

## Supplementary Figures:

**Supplementary Figure S1:** Distributions of the  $\sum_i P_{i \times j}$  in the three cancer types.

**Supplementary Figure S2:** Bar plot shows the significant eigenvalues of the variance matrix of the expression profile of the 62 HRM genes in the three cancer types. Significant eigenvalues are shown in red.

**Supplementary Figure S3:** Gene expression profile of ER, AR and PR in multiple breast cancer subtypes and population proportion calculate by NMF on the gene expression profile. A clear multi-modal distribution can be found in the distribution of one selected population's proportion, which corresponds to samples from different cancer subtypes.

**Supplementary Figure S4:** (A) Heatmap of the expression of HRM genes of each bicluster identified in each cancer type. The biclustering tools applied in this study will output multiple biclusters that may overlap each other. Significance level are calculated for each bicluster. In the heatmap, each row is one HRM gene while each column is one sample. Green and red respectively indicate high and low expression. (B) Permutation test of the bicluster significance. We have run Qubic on 100 randomly shuffled (by samples for each gene) data set for each cancer type and use log significance level of the top 100 biclusters in each run as the empirical distribution of the significance level. The histogram in the figure shows the distribution of the log significance level of biclusters identified in randomized data while the red lines indicate the significance level of the biclusters identified in the real data. Lower log significance level indicates more significant result.

**Supplementary Figure S5:** (A) Distribution of the mutation rates in the four major biclustering classes of colon adenocarcinoma. In the boxplot, each bar from left to right shows the distribution of mutation rate of non-hypoxia/reoxygenation, hypoxia and reoxygenation group, respectively. (B) The gene expression profile of the HRM genes in the four major biclustering classes of colon adenocarcinoma. In the heatmap, the reoxygenation, hypoxia and non-hypoxia/reoxygenation samples are labelled by green, red and pink, respectively. Hypoxia and reoxygenation markers are labelled by red and green, respectively. 11

**Supplementary Figure S6:** (A) Distribution of the mutation rates in the four major biclustering classes of lung adenocarcinoma. In the boxplot, each bar from left to right shows the distribution of mutation rate of non-hypoxia/reoxygenation, angiogenesis, hypoxia and reoxygenation group, respectively. (B) The gene expression profile of the HRM genes in the four major biclustering classes of lung adenocarcinoma. In the heatmap, the reoxygenation, angiogenesis, hypoxia and non-hypoxia/reoxygenation samples are labelled by green, blue, red and pink, respectively. Hypoxia and reoxygenation markers are labelled by red and green, respectively.

**Supplementary Figure S7:** (Unimodal) Distributions of the population proportions in the three cancer types.

**Supplementary Figure S8:** Gene-expression signatures for three cell subpopulations in the three cancer types. In the plot of each cancer type, the columns represent the gene expression pattern of the reoxygenation, background and hypoxia subpopulation, from left to right. The color code of each heat-map represents down or up-regulation with the detailed definition given in the top of the figure.

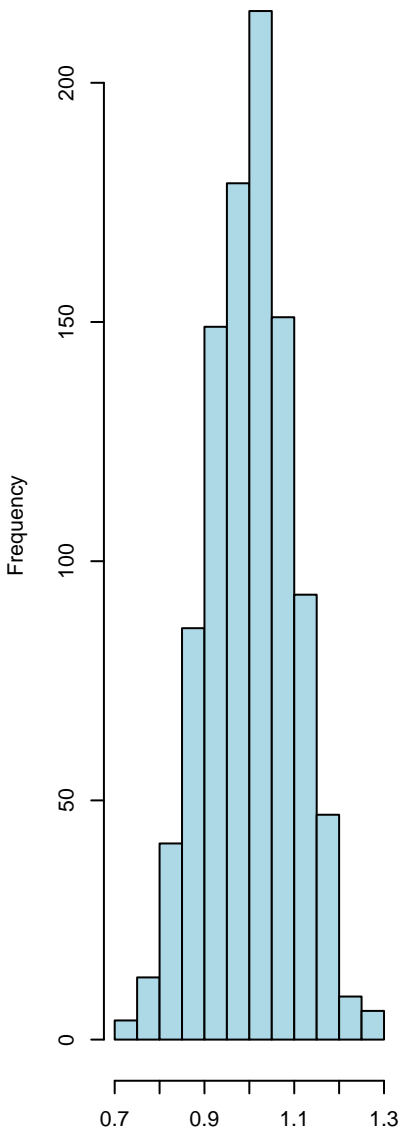
**Supplementary Figure S9:** Histogram of the Pearson correlation coefficients between the population proportions and expression level of oxygen enzymes. 141 genes of the enzymes catalysing oxygen consuming reactions are extracted from KEGG database. Pearson correlation coefficients are calculated between the expression level of these genes and the proportion of hypoxia and reoxygenation populations in each cancer type.

**Supplementary Figure S10:** (A) correlation of the gene expression level of ESR1, AR and PGR with the proportion of sub-populations. (B) Distribution of the gene expression level of ESR1, AR and PGR in each cancer type. The expression level of each gene is fitted by mixture Gaussian model by mclust package in R.

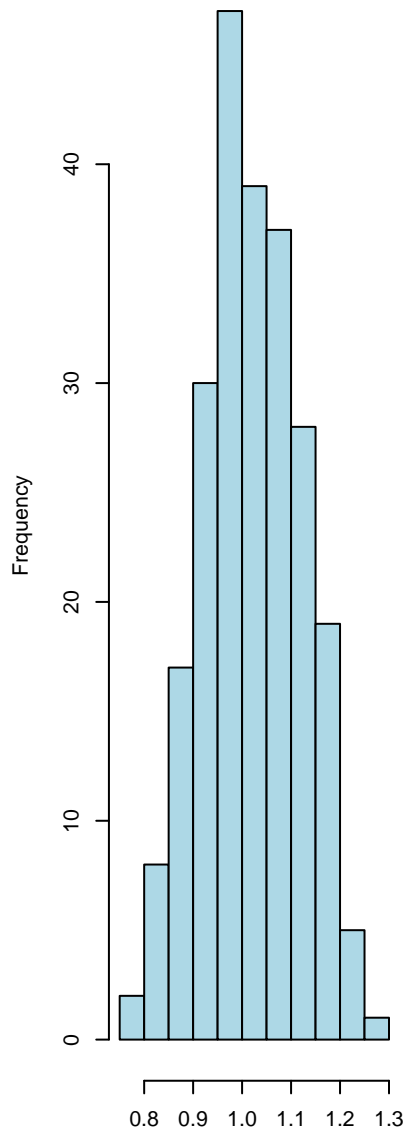
**Supplementary Figure S11:** Boxplot of the mutation rates versus cancer pathological stages. In the boxplot, each bar shows the distribution of mutation rates of the samples in certain cancer pathological stage shown in x-axis.

S1

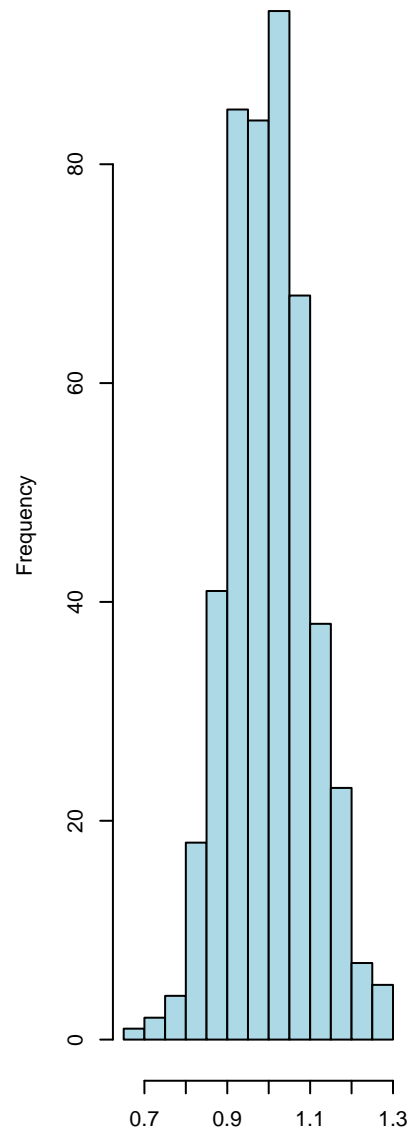
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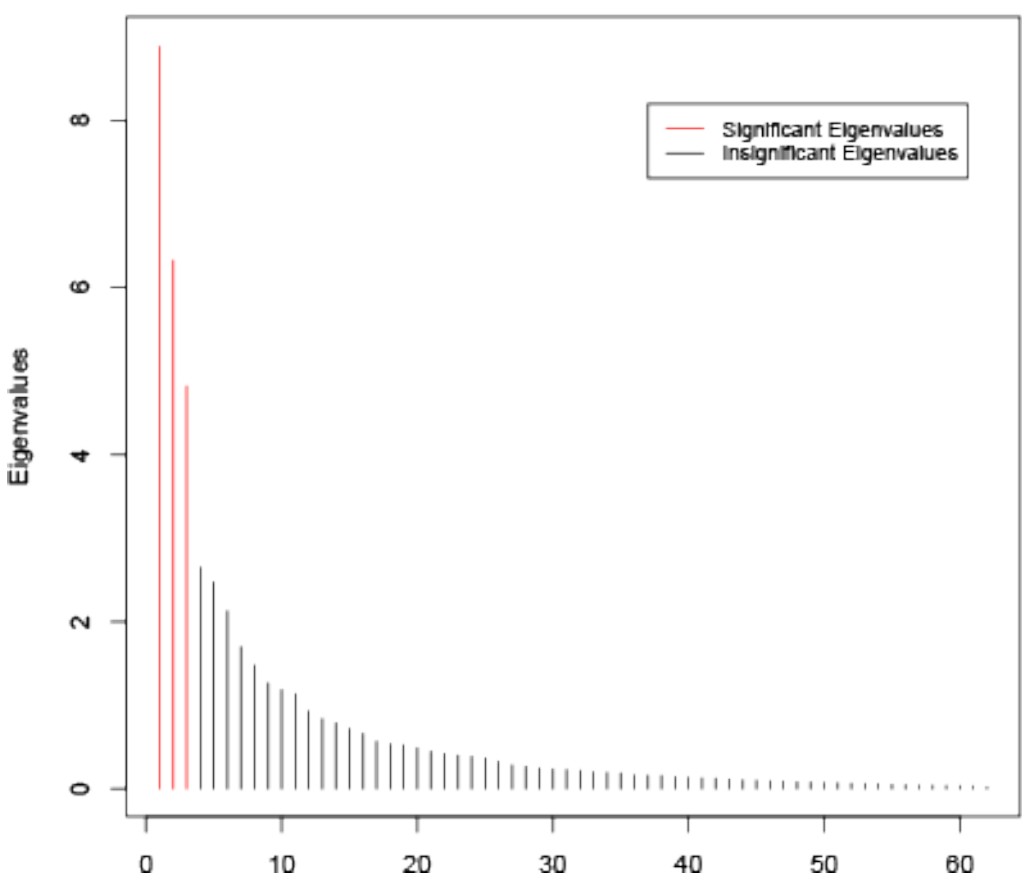
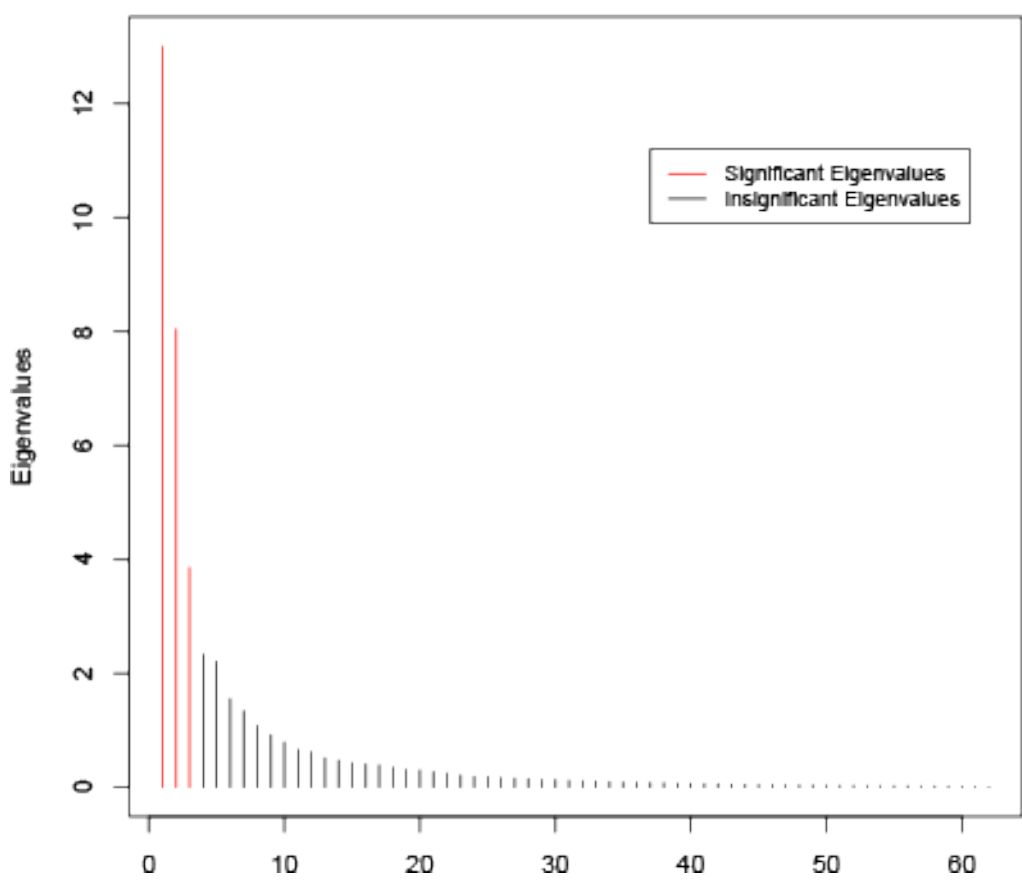
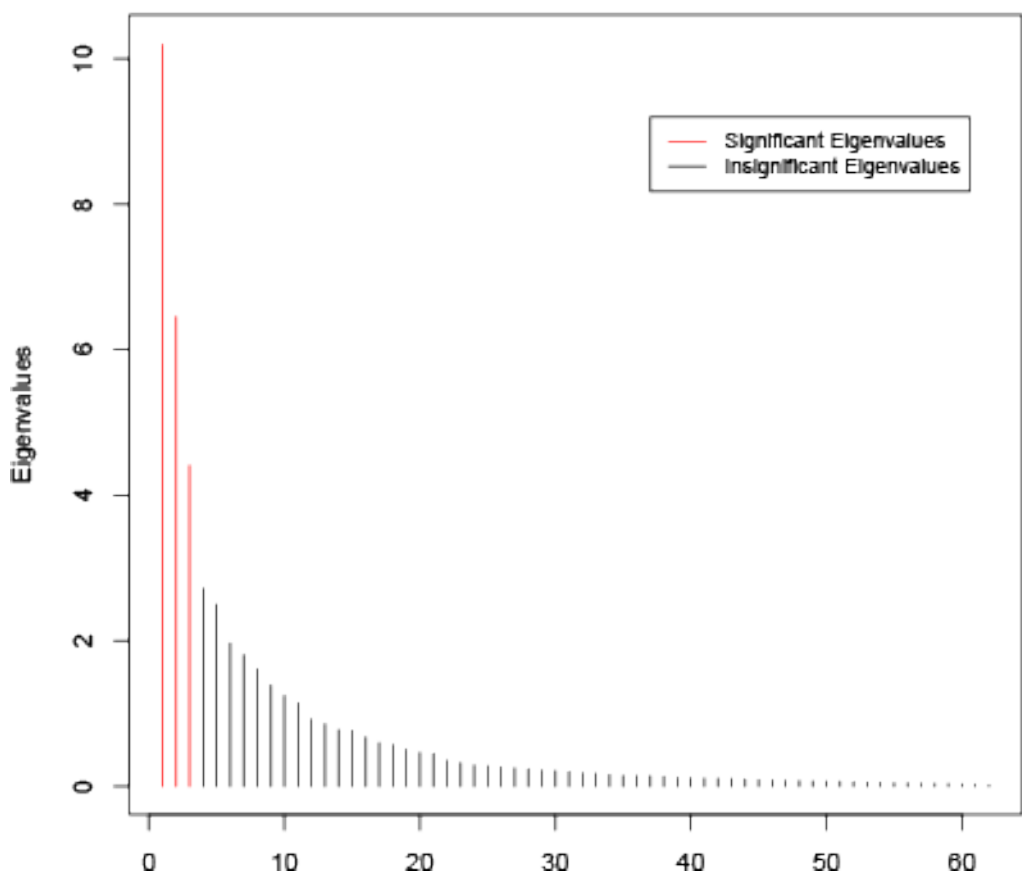


