**Adult low hypodiploid acute lymphoblastic leukemiaemerges from pre-leukemic *TP53*-mutant clonal hematopoiesis**

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**Supplementary data**

**Supplementary Figures**

**Supplementary figure 1. Sequencing-based analysis of CNA and LOH in adult LH-ALL.**

**Supplementary figure 2. Representation of mutations in the frequent targeted genes in adult LH-ALL.**

**Supplementary figure 3. Longitudinal assessment of *TP53*-mutant cell fraction as determined by ddPCR along with clonal *IG/TR*-based MRD quantification in three patients with undetectable *TP53* mutation at remission.**

**Supplementary figure 4. Merged single-cell analysis of cell-surface markers by ADT-sequencing of remission samples from three LH-ALL patients.**

**Supplementary figure 5. Individual single-cell analyses of cell-surface markers by ADT-sequencing of remission samples from three LH-ALL patients.**

**Supplementary figure 6. Individual analyses of single-cell immunophenotyping and genotyping of remission samples from three LH-ALL patients.**

**Supplementary figure 7. Evaluation of allelic dropout rate on heterozygous single nucleotide polymorphism (SNPs) in remission samples.**

**Supplementary figure 8. Individual single-cell analysis of cell-surface markers by ADT-sequencing of diagnosis samples from three LH-ALL patients.**

**Supplementary figure 9. Single-cell genotyping of heterozygous SNPs allowing LOH assessment in diagnosis samples from three LH-ALL patients.**

**Supplementary Figure 10. Distribution of single-cell genotypes of two LH-ALL patients with persistent *TP53* and *JAK2* (EI\_046) or *DNMT3A* (EI\_035) mutations in remission samples.**

**Supplementary Tables (see attached file)**

**Supplementary Table 1. Karyotypes of LH-ALL patients at diagnosis**

**Supplementary Table 2. Somatic variants detected in LH-ALL patients at diagnosis**

**Supplementary Table 3. ARCH related variants detected in LH-ALL patients at remission**

**Supplementary Table 4. Minimal residual disease values of remission samples used for mutation analysis**

**Supplementary Table 5. Somatic alterations in cell populations from diagnostic samples (BMMC) based on single-cell analyses**

**Supplementary Table 6. Somatic alterations in FACS-sorted cell populations from diagnostic samples**

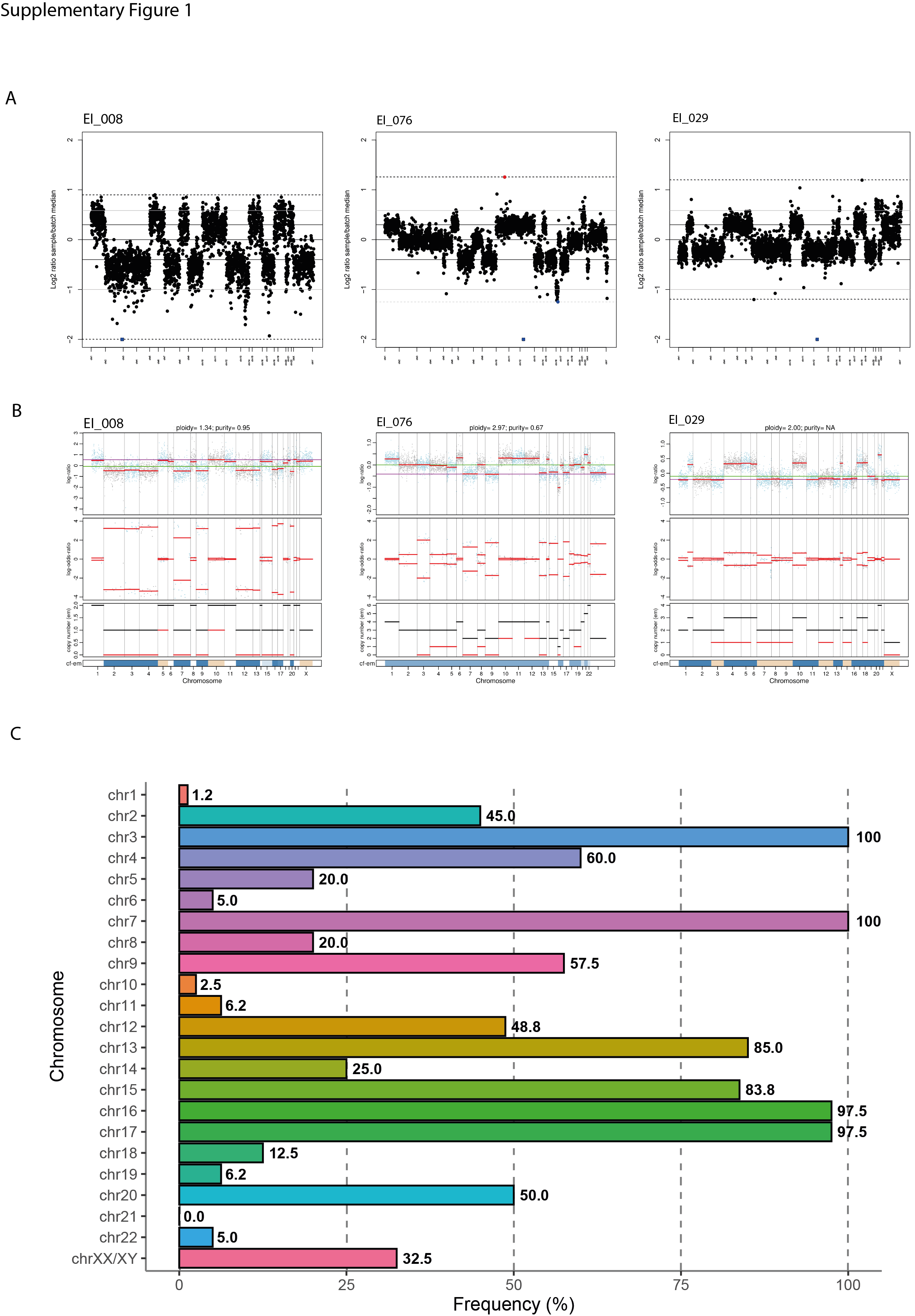
**Supplementary Table 7. Panel of genes for targeted sequencing**

