

Systematic Expression Profiling of Chronic Lymphatic Leukemia Transcriptomes

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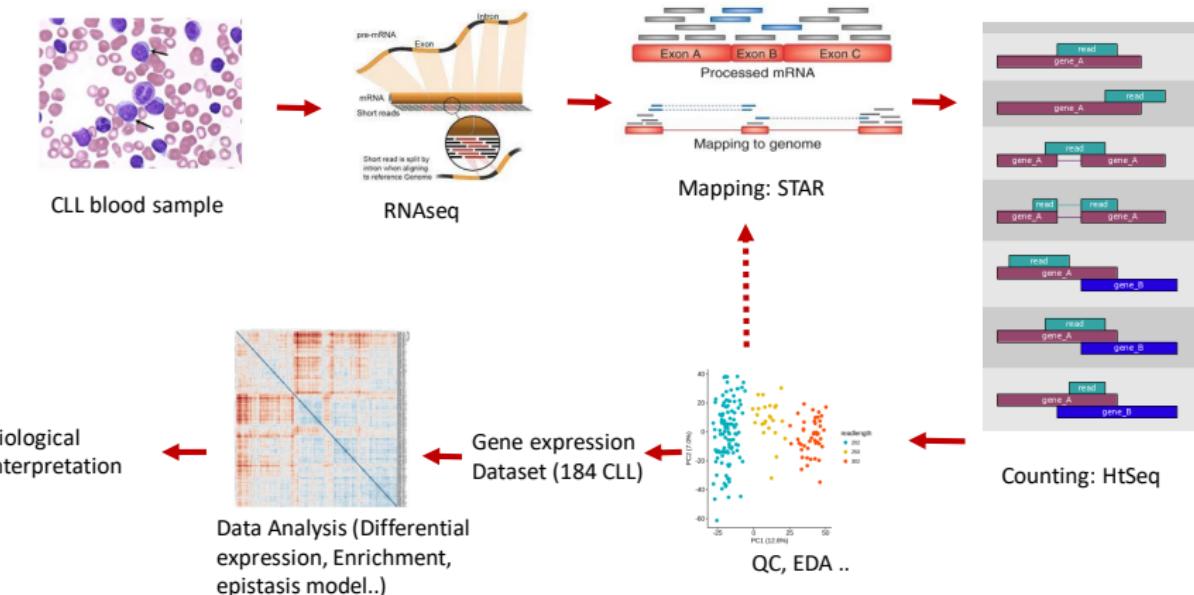
Chronic lymphatic leukemia

- Phenotypic and genotypic **heterogeneity**
- Individual therapeutic strategies: "**personalized medicine**"
- Specific molecular targets

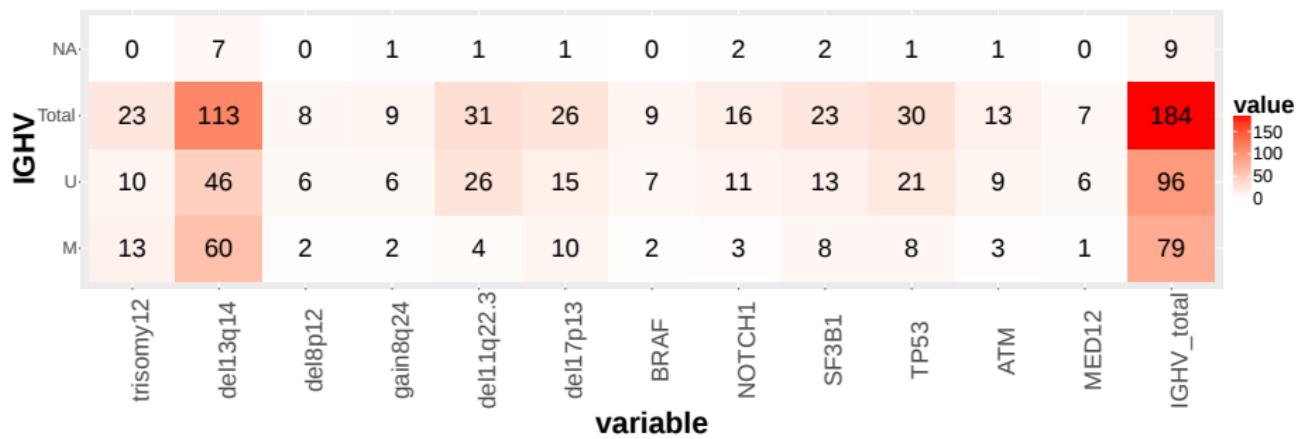
Aim of the study: Characterization of gene expression changes in common genetic variants in chronic lymphatic leukemia (CLL)

