Contribution of copy number to improve risk stratification of adult T-cell acute lymphoblastic leukemia patients enrolled in measurable residual disease-oriented trials

T-cell acute lymphoblastic leukemia (T-ALL) is a genetically heterogeneous disease characterized by a complex multistep mutagenic process in which different alterations cooperate to transform T-cell precursors. However, the clinical impact of most of these alterations remains unclear, which partly explains why T-ALL subtypes are still defined on morphological and immunophenotypic grounds in the current World Health Organization (WHO) 2022 classification. Here, we used single nucleotide ploymorphism (SNP) arrays to investigate the frequency of common copy number variations (CNV), and integrated the results obtained with single nucleotide variants (SNV)/insertions deletions (indel) data on the same homogeneously treated T-ALL cohort, to evaluate their impact on disease outcome.

A total of 146 T-ALL samples were previously analyzed by target deep sequencing.[1] From those, 134 patients were further studied by SNP arrays to identify CNV (CytoScan™ HD, Thermo Fisher). Samples and clinical data were obtained and stored in accordance with the declaration of Helsinki. The study was approved by the Institutional Review Board of the Hospital Germans Trias i Pujol. CNV and SNV results were integrated to assess their prognostic value in a group of 107 patients, homogeneously enrolled in two consecutive Spanish PETHEMA trials.[2,3] Only recurrent alterations found in ≥5 patients were considered. Patient's characteristics at diagnosis and follow-up are summarized in Table 1.

Focusing on SNP array data, among patients with CNV, 124 of 130 (95.4%) had deletions (del) and 72 of 130 (55.4%) duplications (dup), 66/130 (50.8%) showing a combination of both events (*Online Supplementary Figure S1*). There were CNV targeting a single T-ALL driver gene (*LEF1*, *CDK6*, *PTPN2*, *ELF1*, *WT1*, *TET2*, *PHF6*, and *MYB*). The smallest alteration identified was the deletion of *LEF1* (22 kbp). Other recurrent alterations were heterogeneous in size and affected multiple genes (*Online Supplementary Figure S2A*). In turn, for another subset of alterations the minimum altered region overlapped with a T-ALL driver gene, suggesting that this would be the target gene of the alteration (*Online Supplementary Figure S2B-M*). Other recurrent and larger CNV detected included del(5q), del(6q), dup(5p) and dup(17q) (*Online Supplementary Figure S2N-Q*). Finally, alterations resulting in *STIL::TAL1* (*Online Supplementary Figure S2R*) and *NUP214::ABL1* (*Online Supplementary Figure S2S*) fusions, as well as trisomy of chromosomes 10 and 19, and gains of chromosome X, were also observed.

Among patients with complete genomic data (N=134), 88.8% (119/134) had both SNV and CNV (*Online Supplementary Figure*

Table 1. Clinical and biological characteristics, response to treatment and outcome of T-cell acute lymphoblastic leukemia patients (N=107)*.

Patient-related features		
Median age in years (range)		37 (16-61)
Sex: M/F, N		79/28
Biological features, N (%)		
Cytogenetics	<3 alterations	59/107 (55)
	≥3 alterations	10/107 (9)
	NE	38/107 (36)
Immunophenotype	ETP-ALL	20/102 (20)
	Pre-T	18/102 (18)
	Cortical	42/102 (41)
	Mature	22/102 (21)
Disease-related features		
Median WBC x10^9/L (range)		52.8 (0.5-525.4)
ECOG score, N (%)	0	40/103 (39)
	1	49/103 (47)
	2	12/103 (12)
	≥3	2/103 (2)
Adenopathy, N (%)		49/90 (54)
Splenomegaly, N (%)		36/102 (35)
Hepatomegaly, N (%)		25/101 (25)
Mediastinal mass, N (%)		44/104 (42)
CNS involvement, N (%)		14/110 (13)
Response-related features, N (%)		
Slow response on day +14		44/91 (48)
Number of induction cycles to CR	1	87 (81)
	2	20 (19)
CR post induction-1		87 (81)
CR (indunction-1 + induction-2)		96 (87)
MRD <0.1% on day +35		68/81 (84)
Post consolidation treatment	Chemotherapy	54/74 (73)
	Allo-SCT	20/74 (27)
Outcome features, % (95% CI)		
OS prob. at 5 years		37 (27-48)
CIR at 5 years		54 (43-64)