**Supplementary Table 8. Single cell DNA amplicons for genotyping and LOH analyses**

**Supplementary Table 9. Single cell DNA amplicons for B-ALL clono-specific IG/TR detection**

**Supplementary Table 10. ADT-seq panel and spike-in antibodies**

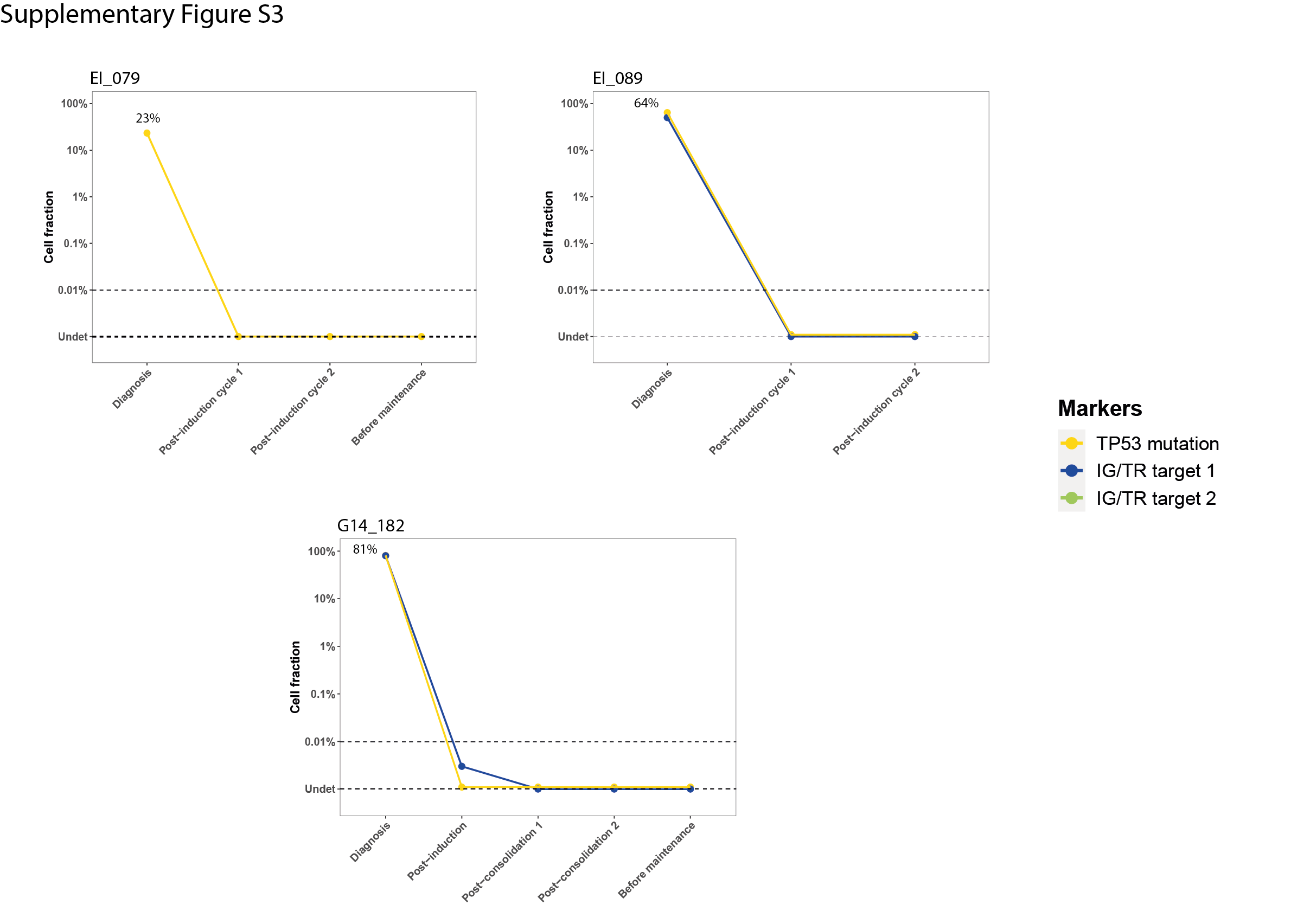
**Supplementary Table 11. Single cell sequencing metrics**



