










# Medulloblastoma


## CKG Notebook Analysis

 **Cancer Cell**

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Proteomics, Post-translational Modifications, and Integrative Analyses Reveal Molecular Heterogeneity within Medulloblastoma Subgroups

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# Re-analysis of Proteomics Data

## Including covariates

- Preprocessing
- Stratification looking at covariates: Age, Gender, Metastatic status and histology
- Differential regulation including covariates
- Functional enrichment

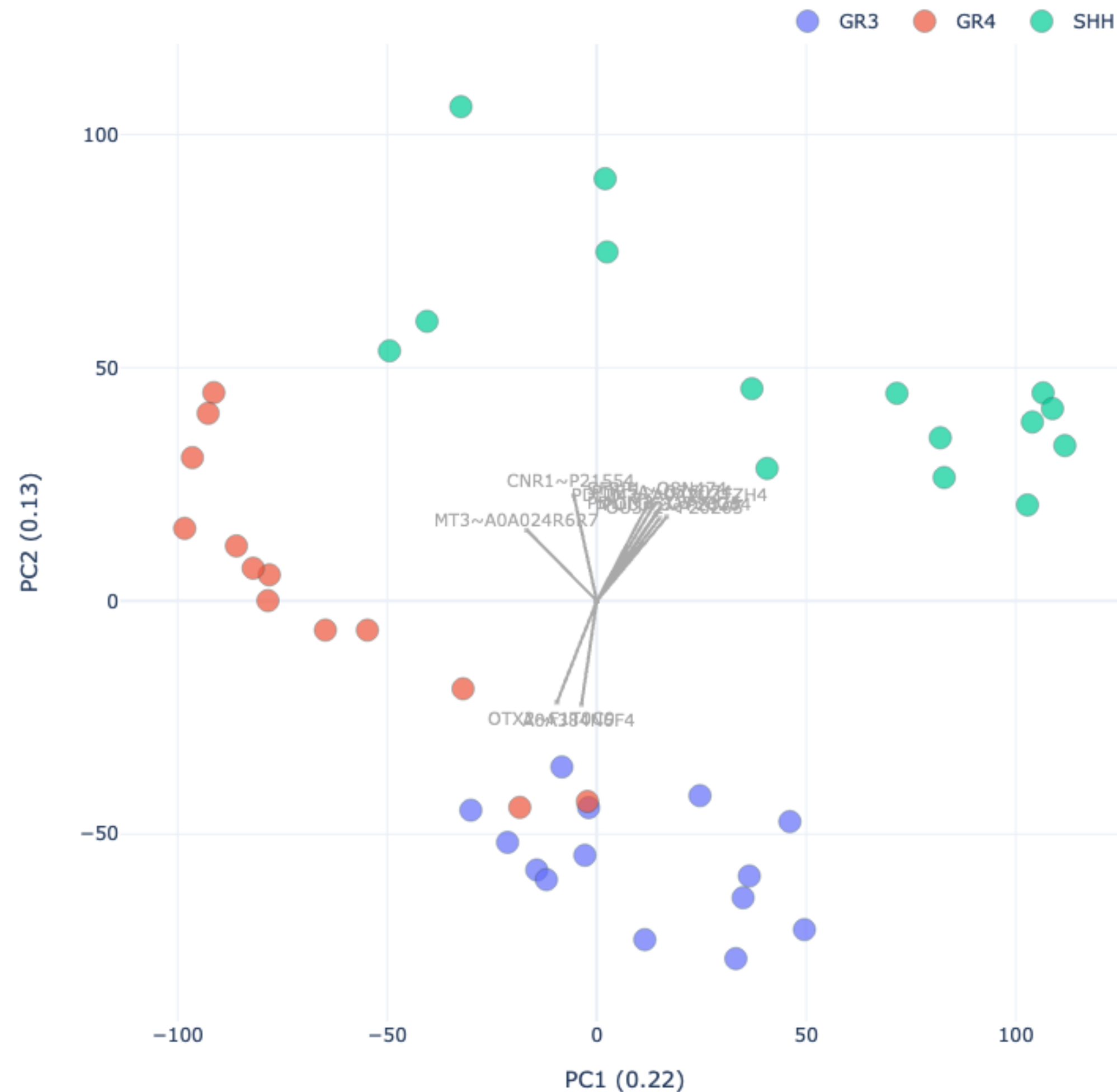
# Pre-processing

- Remove WNT samples (low number of samples)
- Filter proteins with more than 80% missing values in all groups
- Normalize data using median-centered normalization
- Impute missing values using a mixed model: K-Nearest Neighbors algorithm (KNN) if at least 60% valid values, otherwise Minimum Probability (MinProb) drawing random values from a down-shifted Gaussian distribution

