

Systematic Expression Profiling of Chronic Lymphatic Leukemia Transcriptomes

Almut Lütge
European Molecular Biology Laboratory

SOUND Meeting

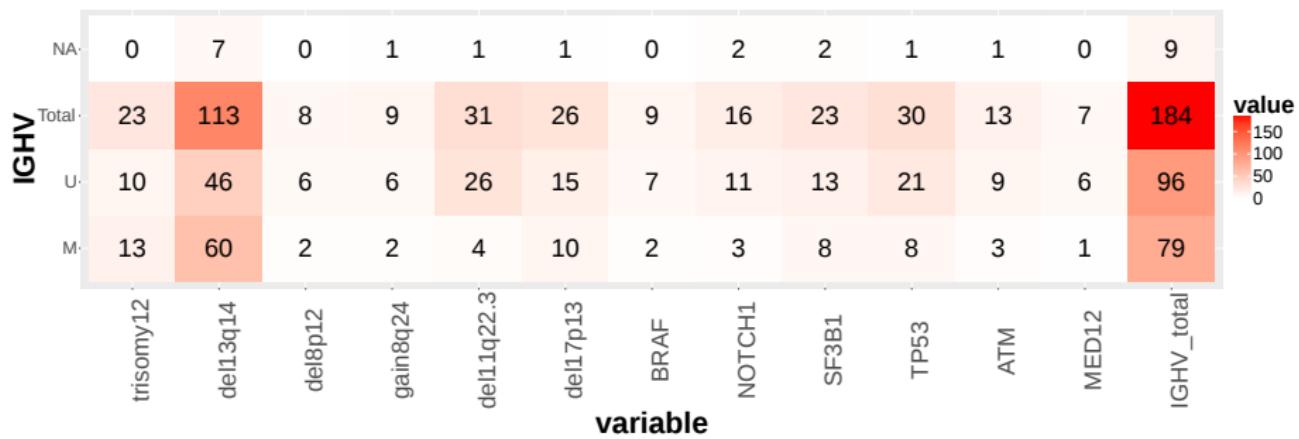
November 2018

Transcriptome analysis in Chronic lymphatic leukemia

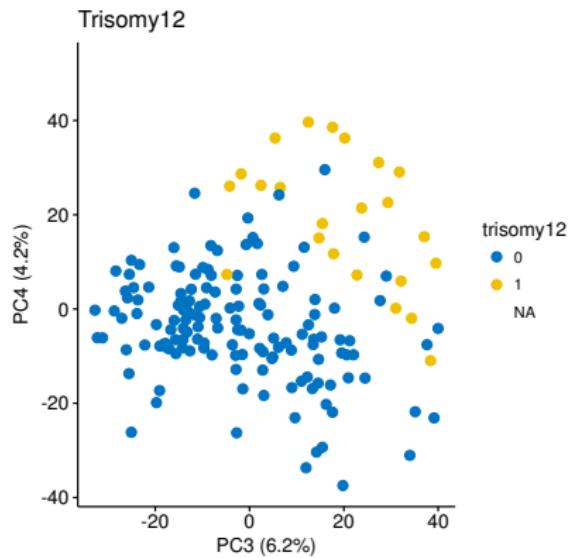
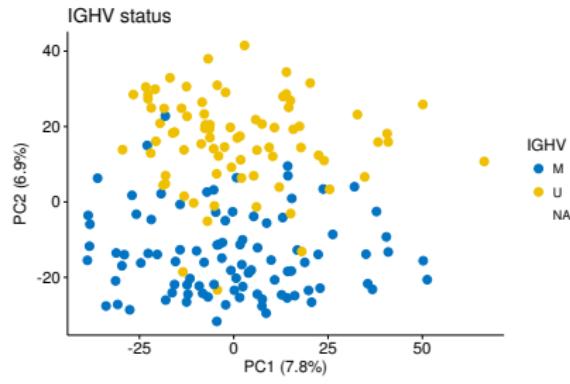
- Phenotypic and genotypic **heterogeneity**
- Identify underlying molecular mechanisms

