

Systematic Expression Profiling of Chronic Lymphatic Leukemia Transcriptomes

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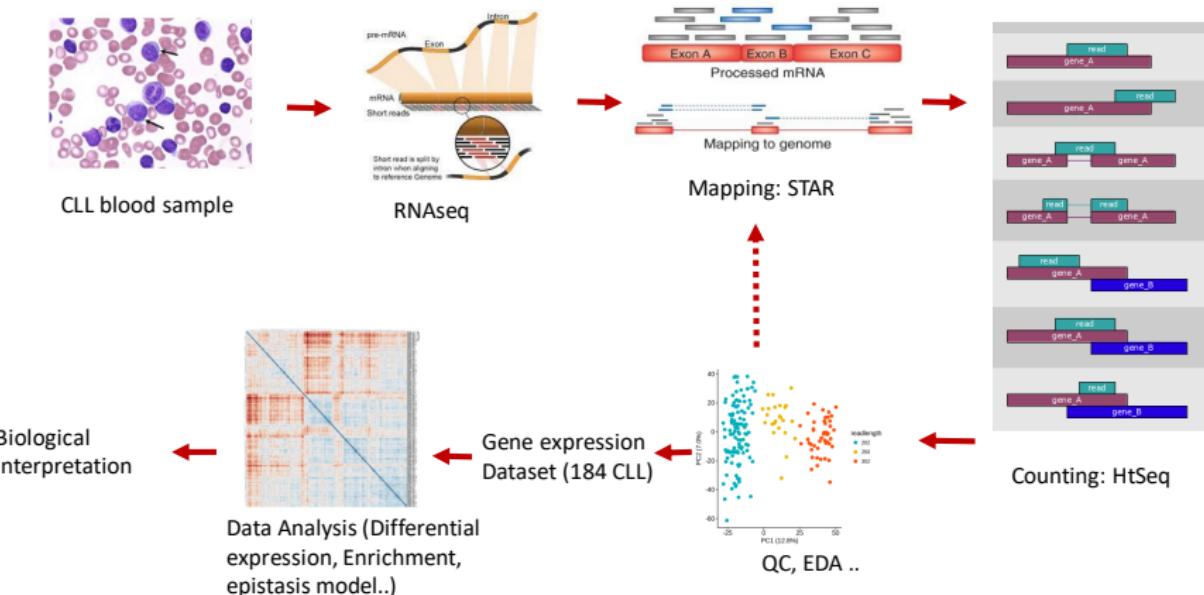
Chronic lymphatic leukemia

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

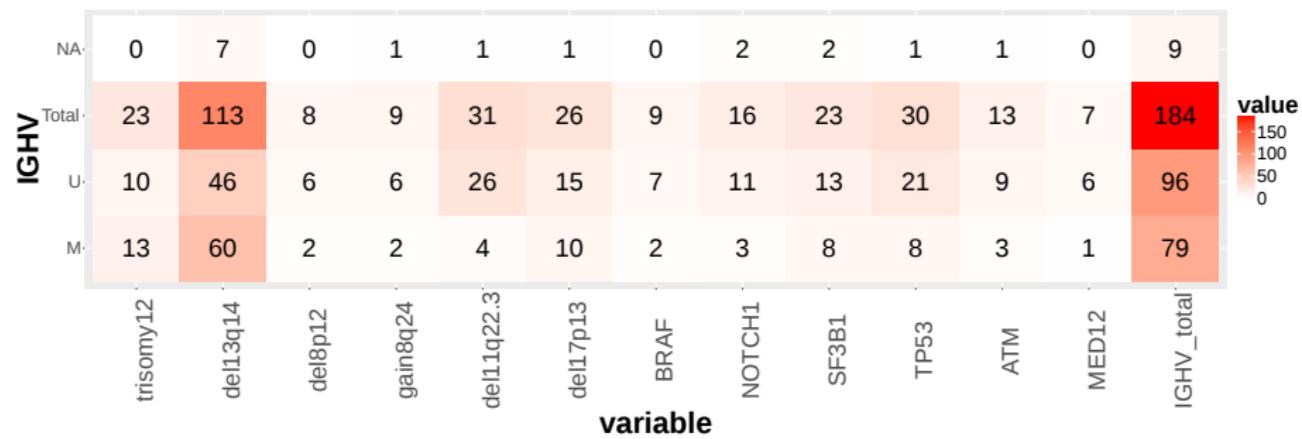
Aim of the study: Characterization of gene expression changes in common genetic variants in chronic lymphatic leukemia (CLL)