# Sample Stratification

## PCA looking at groups: GR3, GR4, SHH

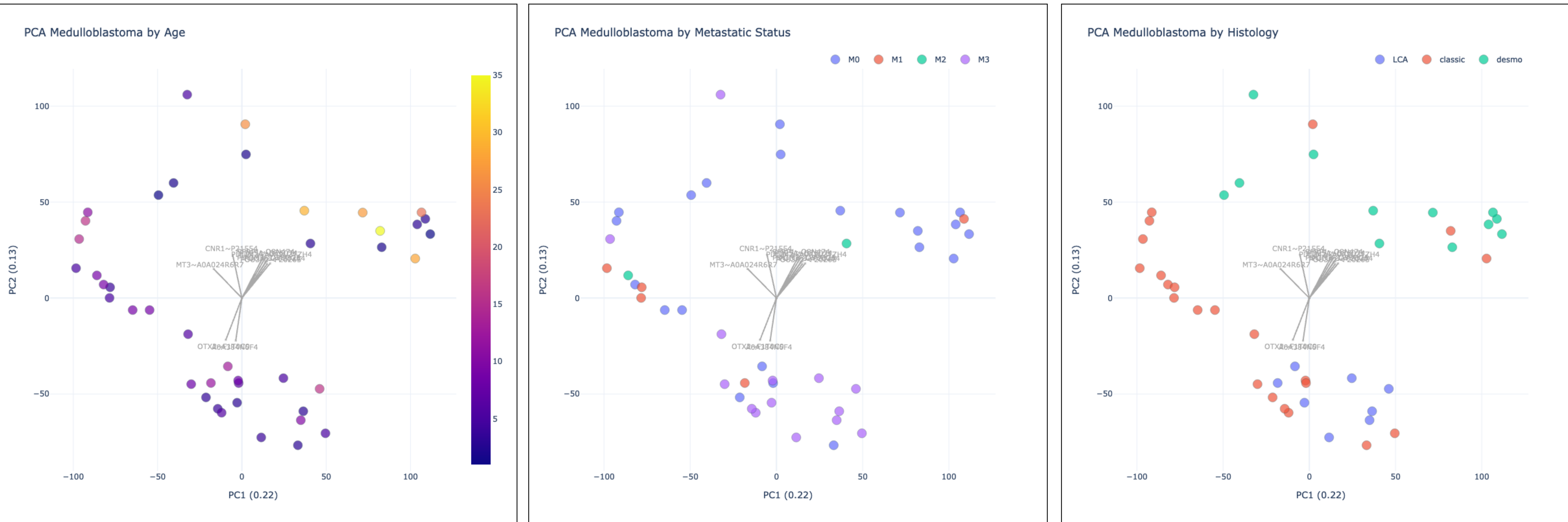
PCA Medulloblastoma groups



- The PCA shows a clear separation of the samples according to the type of Medulloblastoma
- Some of the proteins driving the separation are: OTX2, MT3, CNR1, SFRP1, PDE5A, PDLIM3, POU3F2, POU3F3
- There seem to be other subgroups among the known groups

