

Clinical and biological features of PTPN2-deleted adult and pediatric T-cell acute lymphoblastic leukemia

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Key Points

- We provide a comprehensive analysis of PTPN2-associated genomic alterations and clinical implications in a large cohort of T-ALL.
- PTPN2 loss associates with mutations in the IL7R/JAK-STAT signaling pathway, PHF6 and WT1, but is exclusive from PTEN deletions.

Protein tyrosine phosphatase nonreceptor type 2 (PTPN2) is a phosphatase known to be a tumor suppressor gene in T-cell acute lymphoblastic leukemia (T-ALL). Because the full clinicobiologic characteristics of PTPN2 loss remain poorly reported, we aimed to provide a comprehensive analysis of PTPN2 deletions within a cohort of 430 patients, including 216 adults and 214 children treated according to the GRAALL03/05 (#NCT00222027 and #NCT00327678) and the FRALLE2000 protocols, respectively. We used multiplex ligation-dependent probe amplification to identify an 8% incidence of PTPN2 deletion, which was comparable in adult (9%) and pediatric (6%) populations. PTPN2 deletions were significantly associated with an $\alpha\beta$ lineage and TLX1 deregulation. Analysis of the mutational genotype of adult T-ALL revealed a positive correlation between PTPN2 deletions and gain-of-function alterations in the IL7R/JAK-STAT signaling pathway as well as PHF6 and WT1 mutations. Of note, PTPN2 and PTEN (phosphatase and tensin homolog) deletions were mutually exclusive. Regarding treatment response, PTPN2-deleted T-ALLs were associated with a higher glucocorticoid response and a trend for improved survival in children, but not in adults, with a 5-year cumulative incidence of relapse of 8% for PTPN2-deleted pediatric cases vs 26% ($P = .177$).

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is an uncommon, aggressive neoplasm that accounts for ~25% and 10% of adult and pediatric acute lymphoblastic leukemias, respectively.^{1,2} T-ALL derives from the clonal transformation and proliferation of lymphoid progenitors with thymic stage of maturation arrest.^{3,4} Cytogenetic and global transcriptomic analyses led to the classification of T-ALL into molecular groups characterized by abnormal expression of specific transcription factors (TAL, LMO1/2, TLX1/3, LYL, HOXA, MEF2C) and a specific stage of differentiation blockade.^{3,5,6} Across all these subgroups, a number of additional recurrent genetic abnormalities are found, including the loss of major tumor

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For original data, please contact vahid.asnafi@aphp.fr. Supplemental data provide additional information regarding clinical trials (supplemental Tables 1 and 2;

supplemental Figure 1), microarray-based comparative genomic hybridization (array CGH), and quantitative real-time reverse transcription-polymerase chain reaction.

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suppressive pathways such as inactivating alterations of PTEN and CDKN2A and activation of oncogenic pathways (eg, activating mutations in NOTCH1, IL7R/JAK).⁶

Protein tyrosine phosphatase non-receptor type 2 (PTPN2; also known as TC-PTP) is another tumor suppressor gene described to be inactivated in T-ALL.⁷⁻⁹ It is a ubiquitous nontransmembrane tyrosine phosphatase whose substrates include various receptor tyrosine kinases, such as the epidermal growth factor receptor, the platelet-derived growth factor receptor β , and the hepatocyte growth factor receptor.¹⁰⁻¹² Moreover, PTPN2 is involved in hematopoietic development and regulation of T-cell activation through the dephosphorylation of c-Src, Fyn, Lck, JAK-1/3, and STAT-1, -3, -5, and -6.¹³⁻¹⁷

In 2011, Kleppe et al¹⁸ identified biallelic inactivation of PTPN2 in 2 out of 39 cases of peripheral T-cell lymphoma “not otherwise specified,” but none in a cohort of 50 cases of Hodgkin lymphoma. They also identified biallelic inactivation of PTPN2 in the Hodgkin lymphoma cell line, SUP-HD1, which was associated with activation of the JAK/STAT pathway.

PTPN2 deletions have been described in up to 6% of combined adult and pediatric T-ALLs,^{7,8} almost exclusively in cases with abnormal expression of the TLX1 transcription factor. Furthermore, PTPN2 loss seems to be associated with the presence of NUP214-ABL1, because PTPN2 negatively regulates this fusion oncogene.⁷ PTPN2 deletion also cooperates with JAK-1/3, increasing the effects of their oncogenic mutations by increasing cytokine sensitivity and JAK-STAT signaling, thus promoting leukemic cell proliferation.^{8,19}

Nevertheless, data regarding the incidence and clinical impact of PTPN2 deletions in large and unbiased T-ALL patient cohorts are lacking. In this study, we aimed to provide a comprehensive analysis of the clinical characteristics, the prognosis, and the genomic landscape of adult and pediatric PTPN2-deleted patients within a consecutive series of 430 T-ALL treated within the French adult (GRAALL03/05; $n = 216$) and pediatric (FRALLE2000; $n = 214$) prospective clinical trials.

