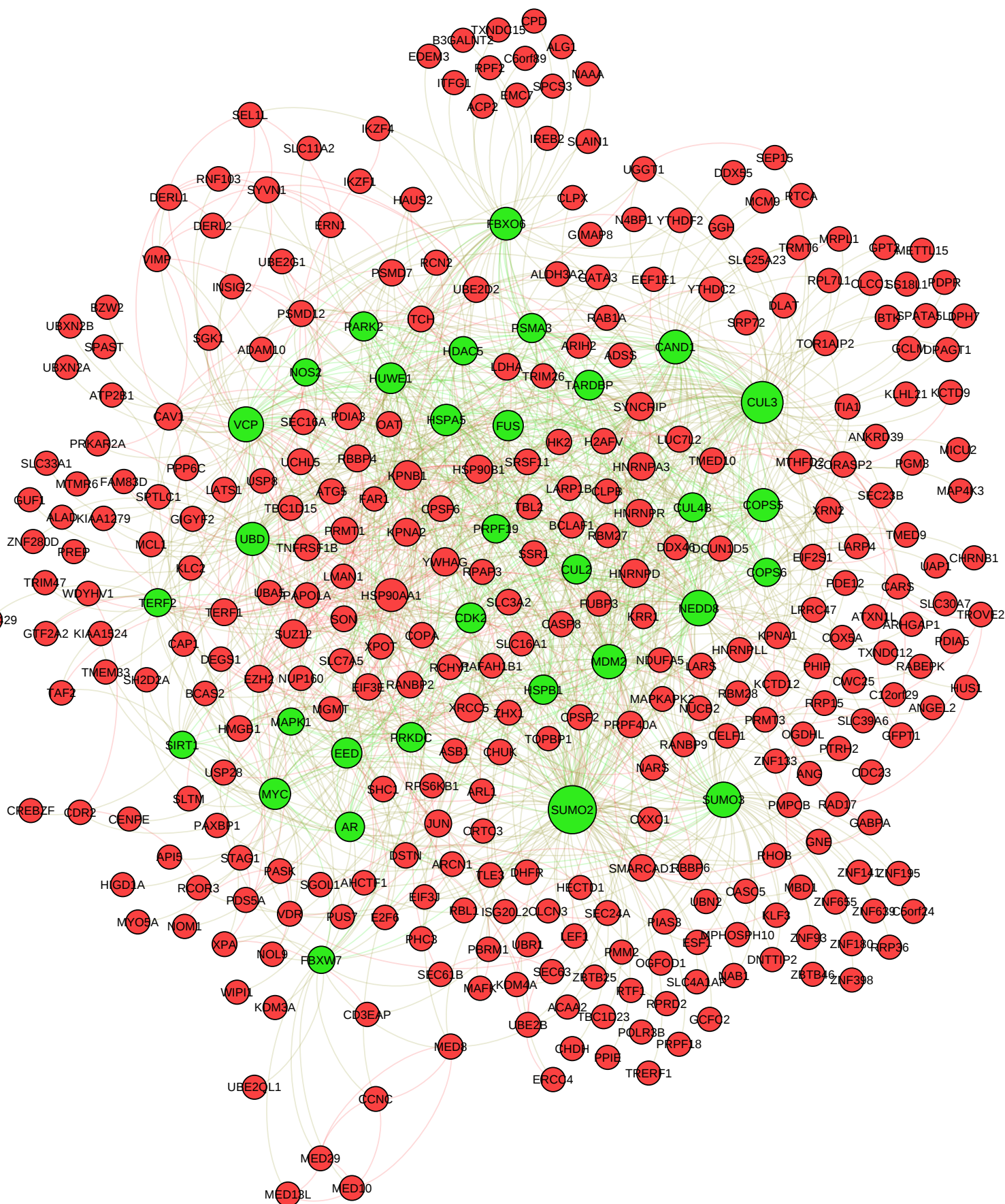
KEGG_CHEMOKINE_SIGNALING_PATHWAY



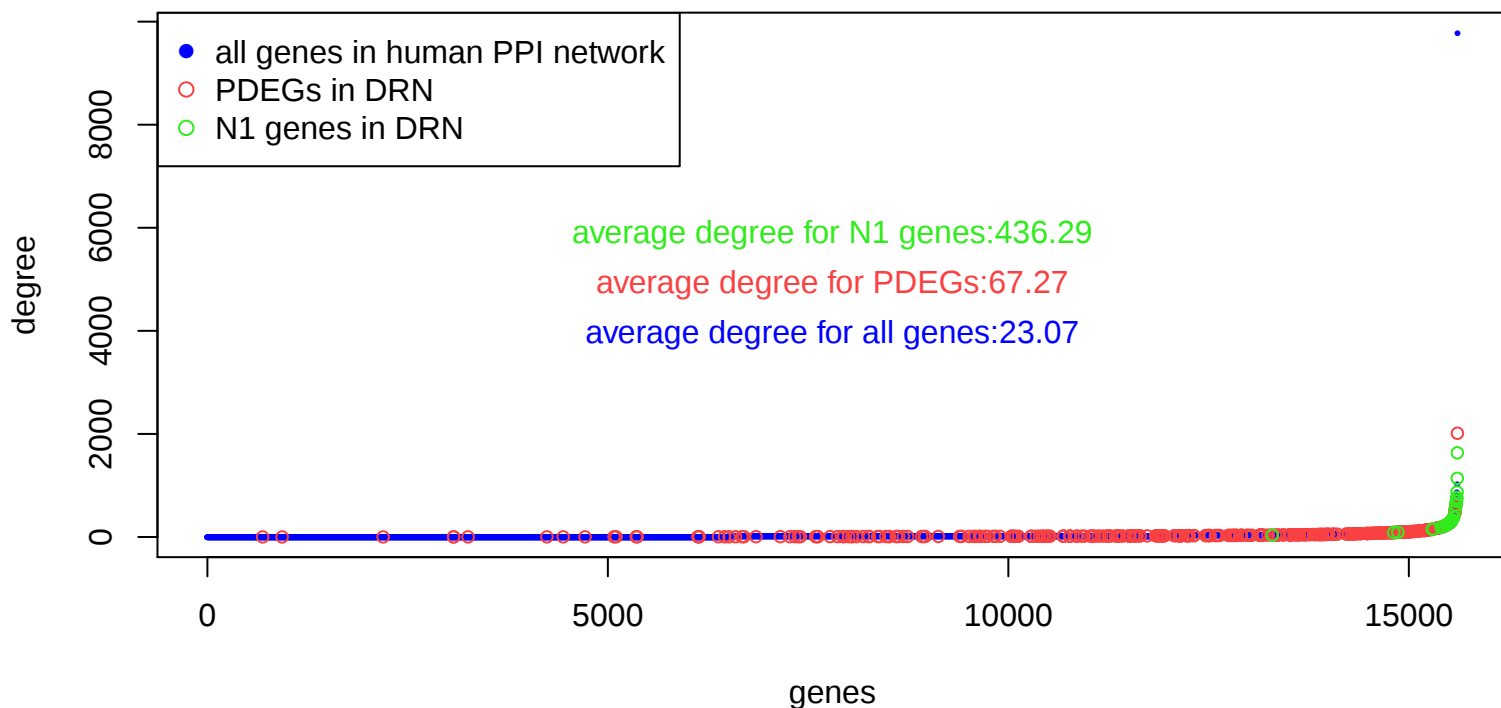
KEGG_FOCAL_ADHESION







Anthracycline Resistant DRN



Taxane Sensitive DRN