# Sample Stratification

## PCA looking at Age, Metastatic status, Histology

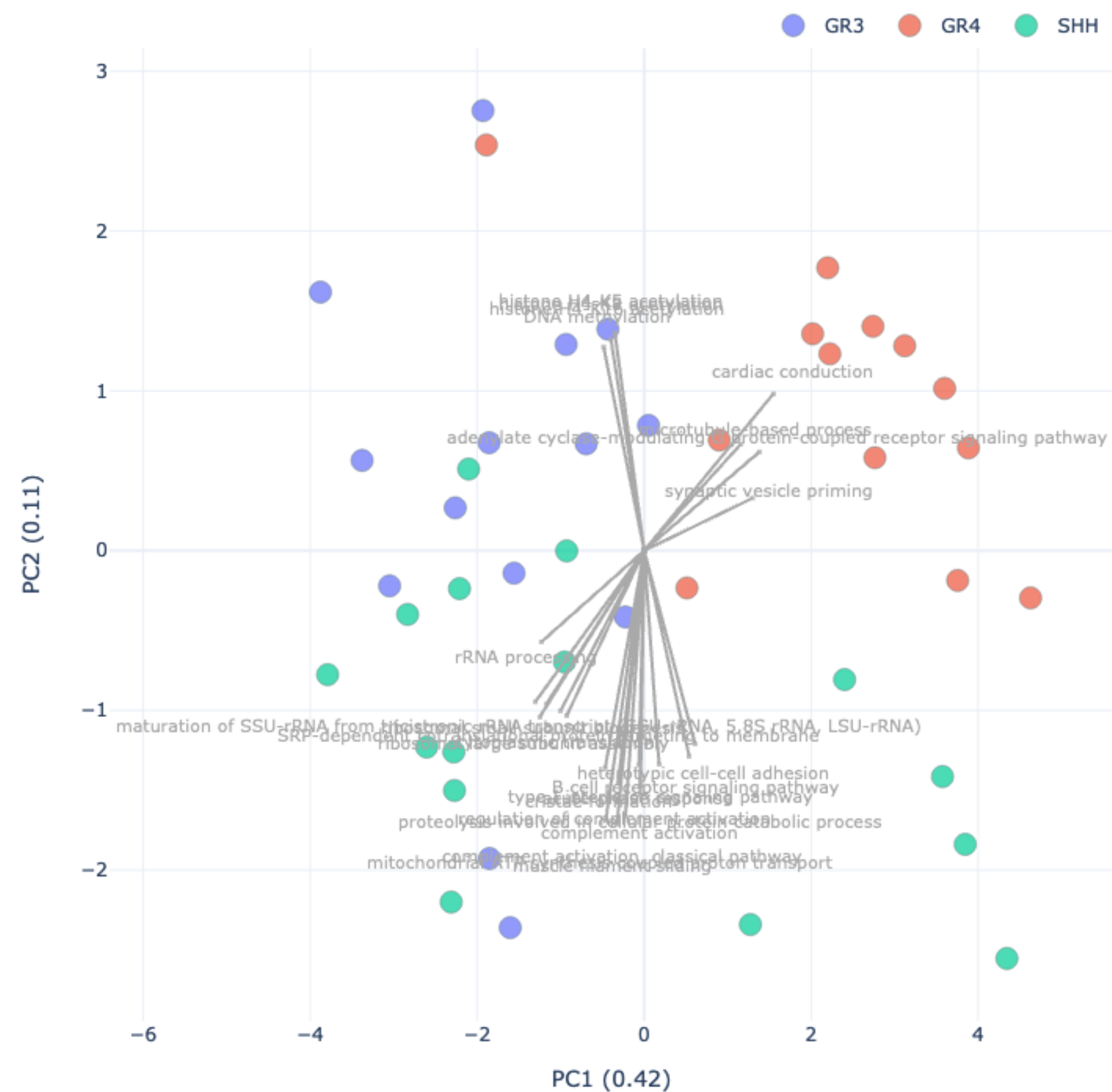


- The PCA seems to also separate the samples according to these covariates

# Sample Stratification

## Stratification based on ssGSEA (GO biological processes)

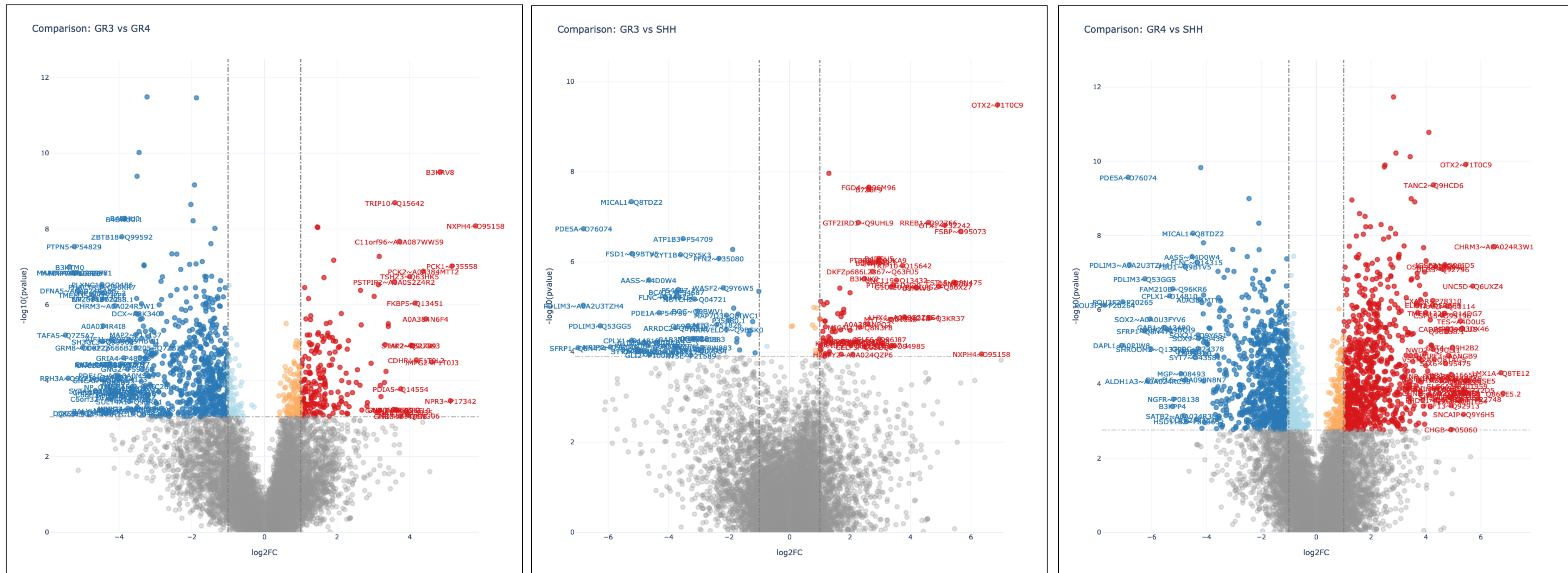
Functional PCA Medulloblastoma groups



- Processes such as methylation seem to drive the separation of GR3 samples
- Proteins involved in rRNA processing characterize SHH samples
- Proteins annotated to microtubule-based process and G-protein coupled receptor signaling pathway cluster the GR4 samples