Patients and methods

Clinical trials

Adult patients (16 to 59 years old) were included in the GRAALL03/05 trials, which were registered at clinicaltrials.gov (GRAALL-2003, #NCT00222027; GRAALL-2005, #NCT00327678). Pediatric patients (1 to 20 years old) were treated in 10 French pediatric hematology departments, members of the FRALLE study group, according to the FRALLE 2000 T guidelines, a German BFM-inspired protocol.²⁰ Patients aged from 16 to 20 years were either treated in the GRAALL (22/216 patients, 10%) or in the FRALLE protocol (12/214 patients, 5.6%) according to the initial health care center (either adult or pediatric departments). Studies were conducted in accordance with the Declaration of Helsinki and approved by local and multicenter research ethical committees.

Immunophenotypic and molecular characterization of T-ALL samples

Diagnostic T-ALL samples were analyzed for immunophenotype, fusion transcripts (SIL-TAL1, CALM-AF10, NUP214-ABL, MLL), oncogenic transcripts (TLX1 and TLX3), T-cell receptor (TCR)

rearrangements, and NOTCH1/FBXW7/RAS/PTEN mutations, as previously described.^{4,21-23}

Multiplex ligation-dependent probe amplification (MLPA) analysis

MLPA analysis was performed using the MRC Holland (Amsterdam, The Netherlands) SALSA MLPA probe mix P383-A1 TALL according to the manufacturer's recommendations. Polymerase chain reaction products were separated by capillary electrophoresis on an ABI-3130 device. Coffalyser software, available at <http://www.mlpa.com>, was used for the analysis.

Next-generation sequencing

A custom capture Nextera XT gene panel (Illumina) targeting complete coding exons and their adjacent splice junctions of 78 genes was designed based on targets known to be mutated in T-ALL and/or important in T lymphopoiesis. DNA Libraries were prepared using Nextera Rapid Capture Enrichment and underwent 2×150 -bp paired-end sequencing on an Illumina MiSeq sequencing system with MiSeq Reagent Kit v2 (Illumina). Briefly, sequence reads were filtered and mapped to the human genome (GRCh37/hg19) using in-house software (Polyweb; Institut Imagine, Paris, France). Annotated variants were filtered according to the following criteria: (1) coverage $< 30\times$, < 10 alternative reads, and variant allelic fraction $< 7\%$ were filtered out; (2) polymorphisms described in dbSNP, 1000Genomes, EVS, Gnomad, and EXAC with a calculated mean population frequency $> 0.1\%$ were removed; and (3) nonfiltered variants were annotated using somatic database COSMIC and ProteinPaint (St. Jude Children's Research Hospital–Pediatric Cancer data portal), published data, and in silico predictions.

Statistical analysis

Group comparison for categorical and continuous variables was performed with Fisher's exact and Mann-Whitney U tests, respectively. The cumulative incidence of relapse (CIR) was calculated from complete remission to relapse date, censoring patients alive without relapse at last follow-up. Overall survival (OS) was calculated from the date of diagnosis to the last follow-up date by censoring living patients. Survival analysis was performed using the Kaplan-Meier method, and the curves were compared using the log-rank test. Statistical analysis was performed with Stata software, version 12 (StataCorp, College Station, TX). All P values were 2-sided, with $P < .05$ considered statistically significant.

Results

PTPN2 deletion incidence in T-ALL

A total of 430 T-ALL was screened for PTPN2 deletions by MLPA analysis. Two hundred sixteen adult patients and 214 pediatric patients were prospectively treated in the GRAALL-2003-2005 and the FRALLE-2000 protocols, respectively. The incidence of PTPN2 deletions in the whole cohort was 8% (33 patients, 48% monoallelic, 52% biallelic), in line with published data^{7,8,24} (Table 1). No significant difference was observed between adult and pediatric T-ALLs, as we identified PTPN2 deletions in 9% of adult patients (50% monoallelic and 50% biallelic; supplemental Tables 3 and 4) and 6% of the pediatric population (46% monoallelic and 54% biallelic; supplemental

Table 1. Clinicobiologic characteristics of adult and pediatric patients with T-ALL (GRAALL and FRALLE protocols) according to PTPN2 status