Project overview

Project overview



Genomic variants



Co-occurrence

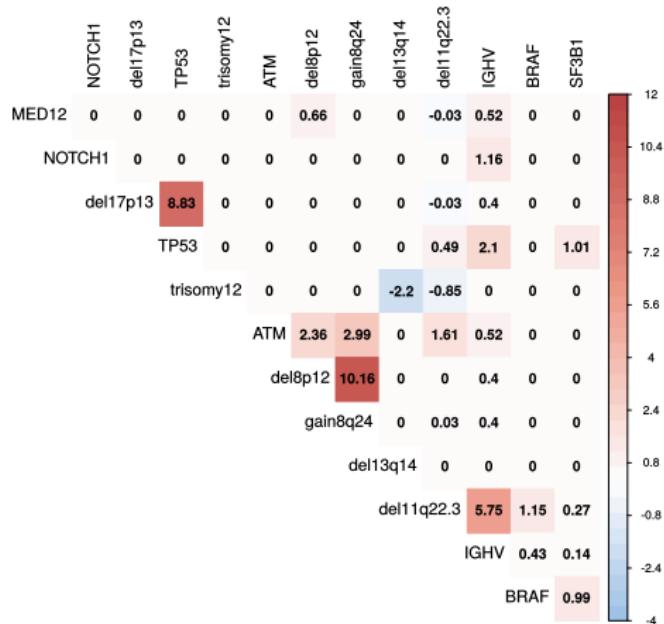
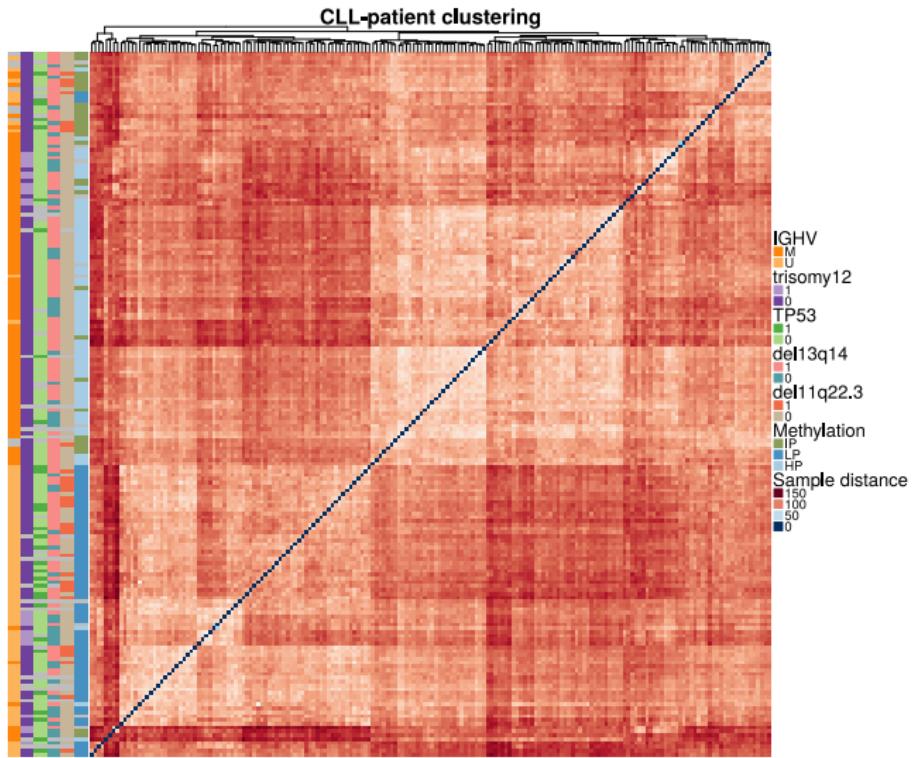
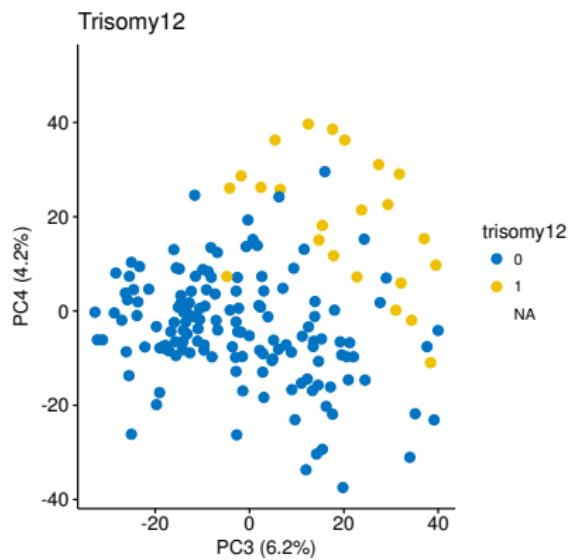
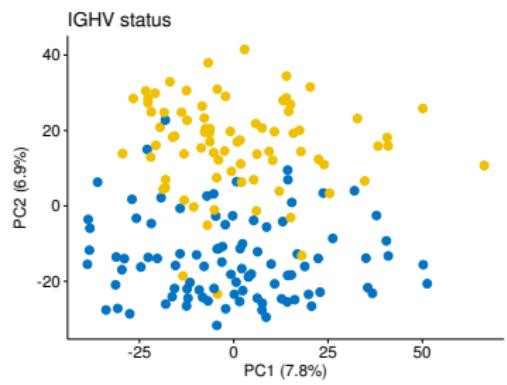


Figure: $-\log_{10}(\text{pvalue})$ for co-occurrence of genetic variants calculated by χ^2 -square test. The sign indicates the direction of association.