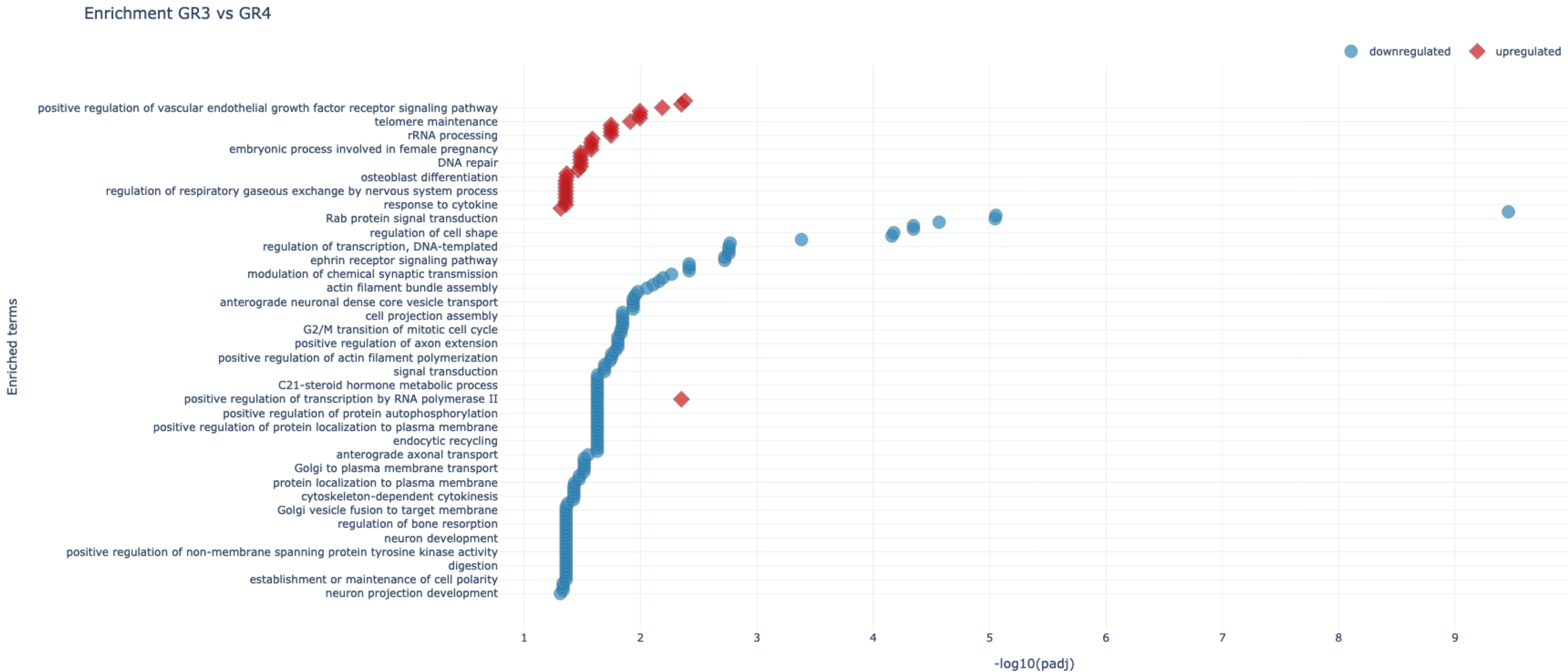


## ANCOVA analysis including covariates: Age, Gender, Metastatic status, Histology



# Functional Enrichment

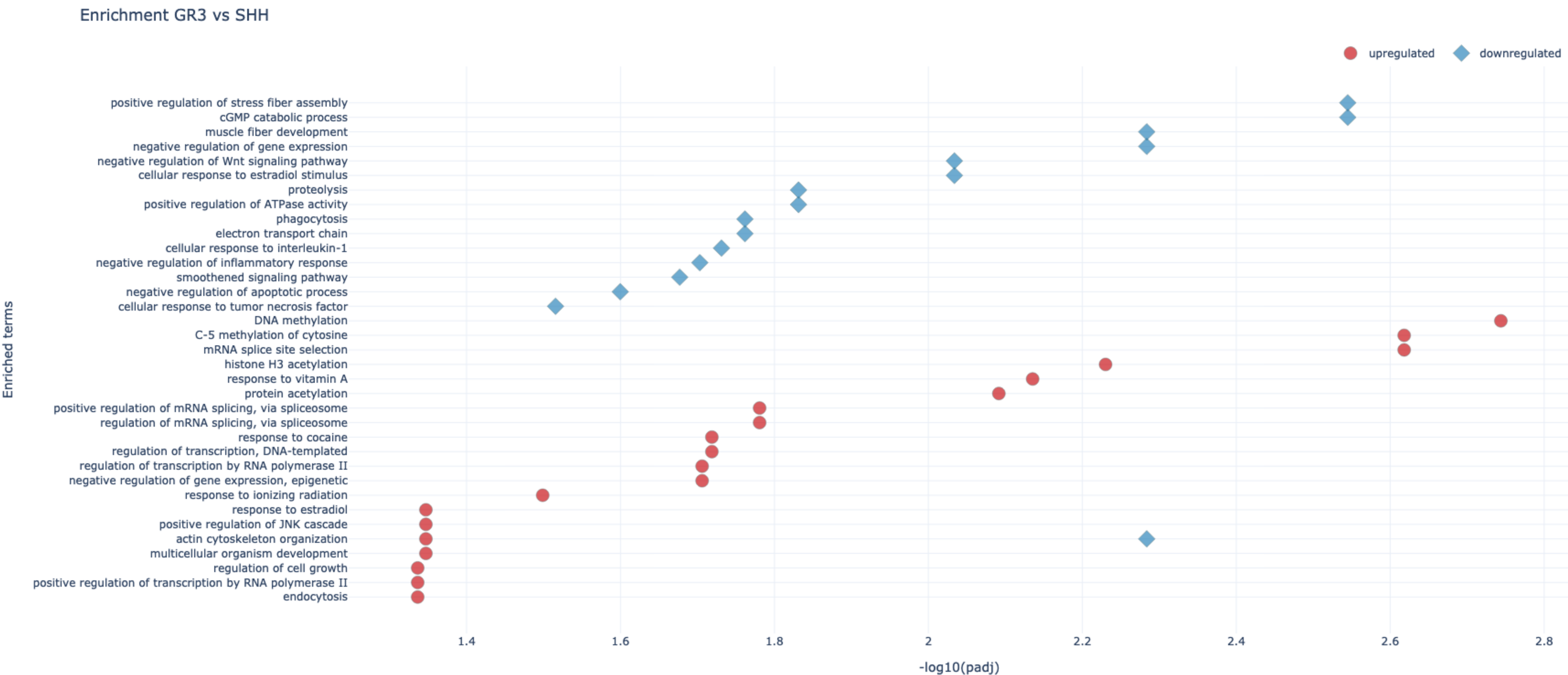
GO biological Processes enrichment of up- and down-regulated proteins in each pairwise comparison