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

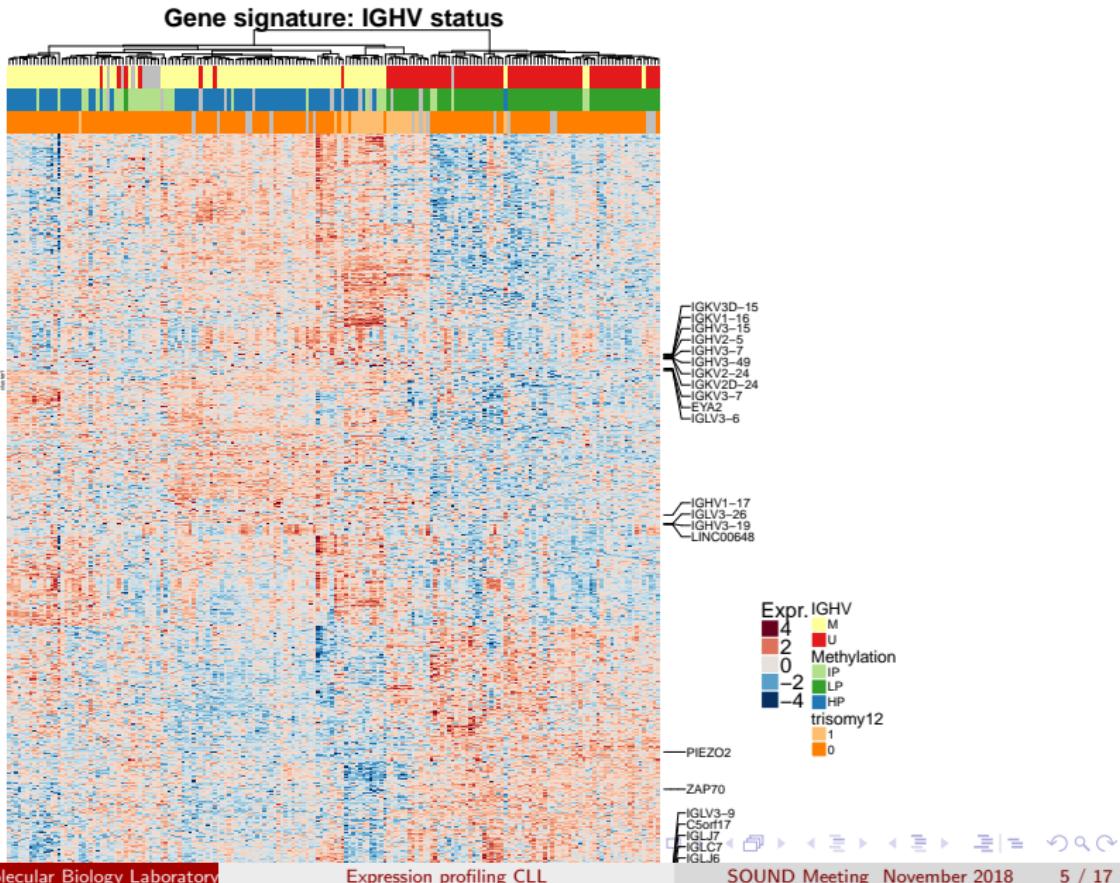
Genomic variants



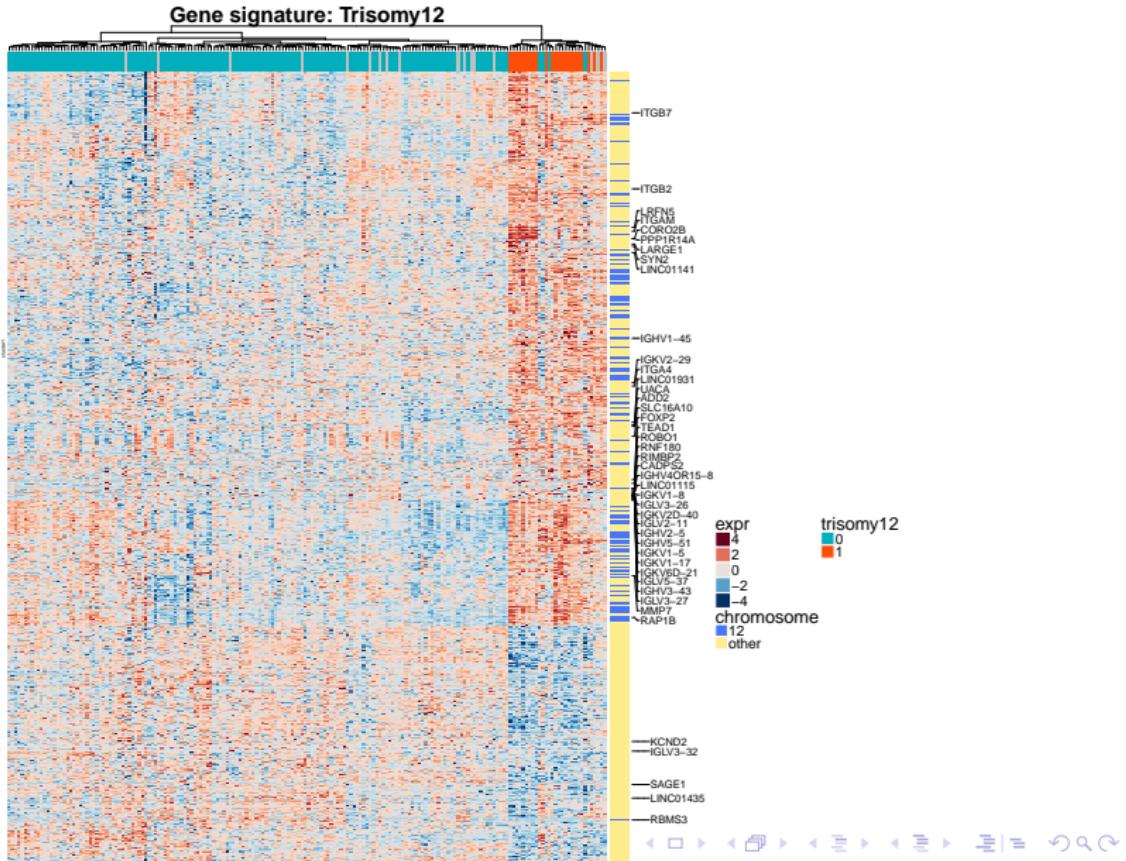
Principal Component Analysis



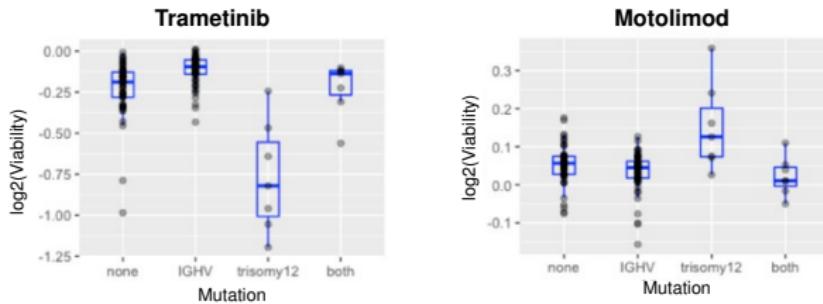
IGHV signature



Trisomy12 signature

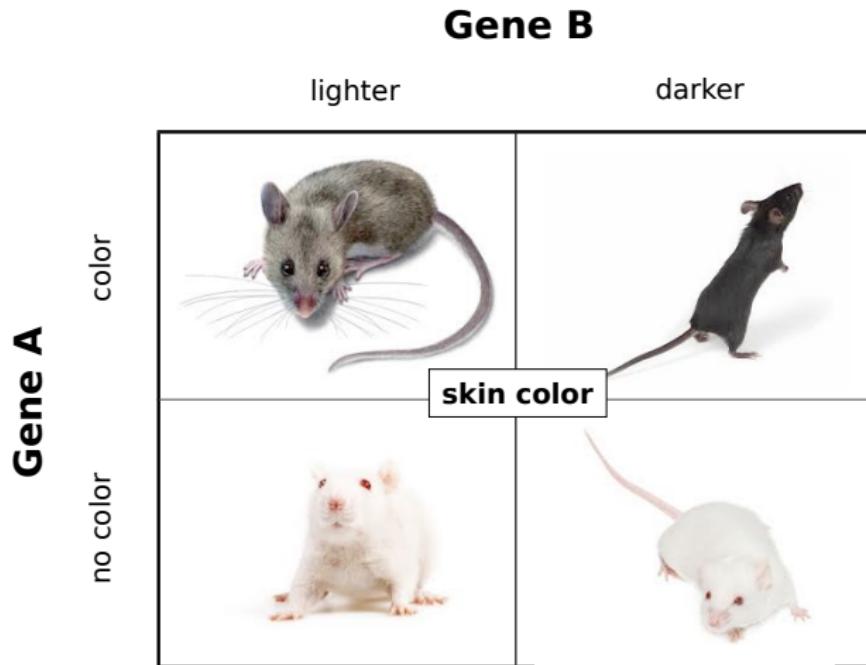


Tumor epistasis - drug sensitivity



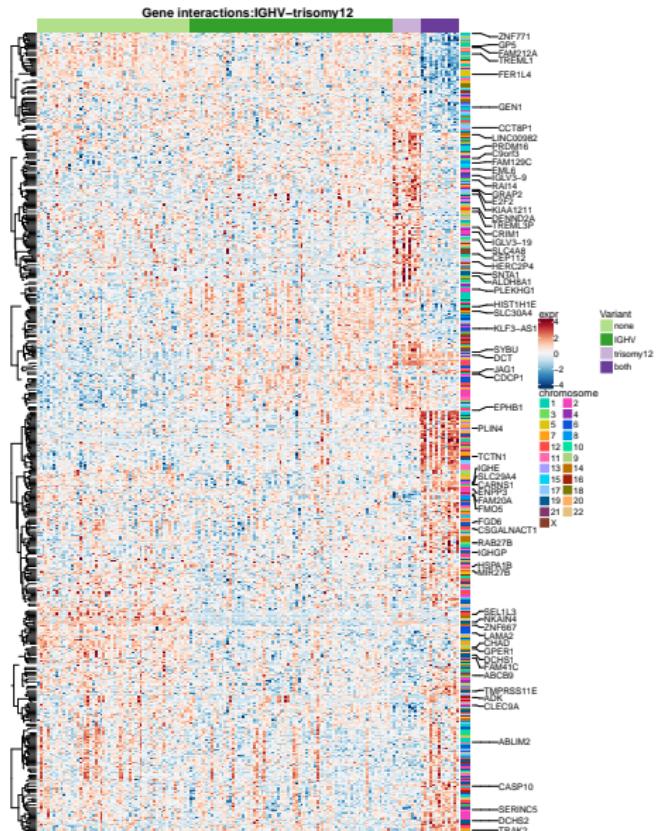
- Trisomy12 sample are less/more sensitive in M-CLL