Hierachical Clustering



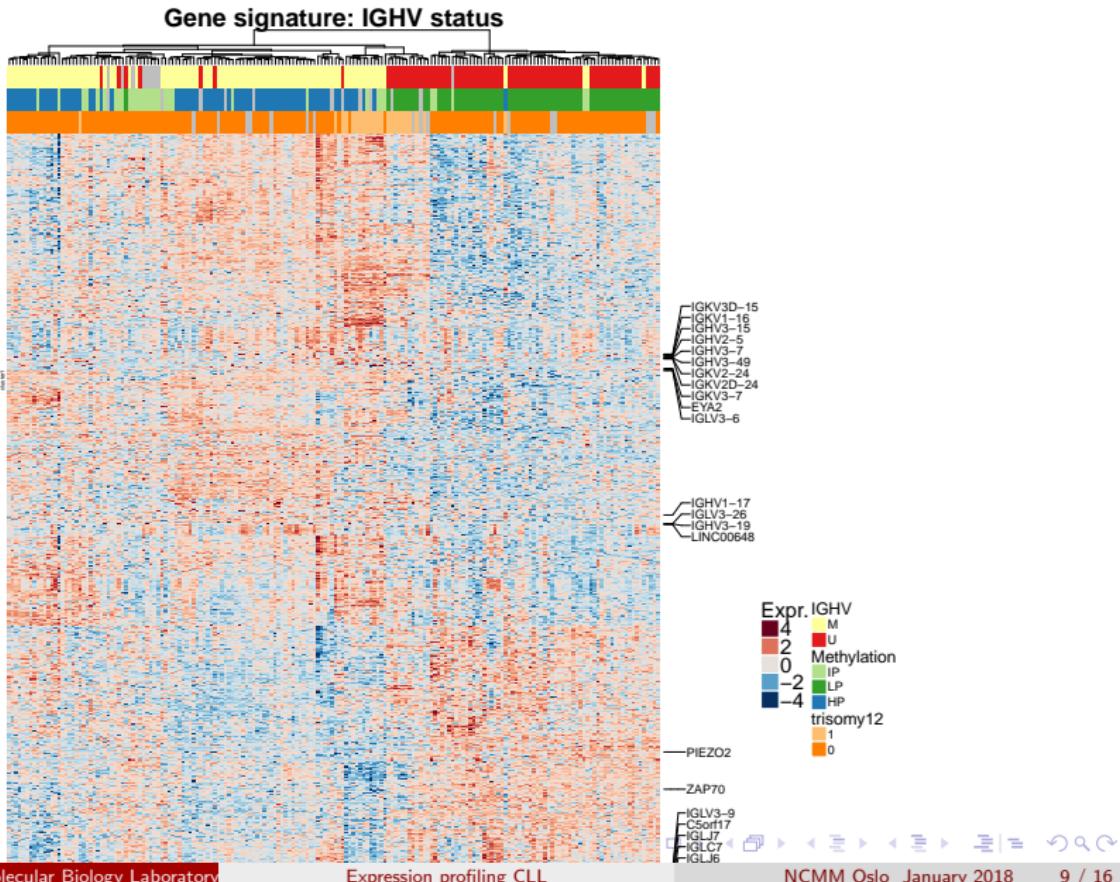
Principal Component Analysis



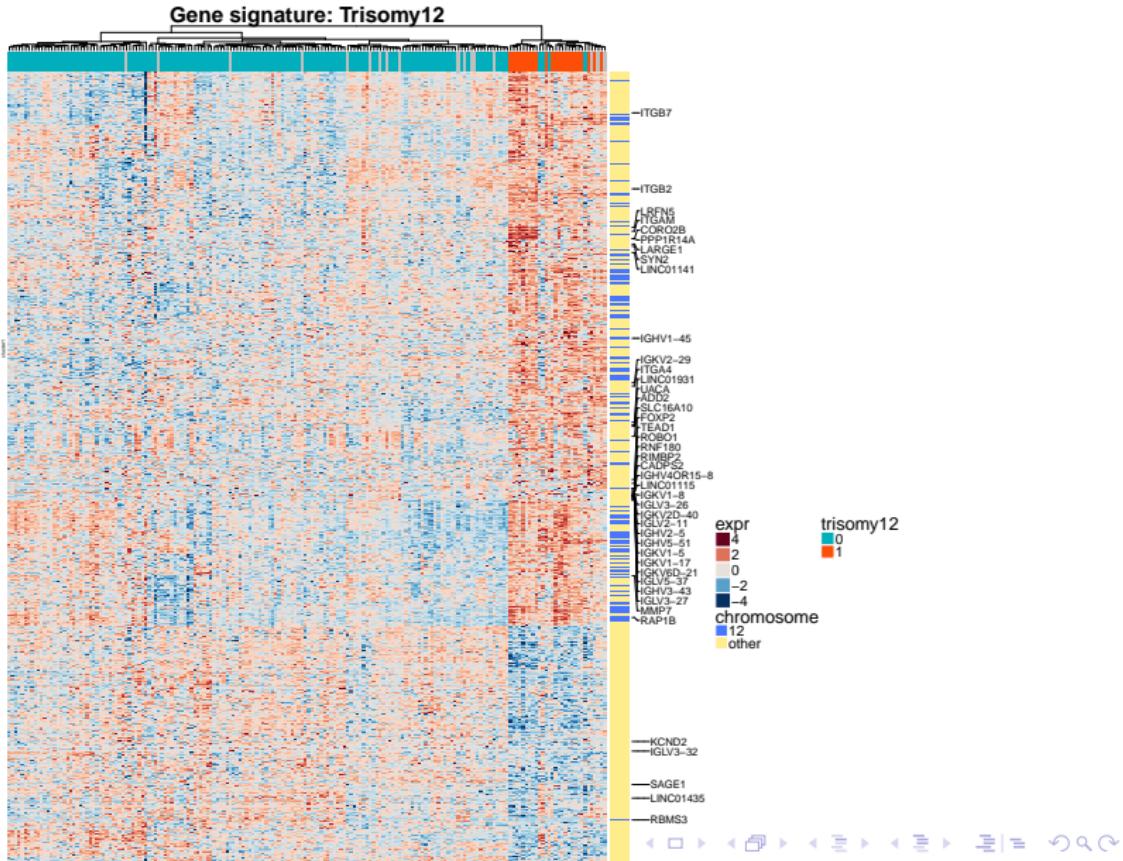
Summary I

- Most comprehensive CLL transcriptome dataset (Primary blood cancer cell encyclopedia)
- **IGHV** status and **Trisomy12** have major impact on gene expression