*Twenty-seven of 134 initial patients were excluded (1 pediatric; 3 intermediate risk; 4 older; 14 patients treated with an ongoing trial; and 4 without clinical data). Results expressed as number of cases/total cases (percentage) when not otherwise indicated. +MRD values were considered for those patients that reached complete remission (CR). M: male; F: female; NE: non-evaluable; ETP-ALL: early T-cell precursor acute lymphoblastic leukemia; WBC: white blood cell count; CNS: central nervous system; MRD: measurable residual disease; day +14: 14 days after induction treatment; day +35: 35 days after induction treatment; allo-SCT: allogeneic stem cell transplantation; OS: overall survival; prob.: probability; CIR: cumulative incidence of relapse; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group.

Table 2. Prognostic impact of genetic alterations and associations in the adult T-cell acute lymphoblastic leukemia cohort.

Alteration	Frequency of alteration		OS prob. time point in years	OS (95% CI)		*P*
	Patients with alteration, N (%)	Patients without alteration, N (%)		Patients with alteration	Patients without alteration	
Del(5q)	8/114 (7)	106/114 (93)	*	0.17 (0.02-0.74)	2.02 (1.53-4.88)	<0.001
ETV6^{alt}	6/107 (5.6)	101/107 (94.4)	5	67 (5-95)	35 (25-46)	0.041
TP53^{alt}	5/107 (4.7)	102/107 (95.3)	*	0.11 (0.05-0.17)	2.02 (0.7-3.32)	0.100
Cortical** & *CDKN2A/B*	33/102 (32.4)	69/102 (67.6)	5	50 (40-60)	34 (27-41)	0.12
N alt >14***	16/107 (15)	91/107 (85)	5	26 (14-38)	40 (34-46)	0.006

*Results are expressed as median of overall survival (OS) as most patients do not reach 1 year of OS. CI: confidence interval. Alt: alterations (sum of single nucleotide variant [SNV]/insertions deletions [indel] and copy number variants [CNV]). OS was estimated using Kaplan-Meier method. **_P_ value =0.189 for OS of cortical _vs_. no-cortical patients. ***We used the maxstat test (R test) to determine that a cutoff of 14 alterations was the most significant threshold to stratify the patients according their OS. prob.: probabilty.

S1) with a median of five alterations/patient (range, 1-13). The frequency and distribution of recurrently identified alterations are in concordance to those previously reported in another adult cohort (Figure 1A).[4] Notably, there were patients with concomitant SNV/indel and CNV affecting *DNMT3A*, *PTEN*, *FBXW7*, *TET2*, *TP53*, *CTCF and RPL5* genes, suggesting that a double-hit event was required for these genes to drive leukemogenesis in T-ALL (Figure 1A).

To evaluate how genetic events cooperate to develop T-ALL in a specific context, we assessed pairwise associations between mutated genes identified in the same patient. We observed co-occurrence of *RB1* with i) *BCL11B* (odds ratio [OR]=13.3, q=0.008), ii) *CDKN2A/B* (OR=102, q=0.07) and iii) *NOTCH1* (OR=92.3, q=0.07) alterations. *BCL11B* gene alterations co-existed with i) *NOTCH1* (OR=169.4, q=0.003) and ii) *CDKN2A/B* (OR=17, q=0.01) alterations. *STIL::TAL1* gene fusion co-occurred with del(6q) (OR=7.1, q=0.09). The strongest association was found between *JAK3* and *JAK1* mutations (OR=115, q=0.003).[5] *JAK3* was also frequently mutated in patients with *PHF6* mutations (OR=5.1, q=0.09). [6] Moreover, mutual exclusion was observed between *CDKN2A/B* and *DNMT3A* alterations (OR=0.09, q=0.01) (Figure 1B, left panel). From the immunophenotypic point of view, *CDKN1B*, *CDKN2A/B*, *RB1* deletions and *MYB* duplications were more frequently observed among cortical T-ALL (OR=10.6, q=0.003; OR=4.8, q=0.005; OR=10.3, q=0.02; OR=7.8, q=0.07 respectively). Conversely, *N/KRAS* mutations and cortical immunophenotype were mutually exclusive (OR=0.1, q=0.07). These mutations were co-occurrent with the ETP-ALL immunophenotype (OR=4.7, q=0.07)[1], similarly like *DNMT3A* and *RUNX1* alterations (OR=8, q=0.01; OR=5.6, q=0.06, respectively). In turn, *CDKN2A/B*, *BCL11B* and *FBXW7* mutations (OR=0.04, q=9x10^{-6}; OR=0, q=0.07; OR=0.1, q=0.07, respectively), were mutually exclusive with ETP-ALL (Figure 1B, right panel).