Project overview

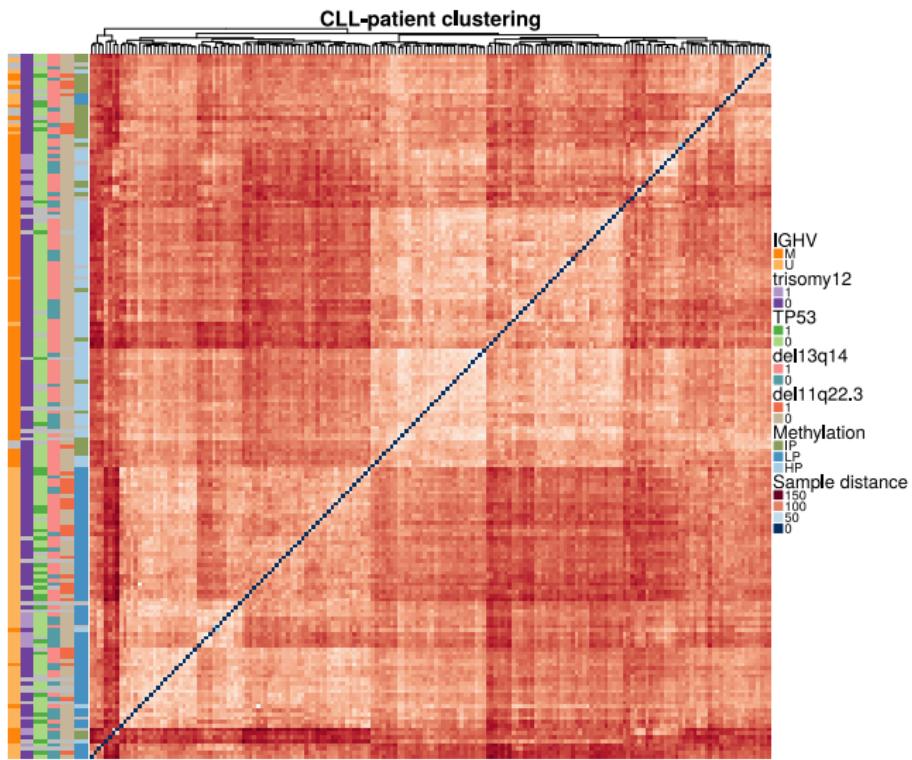
Project overview



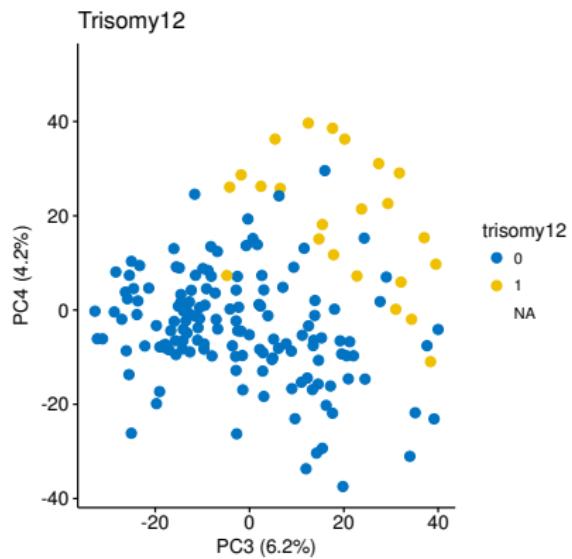
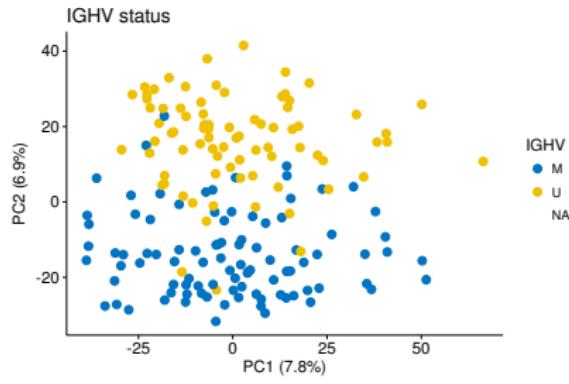
Genomic variants



