Sensitive detection of novel structural variants and 3D chromosome conformation suggests novel drivers including enhancer hijacking in AML

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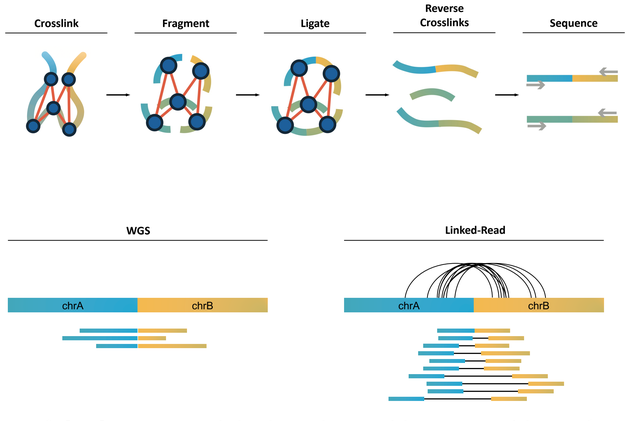
Background

Extensive characterization of the genetic landscape in AML has revealed a set of driver mutations sufficient to initiate leukemic transformation. However, some cases do not contain any of these known drivers and thus pose a clinical challenge for prognostication and targeted therapy. To address this, we employed a novel, proximity ligation based, linked-read whole genome NGS assay to identify single nucleotide variants (SNVs), short Insertions/Deletions (InDels), copy number variation (CNV), structural variants (SVs) and 3D genome contact maps in AML. By employing this approach, we investigate whether comprehensive detection of genetic alterations in conjunction with insights into the epigenetic state of leukemic cells can reveal important biological information in cases lacking canonical driver mutations.

Papaemmanuil, et al., NEJM 2016

Methods



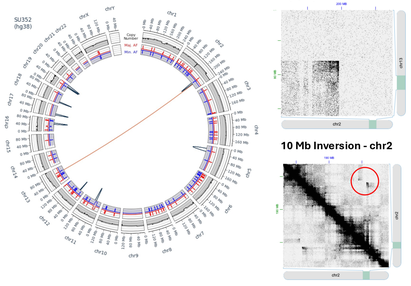
Potential advantage: Linked-reads provide more evidence for SVs enabling data points even at low sequencing depth