To infer the potential sequence of acquisition of the different genetic events, we used variant allele frequency (VAF), CN values and tumor cell contents to calculated the cancer cell fraction (CCF) for each sample. All patients had at least one clonal alteration, defined by a CCF >50% (Figure 1C). The median CCF of the CNV was higher than that of SNV/indel (1 ; [range, 0.15-1] *vs*. 0.83 [range, 0.04-1]; *P*<0.0001), indicating earlier occurrence of the former. In fact, only two genes altered by CNV had more than 35% of their variants as subclonal, *CDK6* and *CTCF* (Figure 1C, left panel). In case of SNV, a large number of genes presented subclonal variants (*IL7R*, *KMT2C*, *PTEN*, *BCL11B*, *NOTCH1* and *JAK1*), suggesting a later acquisition of these events, according to the CCF model[7] (Fig. 1C, right panel). Similarly, the clonal profile of *PTEN* varied according to the type of alteration, with CNV having higher CCF than SNV/indel (1 [range, 0.4-1] *vs*. 0.51 [range, 0.08-1]; *P*=0.001).

Subsequently, we explored potential genetic-clinical correlations based on a total of 44 different genetic subgroups (Table 2; *Online Supplementary Table S1*). Thus, we focused on those alterations that affected >5 patients (Figure 1A) and their correlation with T-ALL biological features at diagnosis, treatment response and survival data. We excluded genes that were only affected by SNV, because their prognostic impact had been previously investigated.[1] In parallel, we also evaluated the clinical impact of the statistically significant pairwise associations described above (Figure 1B). Finally, we assessed the impact of genetic complexity, defined as the sum of SNV and CNV per patient.

Regarding individual alterations, del(5q) (N=8) and *ETV6* gene alterations (*ETV6*^{alt}, 4 SNV and 2 CNV) had an impact on overall survival (OS), while alterations in *TP53* (*TP53*^{alt}, 4 CNV, 1 SNV plus CNV) showed a trend (Table 2). Of note, patients with del(5q) showed worse response to treatment: slower response after 14 days of induction (≥10% blasts) (100% of deleted patients *vs*. 40% of non-deleted; *P*=0.005), lower complete remission (CR) rates even, after two cycles of induction therapy (50% of deleted patients *vs*. 91% of

non-deleted; *P*=0.008), resulting in an increase of deaths during induction therapy (62.5 % of deleted patients *vs*. 5.7% of non-deleted; *P*=0.0002). Such an adverse response and outcome was also observed among patients with *DNMT3A/N/KRAS/MSH2/U2AF1* SNV, collectively defined as variable as the worse outcome genetic profile (WOG), previously described for the same study cohort.[1] In fact, six of eight patients with del(5q) had WOG mutations and consequently, patients with both alterations (WOG + del(5q)) exhibited significantly shorter OS compared to those with only WOG mutations (median OS of 0.16 [range, 0.02- not applicable (NA)] *vs*. 0.81 [range, 0.45-1.75]; *P*<0.001), emphasizing the deleterious effect of an additional del(5q) in the WOG patient group.

In T-ALL, the prognostic significance of *PTEN* alterations remains controversial. Our results showed that neither PTEN CNV nor SVN nor CNV plus SNV had an impact on patient outcome (*Online Supplementary Table S1*), consistent with previous studies.[8,9] Thereby, the genetic signature *NOTCH1/FBXW7*^{wt} and/or *N/KRAS*^{mut} and/or *PTEN*^{alt} did not have prognostic value in our series (*data not shown*), and, therefore, our results do not validate the genetic score proposed by Trinquand A. *et al*.[10] to stratify adult T-ALL patients.