Hierachical Clustering



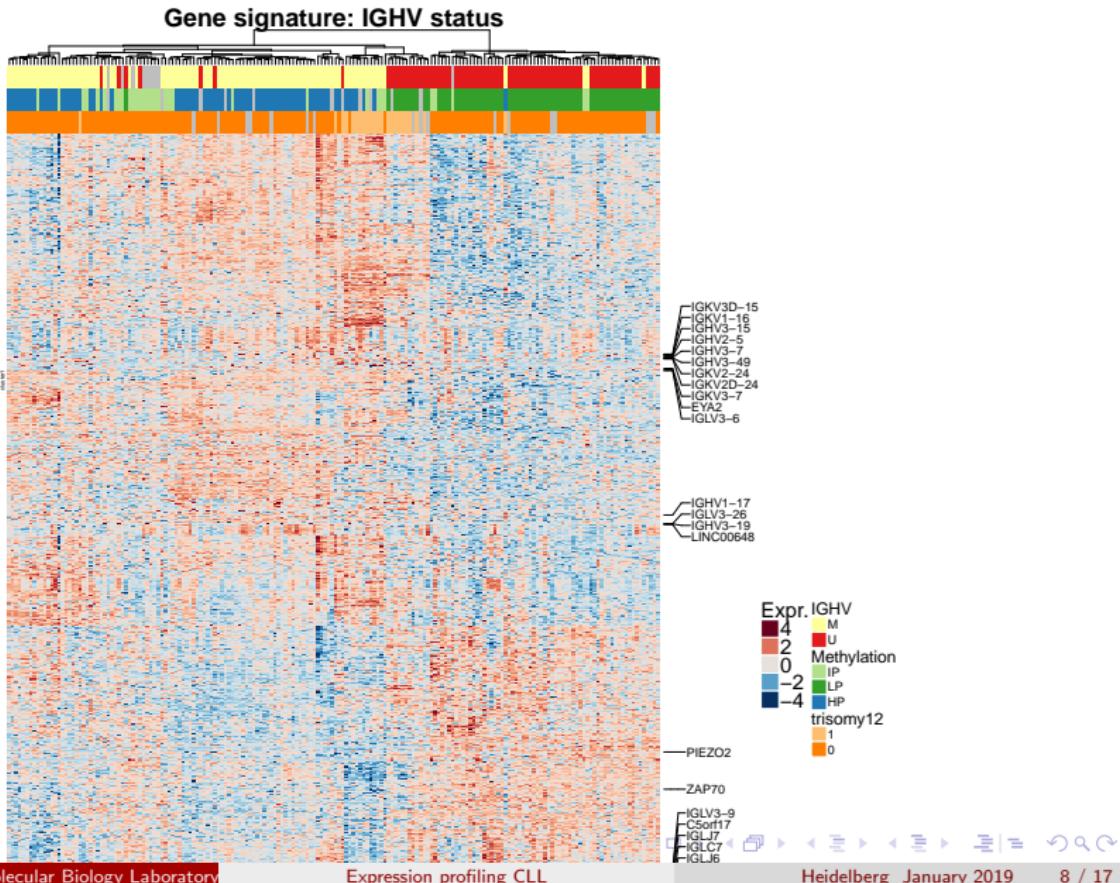
Principal Component Analysis



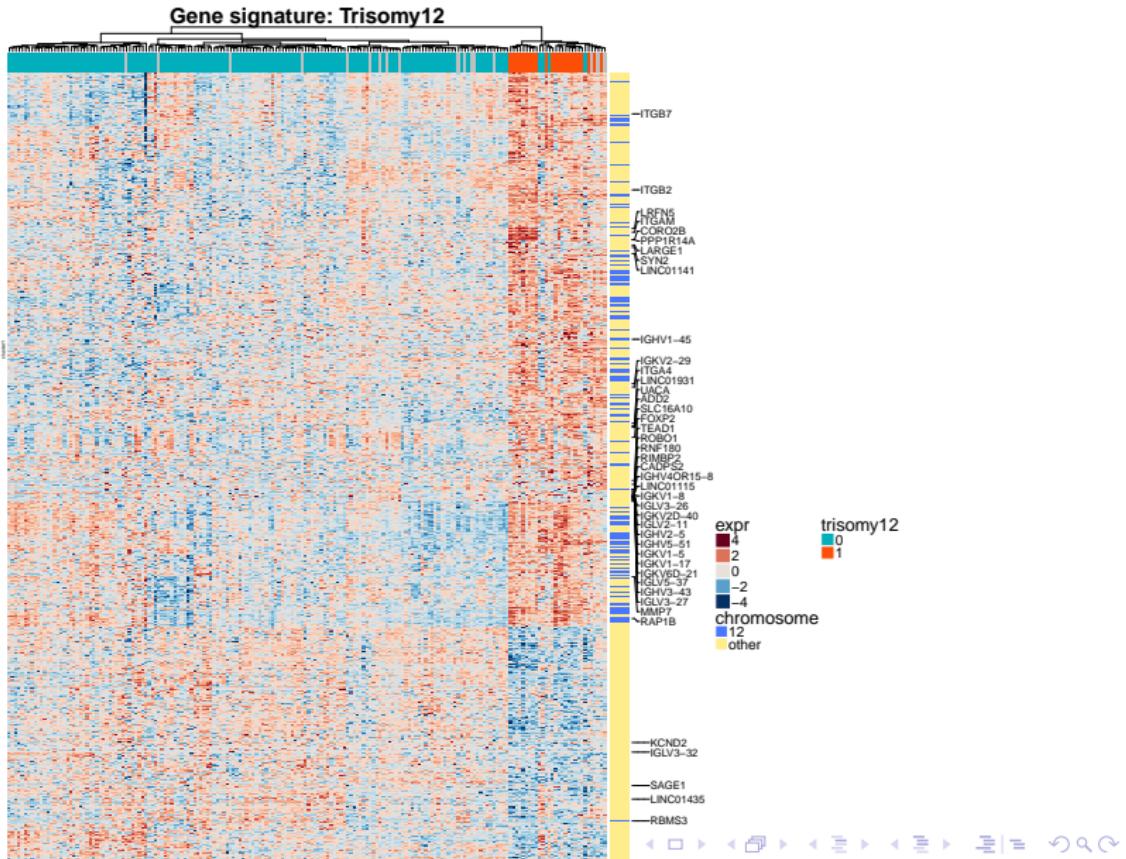
Summary I

- 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

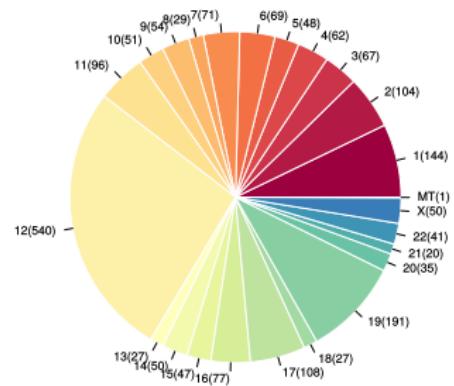


Trisomy12 signature

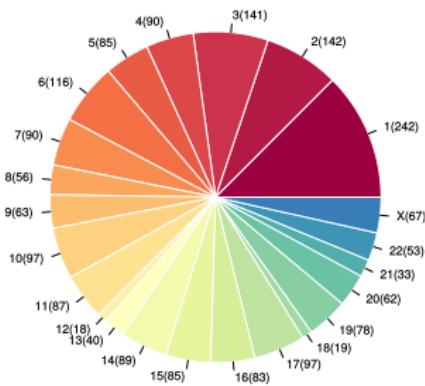


Trisomy12 signature

Chromosomal gene distribution in tri12: up

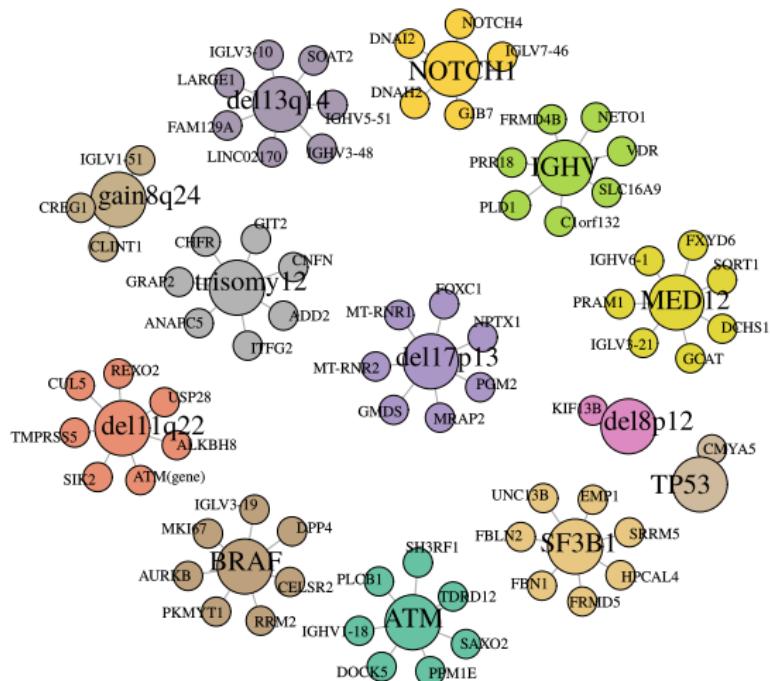


Chromosomal gene distribution in tri12: down

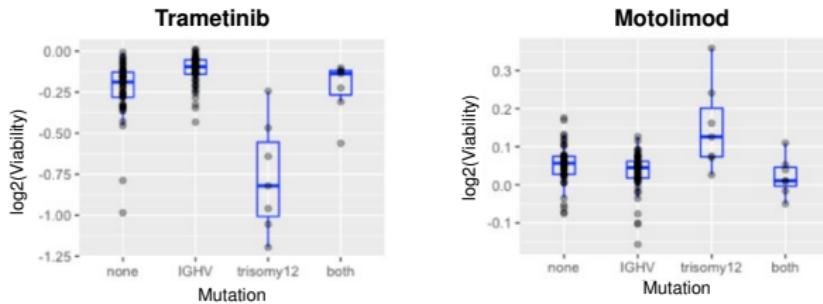


Multivariate model

- Individual effect of each variant
 - Likelihood ratio test of complete and reduced model