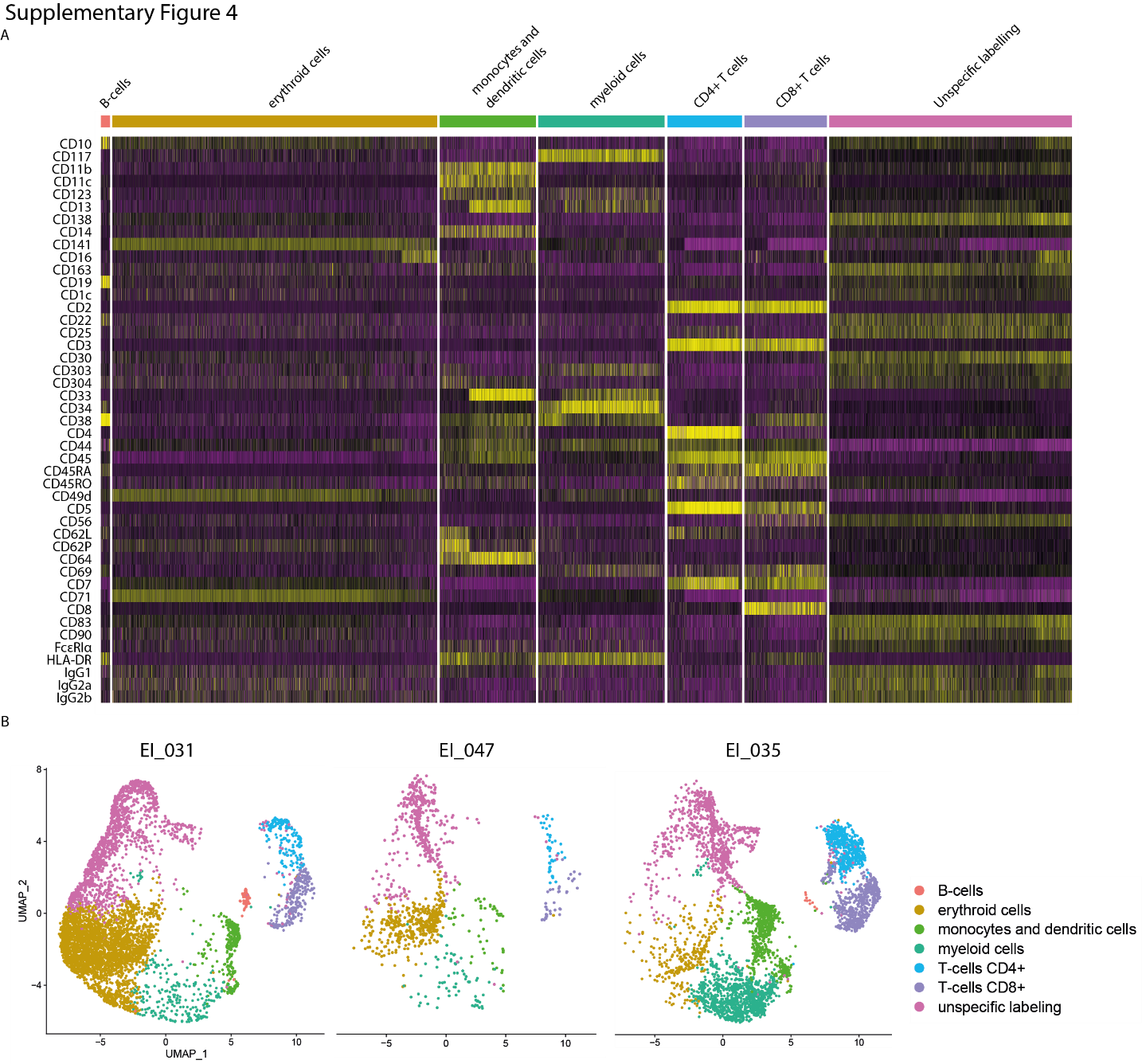
**Supplementary figure 1. Sequencing-based analysis of CNA and LOH in adult LH-ALL.** (A) Sequencing-based assessment of CNA using Viscap tool for three representative cases: low hypodiploid (left), duplicated low hypodiploid (middle) and high hyperdiploid ALL (right). (B) Sequencing-based assessment of LOH using Facets tool for the three same representative cases. (C) Frequency of specific chromosomal losses in the 80 LH-ALL cases. For duplicated LH-ALL cases, only primitive losses in the hypodiploid clone, as inferred by LOH were considered.