Regarding the clinical impact of pairwise genetic associations, we observed that patients with deletions in *CDKN2A/B* genes and cortical immunophenotype exhibited a trend for better OS (Table 2). Finally, patients with a complex tumor genome, defined as >14 alterations (14^{alt}), had poorer OS (Table 2) and lower CR rates (68.8% patients with >14^{alt} achieved CR *vs*. 97.8% of patients with ≤14^{alt}; *P*=0.002).

Overall, our results suggest that CNV seem to cooperate with specific SNV/indel, delineating recurrent onco-genet-

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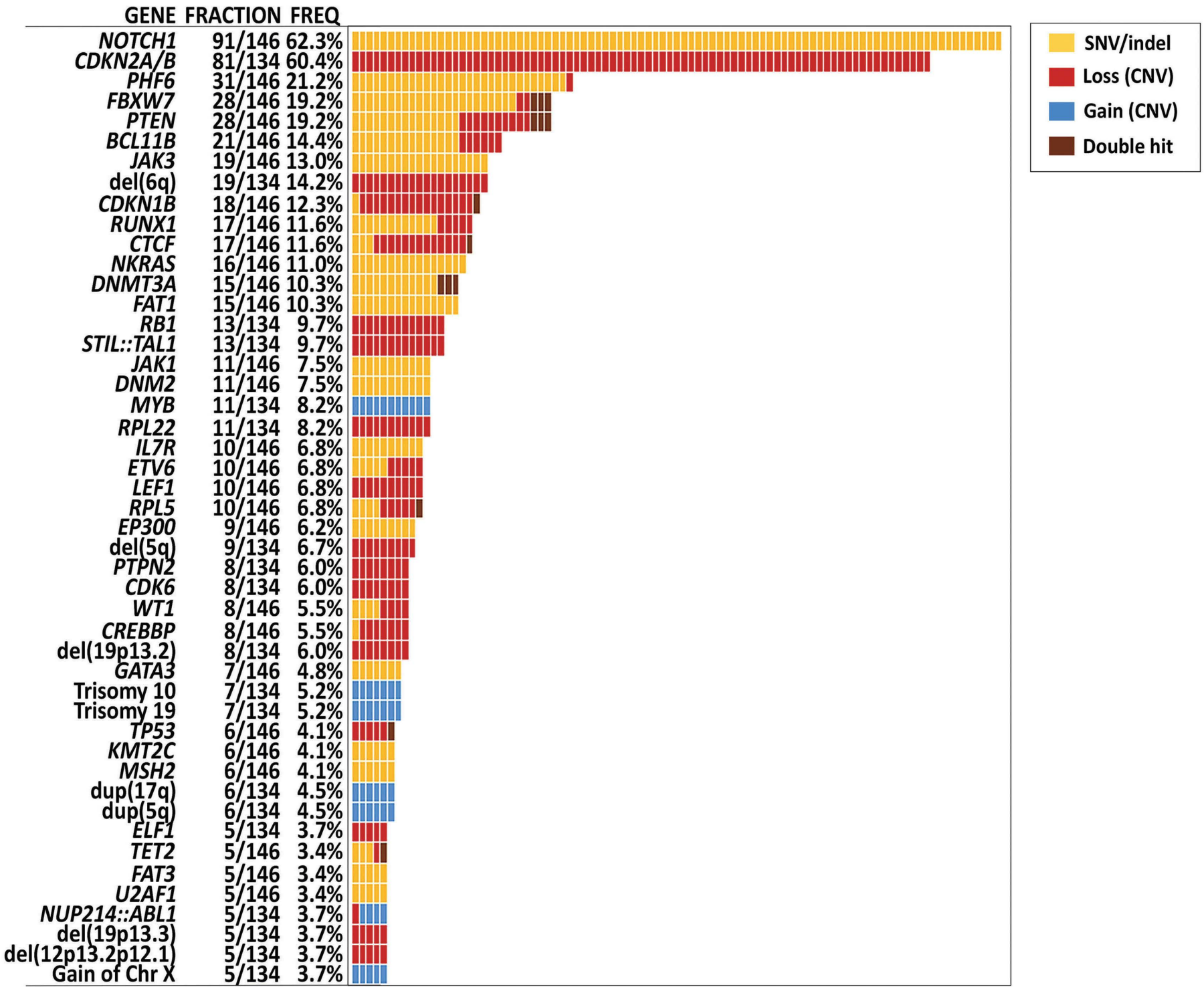