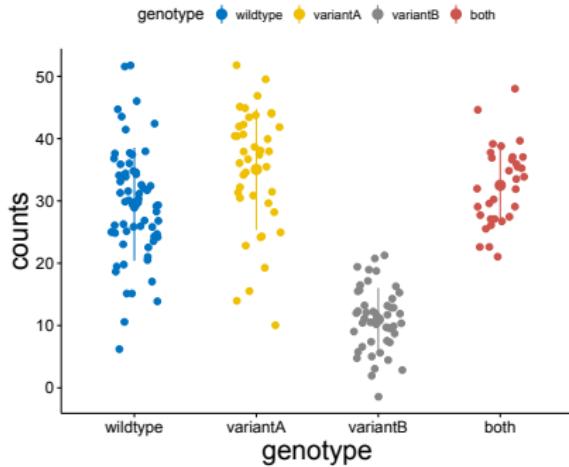


Tumor epistasis - drug sensitivity



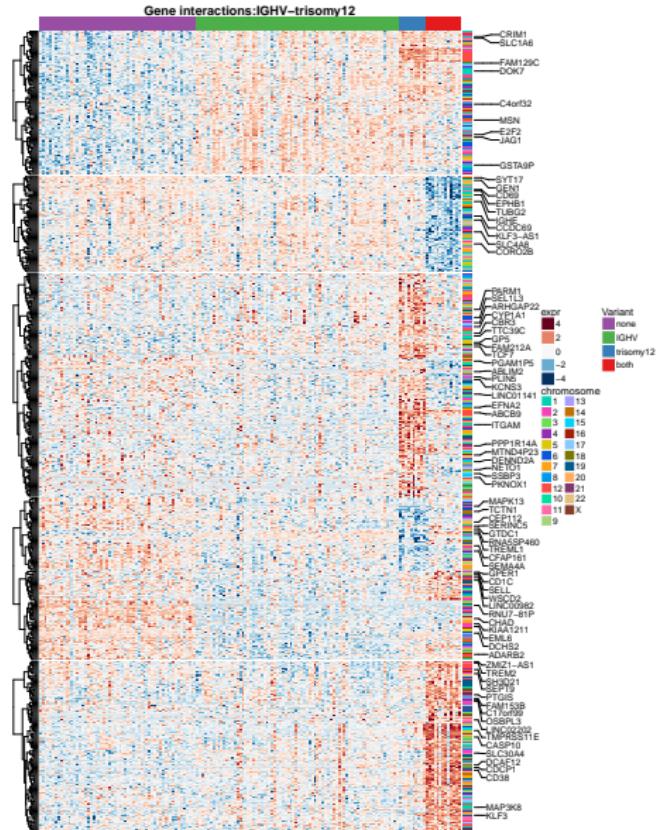
- Trisomy12 sample are less/more sensitive in M-CLL

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



Mixed epistasis model

RMC Biol. 2015; 13: 112.

Published online 2015 Dec 23. doi: [10.1186/s12915-015-0222-5](https://doi.org/10.1186/s12915-015-0222-5)

PMCID: PMC4690272

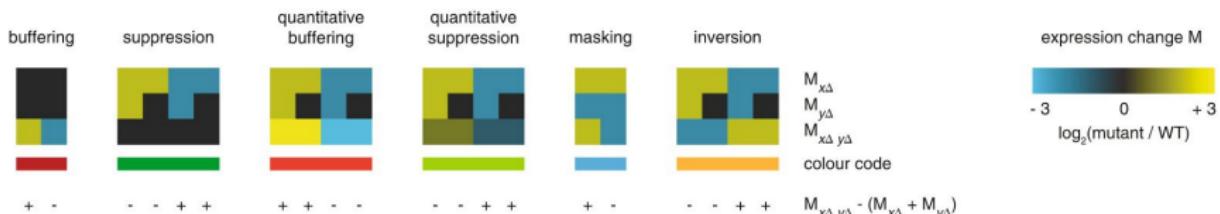
A high-resolution gene expression atlas of epistasis between gene-specific transcription factors exposes potential mechanisms for genetic interactions

Katrin Sameith, Saman Amini, Marian J. A. Groot Koerkamp, Dik van Leenen, Mariel Brok, Nathalie Brabers, Philip Lijnzaad, Sander R. van Hooft, Joris J. Benschop, Tineke L. Lenstra, Eva Apweiler, Sake van Wageningen, Berend Snel, Frank C. P. Holstege, and Patrick Kemmeren*

Cell 2010 Dec 10;143(6):991-1004. doi: 10.1016/j.cell.2010.11.021.

Functional overlap and regulatory links shape genetic interactions between signaling pathways.

van Wageningen S¹, Kemmeren P, Lijnzaad P, Margaritis T, Benschop JJ, de Castro LJ, van Leenen D, Groot Koerkamp MJ, Ko CW, Miles AJ, Brabers N, Brok MO, Lenstra TL, Fiedler D, Fokkens L, Aldecoa R, Apweiler E, Taliadiourous V, Sameith K, van de Pasch LA, van Hooft SR, Bakker LV, Krogan NJ, Snel B, Holstege FC.



Mod. from Sameith et al.

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 ..

AG Huber

Wolfgang Huber
Junyan Lu
Jennifer Huellein

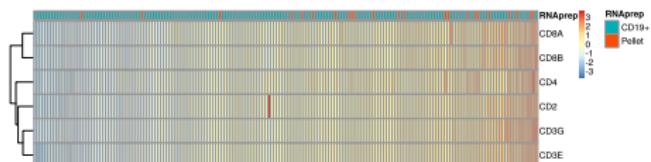
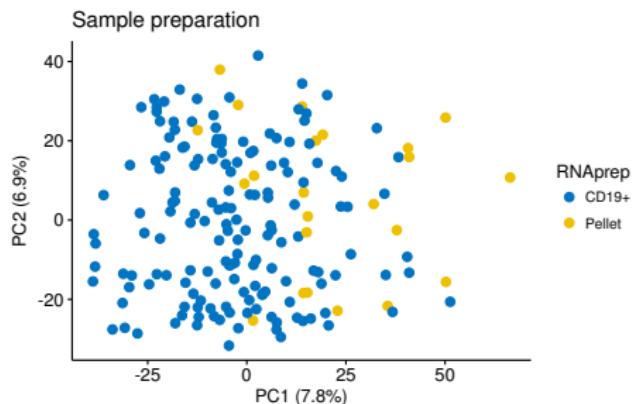
AG Zenz

Thorsten Zenz

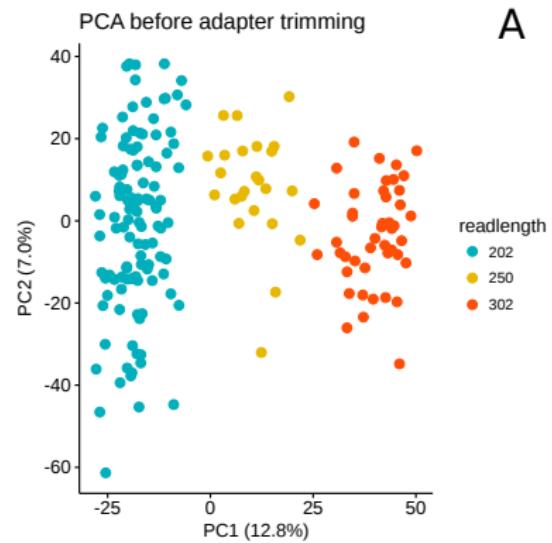
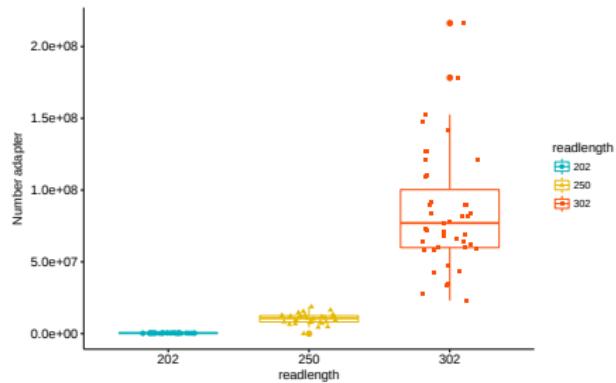
Matthias Schlesner