Concept of epistasis



A is epistatic to B

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

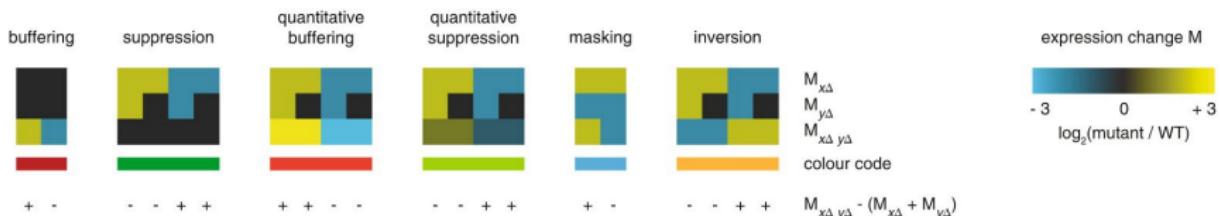
A high-resolution gene expression atlas of epistasis between gene-specific transcription factors exposes potential mechanisms for genetic interactions

Katrin Sameith, Saman Amini, Marian J. A. Groot Koerkamp, Dik van Leenen, Mariel Brok, Nathalie Brabers, Philip Lijnzaad, Sander R. van Hooff, 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.

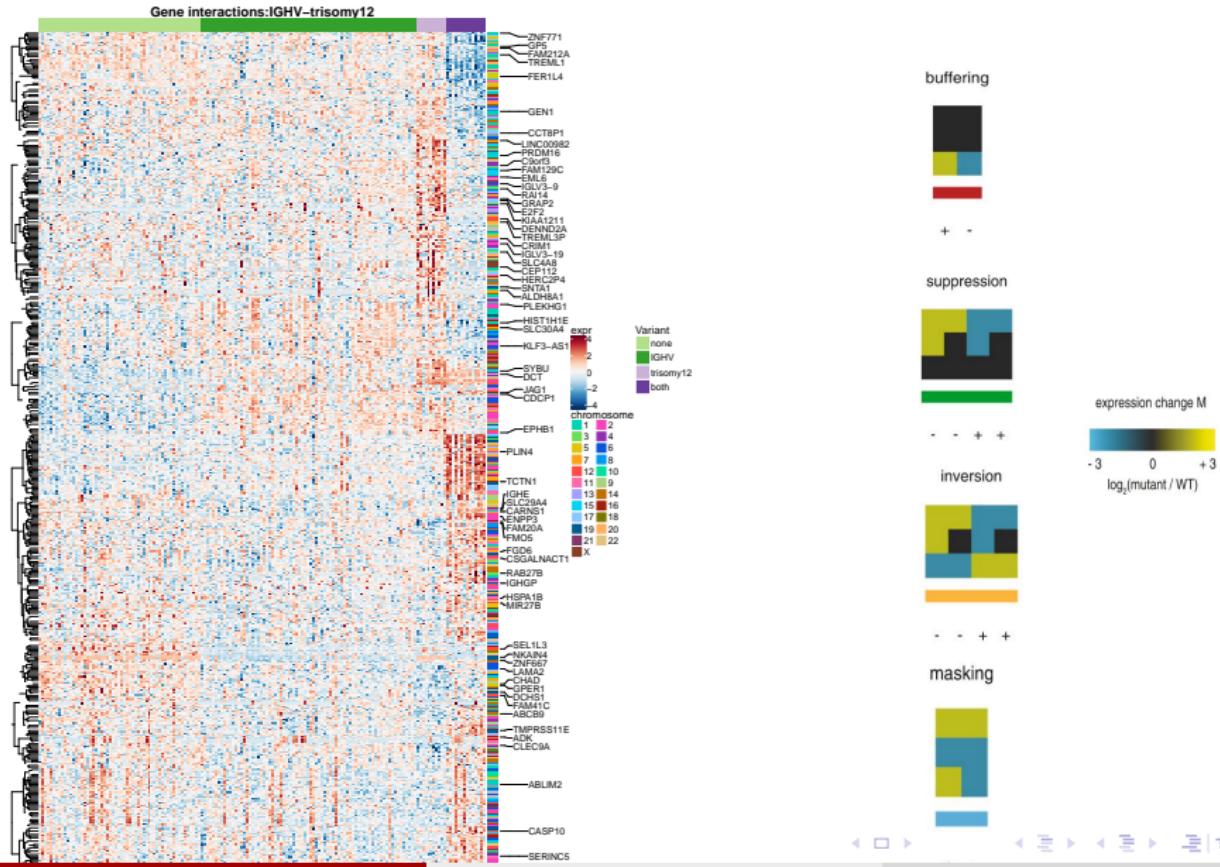
Functional overlap and regulatory links shape genetic interactions between signaling pathways.

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 Hooff SR, Bakker LV, Krogan NJ, Snel B, Holstege FC.

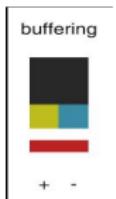
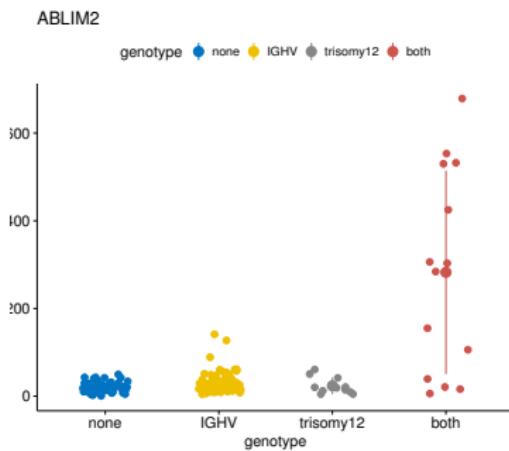
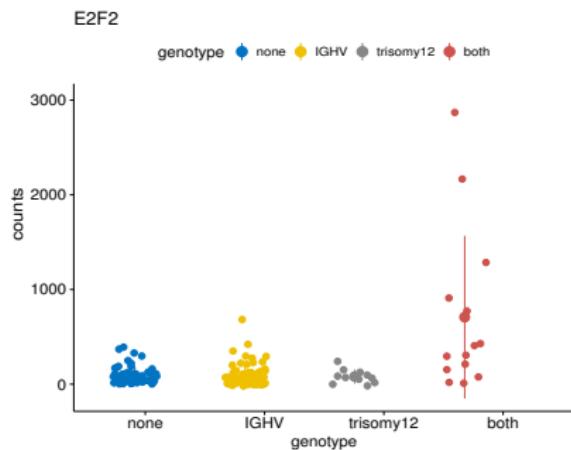


Mod. from Sameith et al.