 - ▶ 6.9% variance are associated to IGHV, compared to 1.5% in previous studies (Feirrera et al. 2014)
- Associations between variants (e.g. Del11q22/IGHV, Del17p13/TP53, ..)

IGHV signature

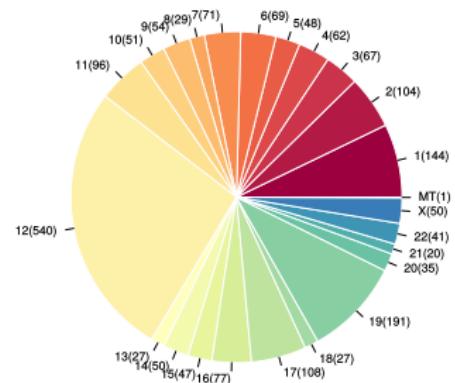


Trisomy12 signature

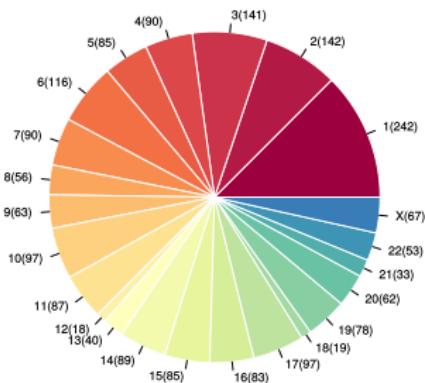


Trisomy12 signature

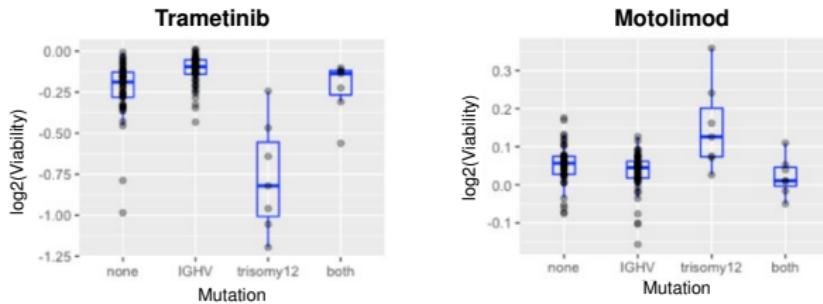
Chromosomal gene distribution in tri12: up