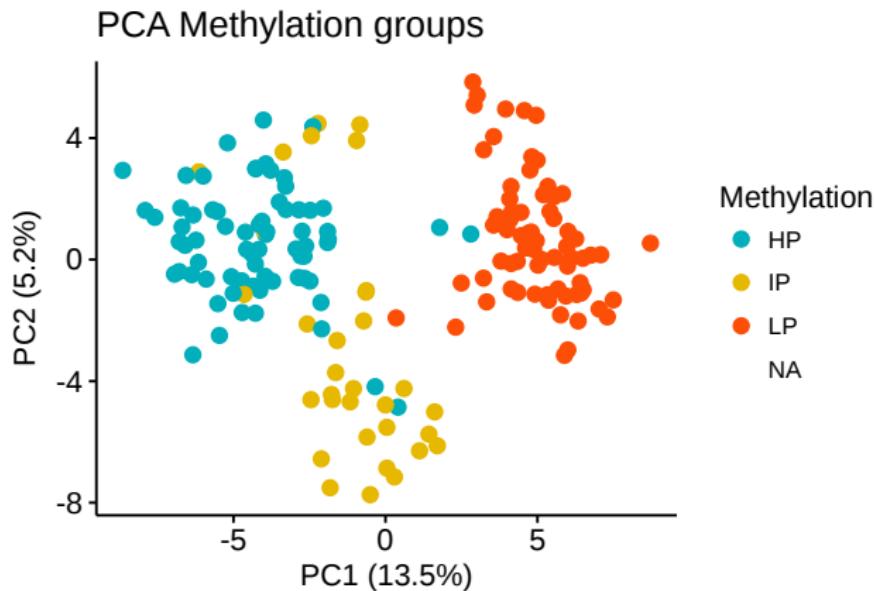
T cell contamination



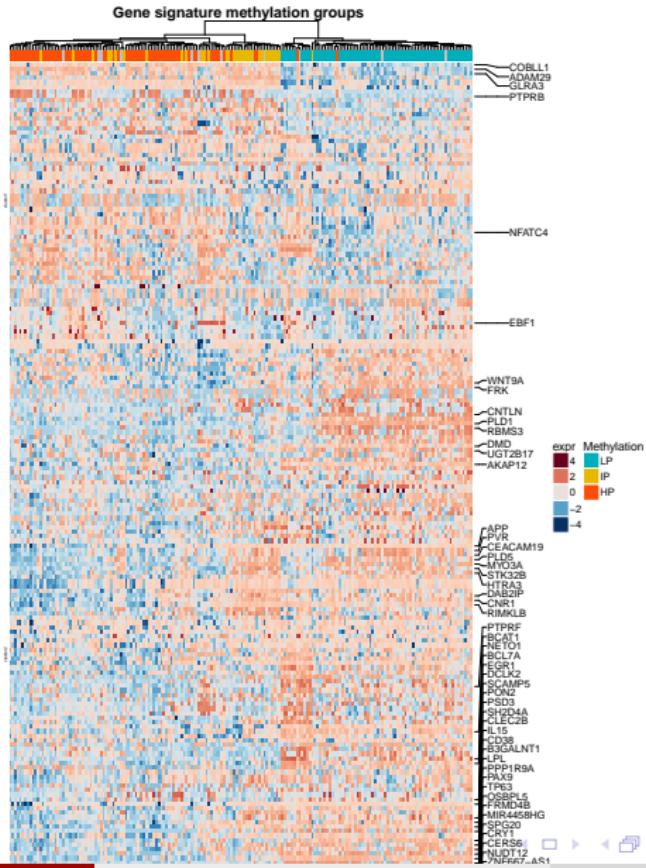
Adapter contamination



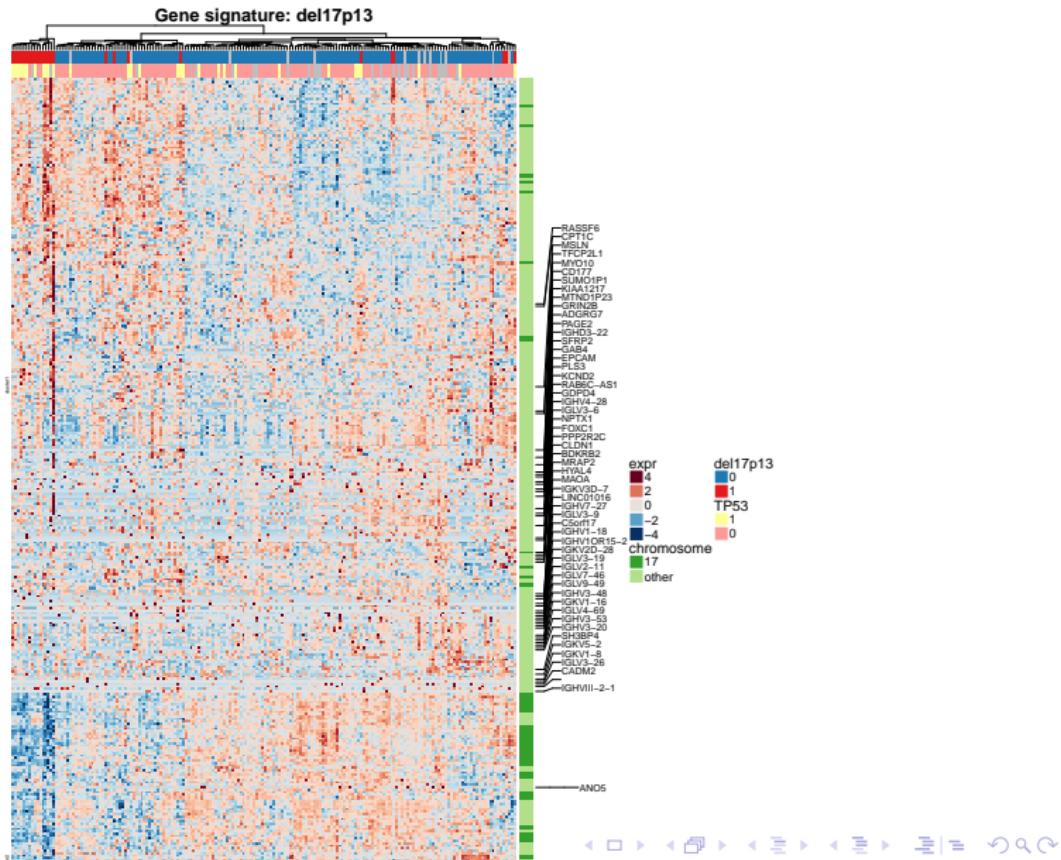
Methylation groups



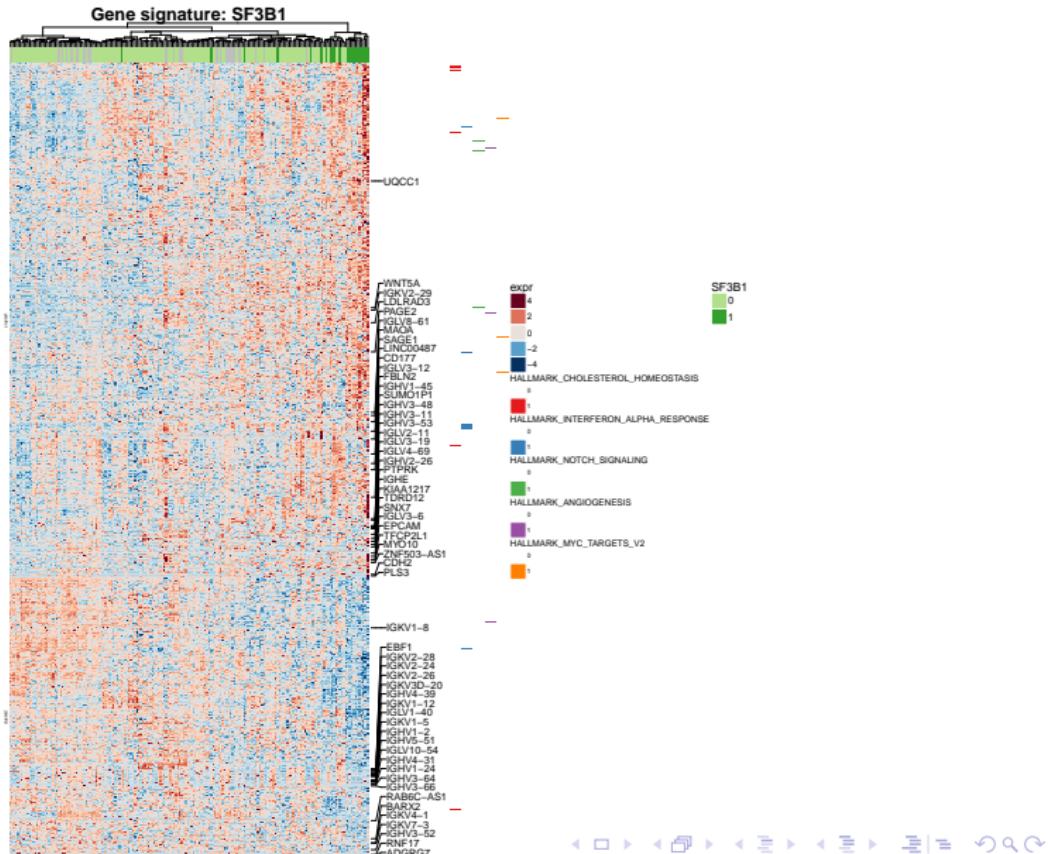
Methylation signature