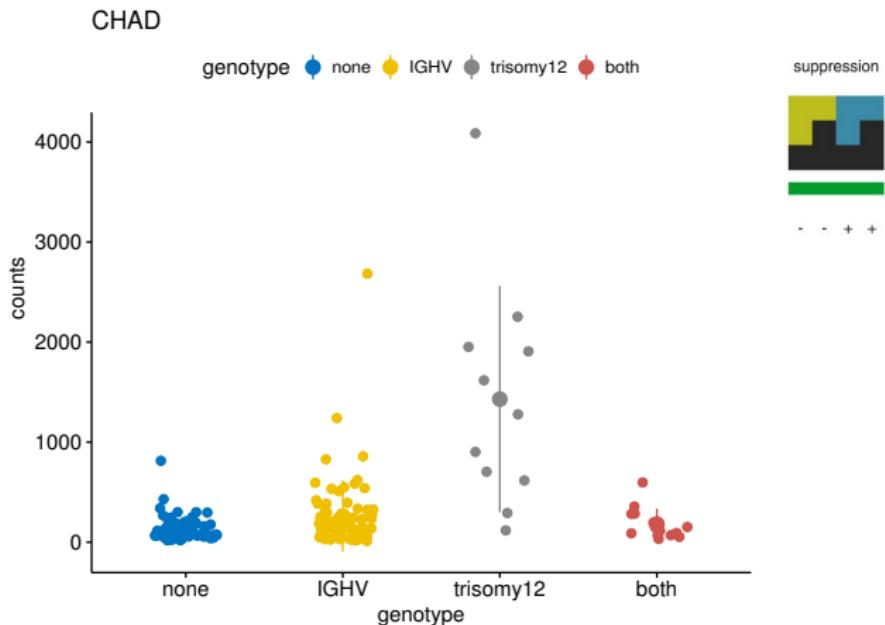
Epistatic interaction of Trisomy12 and IGHV



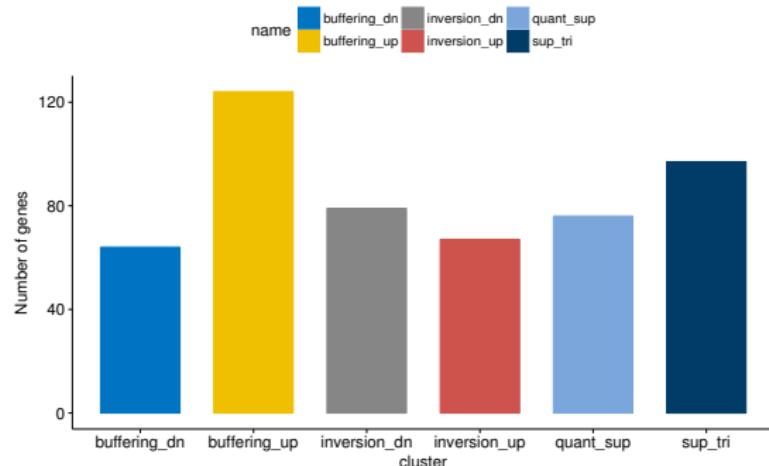
Buffering



Suppression



Mixed epistasis



Summary

- 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 (Feirreira et al. 2014)
- Differential gene expression pattern in 8 of 13 variants
- **Epistatic interaction between IGHV and Trisomy12**
 - ▶ mixed epistasis on gene expression level e.g. buffering, suppression...

Outlook

- What genes are represented by epistatic cluster?
- Do we find evidence for MEK/ERK pathway genes?
- Epistatic phenotypes in other datasets? metabolism?..

Thanks to ..

AG Huber

Wolfgang Huber

Simone Bell

Dorothee Childs

Jennifer Huellein

Vladislav Kim

Bernd Klaus

Junyan Lu

Andrzej Oles

Mike Smith

Arne Smits

Britta Velten

Cecile Le Sueur

Frederik Ziebell

Thomas Schwarzl

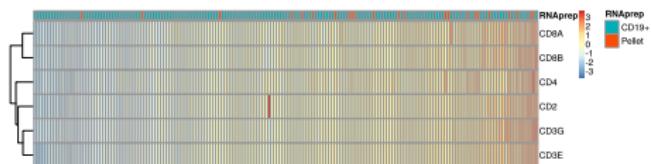
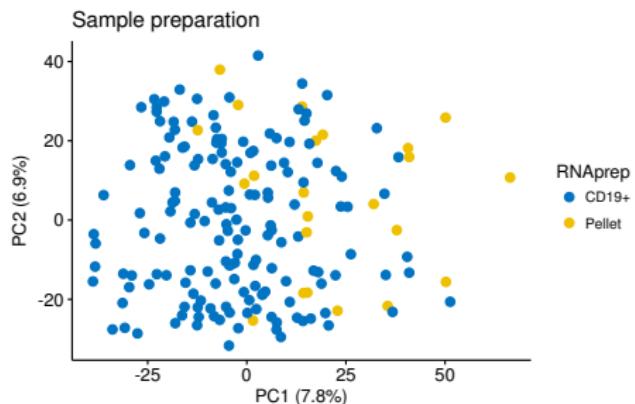
Matthias Schlesner

AG Zenz

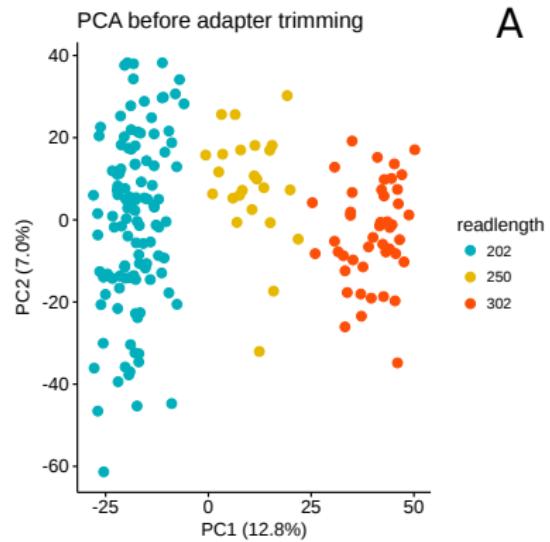
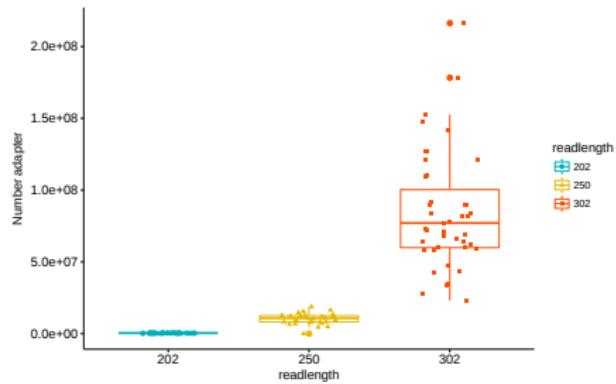
AG Dietrich



