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Acute Leukemias

TARGETED DIGITAL ANALYSIS PROVIDES HIGH-RESOLUTION, CLINICALLY-RELEVANT COPY NUMBER ALTERATIONS AND ENABLES THE IDENTIFICATION OF HIGH-RISK LESIONS ALREADY KNOWN IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Acute lymphoblastic leukemia (ALL) is characterized by recurrent copy-number alterations (CNAs) and ploidy changes that influence risk assessment and therapy. Using a targeted digitalMLPA assay (NXtec D007 ALL), we evaluated the detection of focal CNAs, whole-chromosome abnormalities, and ploidy changes, including cases with non-informative karyotypes or genetic events leading to fusion transcripts.

Methods: We applied the digitalMLPA assay NXtec D007 ALL (MRC Holland; copy number probes covering 73 genes plus 250 karyotyping probes) to 215 adult B/T-ALL cases. dMLPA results were compared with those of conventional cytogenetics and molecular tests (karyotype, MLPA, SNP array, and IKZF1-PCR) when available. In 171 cases, parallel RNA-seq and fusion detection were performed using a four-tool in-house pipeline to assess whether intrachromosomal dels generate fusion transcripts.

Results: After exclusion of 43 failed/unevaluable samples (11 of which exhibited hyper/hypodiploidy), 192 cases remained (170 B-ALL, 15 T-ALL, 3 MPAL, 2 AUL). dMLPA identified CNAs in 86% of cases (Figure 1A). Whole-chromosome dels occurred in 5.8% (predominantly chromosomes 7 and 9); hyperdiploidy was observed in 17.3% (notably chromosomes 8, 10, 14, 21, X) (Figure 1B,C). IKZF1 dels were detected in 37% (71/192), including 40 cases with an IKZF1plus profile. MTAP, a prognostic marker linked to PRMT5i response, was co-deleted with CDKN2A/B in 62 cases. Dels of ETV6, BTG1, and RB1 were found in 12%, 12%, and 10.4% of cases, respectively. BTLA and CD200 were deleted in 15 and 16 cases (co-deletion was common; only 4 cases lacked co-deletion). NR3C1 deletions, implicated in glucocorticoid resistance, were present in 7.5% of diagnostic samples and 23.9% of relapses, showing a significant association with relapse ($p = 0.0067$). Amplifications and dels affecting the iAMP21 locus and the PAR1 region were also observed (Fig. 1D). Comparison with RNA-seq indicated that frequent PAR1 region fusions (e.g.CRLF2-CSF2RA, P2RY8-CD99) are not primarily driven by CN changes (Figure 1B). A recurrent PAX5–ZCCHC7 deletion was detected in 29 patients, persisted in all six available diagnosis–relapse pairs, and was shown to generate a fusion transcript in 3 cases.

Conclusions: Targeted dMLPA provides high-resolution, clinically actionable CNA and ploidy profiling in adult ALL, including cases with non-informative karyotypes. It reliably detects established high-risk lesions (e.g.IKZF1/IKZF1plus), codels with therapeutic relevance (MTAP/CDKN2A/B), and recurrent deletion events that can produce fusion transcripts (e.g.PAX5–ZCCHC7). However, a limitation in accurately detecting aneuploidies requires further validation and methodological refinements. Ongoing analyses, integrating orthogonal data, aim to improve interpretation, increase assay reliability, and expand clinical utility for better risk stratification and personalised treatment.

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ACUTE LEUKEMIAS

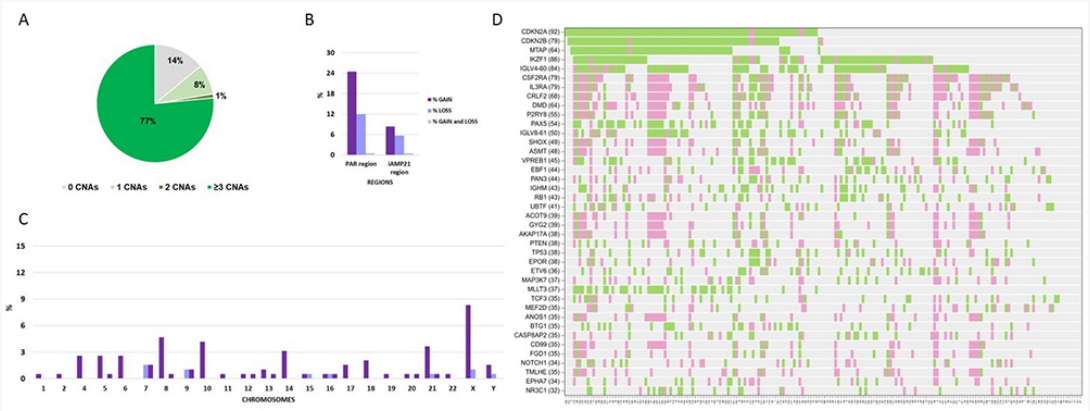

Fig. 1 (A) Pie chart illustrating the proportion of cases with and without CNAs. (B,C) Distribution of ploidy status alterations. (D) Heatmap illustrating the most recurrent copy number alterations in the cohort of 192 adult B-T ALL cases. The figure displays the 40 genes that show the highest frequency of modifications within the analysed samples.