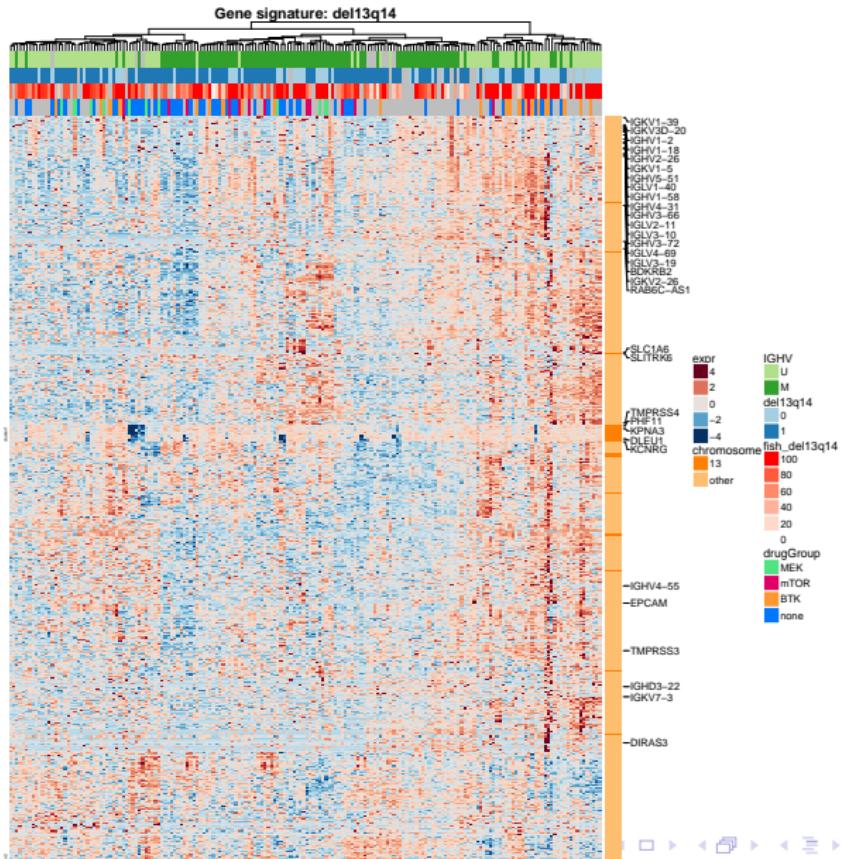
TP53/Del17p13



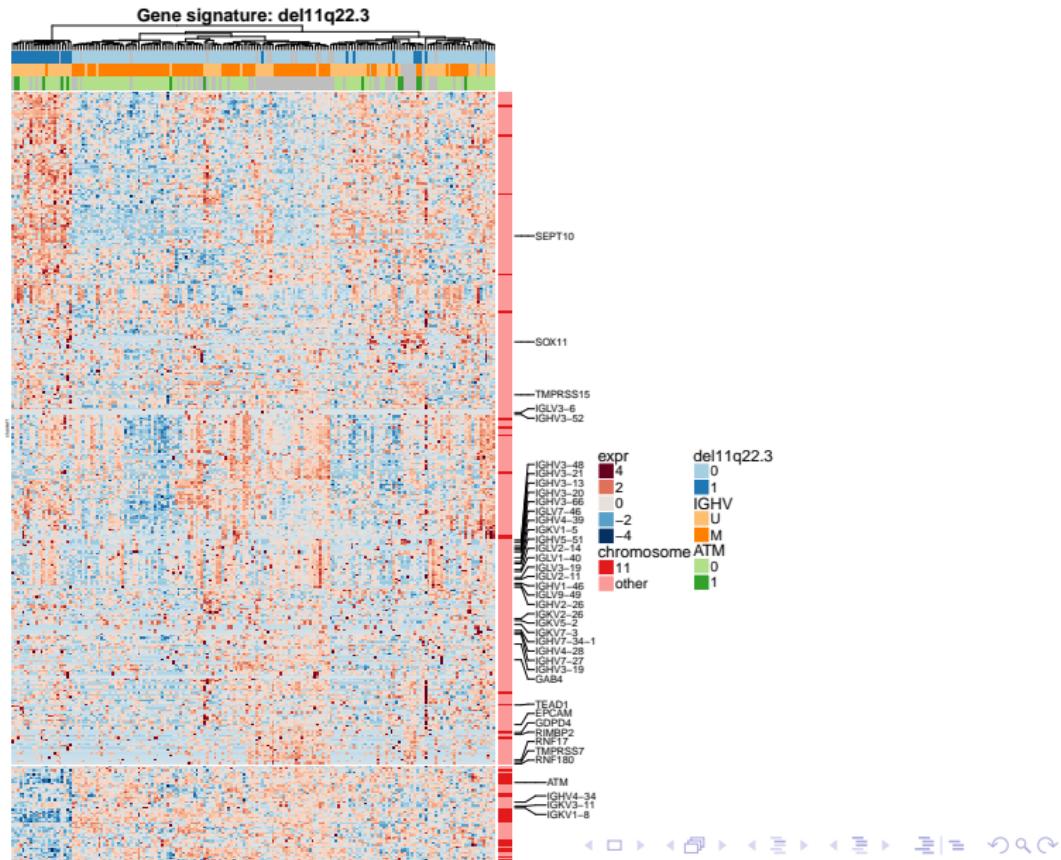
SF3B1 signature



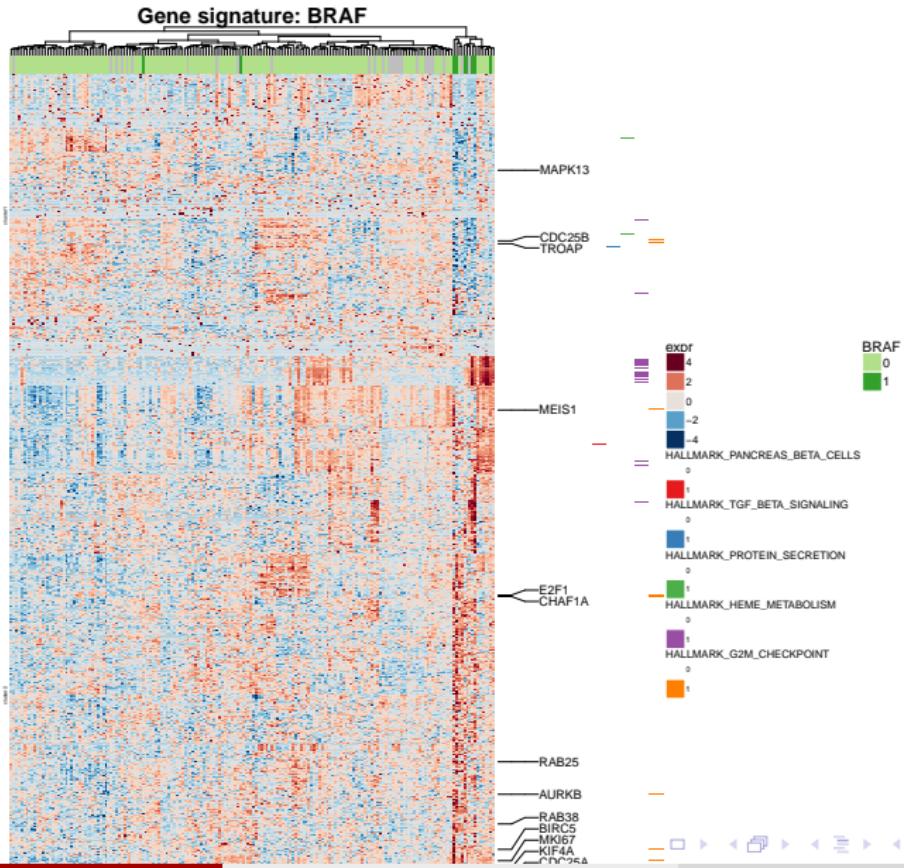
Del13q14 signature



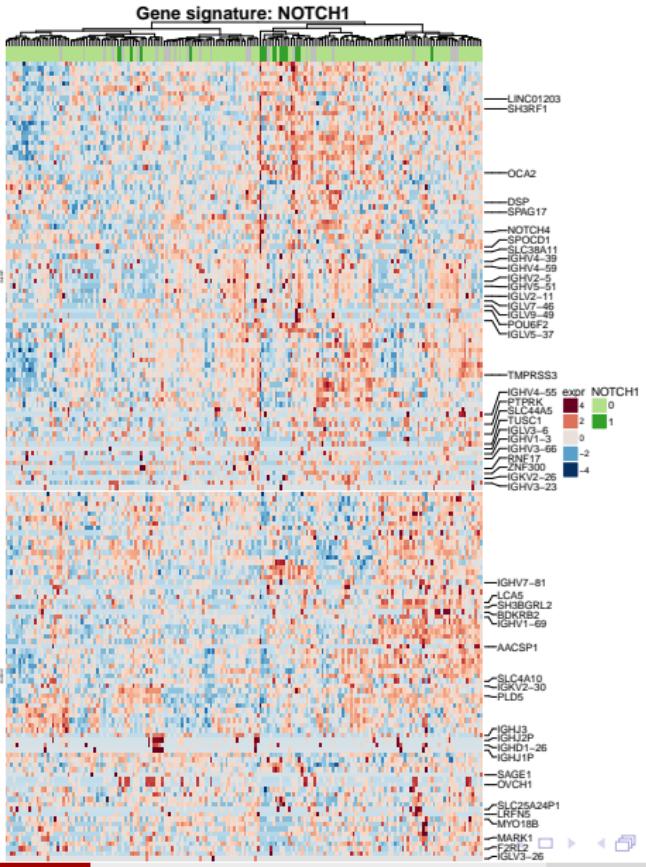
Del11q22 signature