**COAD**



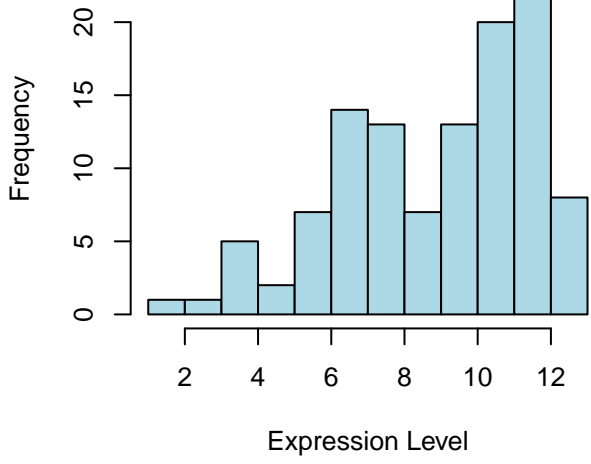
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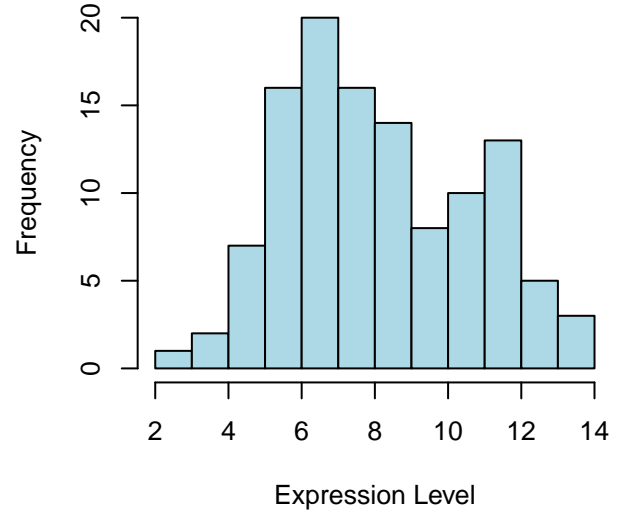


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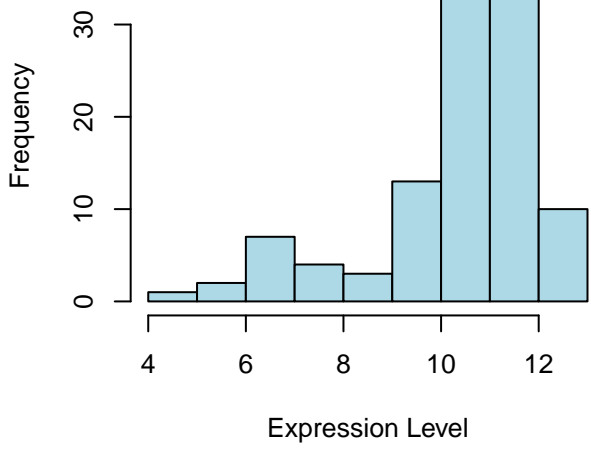
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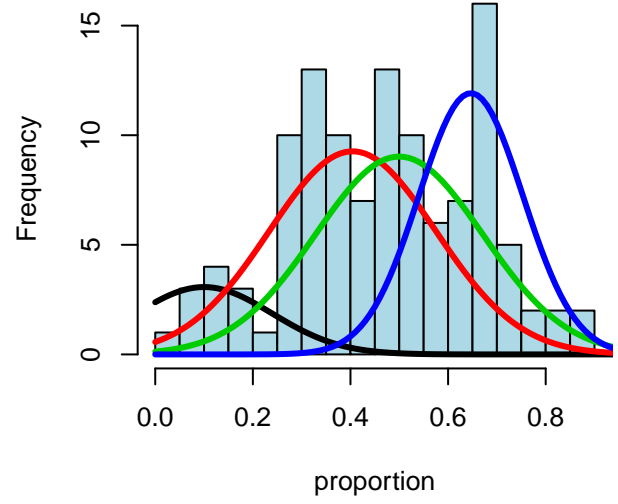
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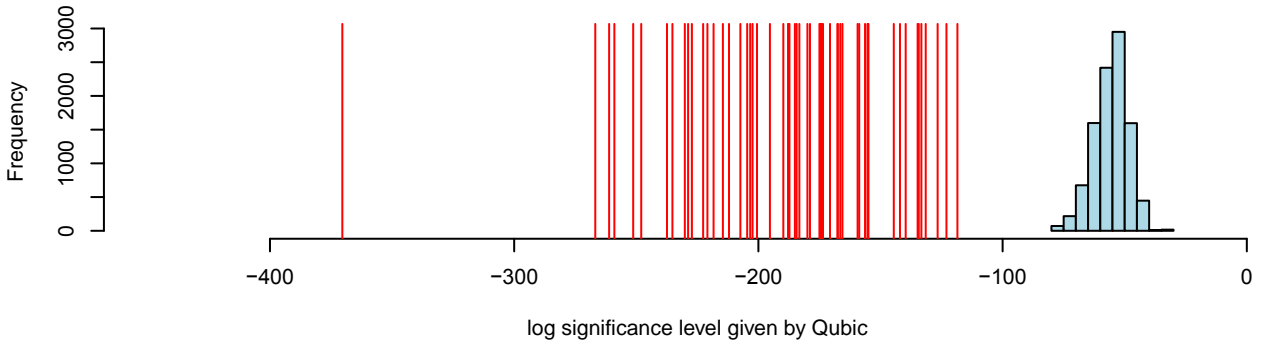
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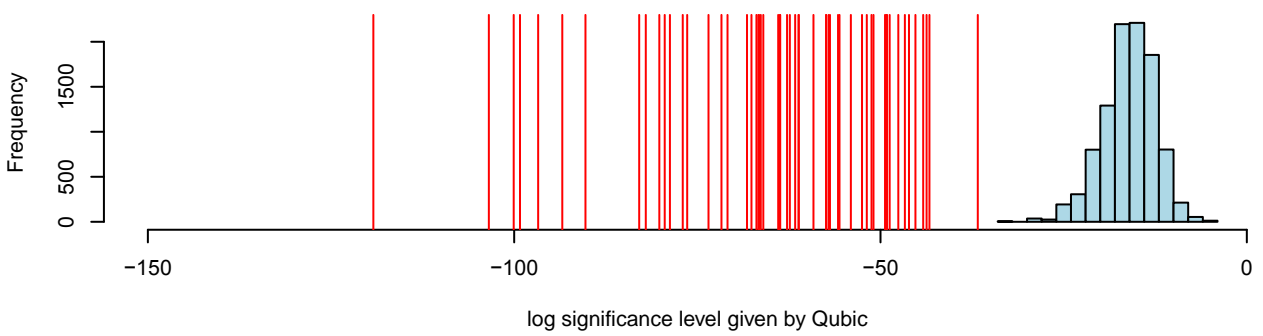
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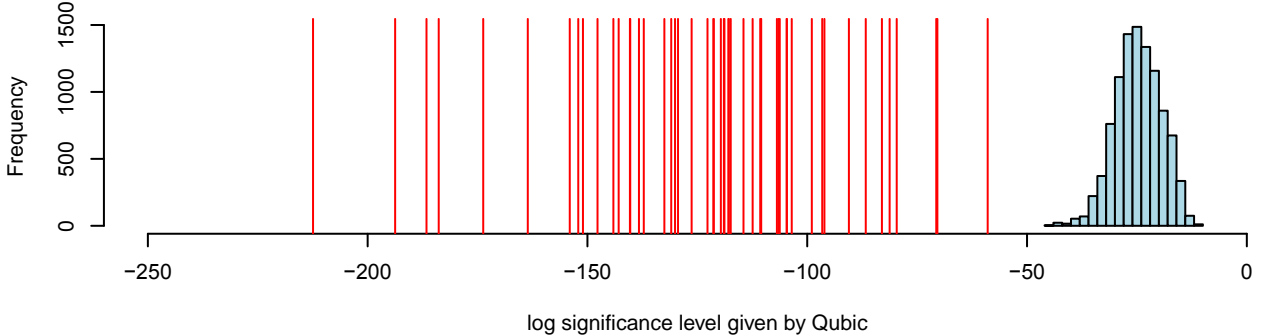
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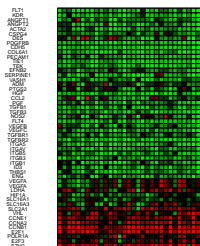
**Permutation test for the significance of biclusters of COAD**



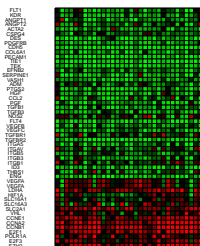
**Permutation test for the significance of biclusters of LUAD**



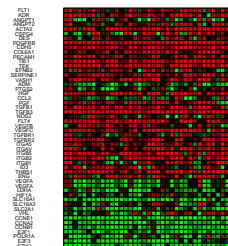
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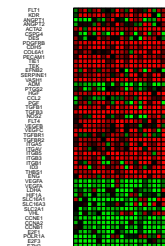
BRCA BC: reoxygenation 8