# Functional Enrichment

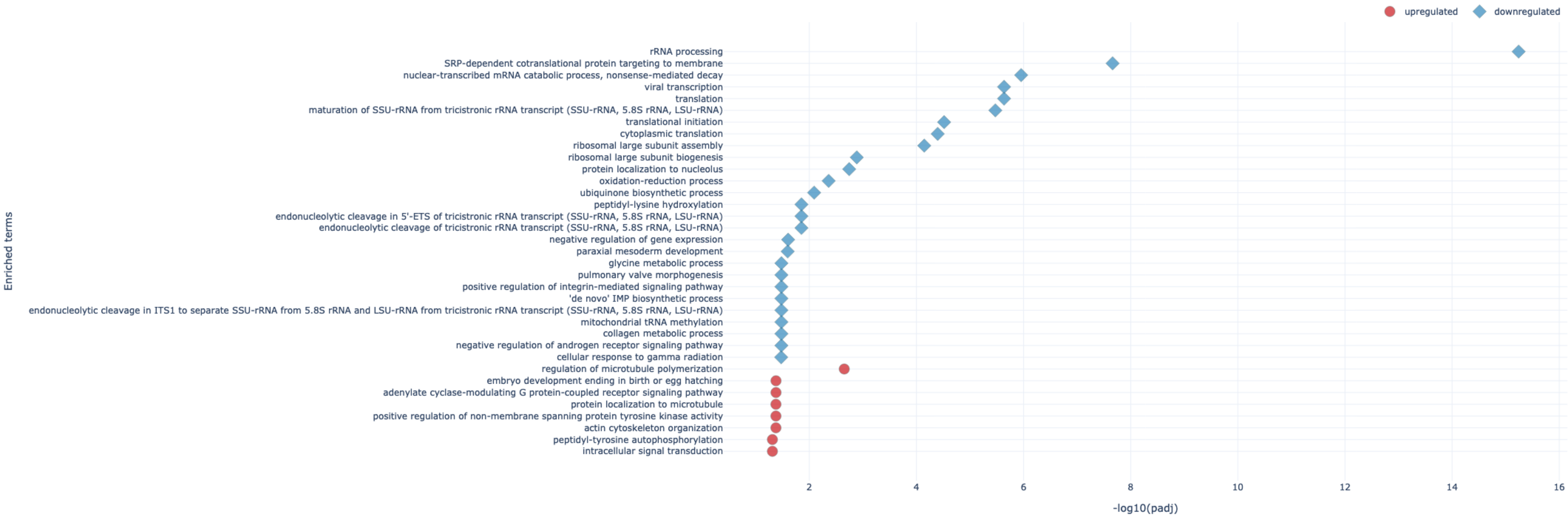
GO biological Processes enrichment of up- and down-regulated proteins in each pairwise comparison