Chromosomal gene distribution in tri12: down

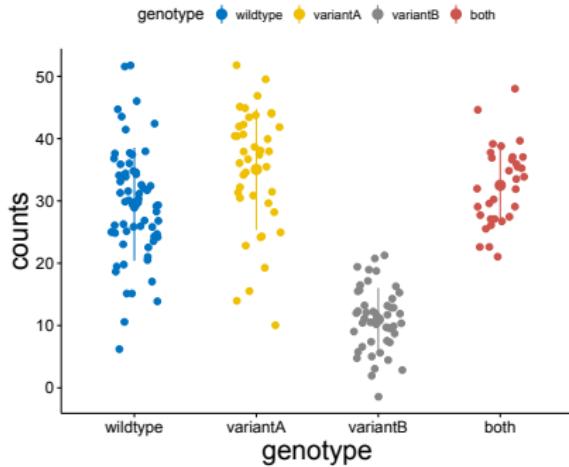


Tumor epistasis - drug sensitivity



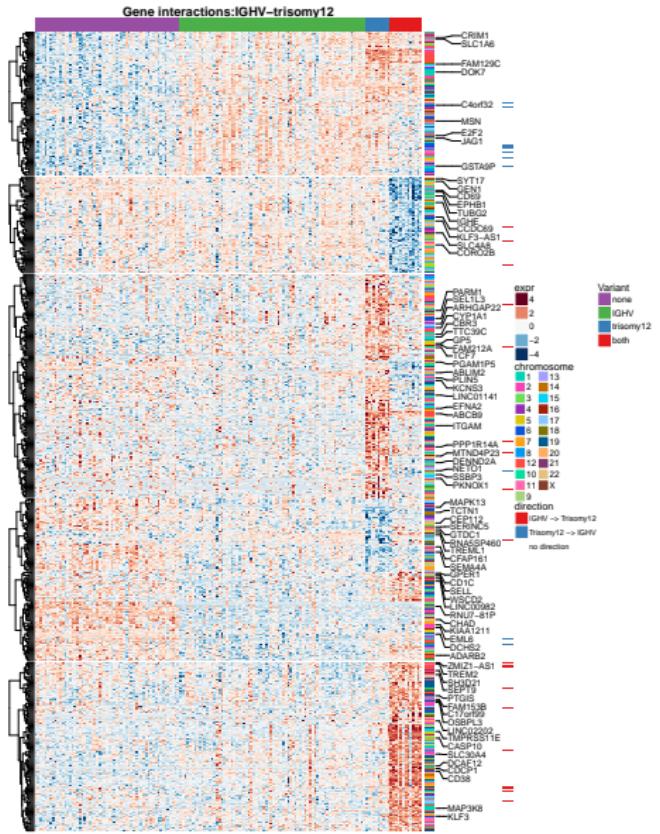
- Trisomy12 sample are less/more sensitive in M-CLL

Tumor epistasis - genetic interaction



- Observed gene expression in a combined genotype differs from the expected expression by combination of the individual effects

Epistatic interaction of Trisomy12 and IGHV



Summary II

- **IGHV** signature

- ▶ Differentially expressed genes are enriched in B cell receptor signaling
- ▶ Marker genes ZAP70 and CD38

- **Trisomy12** signature

- ▶ Up regulation of integrins (ITGAM, ITGB2,...)
- ▶ CD49d
- ▶ Increased lymphnode homing?

- Differential gene expression pattern in 8 of 13 variants

- **Tumor epistasis** (drug sensitivity, gene expression)

Thanks to ..

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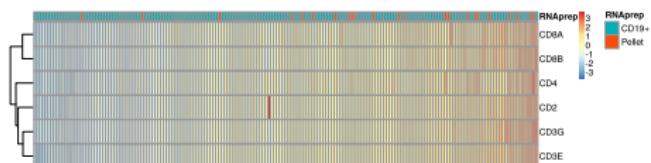
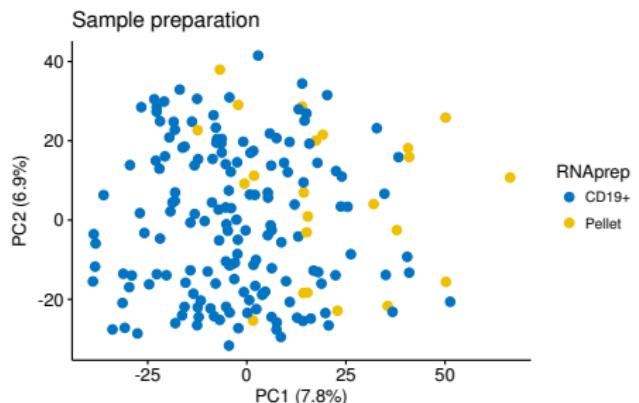
Thomas Schwarzl

AG Zenz

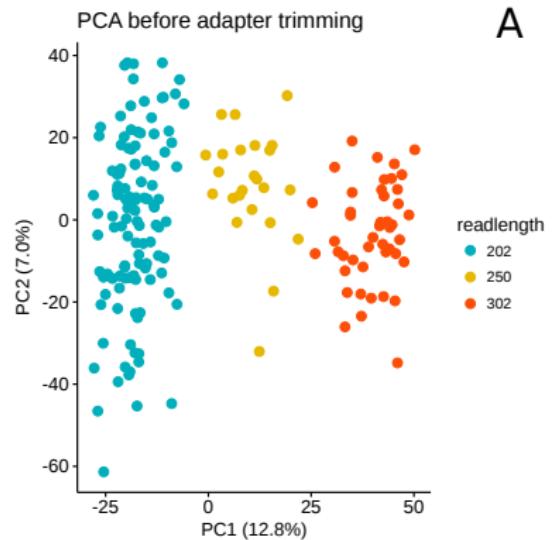
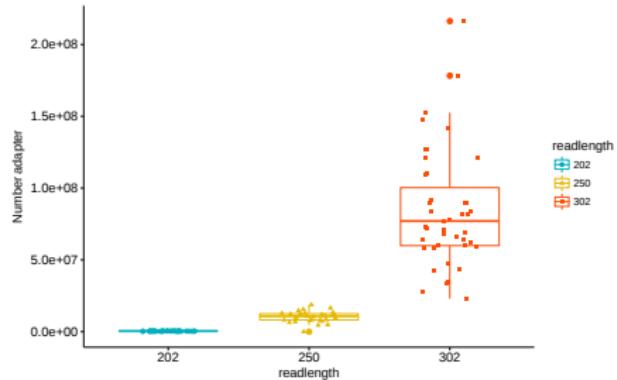
AG Dietrich