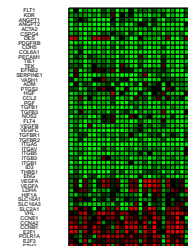
BRCA BC: hypoxia 9



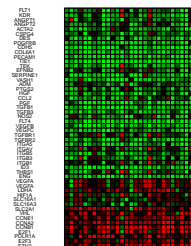
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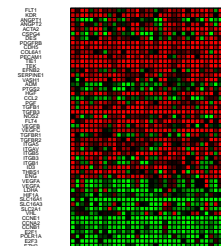
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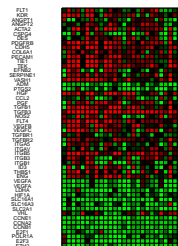
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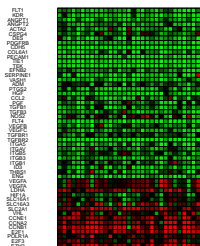
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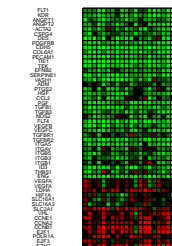
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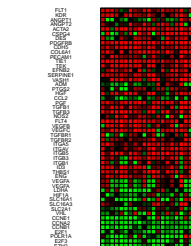
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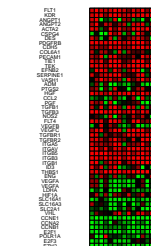
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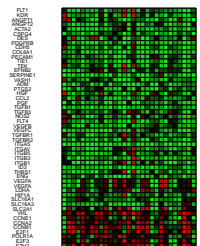
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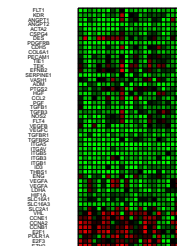
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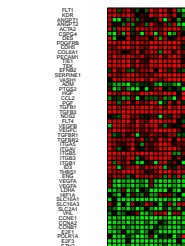
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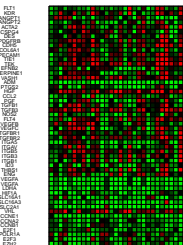
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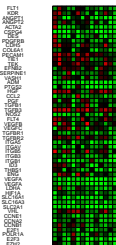
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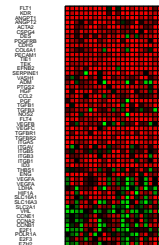
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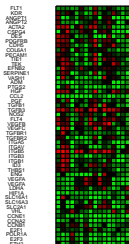
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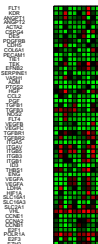
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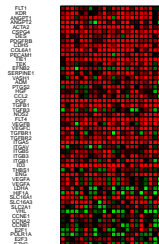
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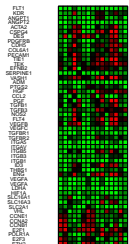
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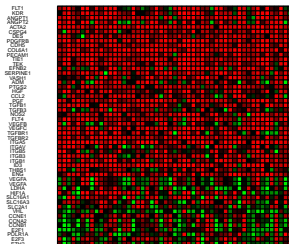
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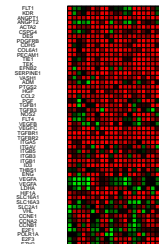
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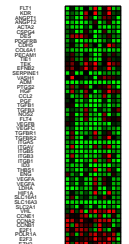
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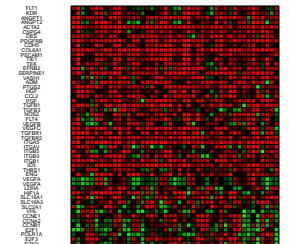
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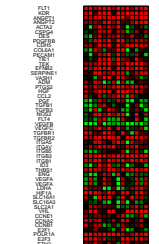
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BRCA BC: background 3



BRCA BC: background 24



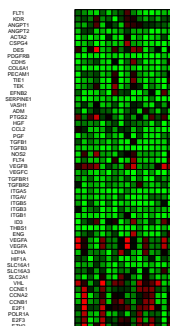




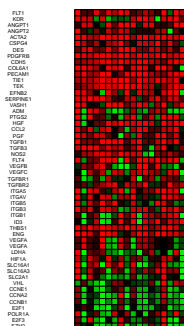
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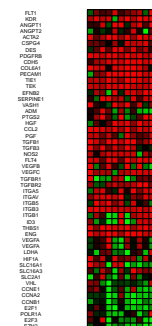
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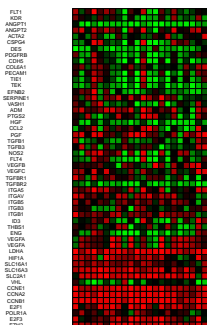
LUAD BC: hypoxia 4



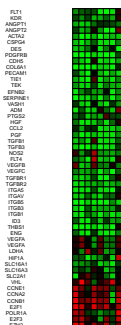
LUAD BC: hypoxia 20



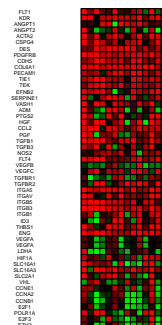
LUAD BC: reoxygenation 2



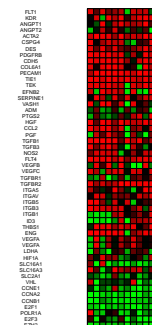
LUAD BC: reoxygenation 14



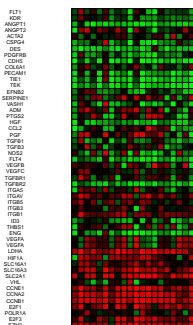
LUAD BC: hypoxia 8



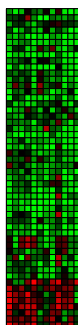
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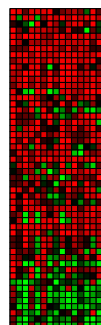
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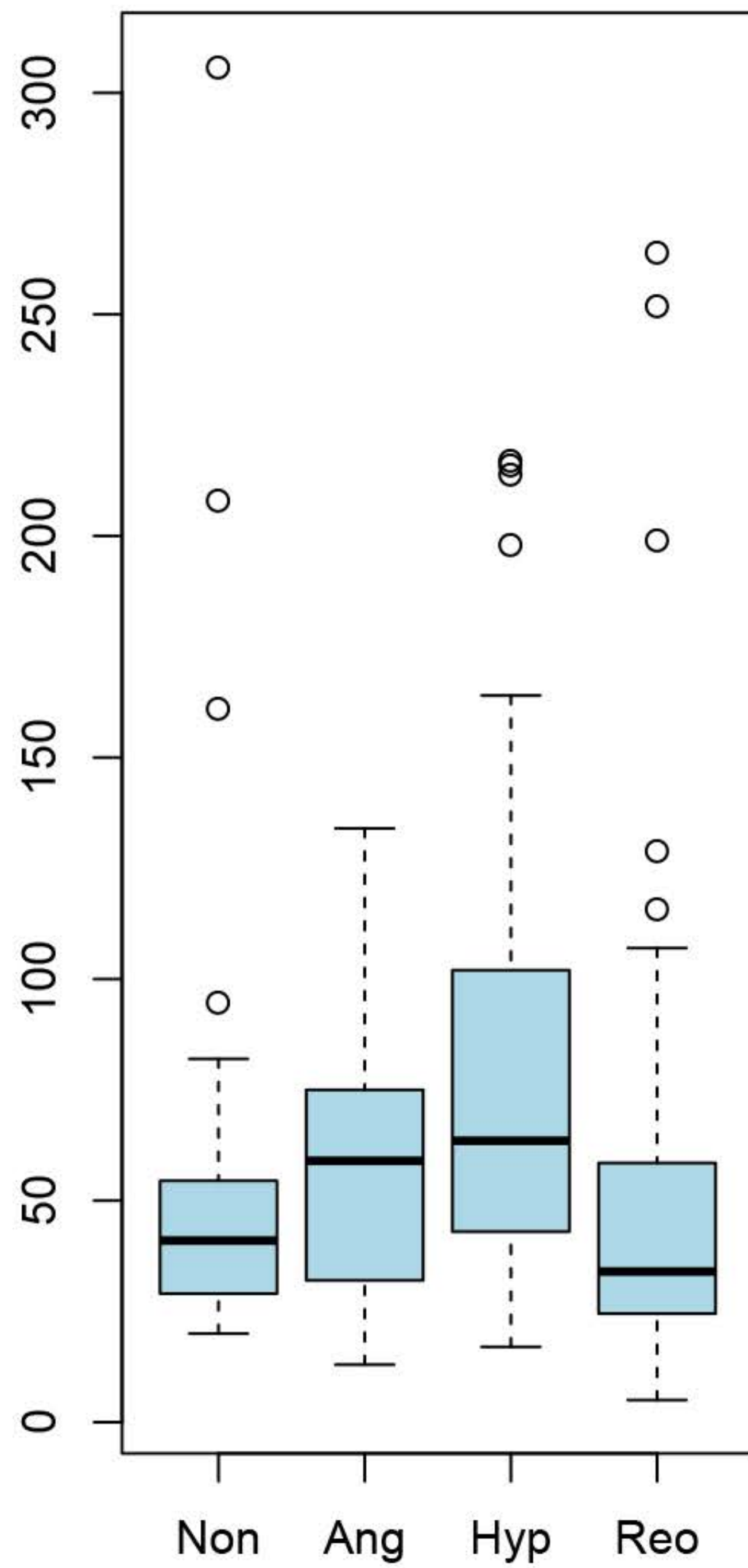
LUAD BC: reoxygenation 18



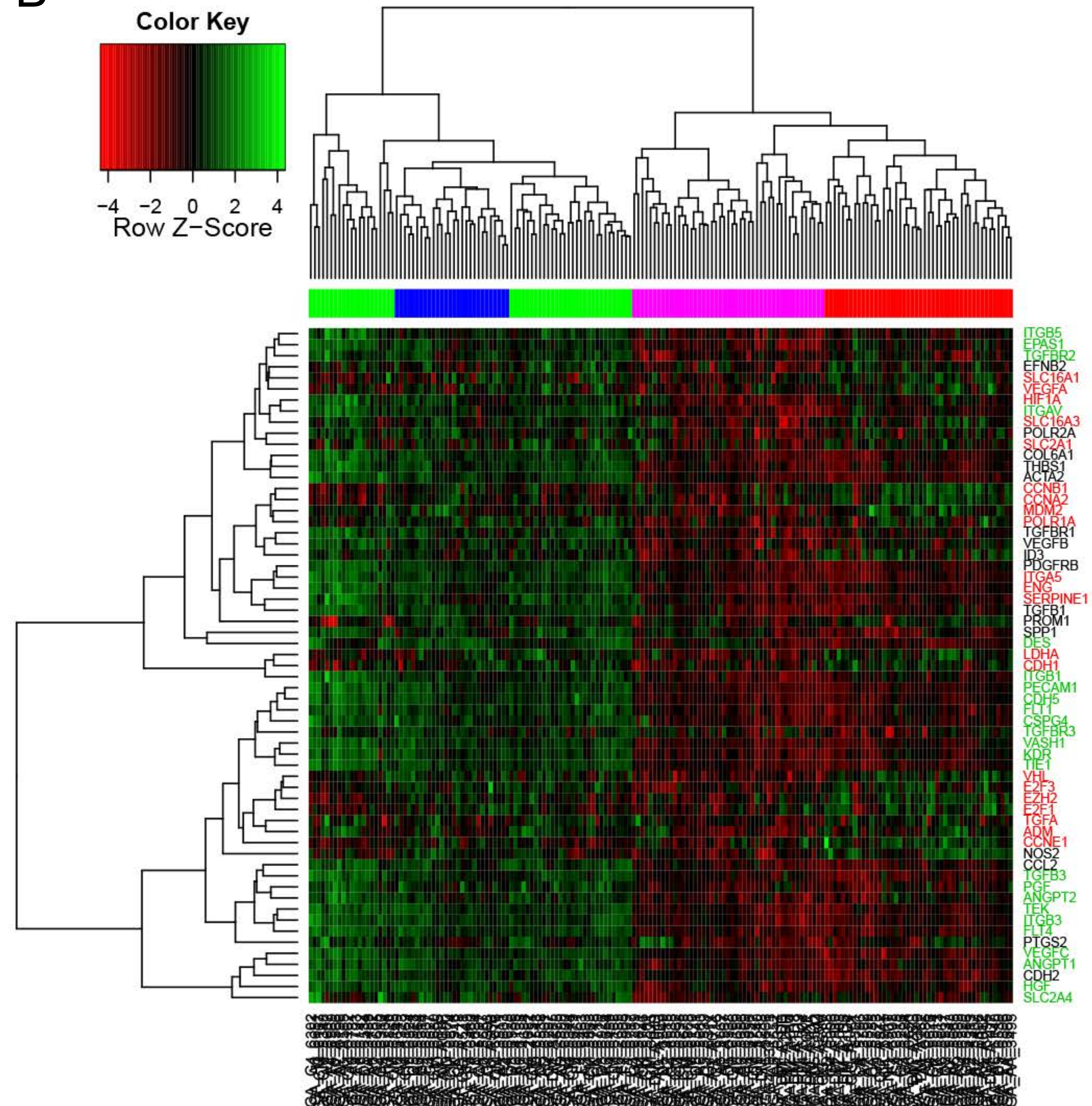
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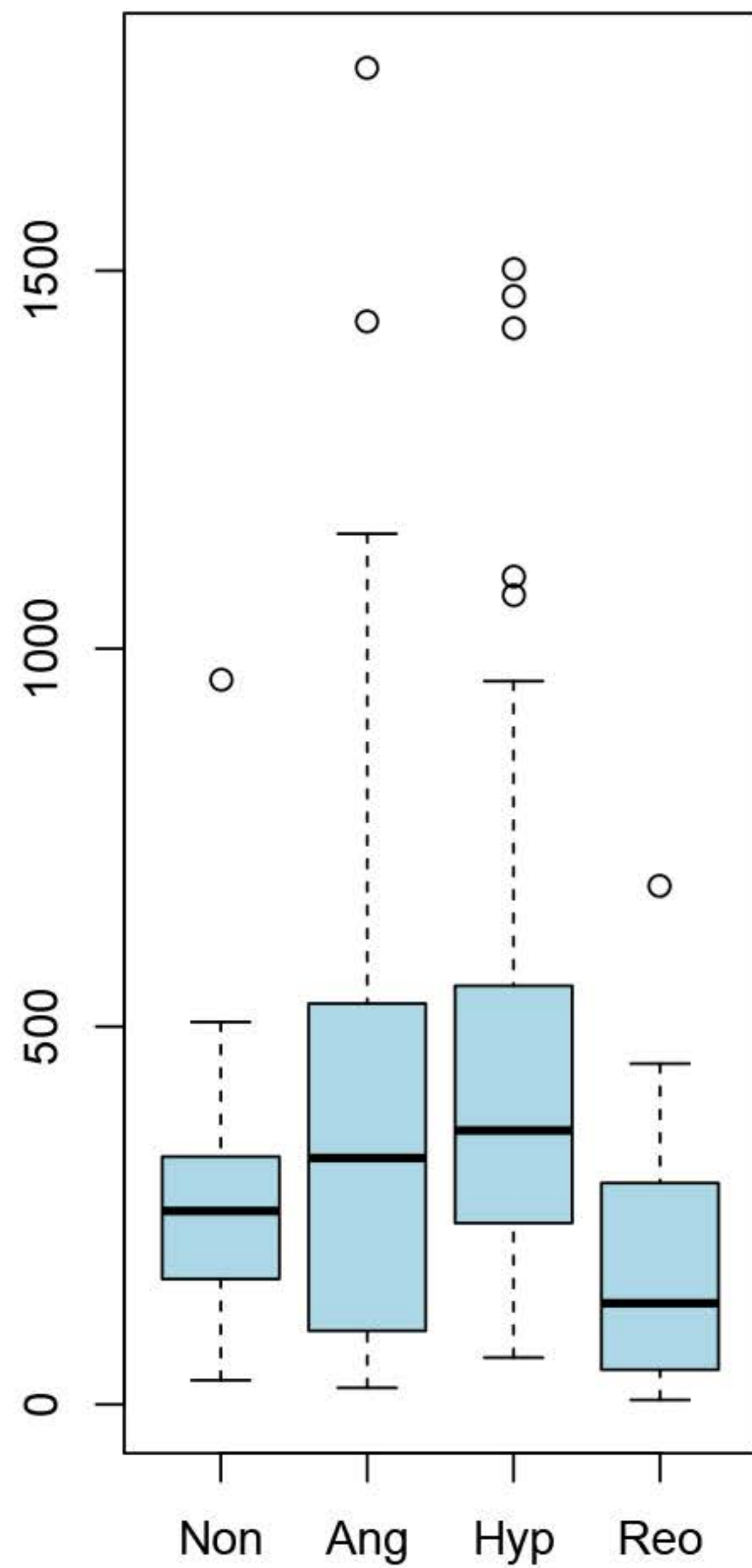