# Functional Enrichment

## GO biological Processes enrichment of up- and down-regulated proteins in each pairwise comparison

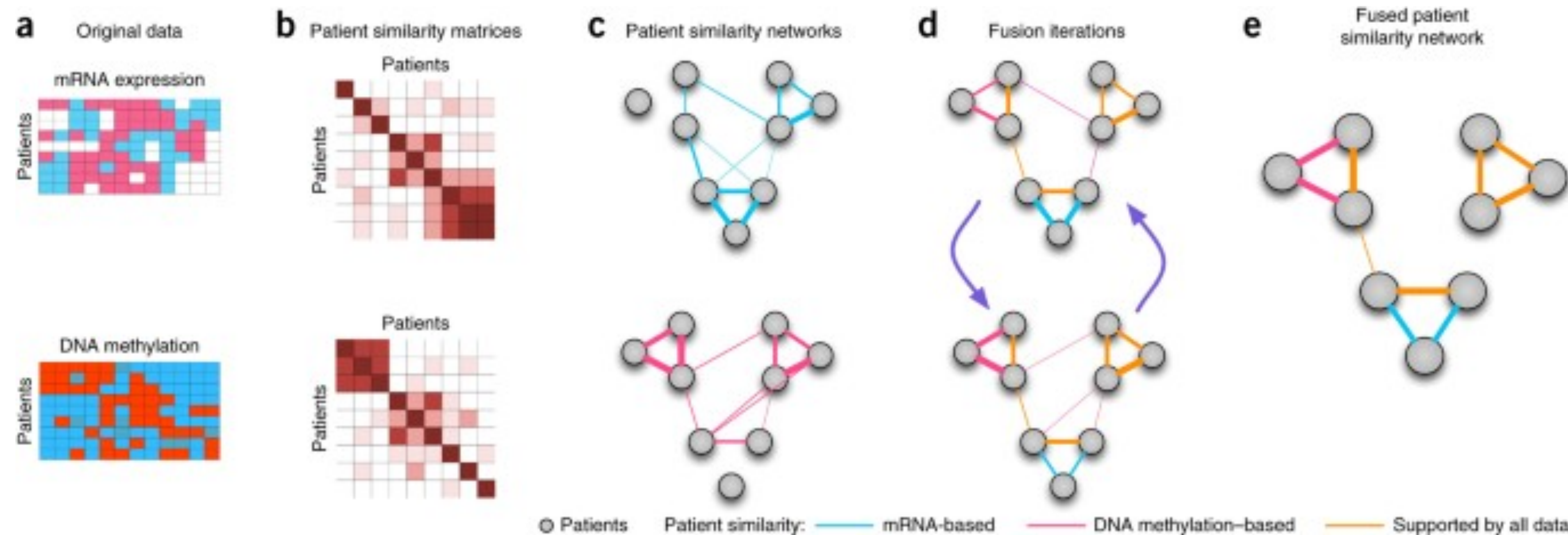
Enrichment GR4 vs SHH



# Identification of Subgroups

## Similarity Network Fusion

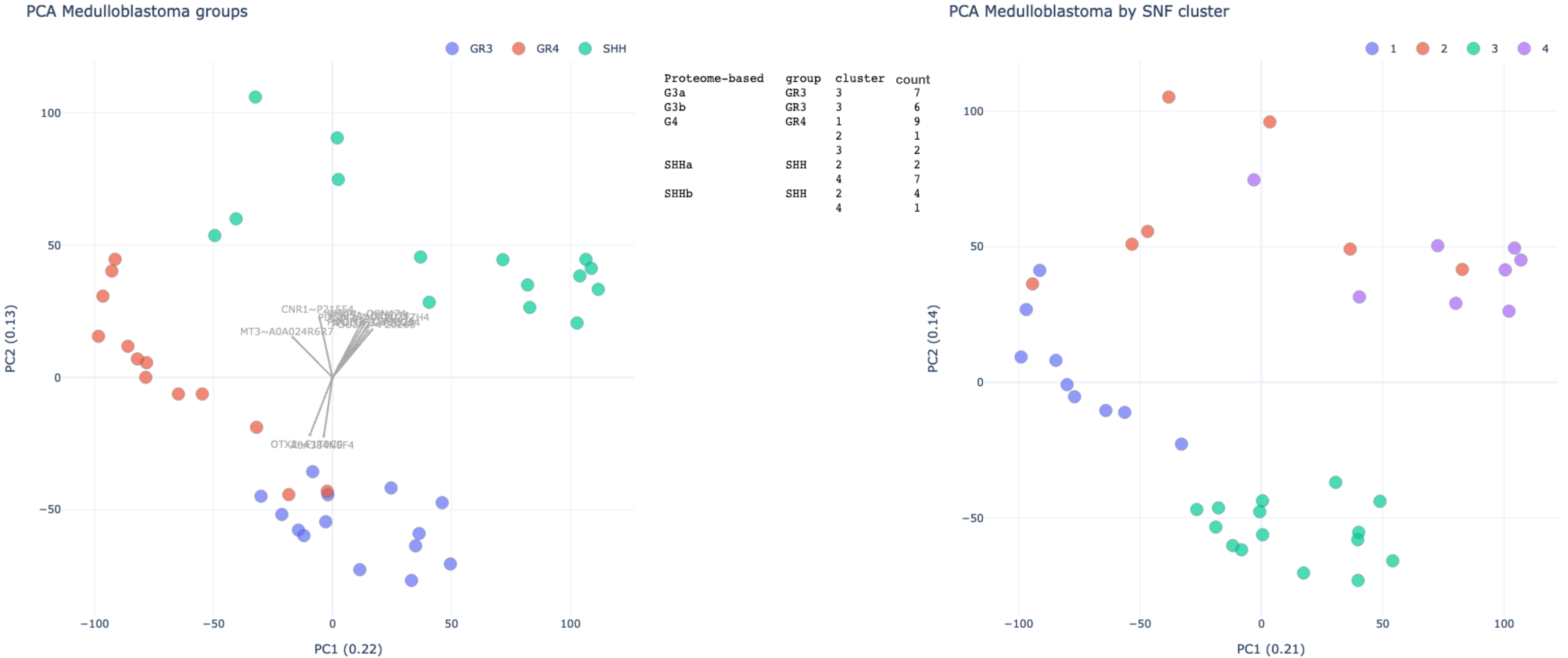
- Integration of all omics data generated using Similarity Network Fusion (SNF):
  - ✦ SNF build sample similarity networks using each omics data (RNAseq, Proteomics, PhosphoSTY, PhosphoY, Acetylomics) and fuses those networks into a single network that uses to identify clusters
  - ✦ We use these clusters to identify subgroups of patients