T cell contamination

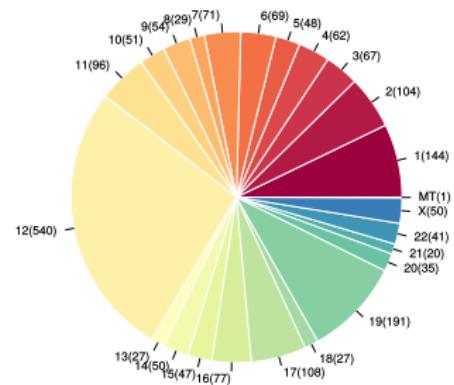


Adapter contamination

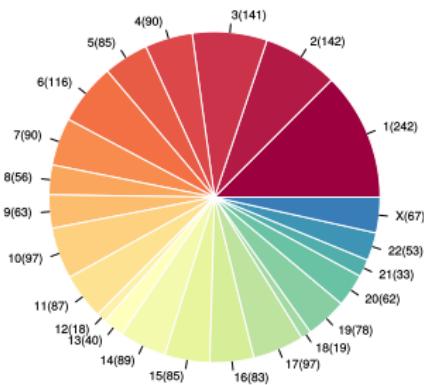


Trisomy12 signature

Chromosomal gene distribution in tri12: up

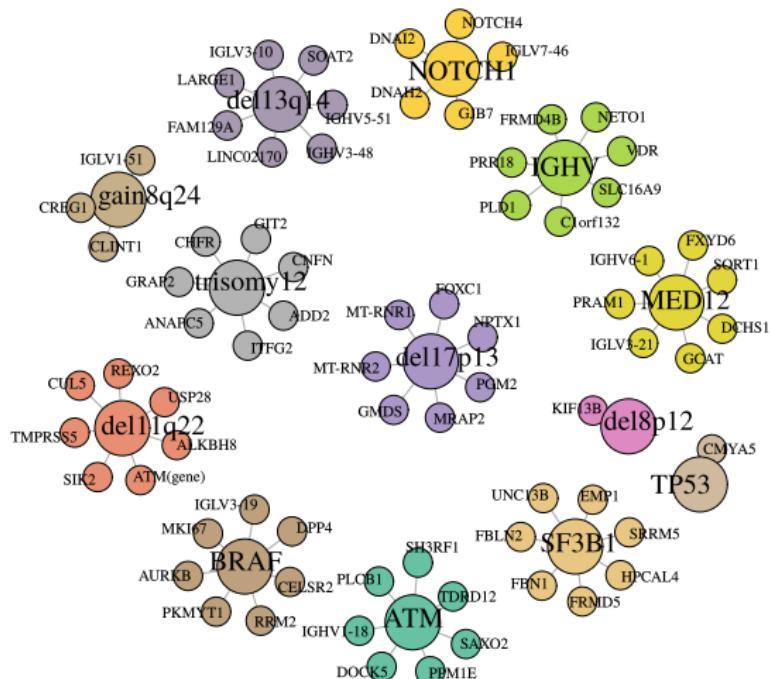


Chromosomal gene distribution in tri12: down

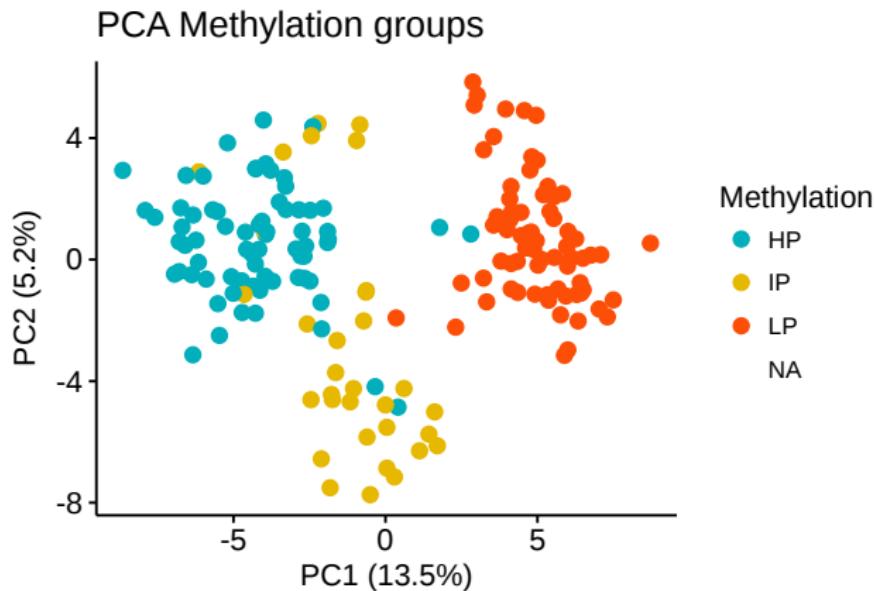


Multivariate model

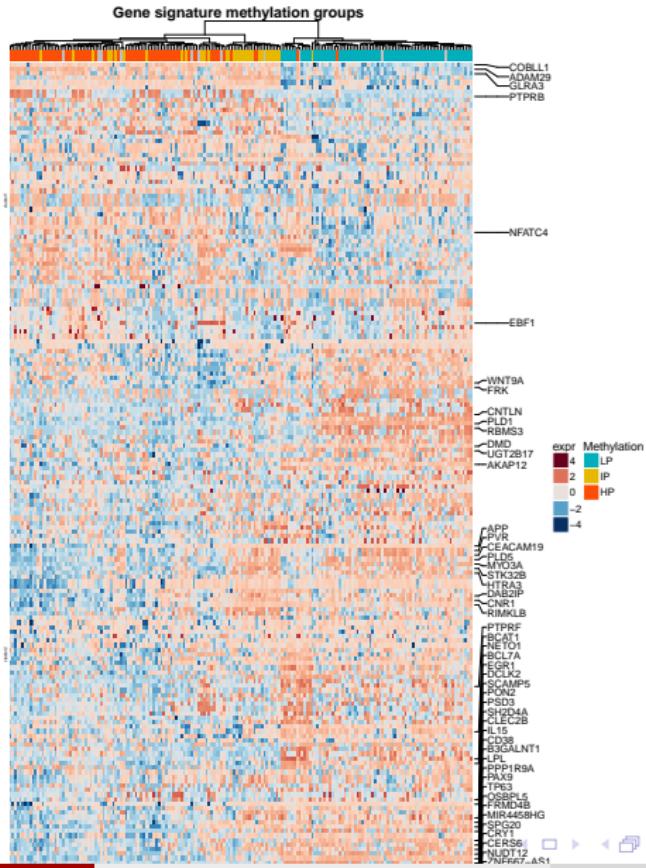
- Individual effect of each variant
- Likelihood ratio test of complete and reduced model



