# JAK-STAT pathway and epigenetic regulators - critical players in BI-ALCL pathogenesis

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## INTRODUCTION

Breast Implant-associated anaplastic large cell lymphoma (BI-ALCL) is a rare T-cell lymphoma arising in association with breast implant, particularly those with textured surfaces. We recently identified two histopathological BI-ALCL subtypes: *in-situ* and tumor-type which correlated with the seroma vs tumor mass clinical presentation, respectively. Although genetic events involving the *JAK/STAT* pathway have been reported and the putative role of local chronic inflammation has been suspected, BI-ALCL pathogenesis remains elusive. To further explore potential molecular mechanisms involved in the pathobiology of these two distinct BI-ALCL subtypes, we performed a genomic characterization of 34 such cases.

## METHODS

Fifty-four BI-ALCL patients have been diagnosed through the *Lymphopath* network and registered in the Lymphoma Study Association Registry from 2010 to 2018. Whole exome sequencing (WES) was performed on 22 samples of BI-ALCL and their matched germline DNA. Sequencing was performed on an Illumina HiSeq4000 with an expected mean depth of 200X and 70X for tumor and germline samples, respectively. Twenty-four BI-ALCL cases including 12 cases already analyzed by WES, were screened by target deep sequencing (TDS) with 500X average depth using the 406 genes FundationOne Heme panel.

## RESULTS

- Nineteen patients presented with *in situ* BI-ALCL whereas 15 were diagnosed with tumor-type BI-ALCL.
- Most patients had a favorable outcome except 3 patients who died of lymphoma progression.
- By immunohistochemistry, all cases were CD30 positive, showed an incomplete T-cell phenotype and a common activated cytotoxic profile. Neoplastic cells were often positive for EMA (90%) and ALK1 was consistently negative.
- Altogether, the entire cohort of 34 BI-ALCL cases sequenced by WES and/or TDS showed:

✓ Recurrent mutations of epigenetic modifiers in 74% of cases, involving notably *KMT2C* (26%), *CHD2* (15%), *CREBBP* (15%) and *KMT2D* (9%).

✓ Twenty cases (59%) showed mutations in at least one member of the JAK/STAT pathway including *STAT3* (38%), *JAK1* (18%), *STAT5B* (3%), and negative regulators like *SOCS3* (6%), *SOCS1* (3%) and *PTPN1* (3%).

✓ Mutations in genes involved in lymphocytes development such as EOMES (12%), PI3K-AKT/mTOR (6%) and loss of function mutations in *TP53* (12%) were also identified.

✓ JAK/STAT alterations were more frequent in tumor-type than *in-situ* samples (p=0.038).

- All BI-ALCL cases expressed pSTAT3 by immunohistochemistry, regardless of *STAT3* mutation status.
- *KMT2C* and *KMT2D* mutations were correlated with a loss of H3K4 trimethylation by immunohistochemistry.
- Copy number aberration (CNA) analysis identified recurrent alterations including gains on chromosomes 2, 9p, 12p and 21 and losses on 4q, 8p, 15, 16 and 20. Regions of CNA encompassed genes involved in the JAK/STAT pathway and epigenetic regulators as well.