# Subgroups

## SNF clusters: PCA on proteomics data



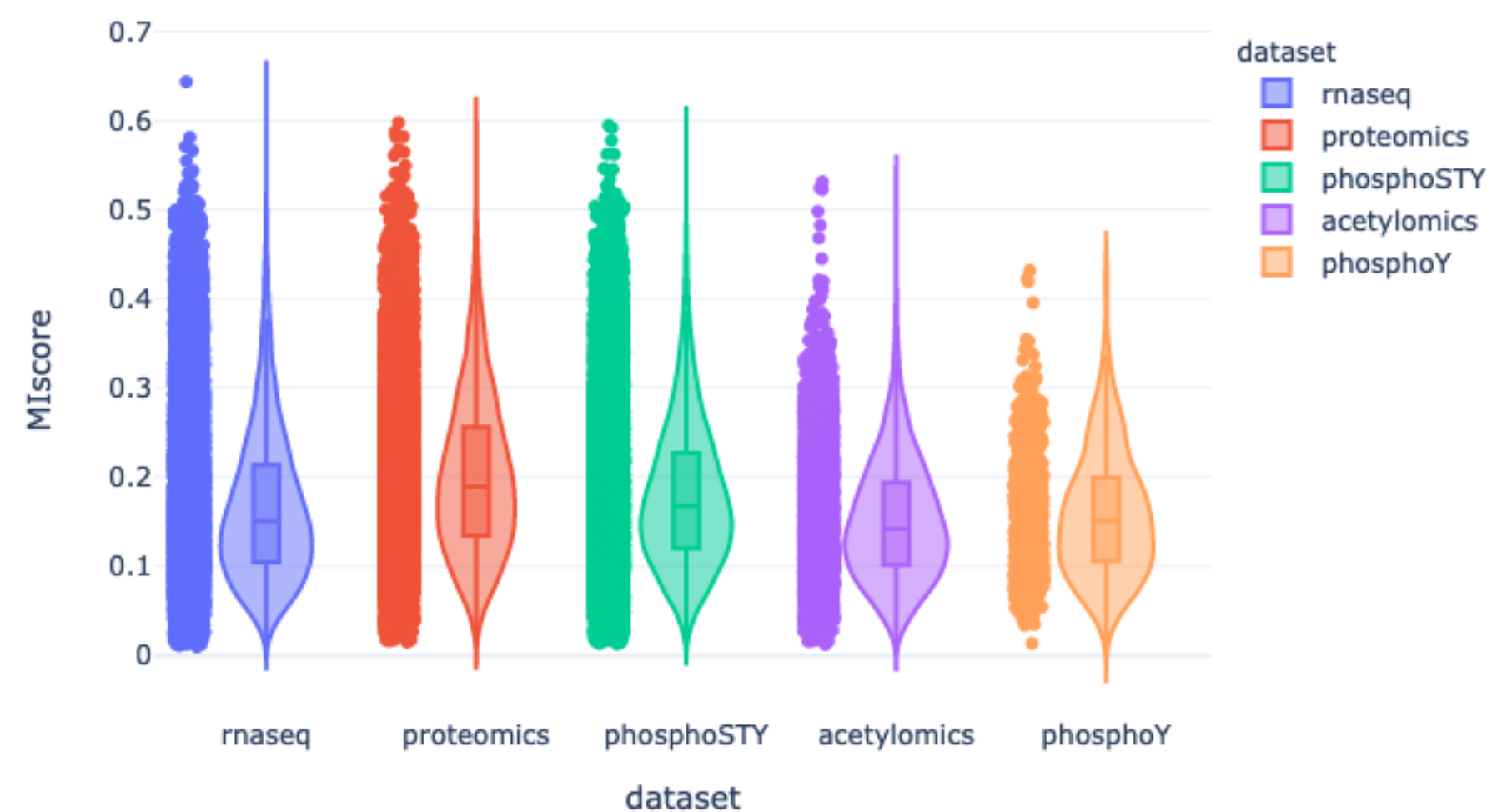
• Including all the omics types SNF identifies subgroups SHHa and SHHb