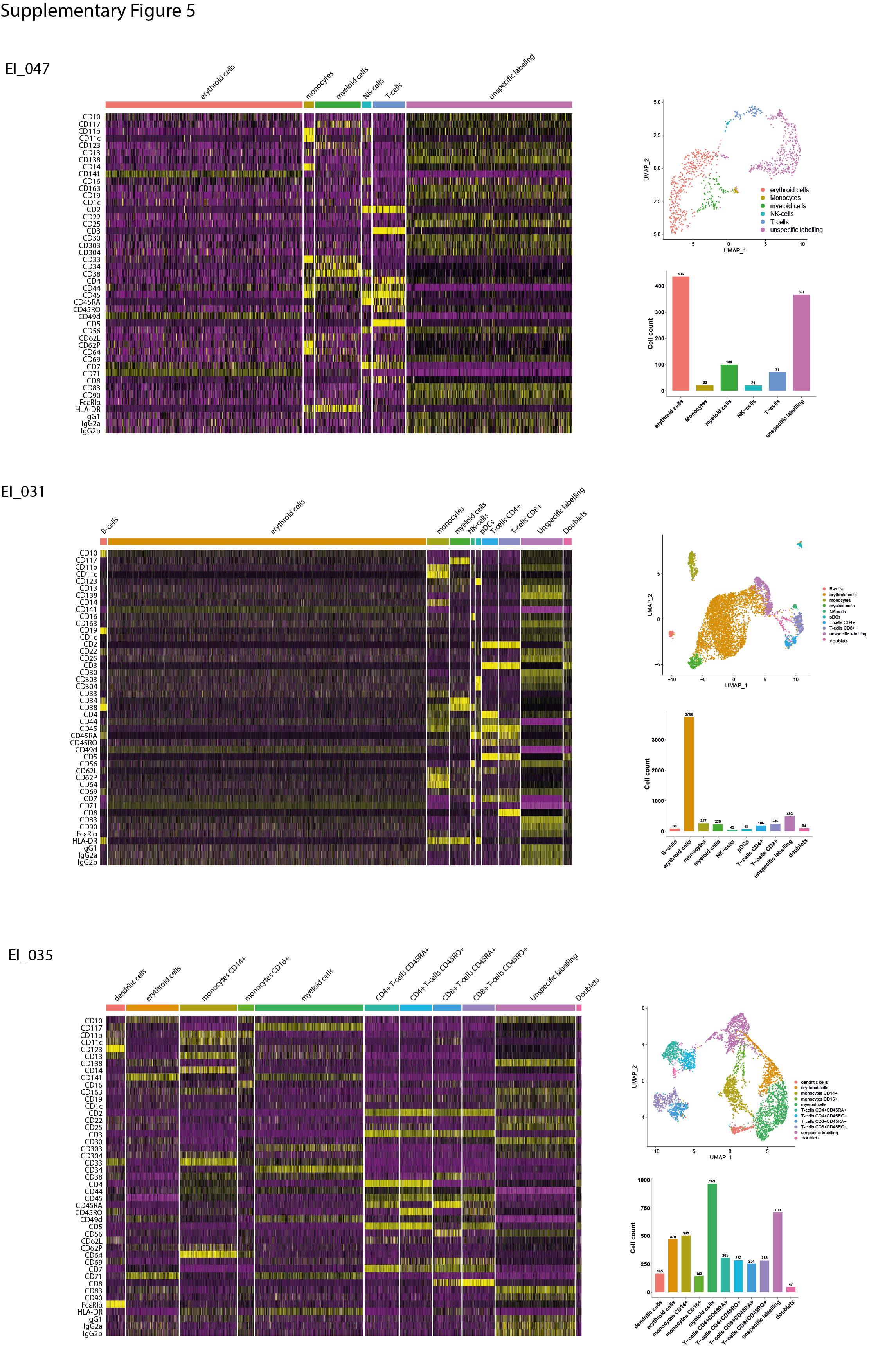
**Supplementary figure 2. Representation of mutations in the frequent targeted genes in adult LH-ALL.** Lollipop plots depicting the distribution of mutations in *RB1* (A), *NF1* (B), *FLT3* (C), *DNMT3A* (D) and *TET2* (E).



