Genetic Screening Of CD30-Positive Lymphoproliferations

- Oncogenic mutations and gene fusions in CD30-positive lymphoproliferations and clonally related mycosis fungoides occurring in the same patients-

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Introduction & Objectives

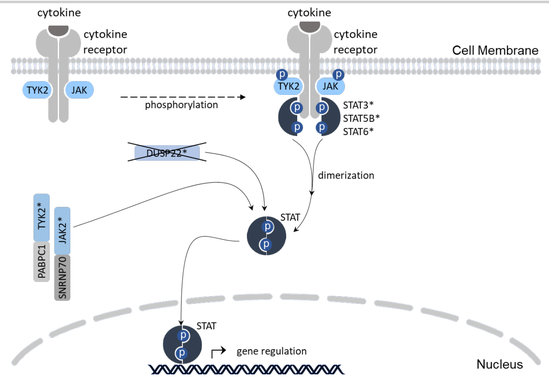
cALCL

- Single cases show *NPM1-TYK2 and TP63* translocations/rearrangements, very rare cases show *ALK* fusions
- Approx. 30% of cases harbor *DUSP22/IRF4* rearrangements

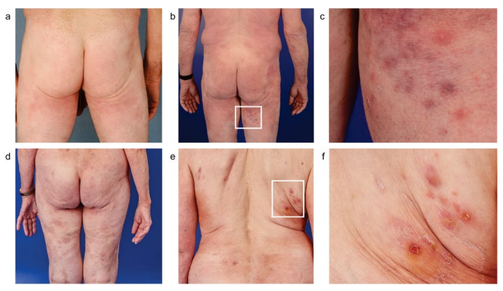
LyP

- Single cases show *NPM1-ALK*, *NPM1-TYK2* rearrangements
- 5% of cases show *DUSP22/IRF4 locus* rearrangements

Karai et al., Am J Surg Pathol. 2013; Feldman et al., Leukemia. 2009; Velusamy et al., Blood. 2014, Maurus et al. , JID. 2020, Melchers et al., Am J Surg Pathol. 2020



→ 50 % of LPD patients exhibit an activating genetic alteration within the JAK-/STAT-signaling pathway



- Two patients with concomitant or sequentially occurring distinct lesions of both CD30-positive LPD as well as CD30-negative MF
- Disease course of at least 5 years and a remarkably long follow-up of over 10 years in total
- corresponding well-documented clinicopathological correlation of each assessed lesion

→ to decipher the molecular alterations of clonally related CD30-positive LPD and MF occurring in the same two patients

Materials and Methods

DNA sequencing

Customer Panel 40 genes | 2 patients/ 16 samples

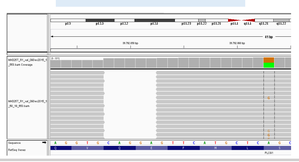
DNA extraction of cryo/FFPE tissue

library preparation → hybrid capture

Next Generation Sequencing (Illumina)

Data analyses and interpretation

Bioinformatics



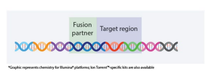
PubMed, Cosmic, ClinVar, dbSNP, onkoKB, Clvic …