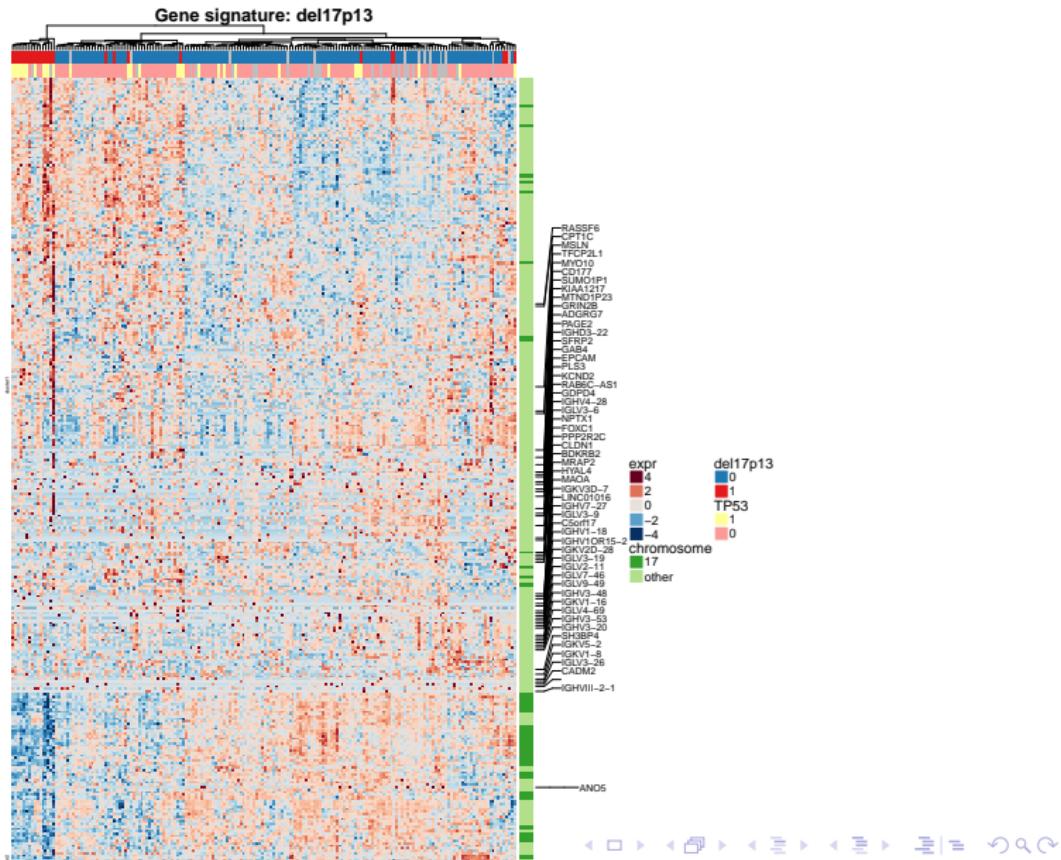
Methylation groups



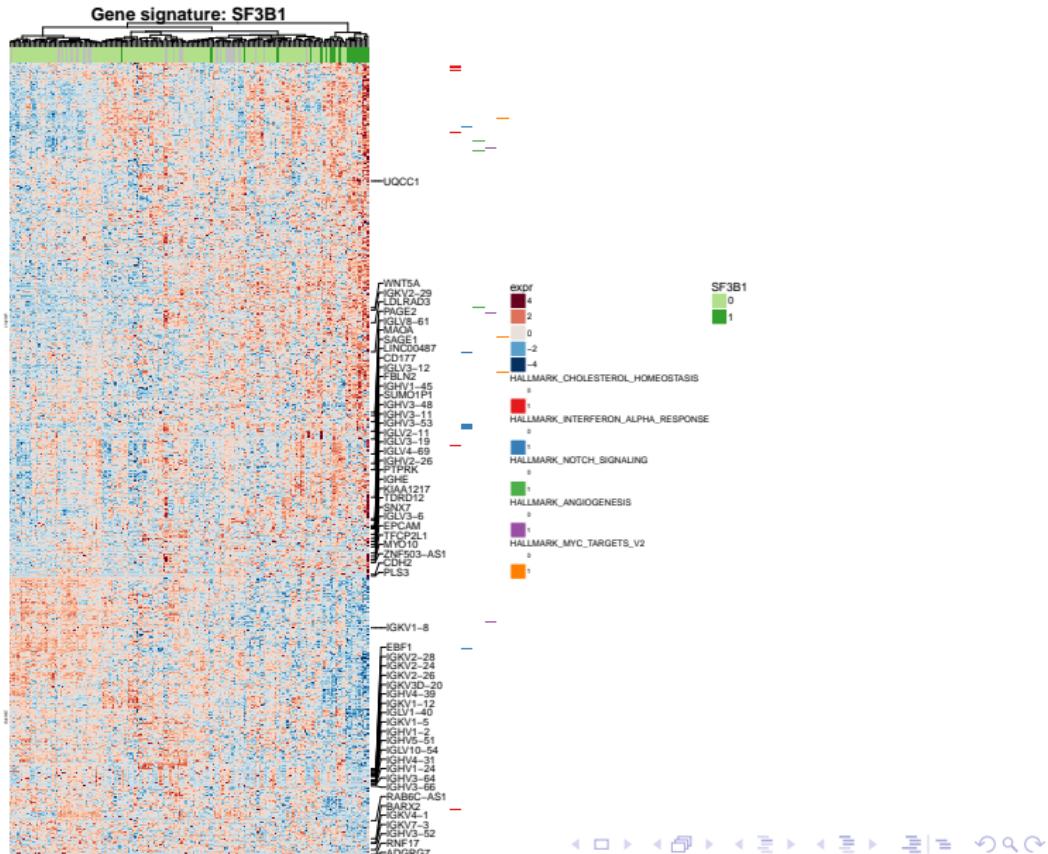
Methylation signature



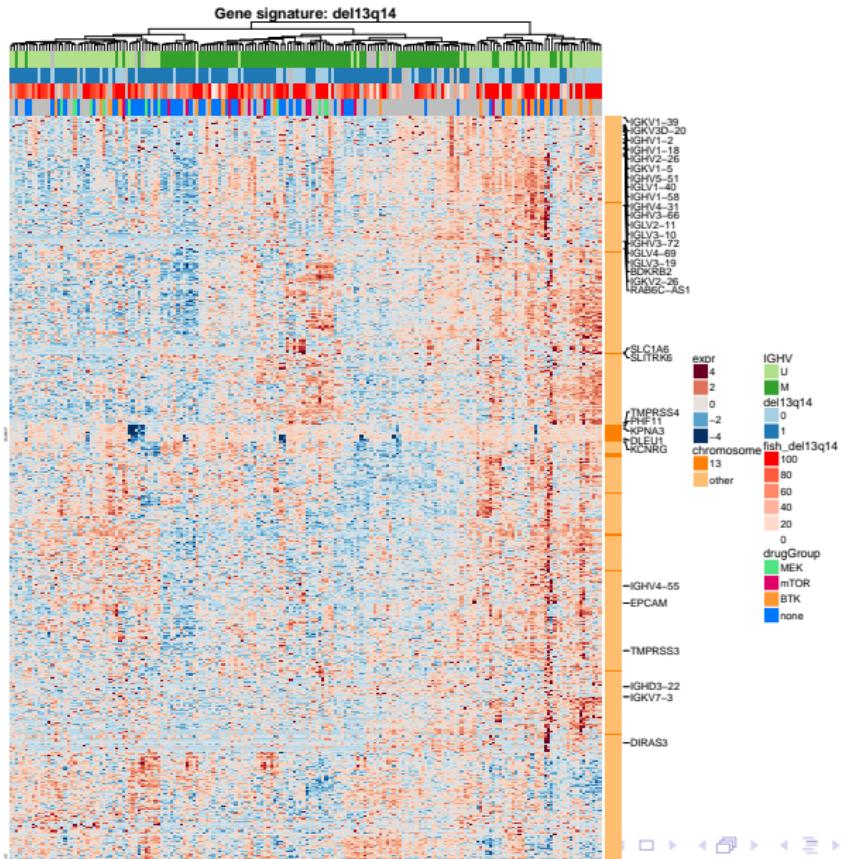
TP53/Del17p13



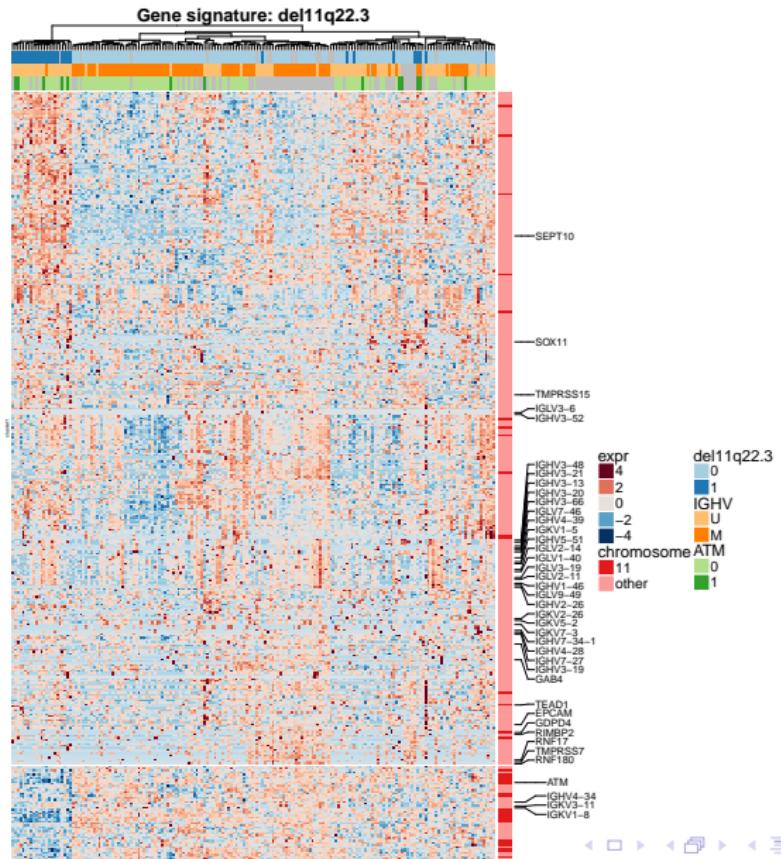
SF3B1 signature