Results

Detection of previously unknown structural variants in AML

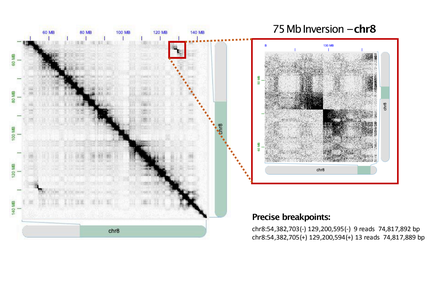
SU352

Sample	Panel Sequencing	Karyotyping
SU352	WT1 p.T365RGX	46, XX

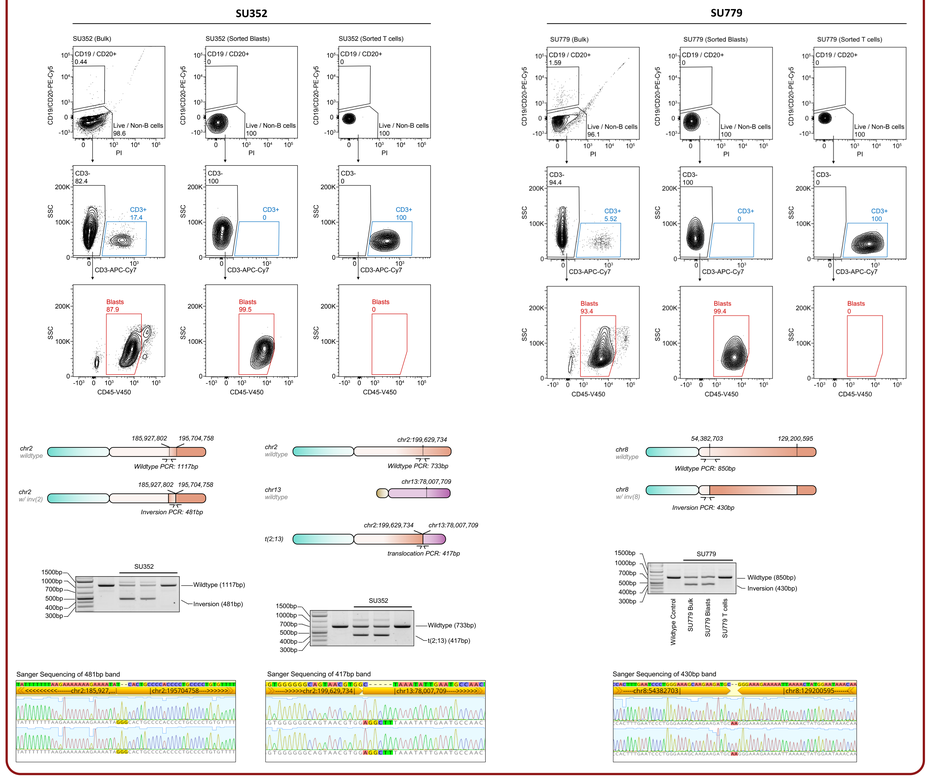


SU779

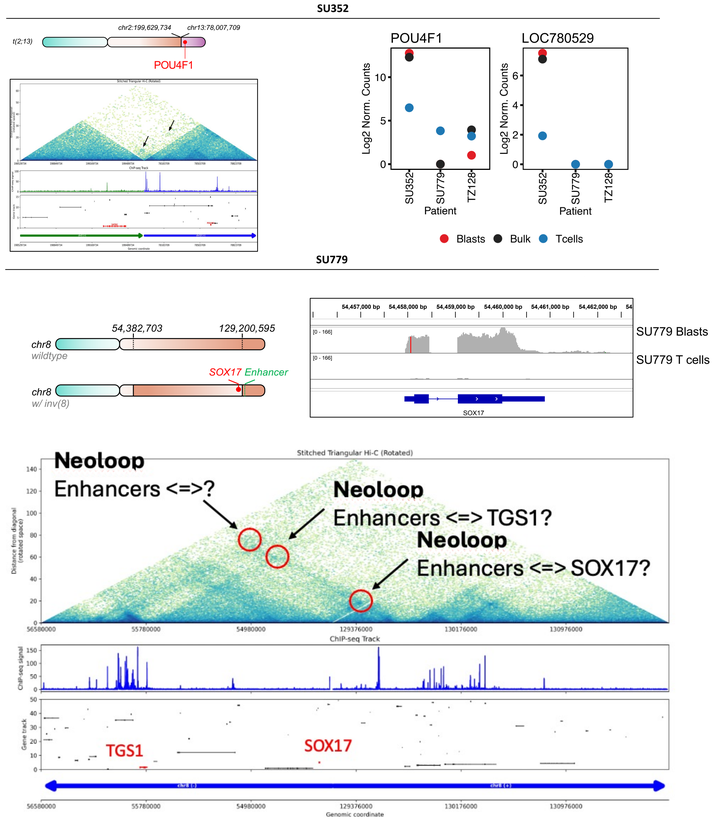
Sample	Panel Sequencing	Karyotyping
SU779	DNMT3A p.R882H TET2 p.V1157M	46, XX



Validation of NGS calls confirms presence of novel structural variants in leukemic clone



Gene expression dysregulation proximal to the SVs suggest potential changes in enhancer activity



Summary

- We find several otherwise undetected structural variants in AML cases without known driver lesions
- By not only detecting genomic variants but also analyzing the epigenetic state through 3D genome contact maps, we can interrogate the biological consequences of these genomic alterations
- The current understanding of the genomic landscape in AML might be underestimating a sizable number of structural variants, implying putative novel driver genes in AML pathogenesis.

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