LONG-READ PROFILING OF STRUCTURAL VARIANTS REVEALS MECHANISMS OF CHEMO-RESISTANCE AND PROGNOSTIC HETEROGENEITY IN ACUTE LYMPHOBLASTIC LEUKEMIA

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INTRODUCTION

Chemoresistance remains a major challenge in acute lymphoblastic leukemia (ALL) treatments, with survival rates for resistant patients falling below 30%. While molecular subtyping based on next generation sequencing (NGS) is a key prognostic indicator of B-cell precursor ALL (BCP-ALL), chemotherapy responses often do not align with expectations based on molecular classification. This discrepancy arises, in part, because certain cases of ALL are driven by structural variants (SVs), which NGS, with its short-read sequencing approach, struggles to detect particularly large insertions, deletions, and complex rearrangements.

AIM

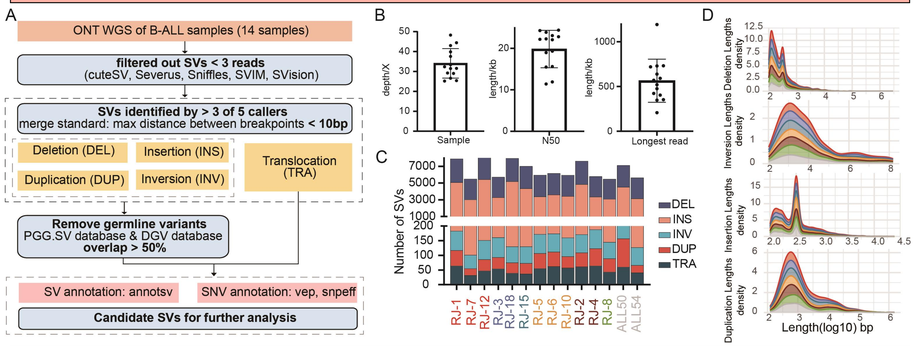
In this study, we performed long-read sequencing (LRS, third-generation sequencing) to identify functional SVs, aiming to elucidate their roles in chemo-resistance and prognostic heterogeneity within defined BCP-ALL subtypes.

METHOD

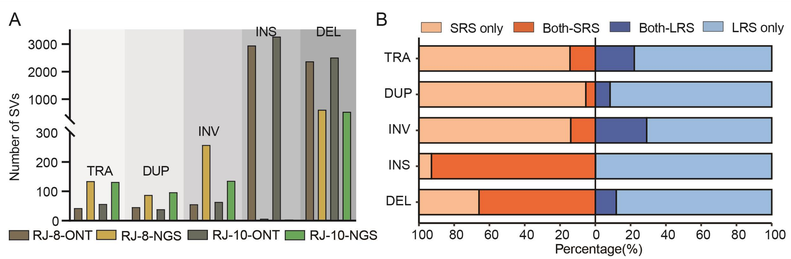
- We established a panel of patient-derived xenografts (PDXs), representing major BCP-ALL subtypes and employed long-read whole-genome sequencing for SV discovery.
- SV calling was carried out using an in-house bioinformatics pipeline that integrated 5 publicly available SV callers. Germline SVs were removed by comparison with the PGG.SV and DGV databases.

RESULTS

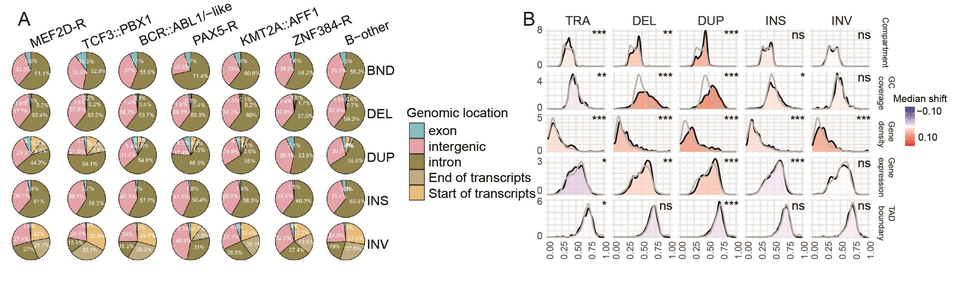
1. Generation of an ONT-based SV calling pipeline and frequencies of SVs in BCP-ALL



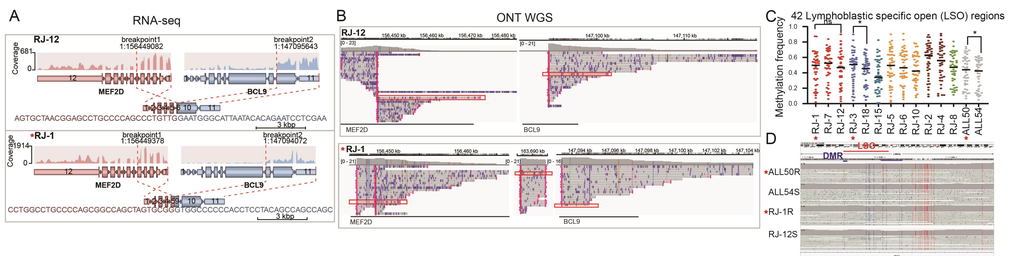
2. Comparison of ONT-based and SRS-based total SVs



3. Genomic distribution and functional features of ONT-based SVs



4. LRS enables complex SVs, methylation detection and reveals chemo-resistance heterogeneity



CONCLUSIONS

- This study identified SVs missed by short-read NGS in BCP-ALL and demonstrated the critical role of these SVs in intra-subtype heterogeneity of drug response across various ALL subtypes.
- Our findings suggest that SV-based stratification could enhance prognostic accuracy and guide therapeutic decisions, offering a novel precision-medicine framework for ALL that transcends traditional subtype definitions.

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