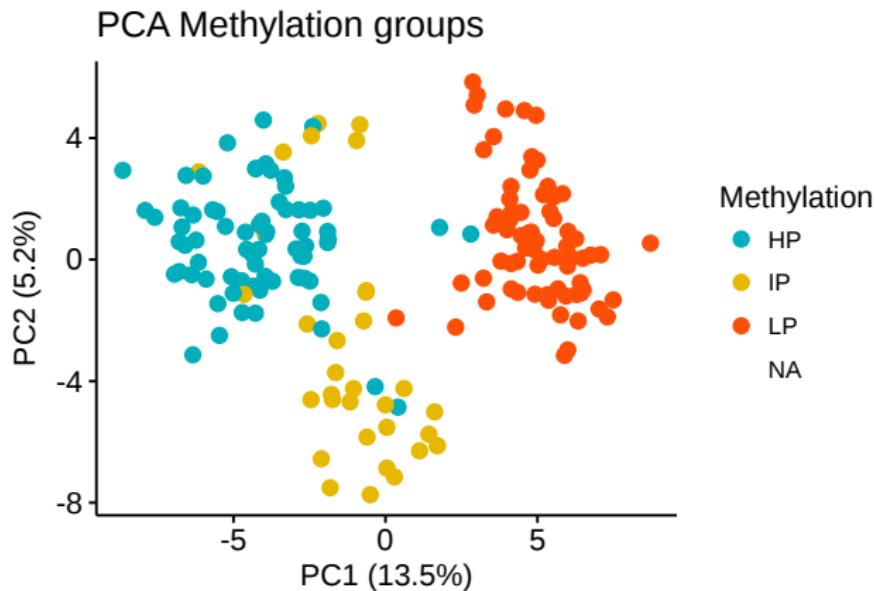
T cell contamination



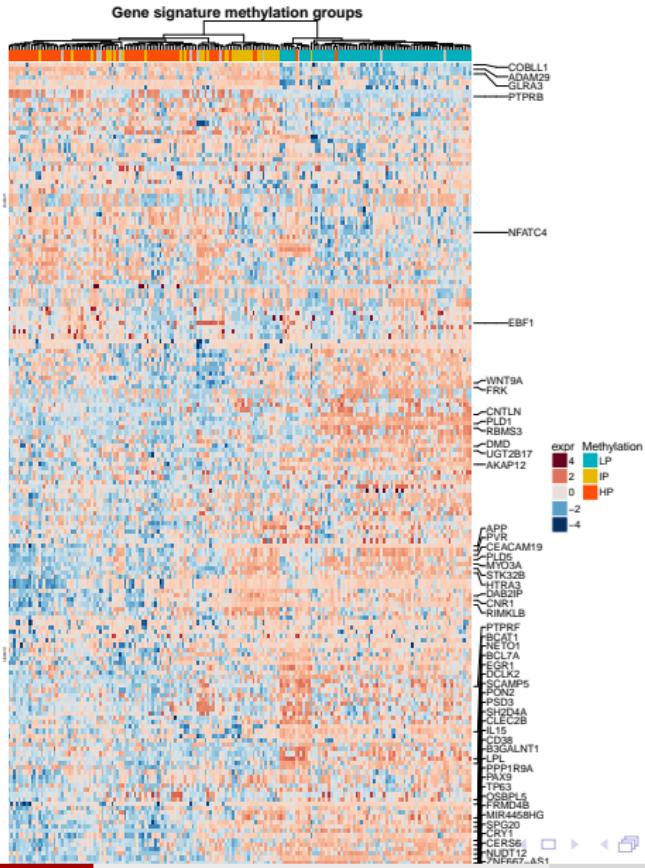
Adapter contamination



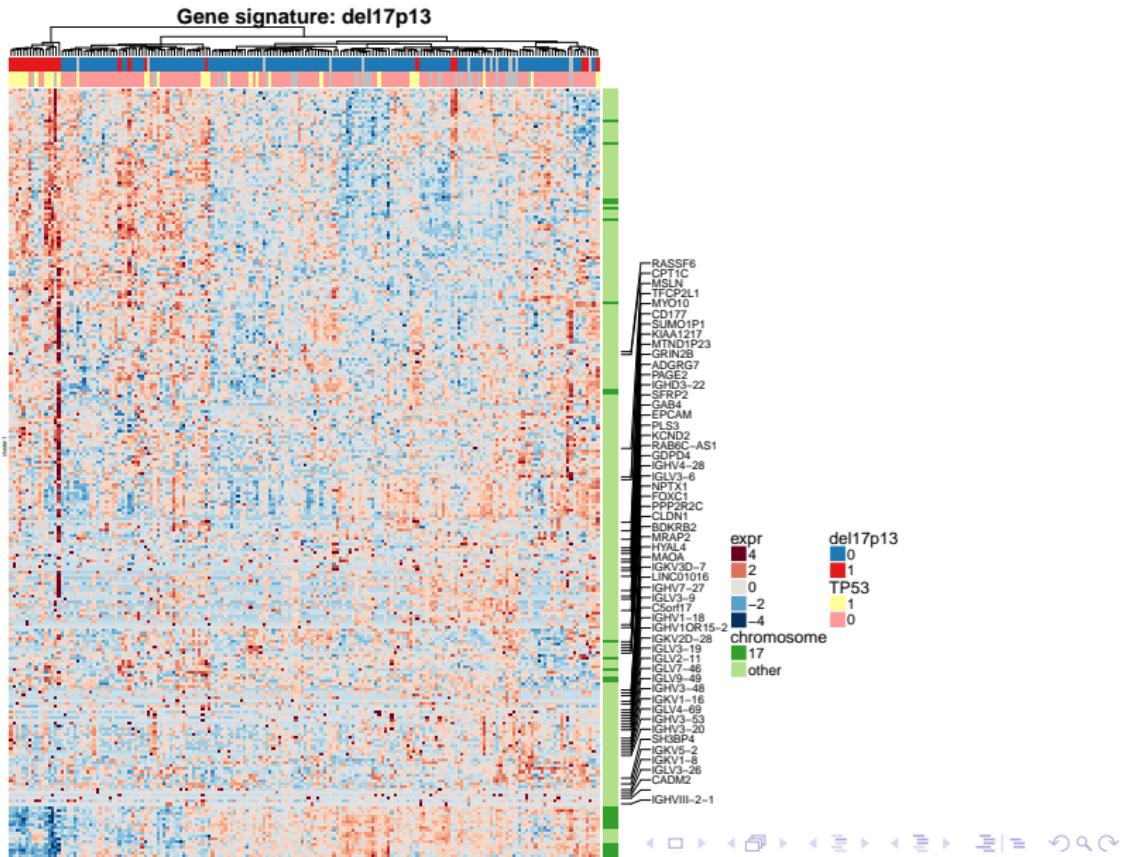
Methylation groups