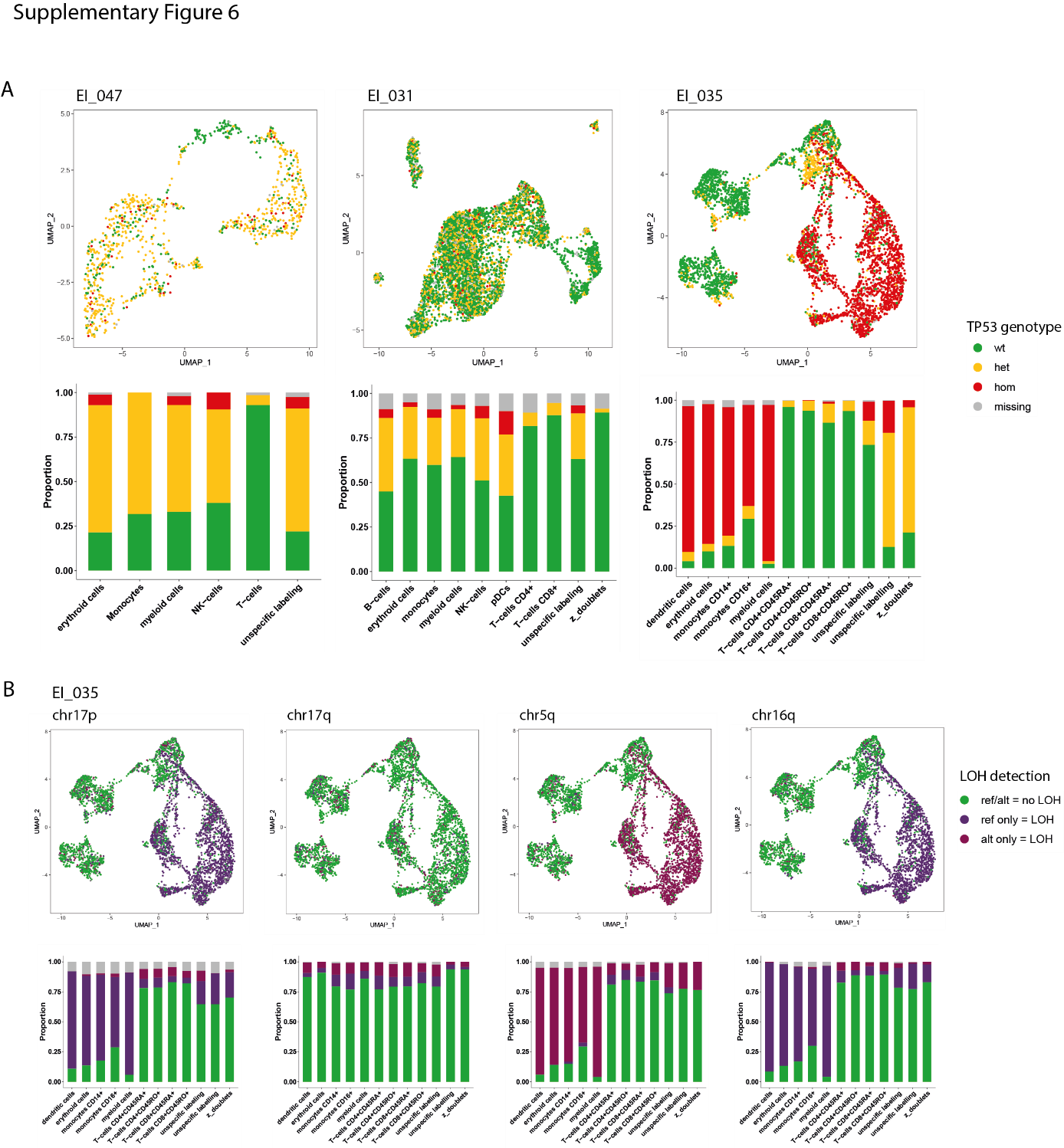
**Supplementary figure 3. Longitudinal assessment of *TP53*-mutant cell fraction as determined by ddPCR along with clonal *IG/TR*-based MRD quantification in three patients with undetectable *TP53* mutation at remission.**

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**Supplementary figure 4. Merged single-cell analysis of cell-surface markers by ADT-sequencing of remission samples from three LH-ALL patients.** (A) Heatmap of expression of cell-surface markers used for cell population assignment. (B) UMAP plots of each individual remission samples clustered by immunophenotype and colored by assigned cell populations. B-cells were recognized as CD10+ CD19+; erythroid cells as CD71+; monocytes and dendritic cells as CD11b+ CD11c+ CD14+ CD64+ CD123+; myeloid cells as CD117+ CD34+ CD33+; T cells as CD2+ CD3+ CD5+ CD7+.