mRNA sequencing

Fusion Panel 199 genes | 2 patients/ 9 samples

RNA extraction of cryo/FFPE tissue

library prep. → anchored multiplex



Next Generation Sequencing

Data analyses and interpretation

Archer Analysis Version 5.1.7

PubMed, Quiver…

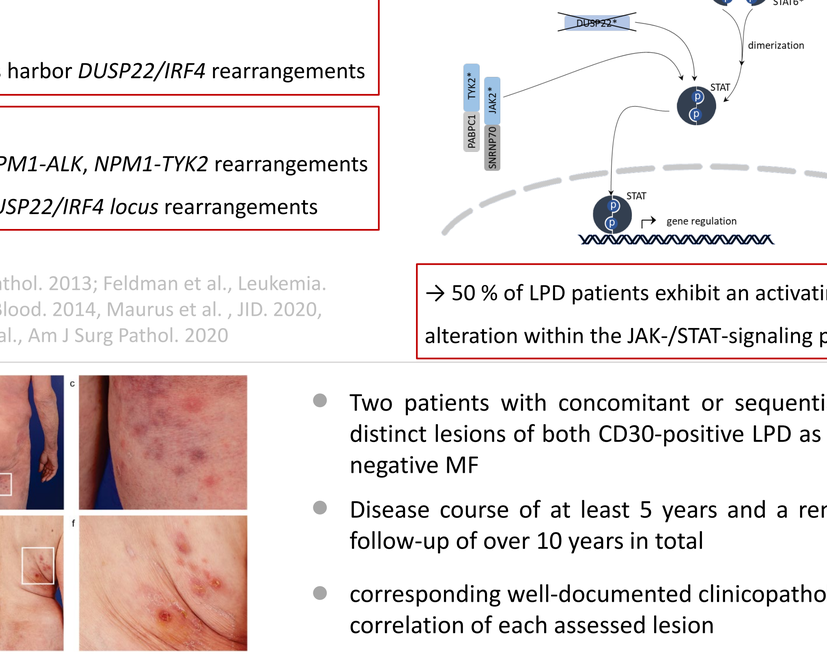
Results

Mutation prevalence

Customer DNA panel

→ whole exonic regions of 40 genes involved in B- and T-cell development and lymphomagenesis

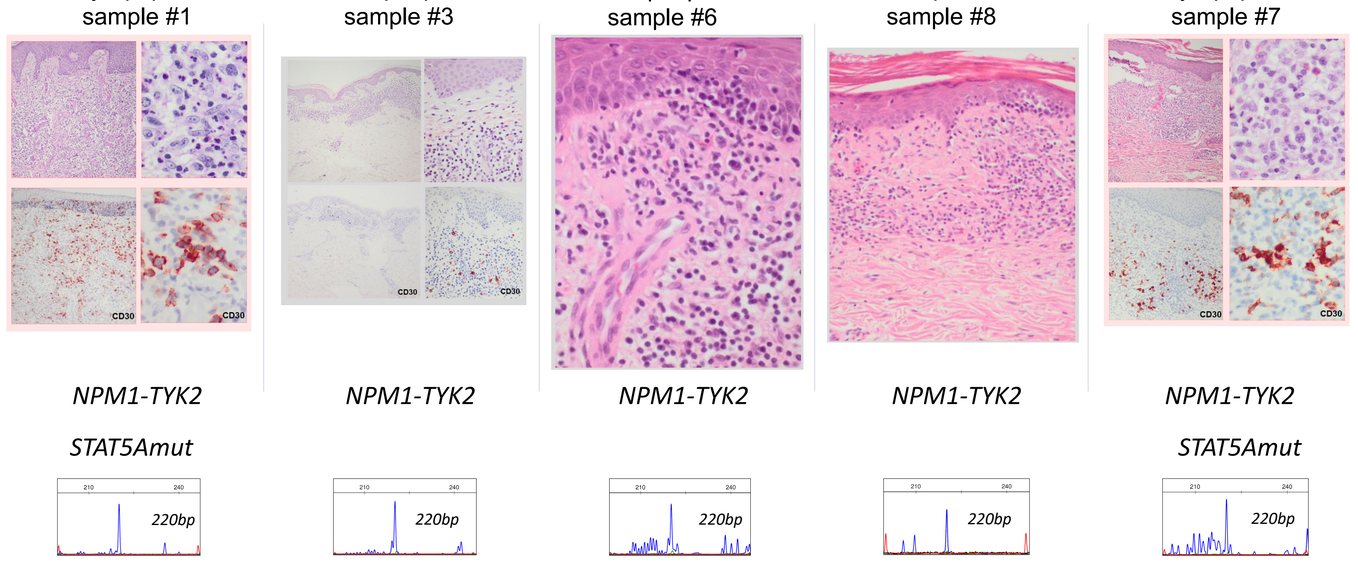
BCL2
CARD11
CCR4
CD79B
CDKN2A
CREBBP
DNMT3A
EP300
EZH2
FAS
FBXO11
FYN
IDH2
JAK1
JAK3
KDM1A
KIT
KMT2D
KRAS
MYC
MYD88
NOTCH1
NOTCH2
NRAS
PAX5
PDCD1
PIM1
PLCG1
PRDM1
RELB
RHOA
RHOH
STAT3
STAT5A
STAT5B
STAT6
TET2
TNFAIP3
TNFRSF14
TP53