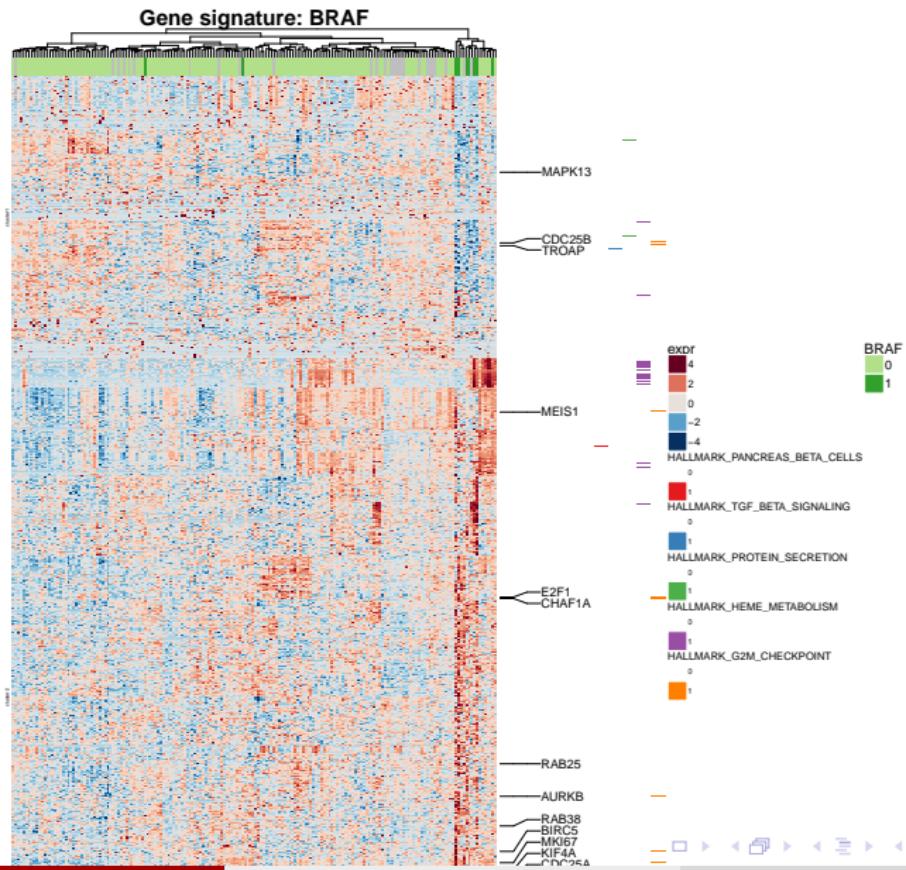
Del13q14 signature



Del11q22 signature



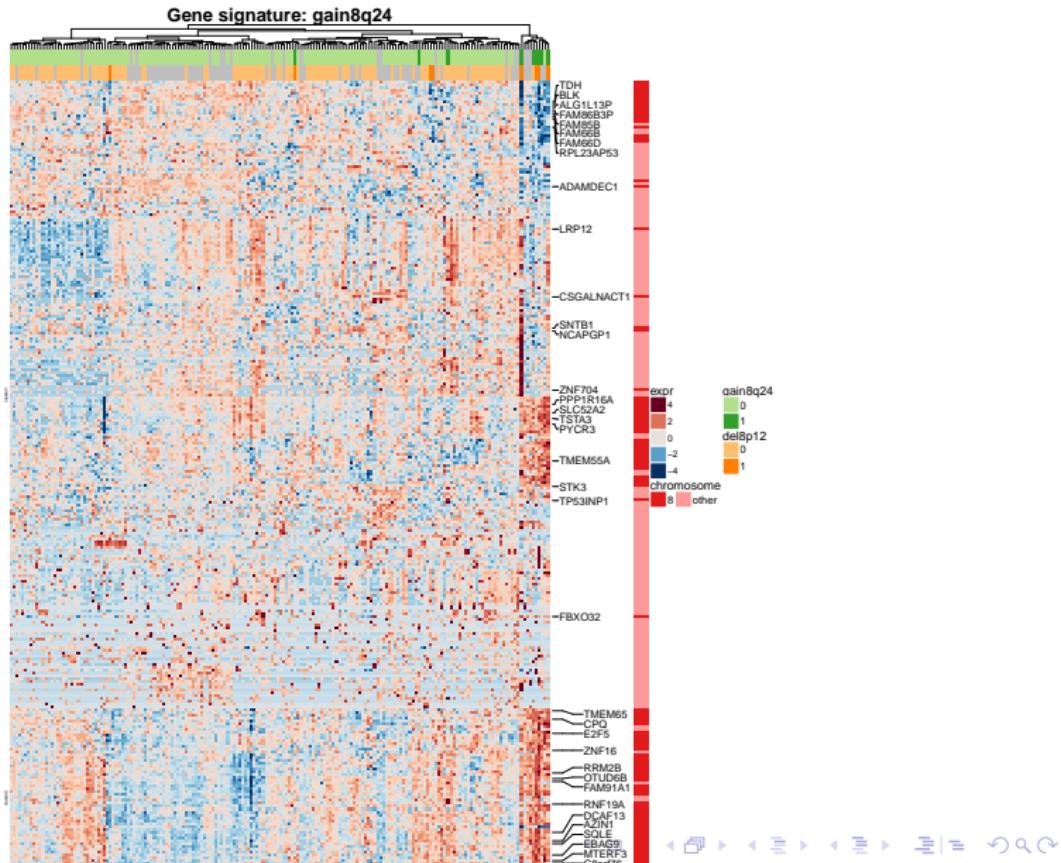
BRAF signature



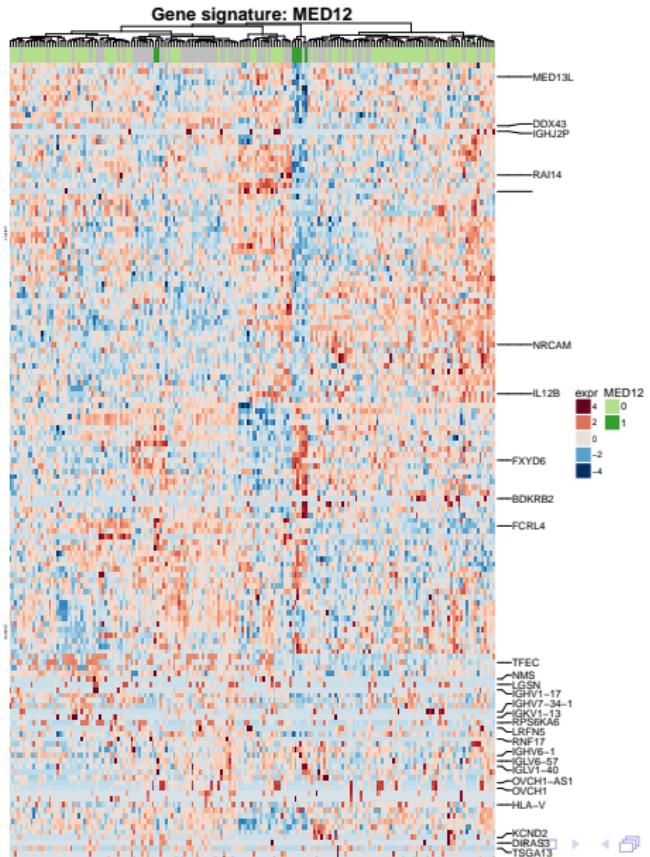
Notch signature



Gain8q24 signature



MED12 signature



Co-occurrence

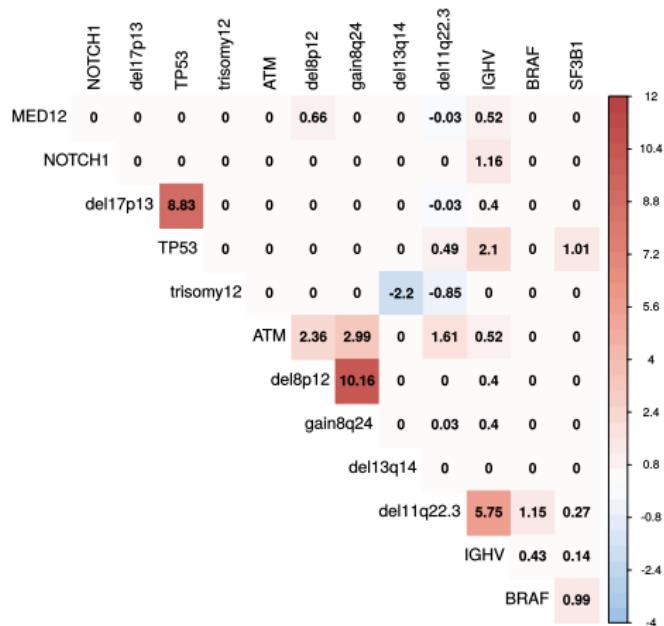