**Figure 2 :** Functional pathways altered by mutations in BI-ALCL .

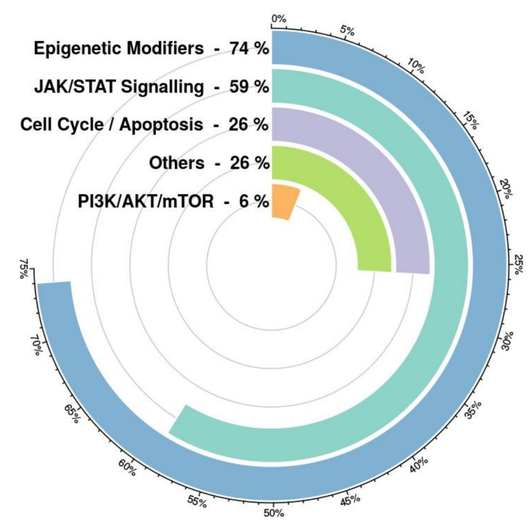



**Figure 1 :** WES and/or TDS of 34 BI-ALCL.

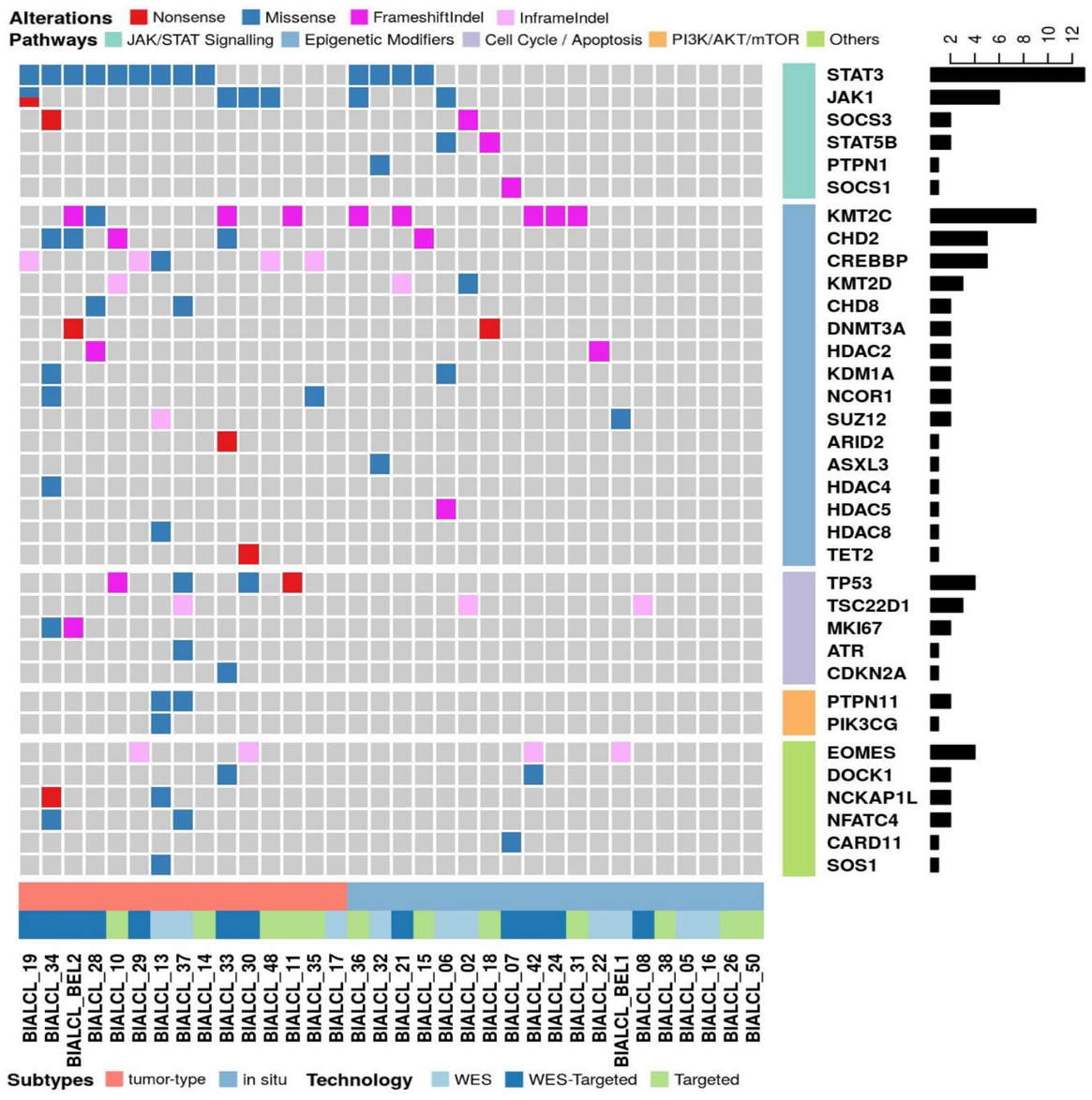



**Figure 3:** Mapping of protein variants produced by most frequent mutated genes.

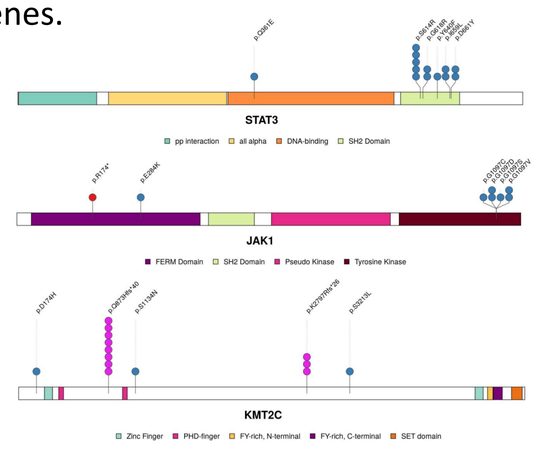



**Figure 4:** pSTAT3 and H3K4me3 immunostaining in BI-ALCL.

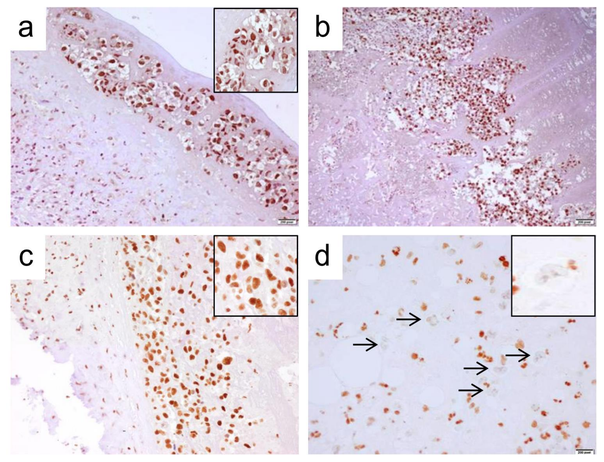
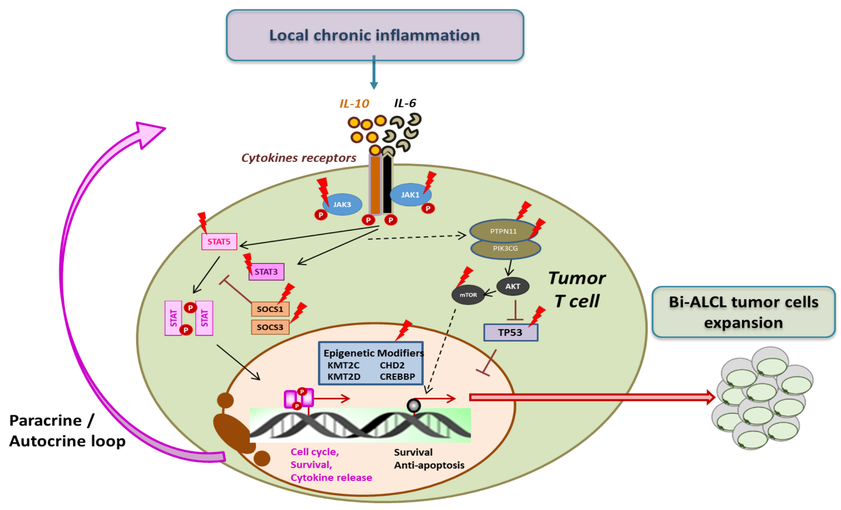



**Figure 5:** Hypothetical mechanisms involved in BI-ALCL pathogenesis.




## CONCLUSIONS

- Dysregulation of cytokine receptor signaling caused by recurrent mutations in the JAK/STAT pathway is a key event in BI-ALCL pathogenesis.
- The finding of STAT3 being less frequent mutated in *in situ* than in tumor-type cases suggests an injury continuum ranging from activation of JAK/STAT pathways through cytokine receptor-ligand interactions at the implant site, to the occurrence of JAK/STAT gain-of-function mutations.
- The frequent mutations in chromatin remodeling genes highlight the importance of epigenome and provide new insights into the complexity of BI-ALCL oncogenesis.

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