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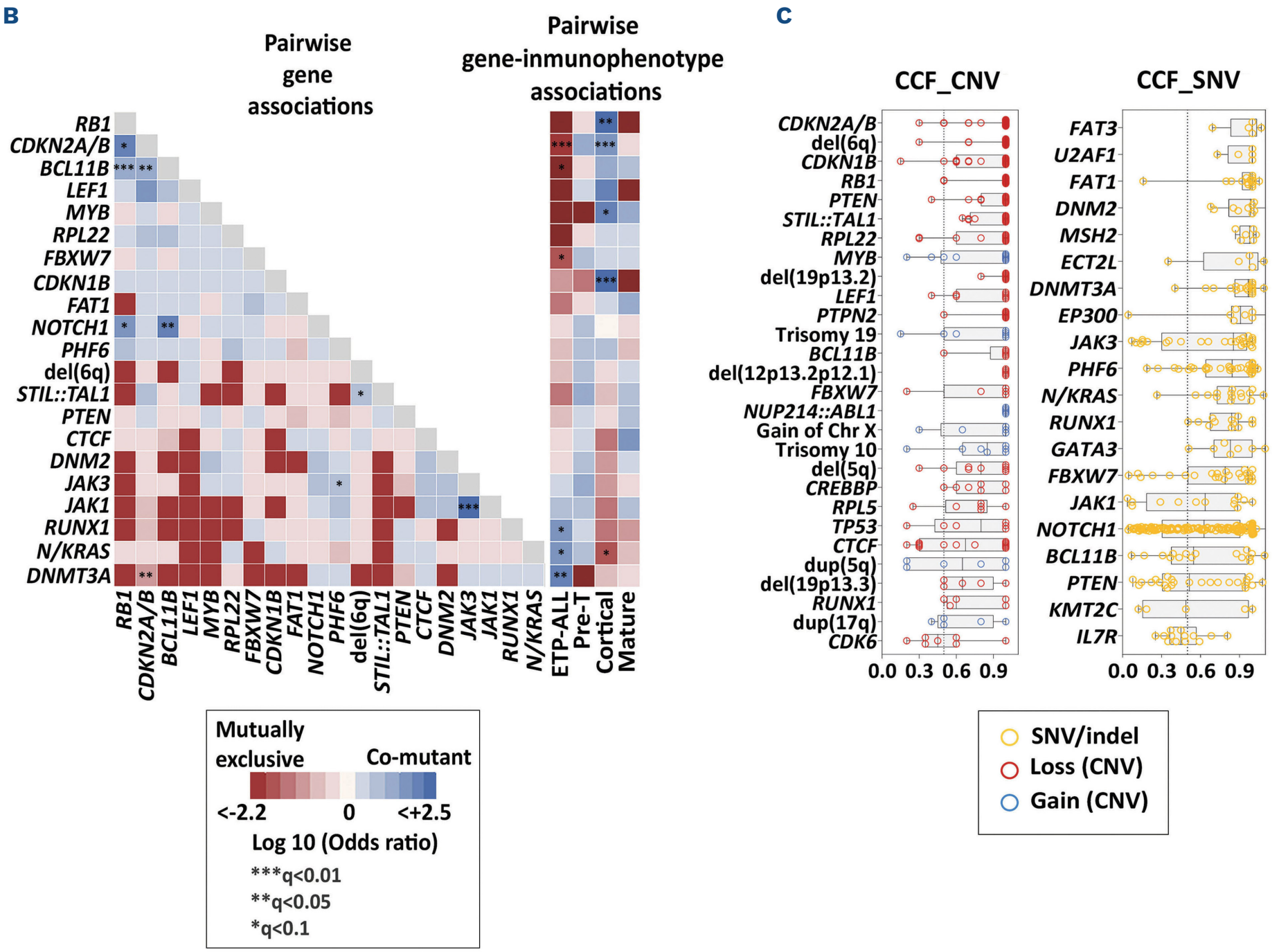