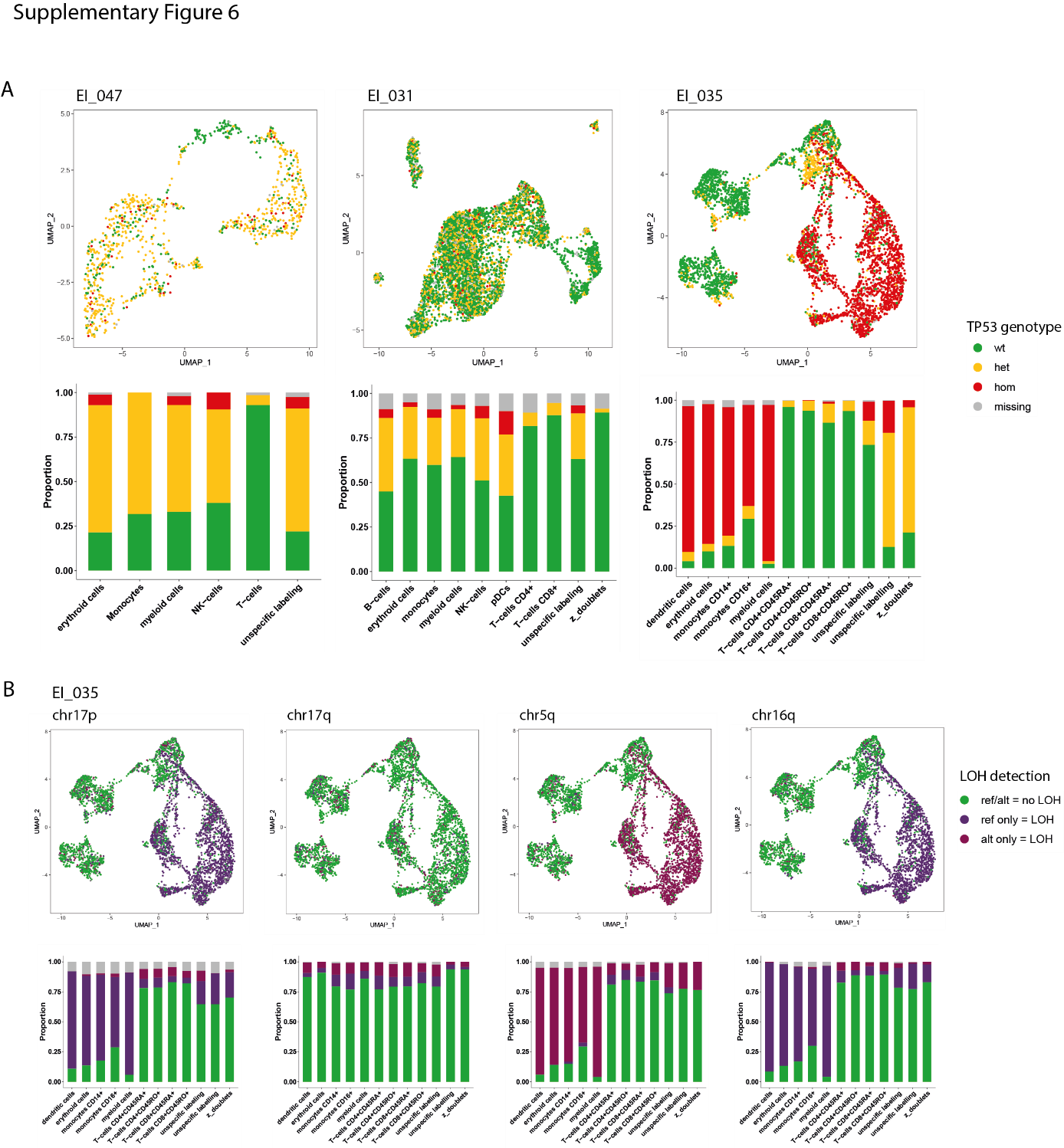
**Supplementary figure 5. Individual single-cell analyses of cell-surface markers by ADT-sequencing of remission samples from three LH-ALL patients.** Cell clusters were assigned as in Supplementary figure 4 and additional populations could be distinguished: NK-cells as CD2+ CD3- CD7+ CD16+ CD56+; monocytes as CD11b+ CD11c+ CD64+; plasmacytoid dendritic cells (pDCs) as CD123+ CD303+ CD304+; dendritic cells as CD123+ CD33+ FcꜪRIα+.

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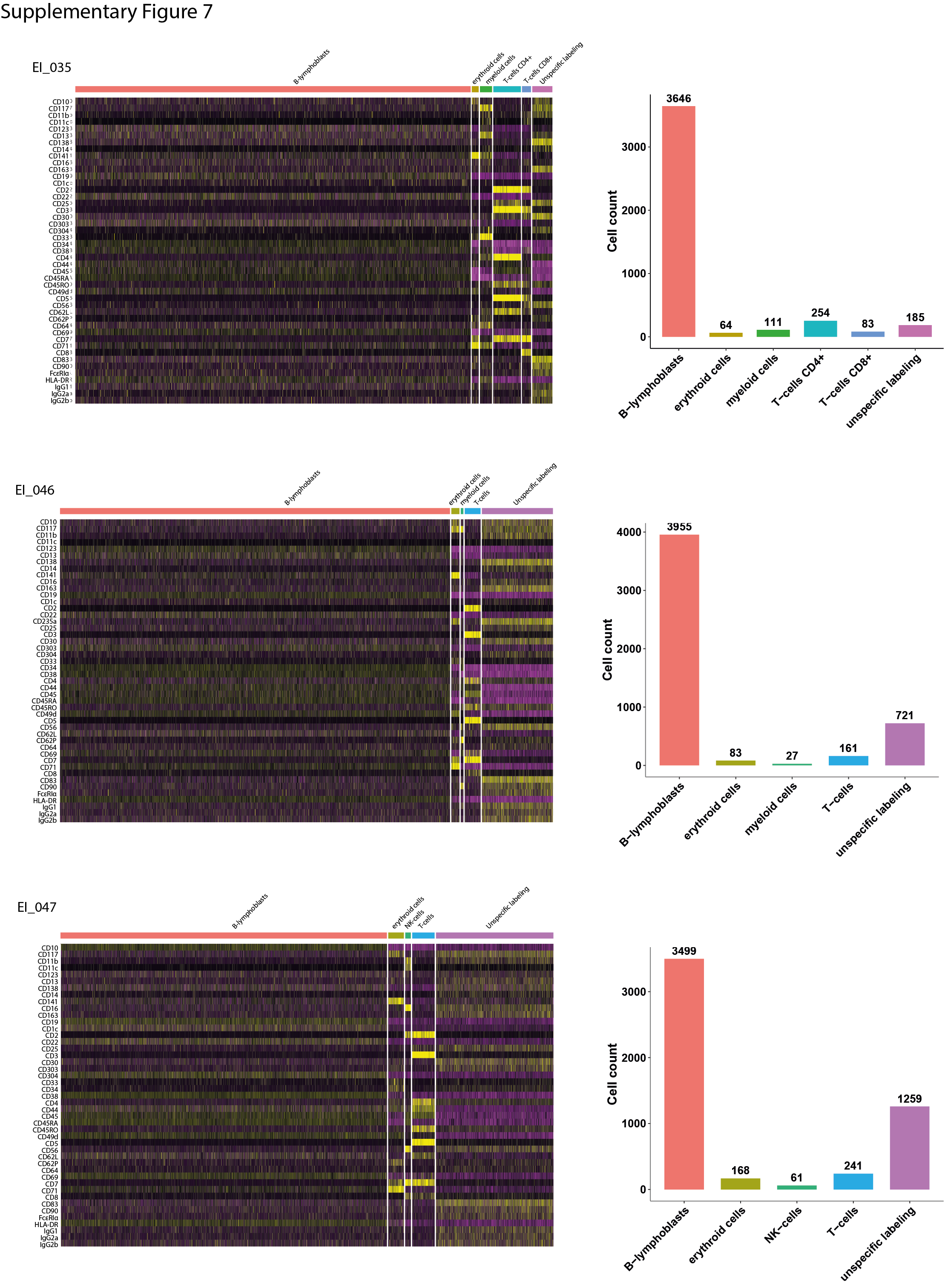
**Supplementary figure 6. Individual analyses of single-cell immunophenotyping and genotyping of remission samples from three LH-ALL patients.** UMAP plots (upper panels) of individual remission samples of three patients, with cells colored according to *TP53* genotype. Histograms (lower panel) show the proportion of each *TP53* genotype within each cell cluster.