S5  
A

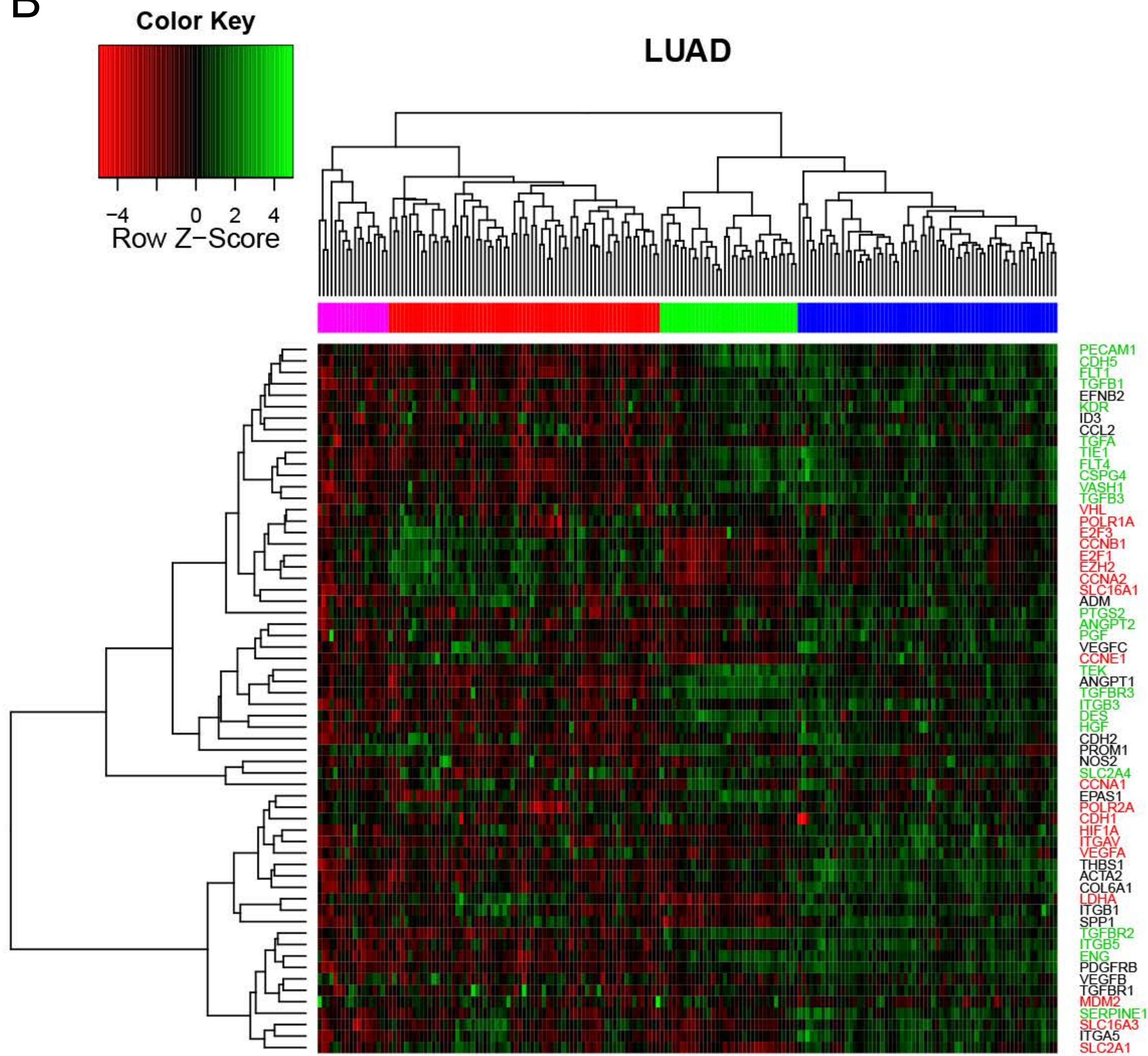
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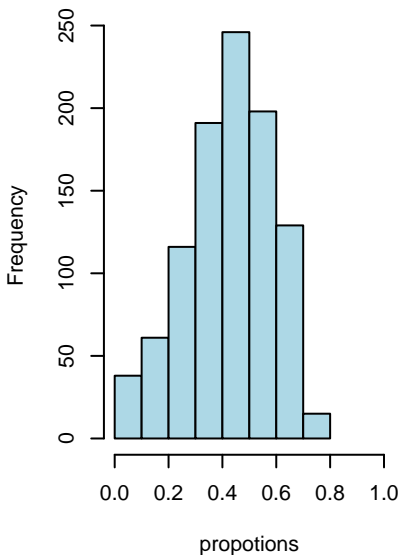
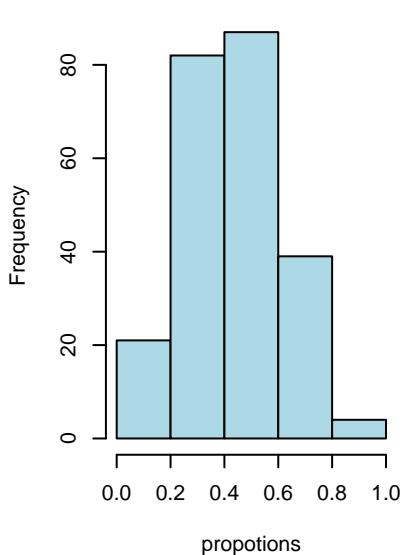
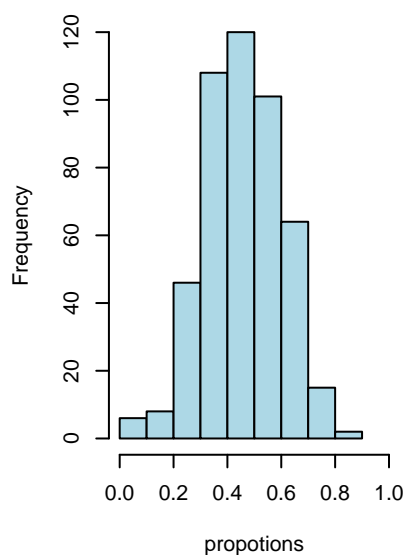
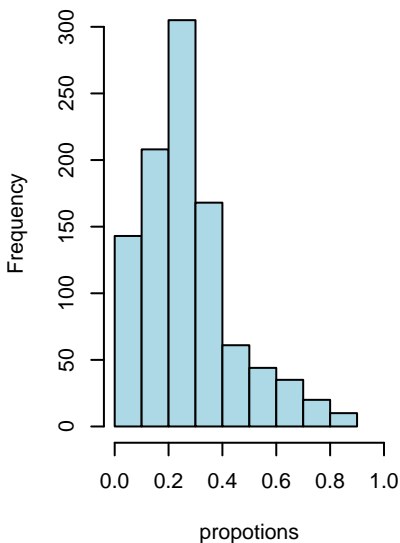
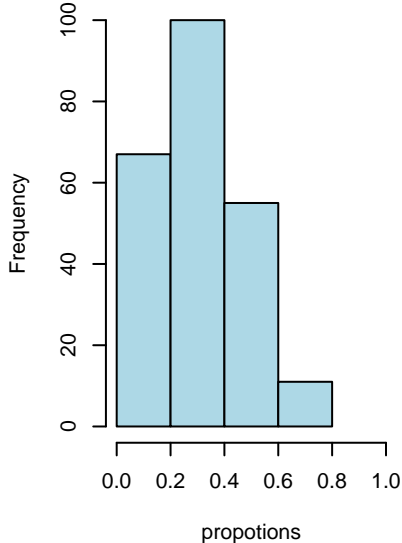
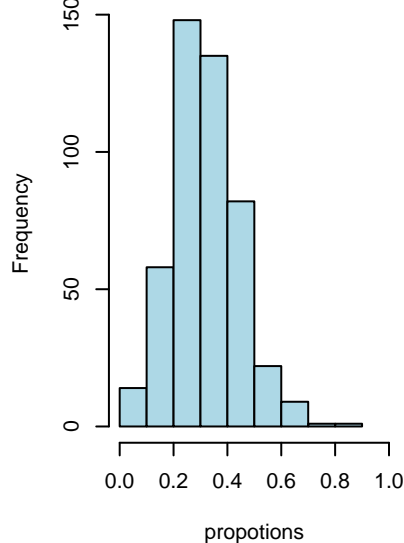


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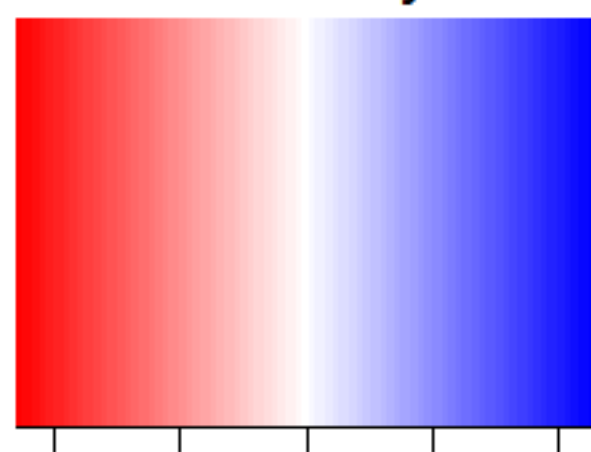