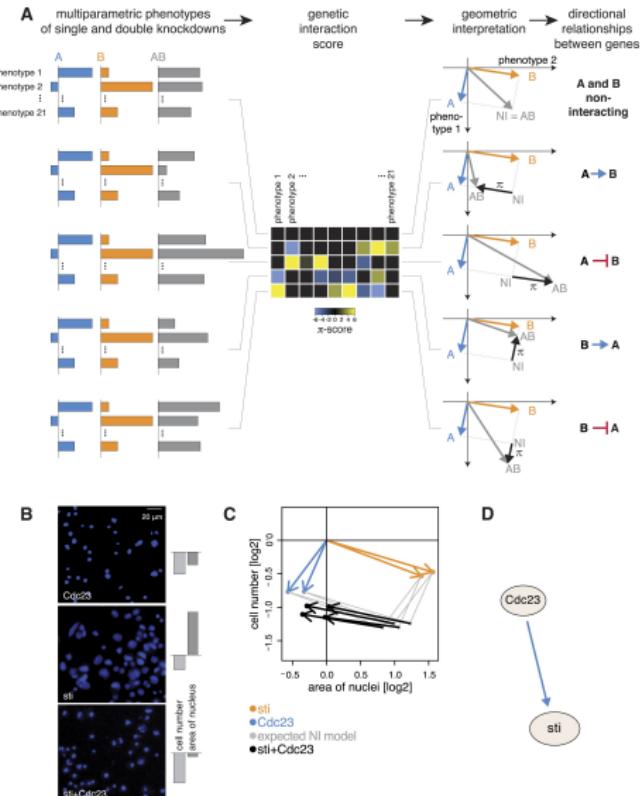


Figure: $-\log_{10}(\text{pvalue})$ for co-occurrence of genetic variants calculated by χ^2 -square test. The sign indicates the direction of association.

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