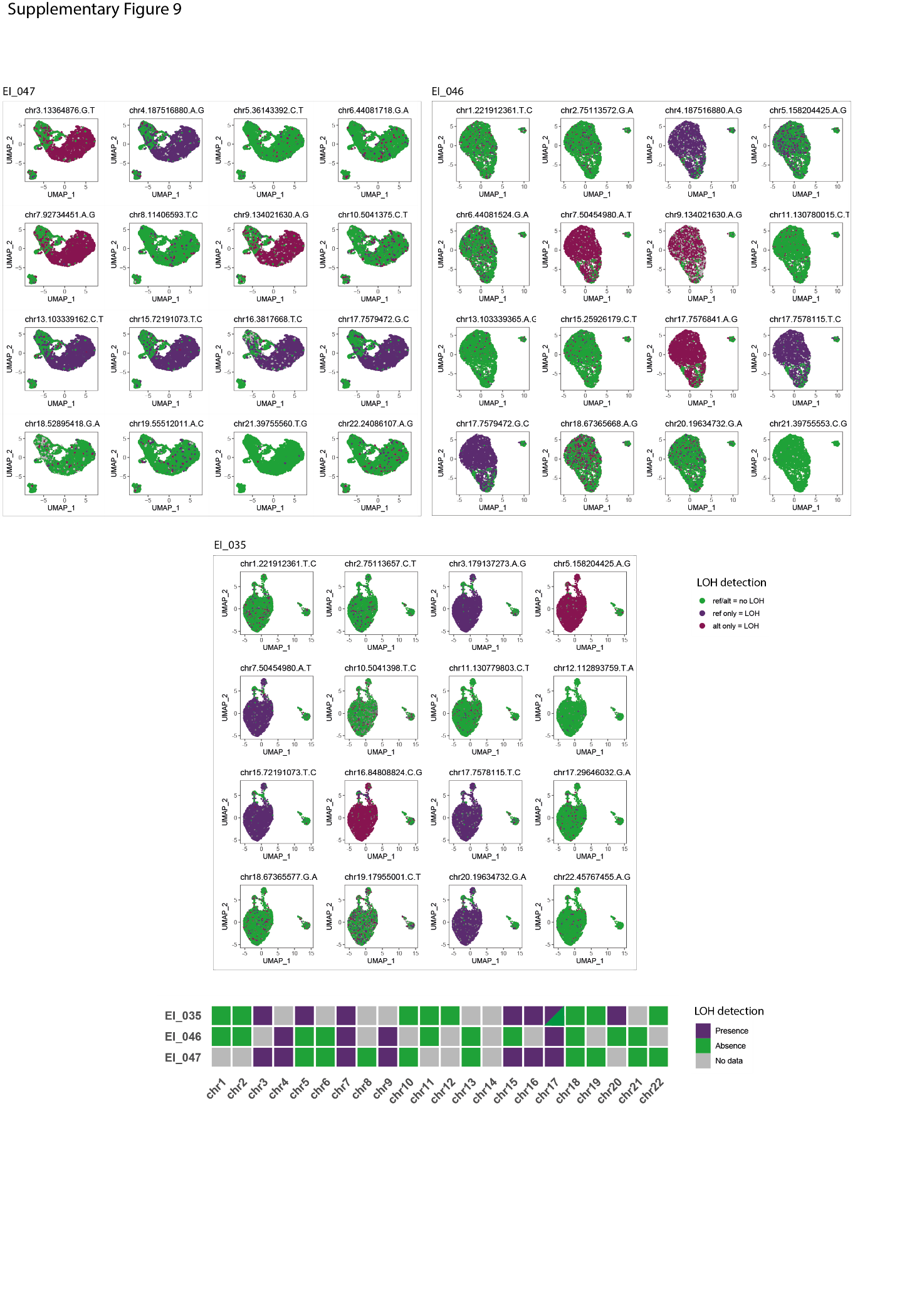
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**Supplementary figure 7. Evaluation of allelic dropout rate on heterozygous single nucleotide polymorphism (SNPs) in remission samples.** Proportions of single-cell genotypes observed for heterozygous SNPs in different cell fractions. False homozygous genotypes related to allelic dropout are observed in 1-18% of cells.