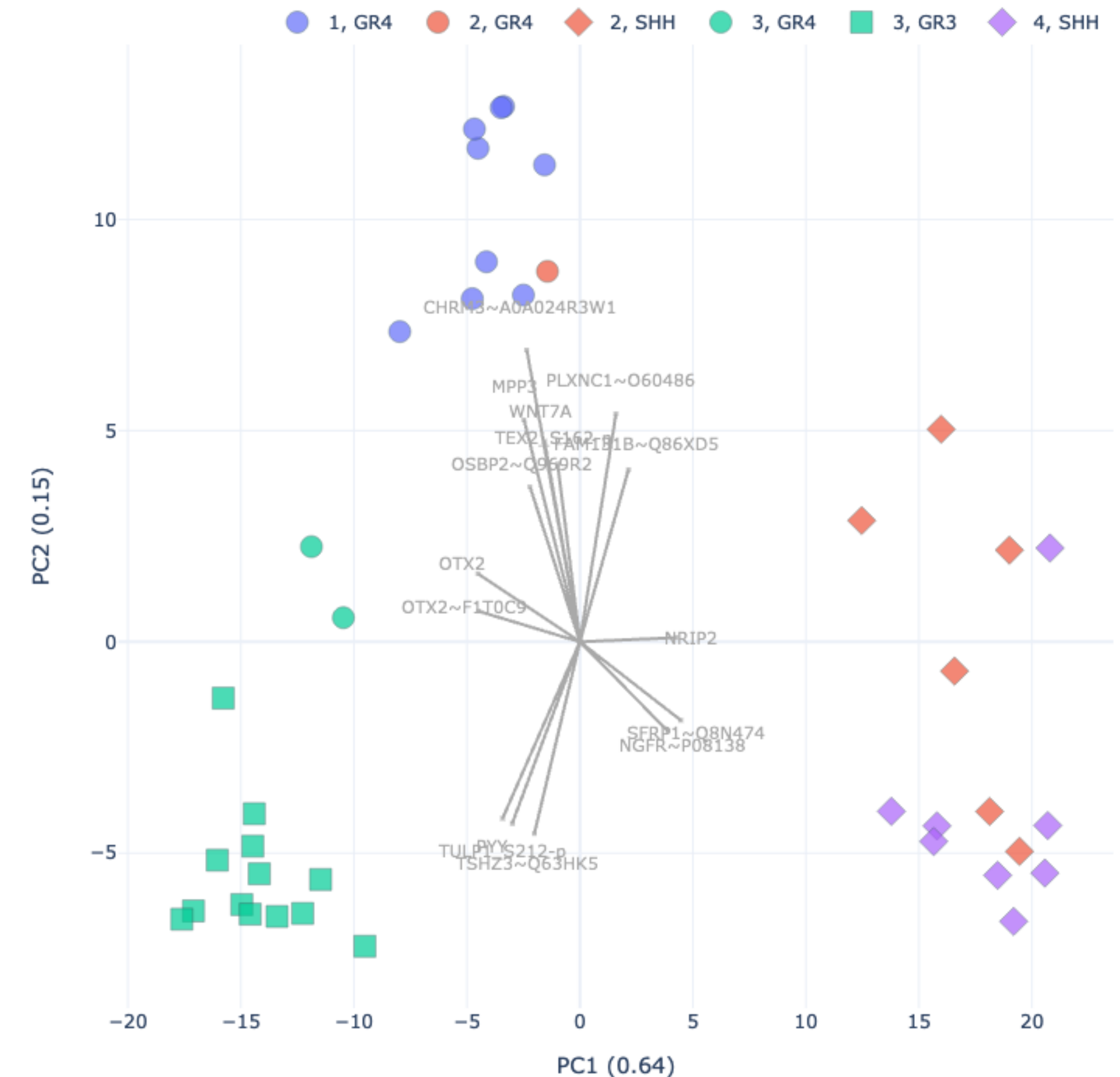
# Drivers for the SNF Clusters

These are the most informative features to distinguish the identified clusters

- **RNAseq:** MPP3, B3KNK0, MAPK10, OTX2-AS1, HIP1R, GRAMD1B, PYY, MAK, OTX2, TTBK1, NRIP2, PCYT1B, BOC
- **Proteomics:** RREB1~Q92766, ZNF609~O15014, MAPK10~P53779, TTBK1~Q5TCY1, PLXNC1~O60486, RALGPS2~Q86X27, OTX2~F1T0C9, THRA~P10827, GRAMD1B~Q3KR37, MAPK10~A0A286YF97, Q59G28, A0A140VKC1, OSBP2~Q969R2, NGFR~P08138, OTX1~P32242, CLTC~A0A087WVQ6
- **Phospho:** PPM1H\_S496-p, OSBP2\_S284-p, AFF3\_S903-p, SLC4A8\_S246-p, Q6ZSD7\_S1367-p, FAM171A2\_T791-p, RREB1\_S1219-p, TSHZ3\_S837-p, RREB1\_S1194-p, PCYT1B\_T337-p
- **Acetylomics:** LDHA\_K228-ac, DPF2\_K207-ac, SMAD2\_K46-ac



PCA Medulloblastoma by SNF cluster



Proteomics dataset contains the most informative features (Mutual Information score)