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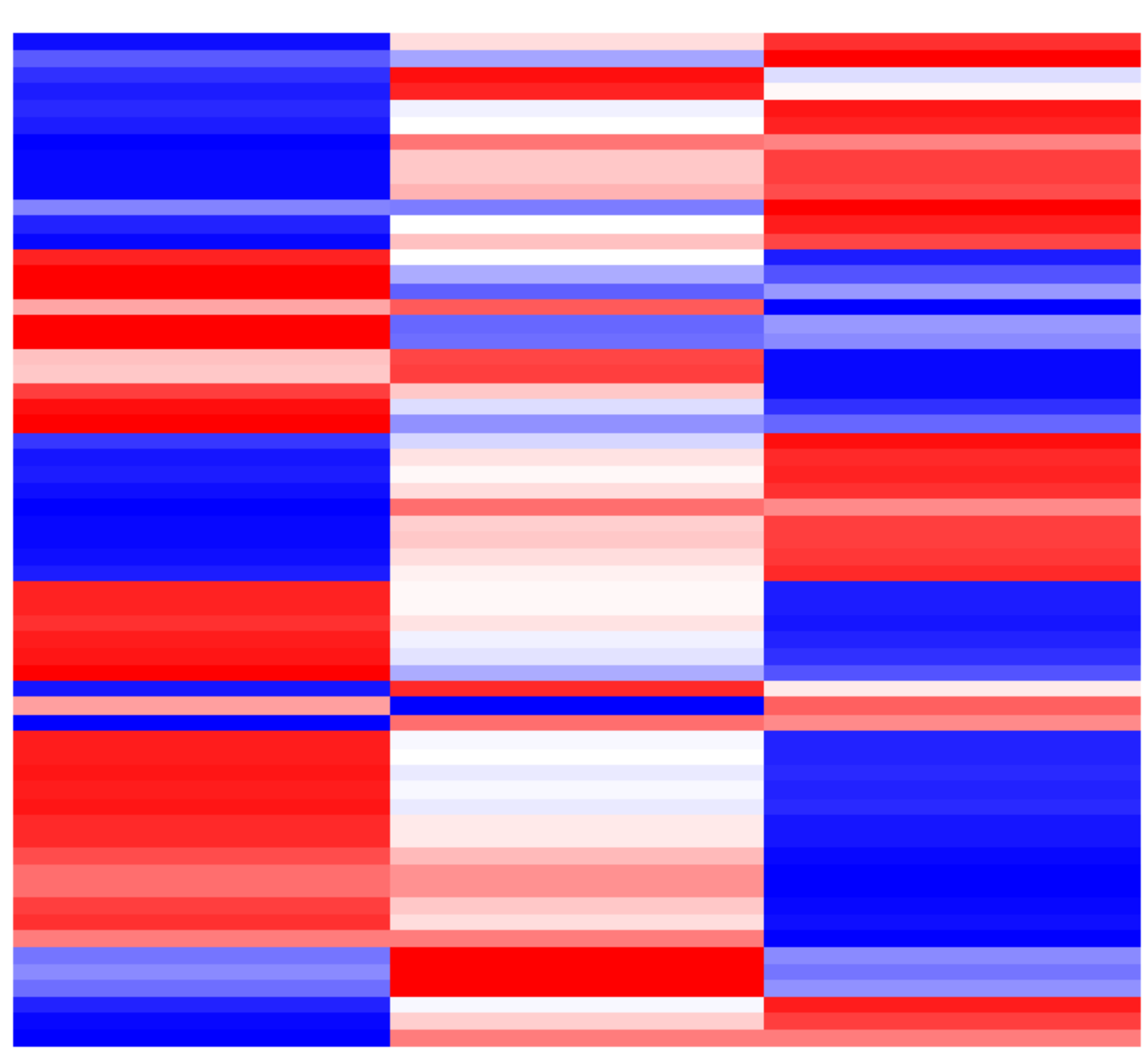
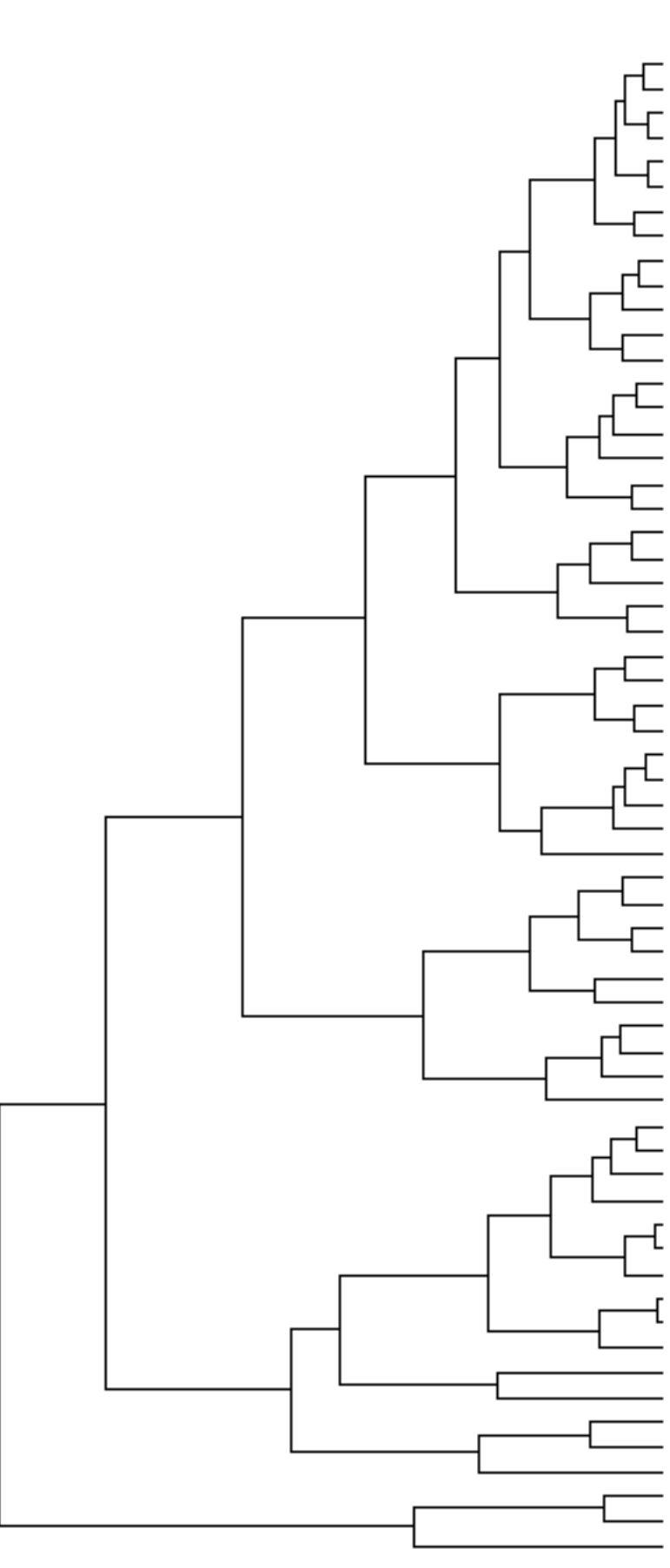


**S7****BRCA\_hypoxia  
propotions****COAD\_hypoxia  
propotions****LUAD\_hypoxia  
propotions****BRCA\_reoxygenation  
propotions****COAD\_reoxygenation  
propotions****LUAD\_reoxygenation  
propotions**

Color Key

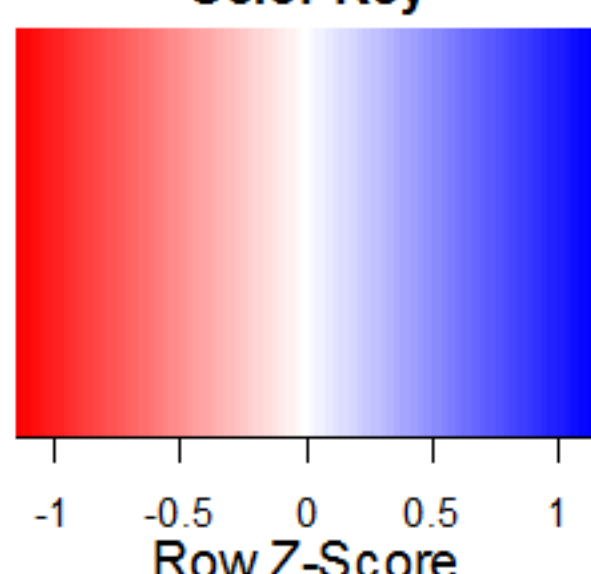


BRCA signatures

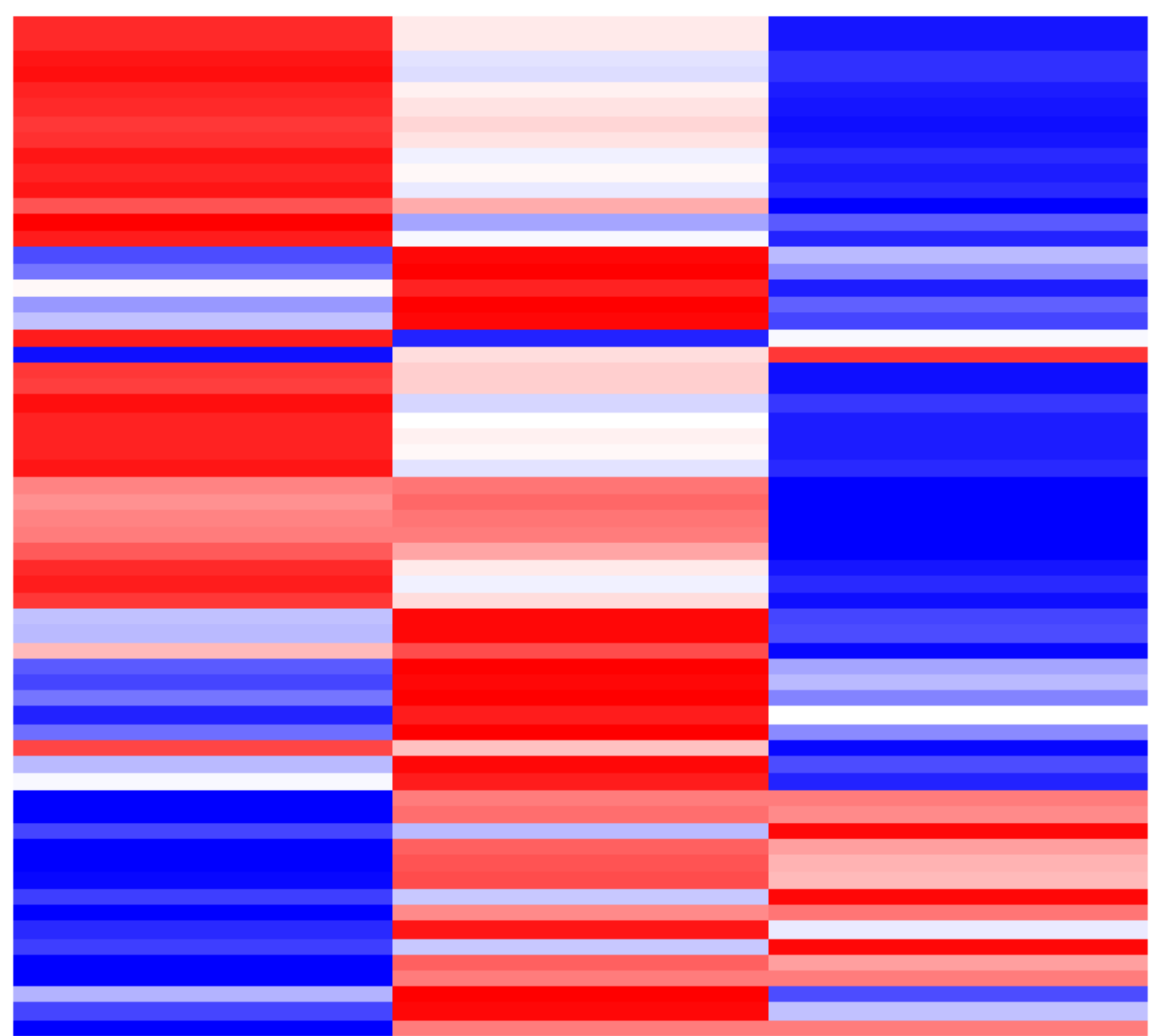
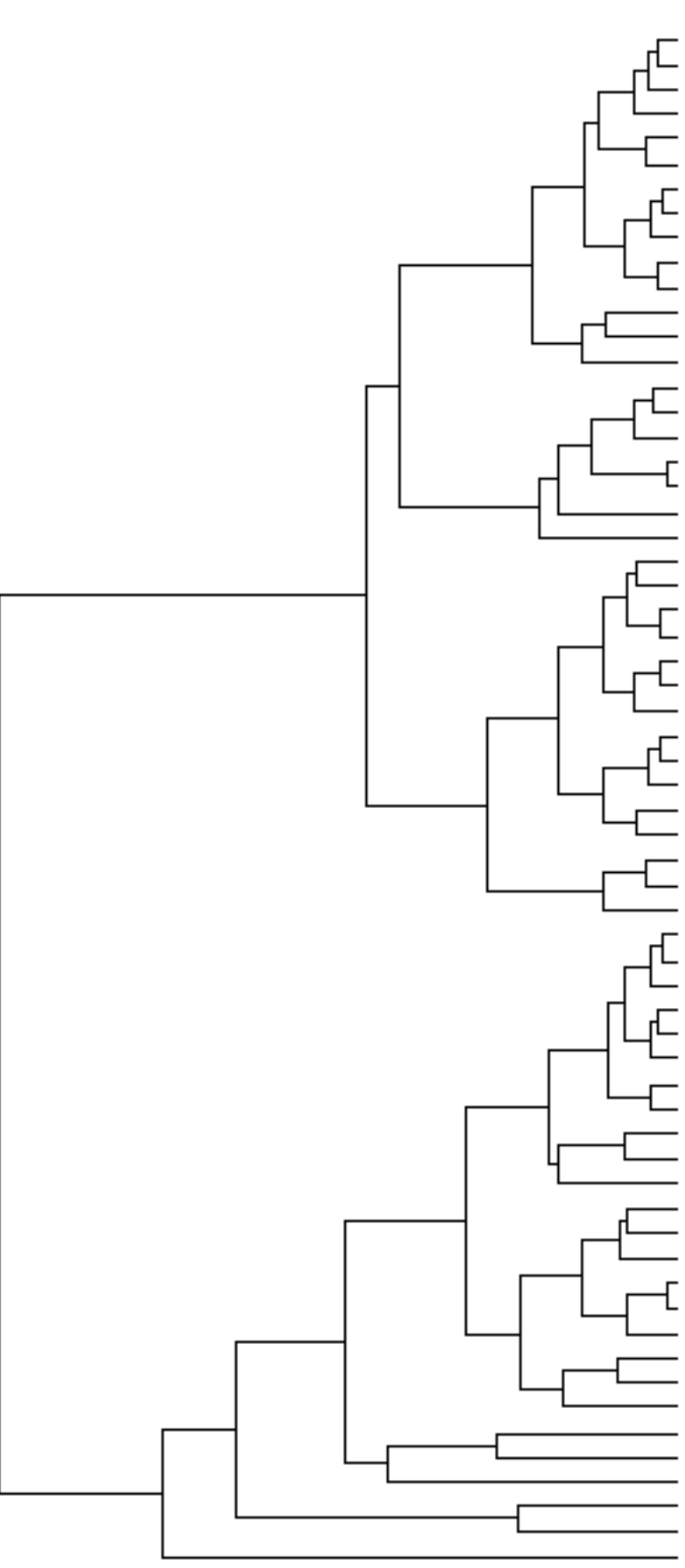