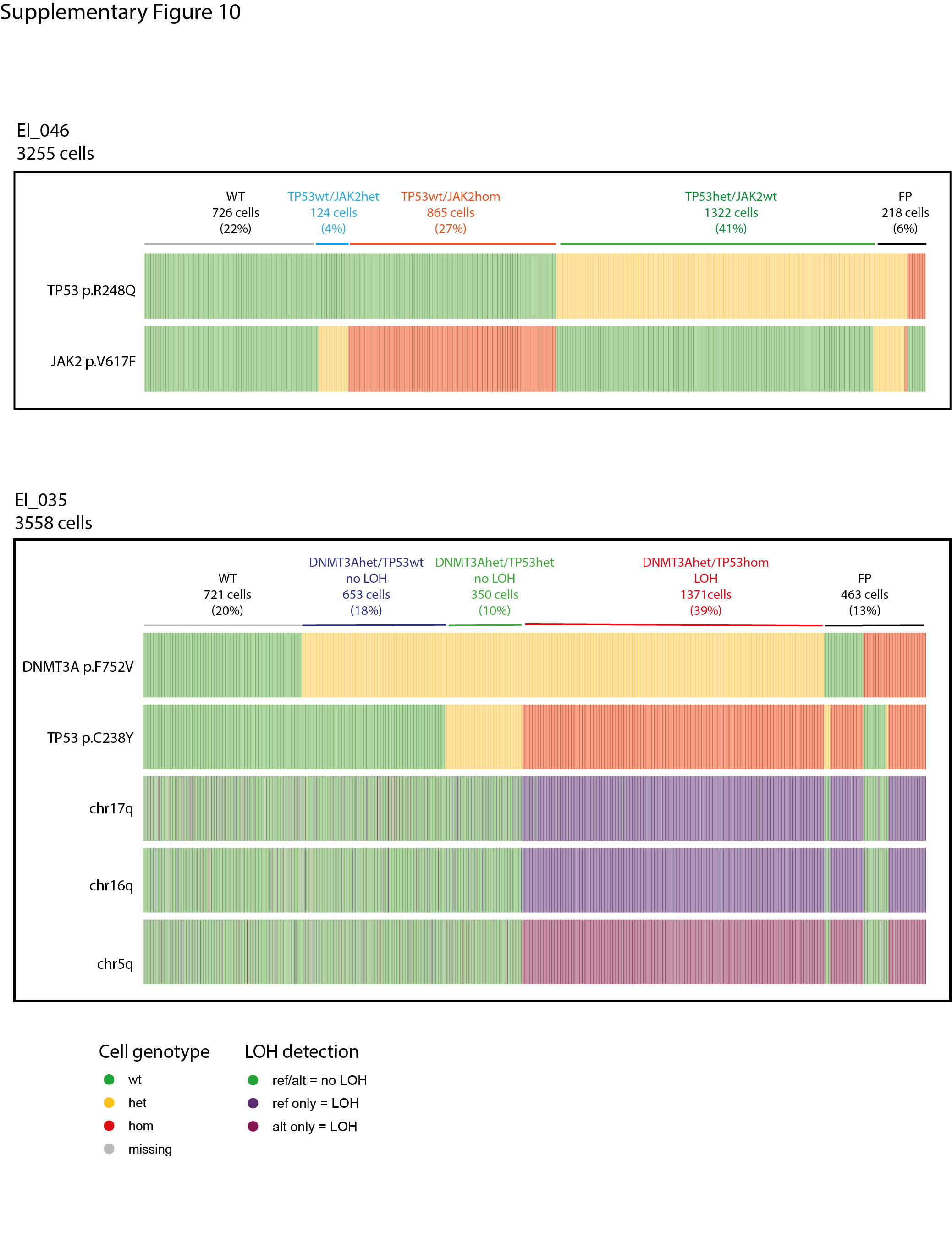
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**Supplementary figure 8. Single-cell protein and LOH analyses of remission sample from patient EI\_035.** UMAP plots (upper panels) with cells colored according to genotype for several heterozygous SNPs allowing LOH assessment. Histograms (lower panel) show the proportion of each genotype within each cell cluster.

**Supplementary figure 9. Individual single-cell analysis of cell-surface markers by ADT-sequencing of diagnosis samples from three LH-ALL patients.**

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**Supplementary figure 10. Single-cell genotyping of heterozygous SNPs allowing LOH assessment in diagnosis samples from three LH-ALL patients.**

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**Supplementary Figure 11. Distribution of single-cell genotypes of two LH-ALL patients with persistent *TP53* and *JAK2* (EI\_046) or *DNMT3A* (EI\_035) mutations in remission samples.** FP,false positive.