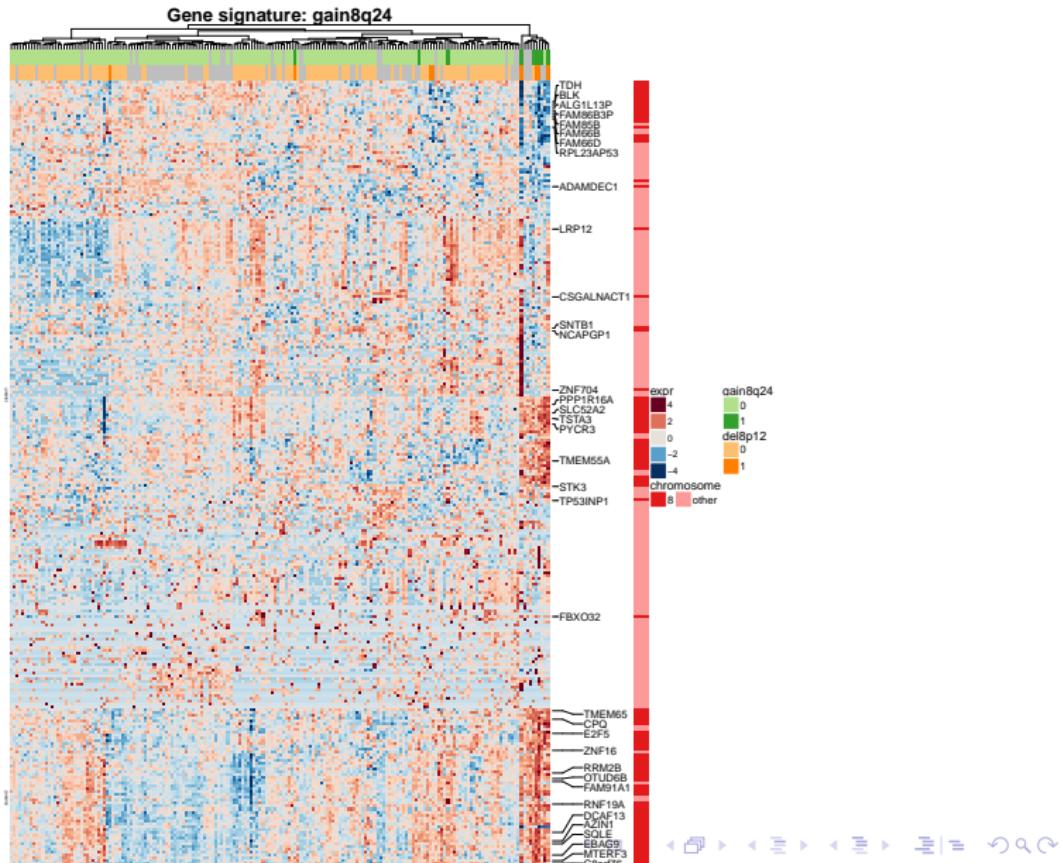
BRAF signature



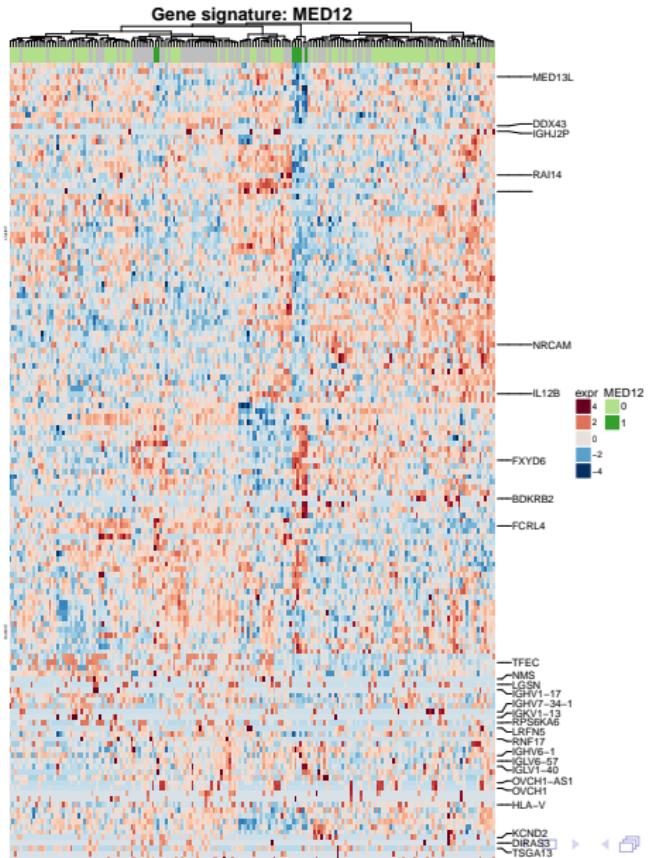
Notch signature



Gain8q24 signature



MED12 signature



Co-occurrence

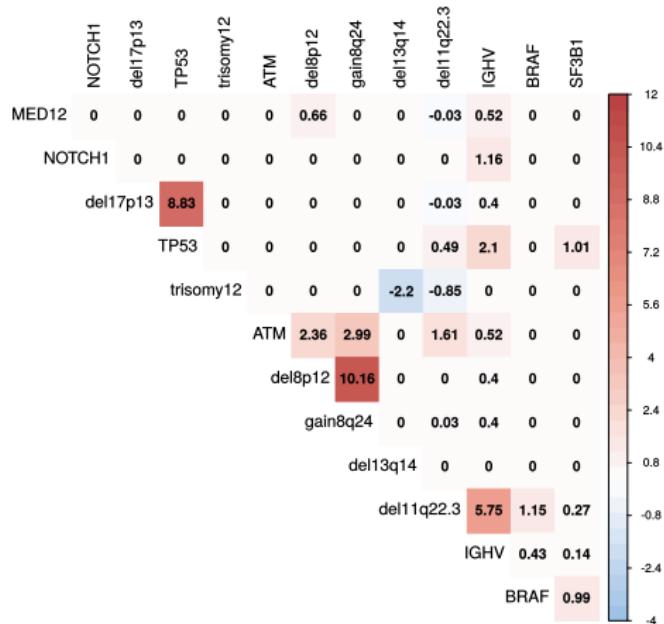
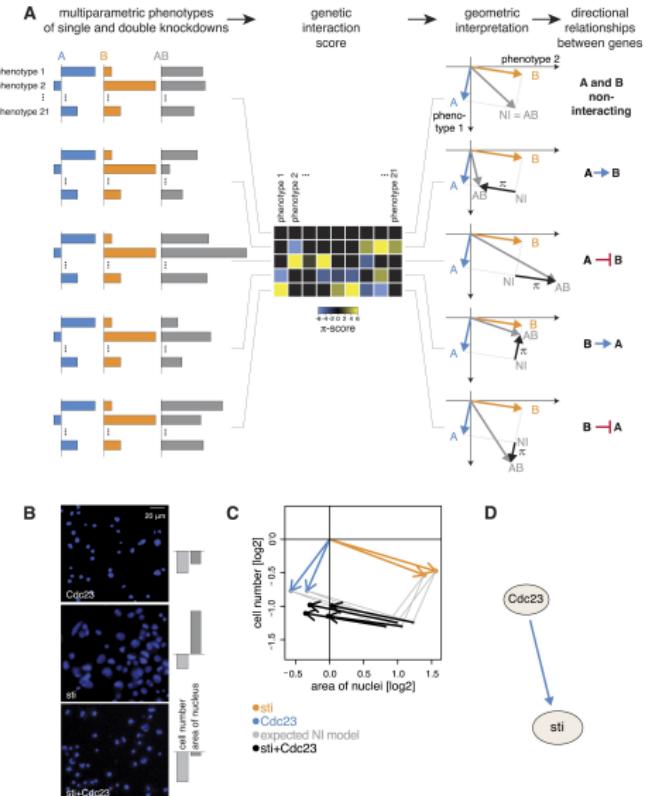


Figure: $-\log_{10}(\text{pvalue})$ for co-occurrence of genetic variants calculated by χ^2 -square test. The sign indicates the direction of association.

Directions of epistatic interactions by Fischer et al.



Outlook

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