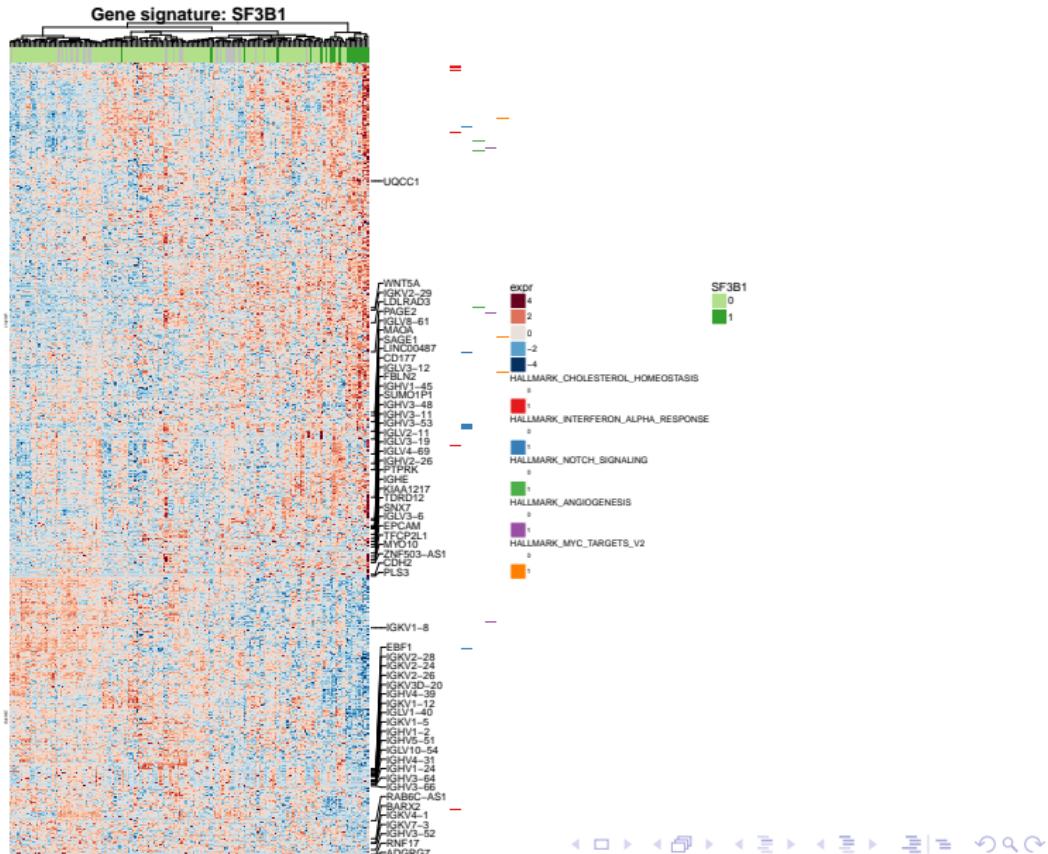
Methylation signature



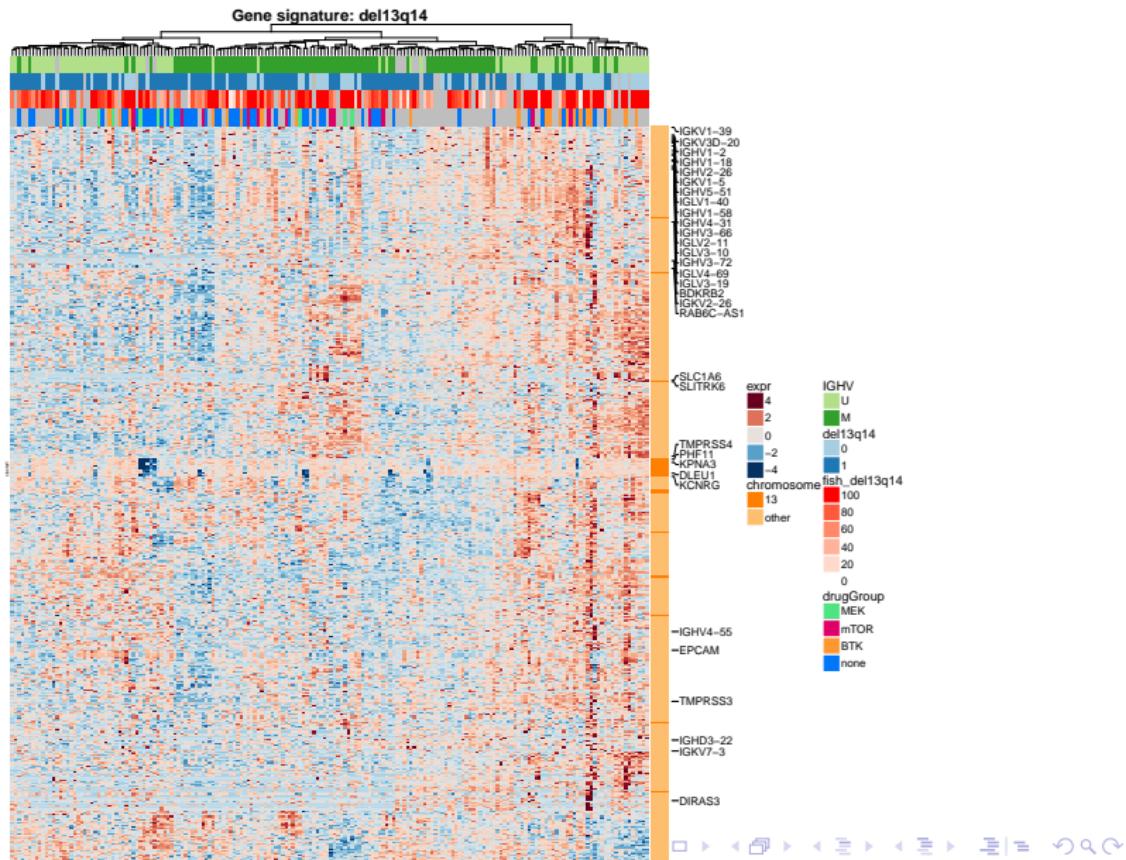
TP53/Del17p13



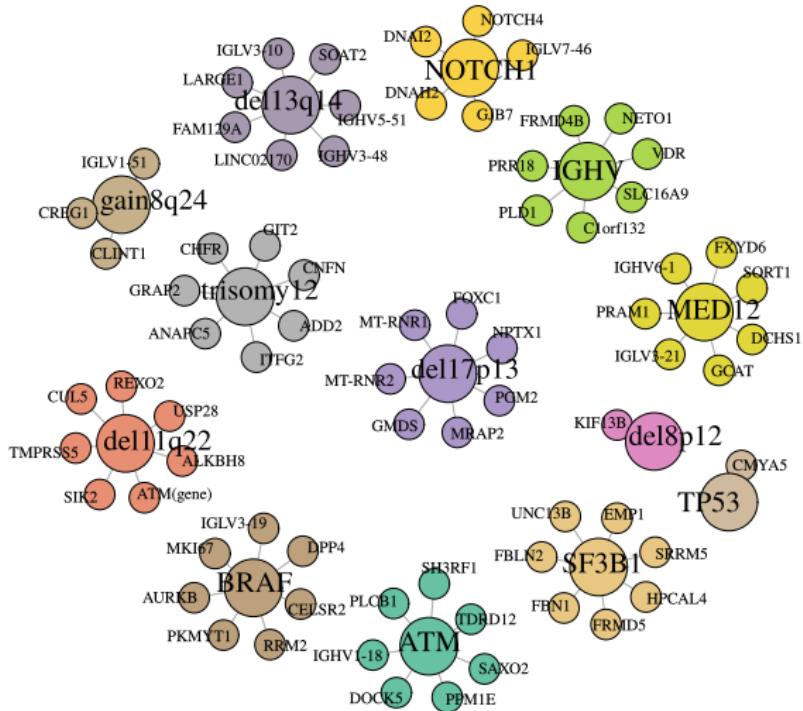
SF3B1 signature



Del13q14 signature



Multivariate model



Outlook

- directions/mixed epistasis model?
- role of TPL2 in Trisomy12 and IGHV-M
- lymphnode homing/integrins in Trisomy12
- enrichment tests