- TGFB1
- FLT1
- EFNB2
- ID3
- KDR
- VASH1
- SERPINE1
- PECAM1
- EPAS1
- ENG
- ITGB5
- PDGFRB
- TGFR2
- TGFR1
- VEGFB
- MDM2
- ITGA5
- POLR2A
- ITGAV
- CSPG4
- CCL2
- ANGPT2
- POLR1A
- VHL
- TGFB3
- CDH5
- TGFR3
- TIE1
- PGF
- VEGFC
- ITGB3
- FLT4
- TEK
- SPP1
- SLC2A1
- HIF1A
- VEGFA
- LDHA
- CDH1
- COL6A1
- THBS1
- ACTA2
- ITGB1
- EZH2
- E2F1
- CCNA2
- CCNB1
- SLC16A3
- E2F3
- SLC16A1
- ADM
- TGFA
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- CCNA1
- PTGS2
- ANGPT1
- NOS2
- HGF
- SLC2A4
- DES

Color Key

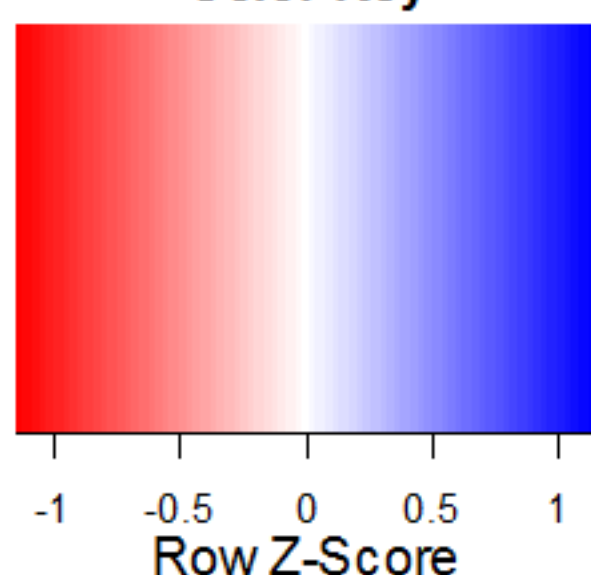


COAD signatures

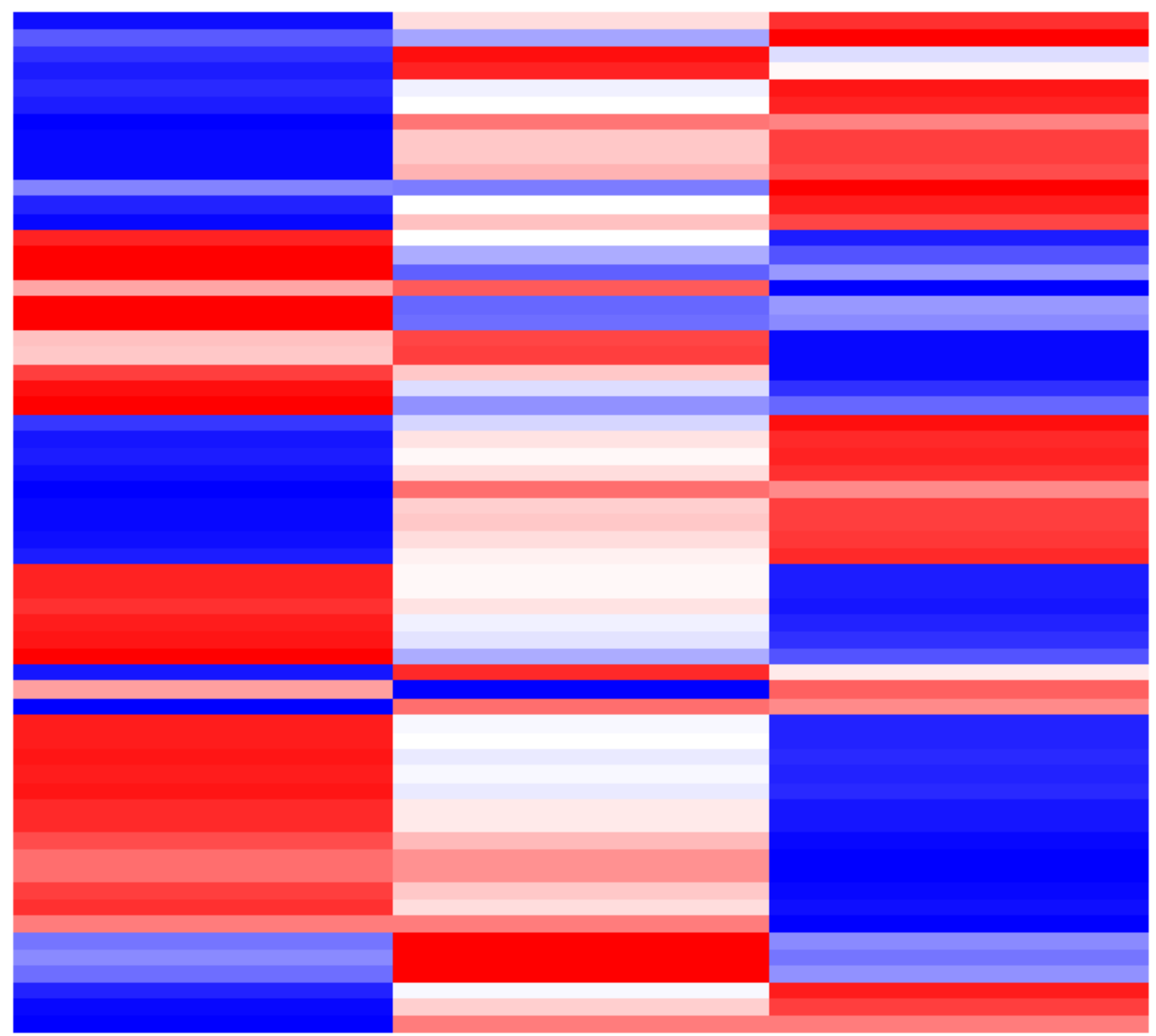
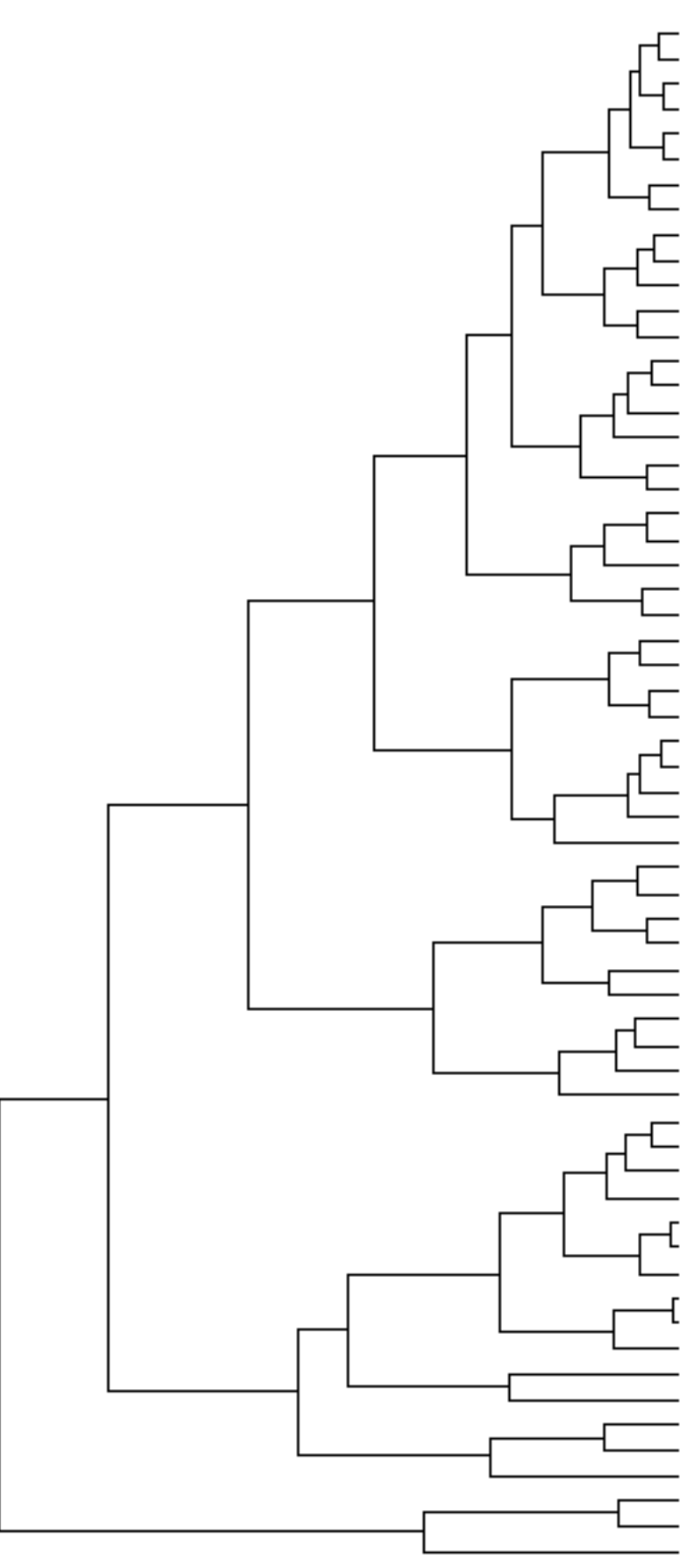


- VHL
- EZH2
- E2F3
- E2F1
- CCNB1
- CCNA2
- MDM2
- ID3
- POLR1A
- TGFR1
- VEGFB
- TGFA
- TGFR3
- CCNE1
- PDGFRB
- ITGA5
- ENG
- COL8A1
- THBS1
- ACTA2
- SPP1
- POLR2A
- EFNB2
- TGFR2
- ITGB5
- SLC2A1
- VEGFA
- SLC16A1
- EPAS1
- HIF1A
- ITGAV
- SLC16A3
- PRDM1
- LDHA
- CDH1
- ITGB1
- PECAM1
- CSPG4
- FLT1
- CDH5
- VASH1
- KDR
- SERPINE1
- TGFB1
- PGF
- ANGPT2
- ADM
- TIE1
- FLT4
- TGFB3
- TEK
- CCL2
- VEGFC
- ANGPT1
- SLC2A4
- CDH2
- HGF
- DES
- NOS2
- PTGS2
- CCNA1

Color Key



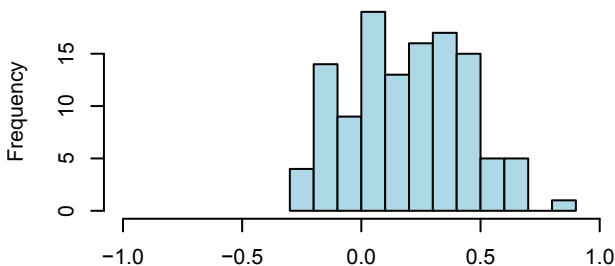
LUAD signatures



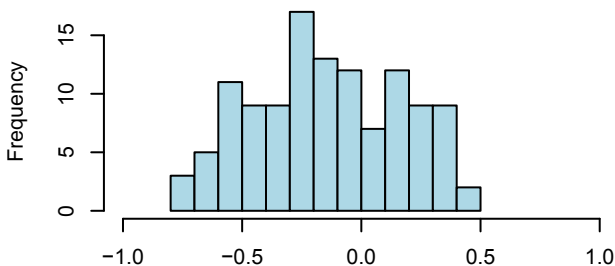
- TGFB1
- FLT1
- EFNB2
- ID3
- KDR
- VASH1
- SERPINE1
- PECAM1
- EPAS1
- ENG
- ITGB5
- PDGFRB
- TGFR2
- TGFR1
- VEGFB
- MDM2
- ITGA5
- POLR2A
- ITGAV
- CSPG4
- CCL2
- ANGPT2
- POLR1A
- VHL
- TGFB3
- CDH5
- TGFR3
- TIE1
- PGF
- VEGFC
- ITGB3
- FLT4
- TEK
- SPP1
- SLC2A1
- HIF1A
- VEGFA
- LDHA
- CDH1
- COL8A1
- THBS1
- ACTA2
- ITGB1
- EZH2
- E2F1
- CCNA2
- CCNB1
- SLC16A3
- E2F3
- SLC16A1
- ADM
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- NOS2
- HGF
- SLC2A4
- DES