Figure 1. Genetic profile of adult T-cell acute lymphoblastic leukemia at diagnosis. (A) Mutational landscape of adult T-cell acute lymphoblastic leukemia (T-ALL) patients. Only alterations found in at least 5 patients are shown. Genes affected by both sum of single nucleotide variant (SNV)/insertions deletions (indel) and copy number variants (CNV) in the same patient are highlighted in brown. (B) Pairwise associations between altered genes identified in the same patient (left panel) and between genetic alterations and immunophenotype (right panel). Associations are shown only for alterations present in at least 10 patients. Combinations were tested using the Fisher test corrected by the Benjamini-Hochberg multiplicity test (considering significant co-existence when q<0.1). Positive correlations are represented by the blue range color and negative correlations by the red range color. (C) Box and whisker representation of cancer cell fractions (CCF) for CNV (left panel) and SNV/indel (right panel). The threshold to define clonality (0.5) is indicated by the dashed line. All statistical analyses were performed using SPSS version 24 (IBM Corp. Armonk, NY), GraphPad Prism® version 10 (GraphPad Software Inc., La Jolla, CA) and R version 4.1.0.

ic pathways that define the transformation of each T-cell precursor at a particular stage of differentiation. Thus, alterations in *RB1*, *BCL11B*, *CDK1NB* lead to a T-cell transformation at a cortical thymocyte, while *N/KRAS* mutations, *DNMT3A* or *RUNX1* alterations, would block the T-cell differentiation process at an earlier stage (ETP-ALL). Based on these findings, we would not expect CNV to substantially improve the risk stratification provided by immunophenotypic groups.[11] Interesting, we observed that patients with *CDKN2A/B* gene deletions and a cortical immunophenotype had a trend for better outcomes.

We have also shown that some CNV identify patients with poor outcome. That is the case of del(5q), the CNV with the highest impact on OS in our cohort. Del(5q) has been previously described in a small cohort of adult T-ALL patients to be associated with an immature immunophenotype and the presence of stem cell/myeloid markers.[12] Most patients showed a WOG signature that mainly identifies patients with ETP-ALL and advanced age,[1] which might explain their poorer outcome. We could not validate the impact, previously shown, of $TP53^{alt}$ in this cohort,[13] due to the limited number of positive cases, although we see a trend to worse outcome. The limited number of patients with $ETV6^{alt}$ also abort the possibility to assess their outcome.

We also studied the value of genomic complexity to stratify adult T-ALL patients, based on the number of CNV and SNV per patient, which could provide information of the plasticity of blast cell. We showed that an increased number of >14[alt] was associated with worse outcomes, similarly to what has been described with karyotype studies.[14,15] This may be due to the higher genetic heterogeneity of leukemic cells in these patients, which provides more opportunities for the leukemia to evade treatment. However, limitations in the cohort size, precluded the evaluation of the prognostic impact of this genetic marker by multivariable analysis.

In summary, herein we show that CNV, that are essential for T-cell leukemia development, help to improve genetic risk stratification of T-ALL. Further studies in larger T-ALL cohorts with complete genomic data (i.e., inclusion of rearrangements) are needed to confirm our findings and to delineate an integrative genetic approach to assess clinically relevant onco-genetic pathways.

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Disclosures

No conflicts of interests to disclose.

Contributions

CG-C analyzed the data, produced the figures and wrote the paper. MM did the statistical analyses. TL collected and prepared DNA samples. FF-T optimized CNV analysis. PM, PB, MD-B, LH, CM, JG-C, TB., MS, LZ, MP, RM, MJL, TA, AT, FV-Ll, M T, CG, AN, PM-S, JR, M-PQ, TG-M, MC, AC and JC provided clinical data and/or DNA samples. AO and J MR reviewed the manuscript. EG designed the study, reviewed the data, co-wrote and reviewed the manuscript.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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