→ patient 1 shows *STAT5A* mutations exclusively in CD30-positive lesions

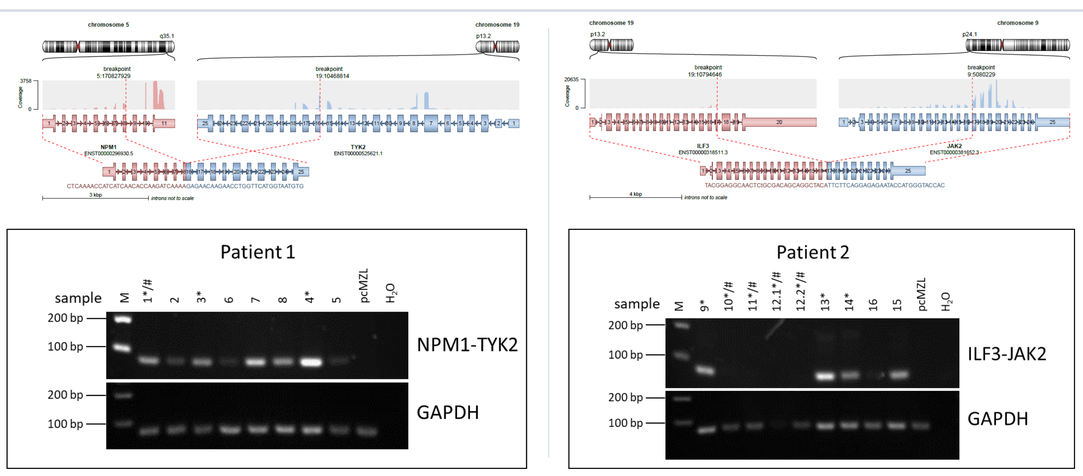
→ patient 2 shows divergent *PLCG1* and unifying *DNMT3A* mutations

Summary - Patient 1



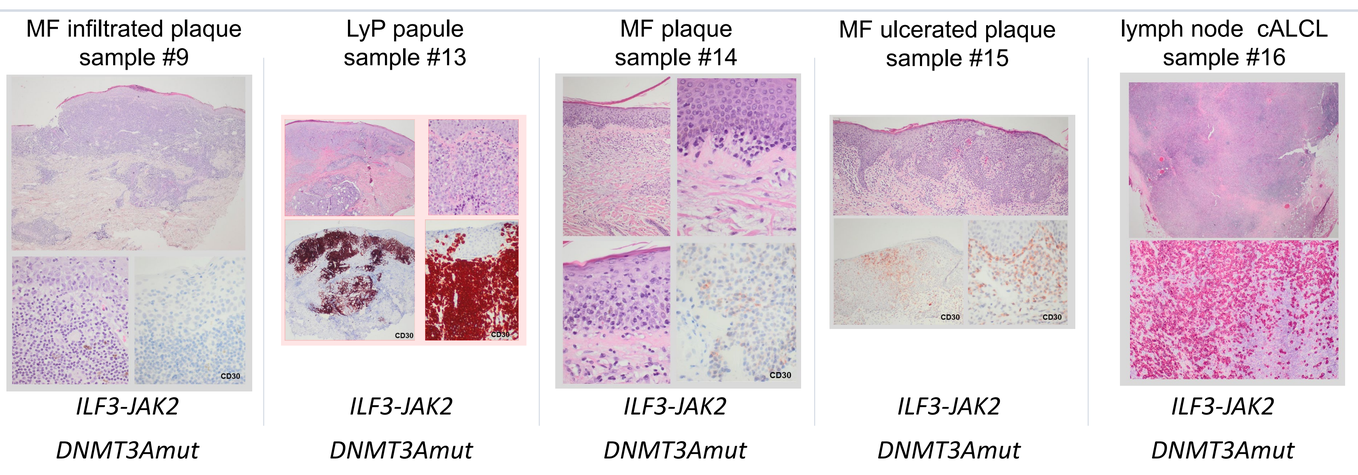
→ T-cell receptor analyses display cognitional monoclonal T-cell populations in MF and CD30-positive LPD (*TRG*)
→ RNA panel sequencing reveals unifying oncogenic *TYK2* Janus kinase fusion transcripts
→ Targeted DNA panel sequencing shows *STAT5A* mutations in CD30-positive LPD, but not in CD30-negative MF

Fusion prevalence



→ all lesions belonging to one patient, including MF, show identical Janus kinase fusion transcripts
→ oncogenic fusion transcripts comprise effector kinase domains of the Janus kinases *TYK2* and *JAK2*
→ oncogenic fusion transcripts contain dimerization domain of fusion partners

Summary - Patient 2



→ T-cell receptor analyses display cognitional monoclonal T-cell populations in MF and CD30-positive LPD (*TRG*)
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→ patient 2 shows divergent PLCG1 and unifying DNMT3A mutations

Conclusion

- LyP, cALCL and MF in the same patient share unifying genetic biomarkers, including T cell receptor rearrangements (*TRG*) and oncogenic Janus kinase fusion transcripts pointing to a common progenitor cell and a common genetic origin
- LyP, cALCL and MF in the same patient additionally show divergent genetic features; this might explain different evolutionary paths towards different entities
- *STAT5A* mutation in patient 1 is strictly associated with CD30 expression

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