S9

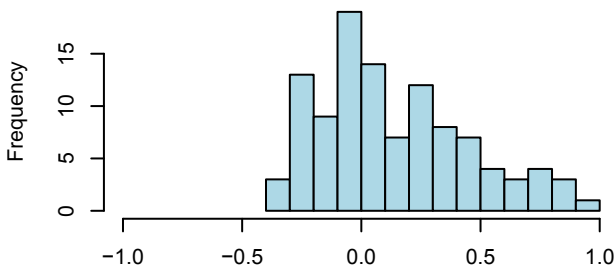
**BRCA: correlation of reoxygenation population and oxygen enzyme expression**



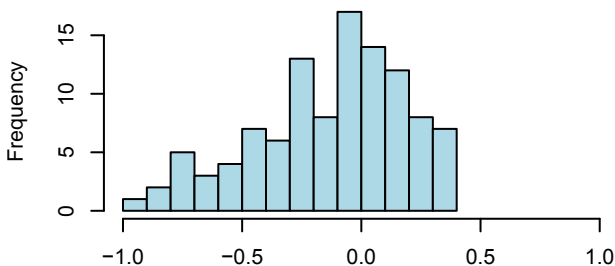
**BRCA: correlation of hypoxia population and oxygen enzymes expression**



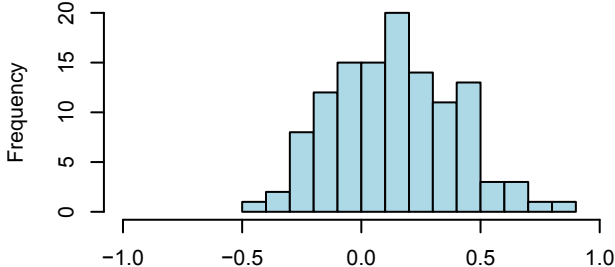
**COAD: correlation of hypoxia population and oxygen enzymes expression**



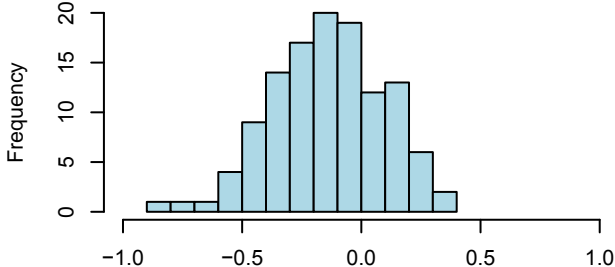
**COAD: correlation of hypoxia population and oxygen enzymes expression**

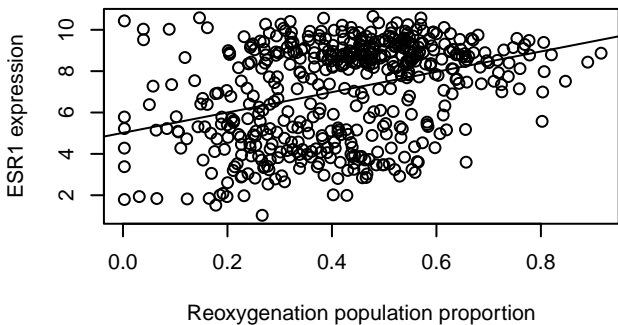
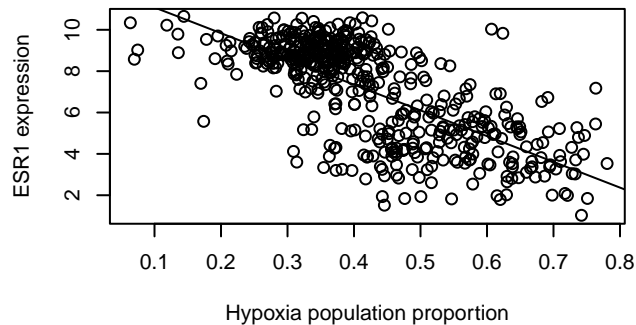
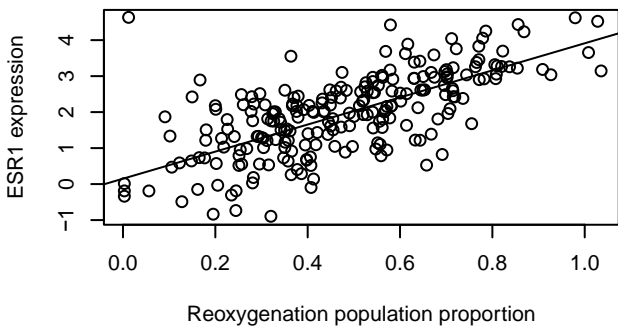
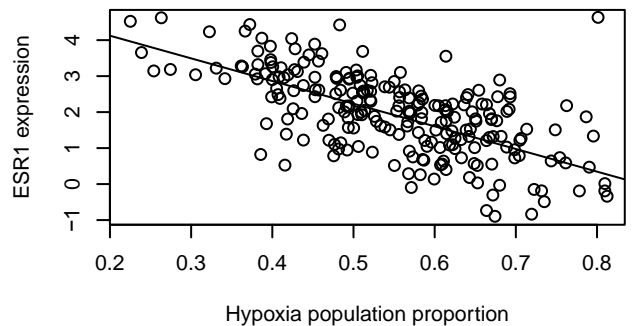
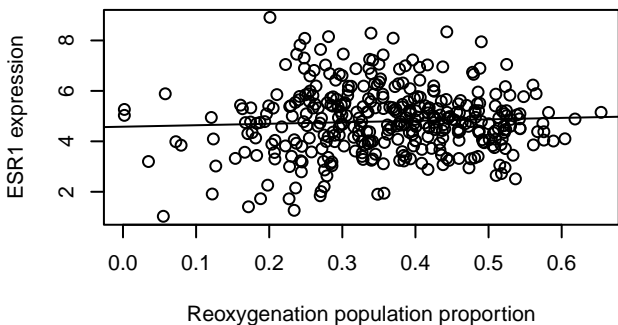
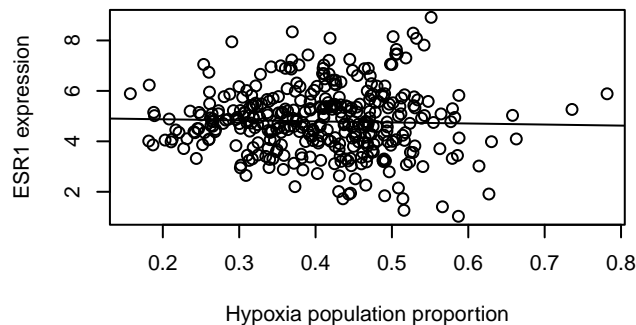


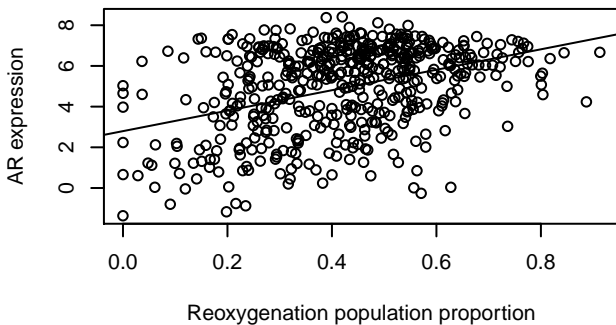
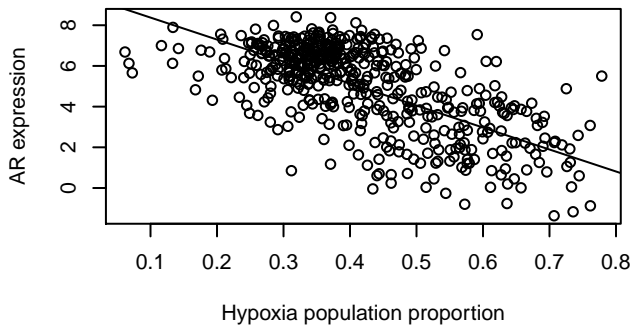
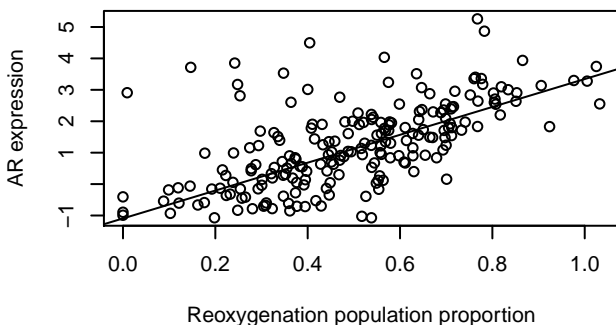
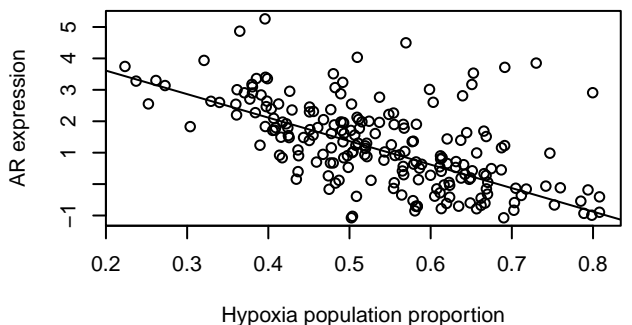
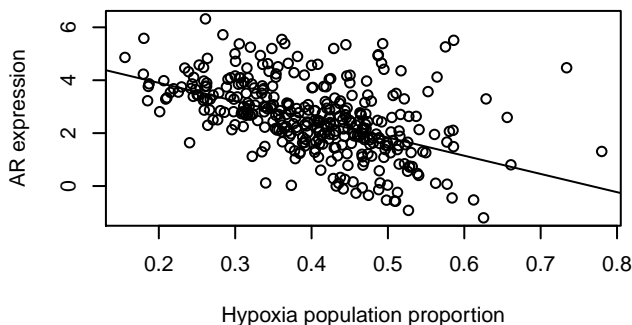
**LUAD: correlation of hypoxia population and oxygen enzymes expression**



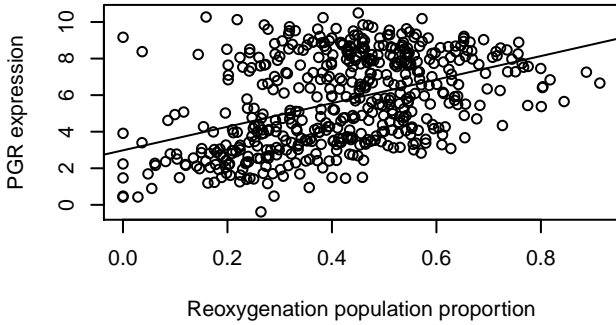
**LUAD: correlation of hypoxia population and oxygen enzymes expression**



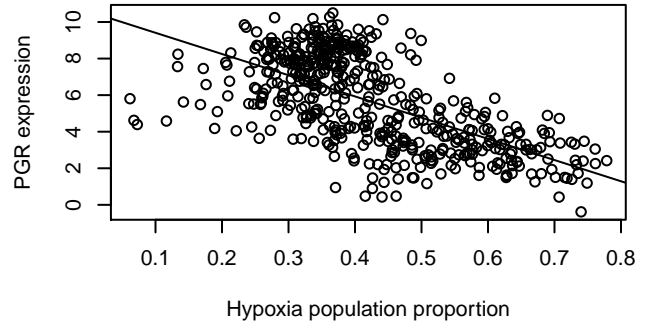
**BRCA reoxygenation ESR1****BRCA hypoxia ESR1****COAD reoxygenation ESR1****COAD hypoxia ESR1****COAD reoxygenation ESR1****COAD hypoxia ESR1**

**BRCA reoxygenation AR****BRCA hypoxia AR****COAD reoxygenation AR****COAD hypoxia AR****LUAD reoxygenation AR****LUAD hypoxia AR**

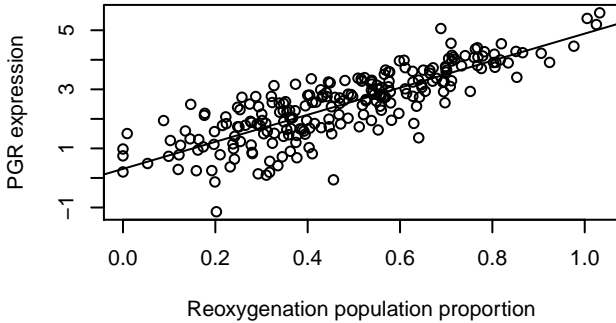
**BRCA reoxygenation PGR**



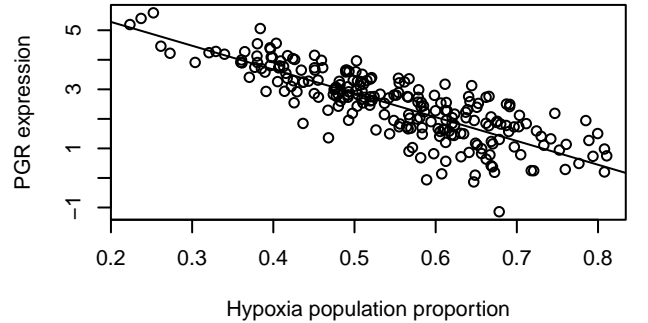
**BRCA hypoxia PGR**



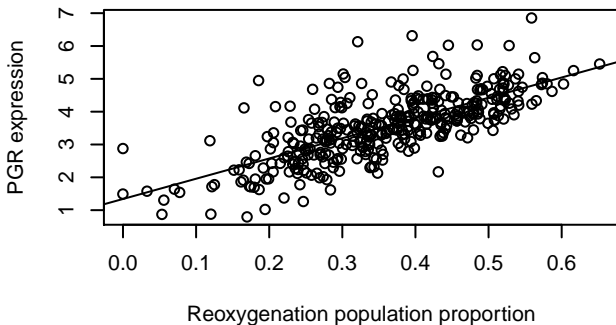
**COAD reoxygenation PGR**



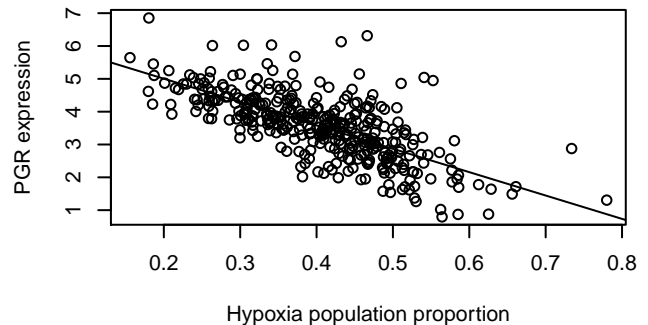
**COAD hypoxia PGR**



**LUAD reoxygenation PGR**

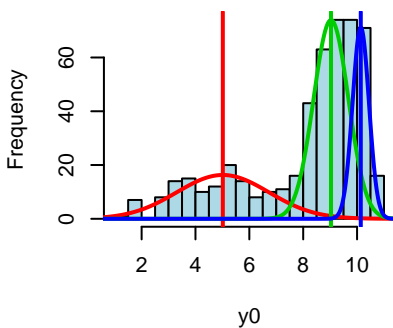


**LUAD hypoxia PGR**

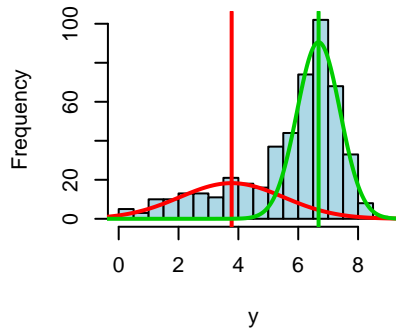


S10B

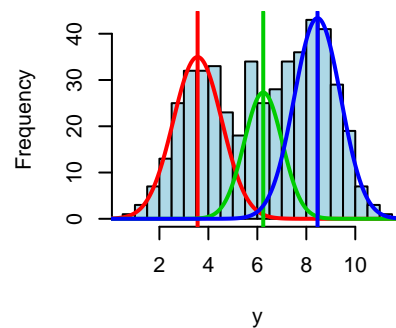
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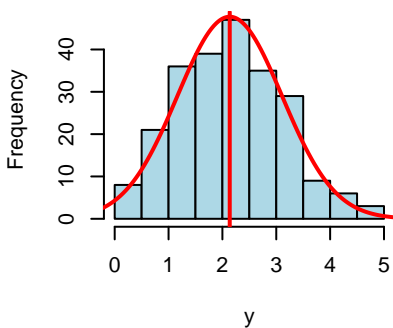
BRCA\_AR



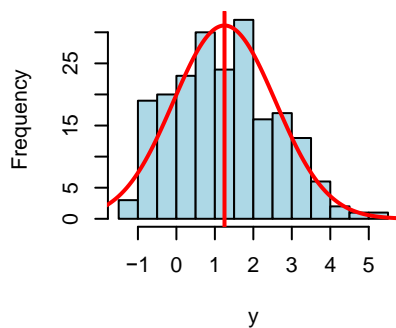
BRCA\_PGR



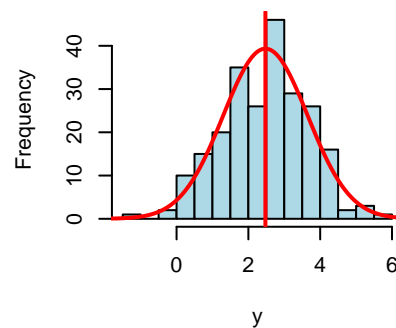
COAD\_ESR1



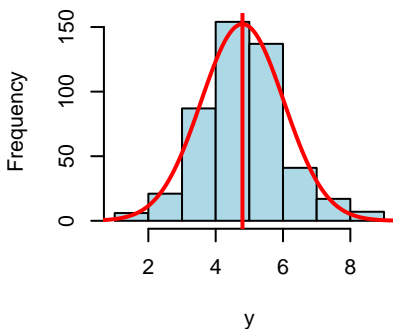
COAD\_AR



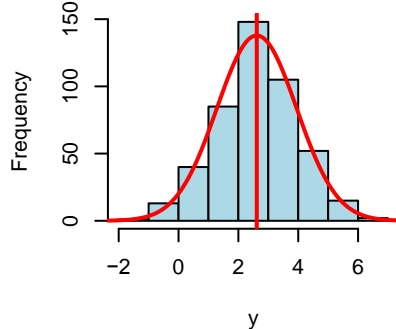
COAD\_PGR



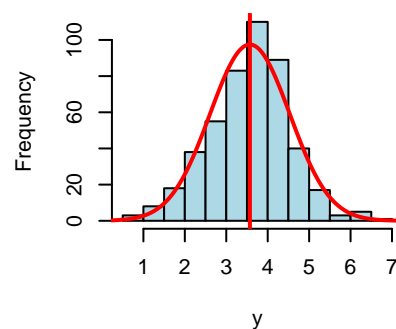
LUAD\_ESR1



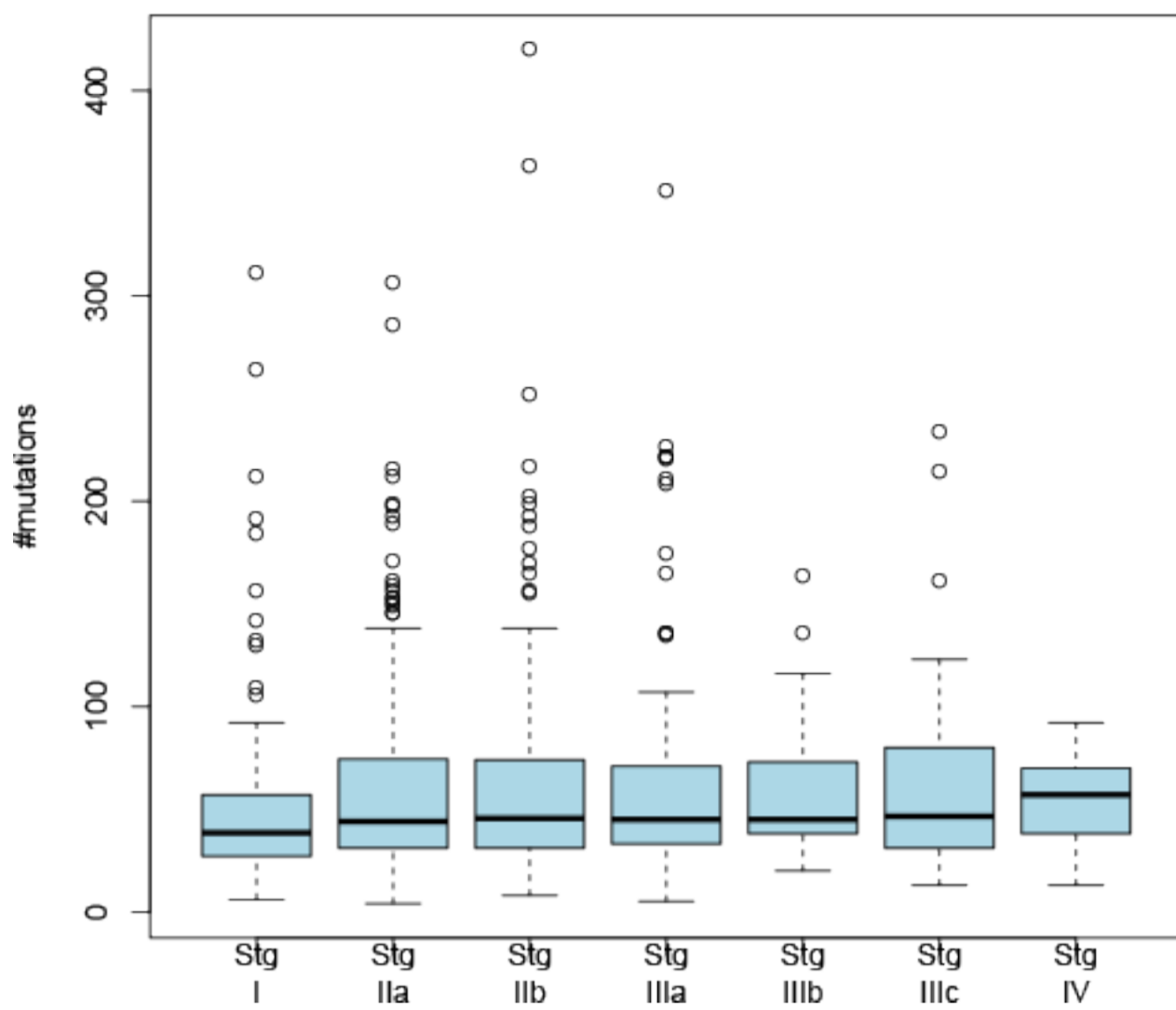
LUAD\_AR



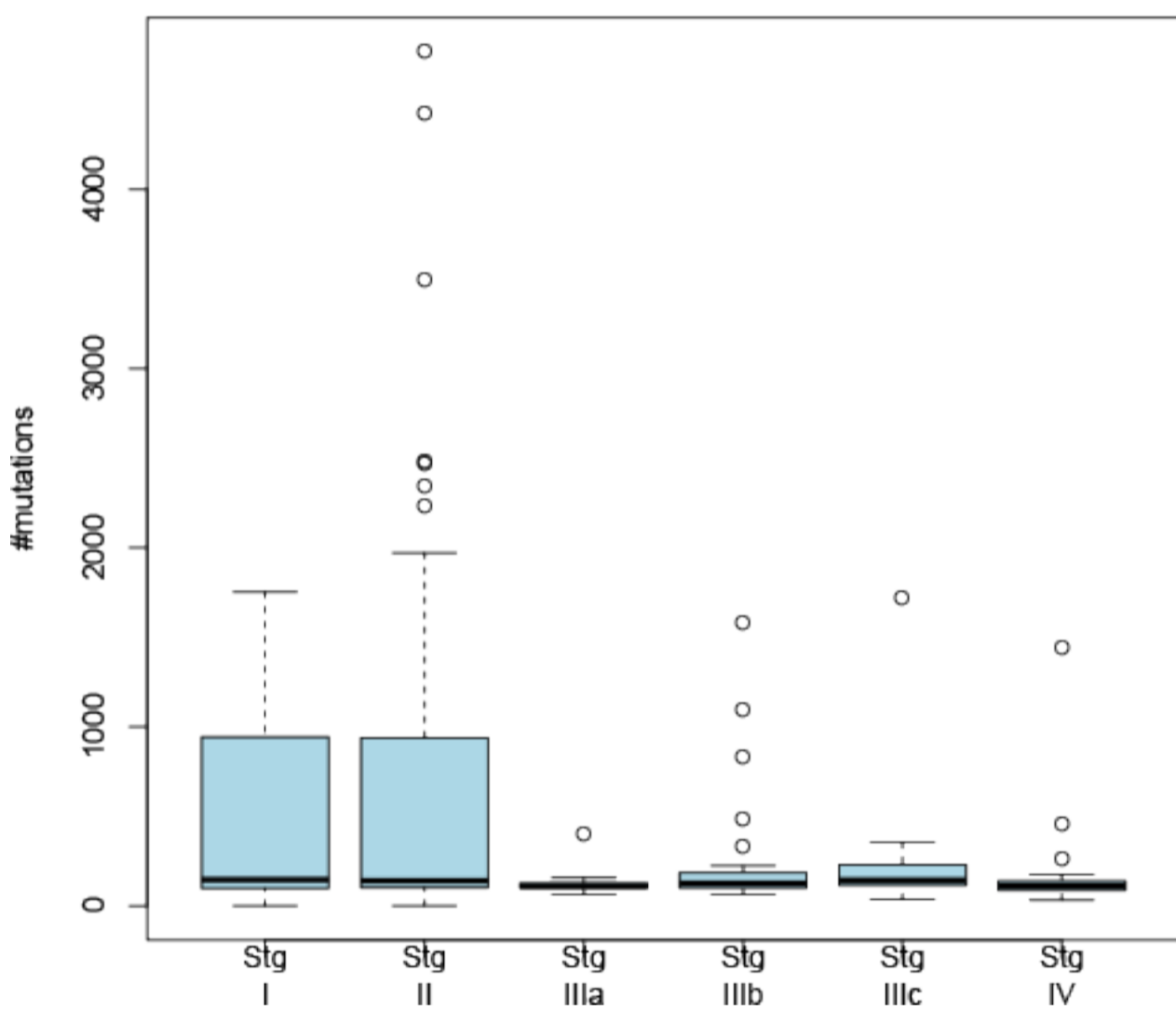
LUAD\_PGR



## BRCA



## COAD



## LUAD