	PTPN2 del, n = 33 (8%)*	PTPN2 WT, n = 397 (92%)	Total, N = 430 (100%)	P
Clinical subsets analyzed				
Male, n (%)	22/33 (67)	306/397 (77)	328/430 (76)	.2
Age, median (range), y	27.4 (4.3-57.0)	16.8 (1.1-59.1)	17.5 (1.1-59.1)	.02
WBC, median (range)	48.1 (4.1-574)	57.8 (0.3-980)	57.7 (0.3-980)	.2
CNS involvement (%)	5/33 (15)	37/394 (9)	42/427 (10)	.3
TCR status (available)†	26/33	277/397	303/430	
Immature (IM0, IMD, IMG), n (%)	2/26 (8)	64/277 (23)	66/303 (22)	.08
αβ lineage (IMB, pre-αβ, TCR αβ), n (%)	23/26 (88)	174/277 (63)	197/303 (65)	.009
γδ lineage (TCR γδ), n (%)	1/26 (4)	39/277 (14)	40/303 (13)	.2
Oncogenetics, n (%)†				
TLX1	13/27 (48)	39/308 (13)	52/335 (15)	<.0001
TLX3	9/27 (33)	52/308 (17)	61/335 (18)	.06
SIL-TAL1	1/27 (4)	37/308 (18)	38/335 (17)	.3
NUP214-ABL	5/24 (21)	17/257 (7)	22/281 (8)	.03
PTEN-deleted/mutated	0/33 (0)	55/396 (14)	55/429 (13)	.01
NOTCH1/FBXW7 mutated	28/33 (85)	250/397 (63)	278/430 (65)	.01
RAS mutated	3/33 (9)	36/397 (9)	39/430 (9)	1
Treatment response, n (%)†				
Corticosteroid sensitivity	25/32 (78)	217/388 (56)	242/420 (58)	.015
CR	32/33 (97)	374/397 (94)	406/430 (94)	1
MRD1 ≥ 10 ⁻⁴ ‡	9/20 (45)	102/274 (37)	111/294 (38)	.5

Comparison of the clinicobiologic characteristics of PTPN2-deleted and wild-type T-ALL patients in the whole cohort. TCR status and oncogenetics were determined as previously described.^{4,21,23} Bold *P* values are statistically significant (*P* < .05).

CNS, central nervous system; CR, complete remission; del, deleted; IM0, no TCR rearrangement; IMB, VDJ rearrangement of TCRβ is observed; IMD, only TCRδ rearrangement is observed; IMG, both TCRδ and TCRγ rearrangements are observed; WBC, white blood cell count; WT, wild-type.

*Monoallelic 16/33; biallelic 17/33.

†Detailed data in supplemental Figure 3.

‡MRD was centrally assessed by real-time quantitative allele-specific oligonucleotide polymerase chain reaction and interpreted according to EuroMRD group guidelines.^{34,35}

Tables 5 and 6). High-resolution array CGH was performed for a subset of 88 of the 430 patients analyzed by MLPA (supplemental Figure 2) and identified 7 PTPN2 deletions all also identified by MLPA analysis. These deletions encompassed the entire gene (Figure 1A), and all were also found by MLPA (Figure 1B). PTPN2-deleted patients had significantly lower messenger RNA (mRNA) expression than those with no alteration of PTPN2 copy number (Figure 1C). No significant difference was seen in mRNA expression levels between samples with monoallelic or biallelic deletion of PTPN2 (data not shown).

PTPN2 deletions associate with IL7R/JAK-STAT mutations and are mutually exclusive from PTEN deletions/mutations

Regarding oncogenetics features, we confirmed the significant association between PTPN2 deletions and TLX1 expression as well as NUP214-ABL fusion^{7,8} (Table 1; supplemental Figure 3). Indeed, 48% and 21% of PTPN2-deleted T-ALLs expressed TLX1 and NUP214-ABL, respectively, vs 13% and 7% of cases with wild-type PTPN2. In line with these observations, a strong association of PTPN2 deletions with the αβ lineage TCR status of T-ALL was observed (*P* = .009; Table 1). In contrast to published data, not all

PTPN2-deleted patients expressed TLX1/3 because at least 11 cases were TLX1/3 negative (Table 1).

Interestingly, in this large cohort of 430 patients, all PTEN abnormalities were restricted to PTPN2 wild-type patients (*P* = .01; Table 1; Figure 2). Moreover, 85% of the PTPN2-deleted population presented mutations of NOTCH1/FBXW7 vs 63% of wild-type patients (*P* = .01; Table 1).

We then took advantage of our published next-generation sequencing data from 194 of the 216 adult patients included in this study.²⁵ Among those 194 patients, 19 harbored PTPN2 deletions. Overall, at least 1 mutation was detected in 19/19 PTPN2-deleted T-ALL and 173/175 wild-type patients. The comparison of the mutation and large deletion frequencies between PTPN2-deleted and wild-type patients is shown in Figure 2, with a focus on alterations presented by at least 5% of the whole cohort. Data regarding all the abnormalities are reported in supplemental Table 7.

A significant association between mutations in IL7R/JAK-STAT signaling pathway (including DNM2, SH2B3, STAT5B, IL7R, JAK3, JAK1) and PTPN2 deletions was observed. Indeed, mutations in the IL7R/JAK-STAT pathway were found in 14/19 (74%) of PTPN2-deleted T-ALL vs 72/175 (41%) of the wild-type cohort (*P* = .008) (Figure 2; supplemental Tables 8 and 9). A higher rate of PHF6 mutations, with 95% of mutations among PTPN2-deleted

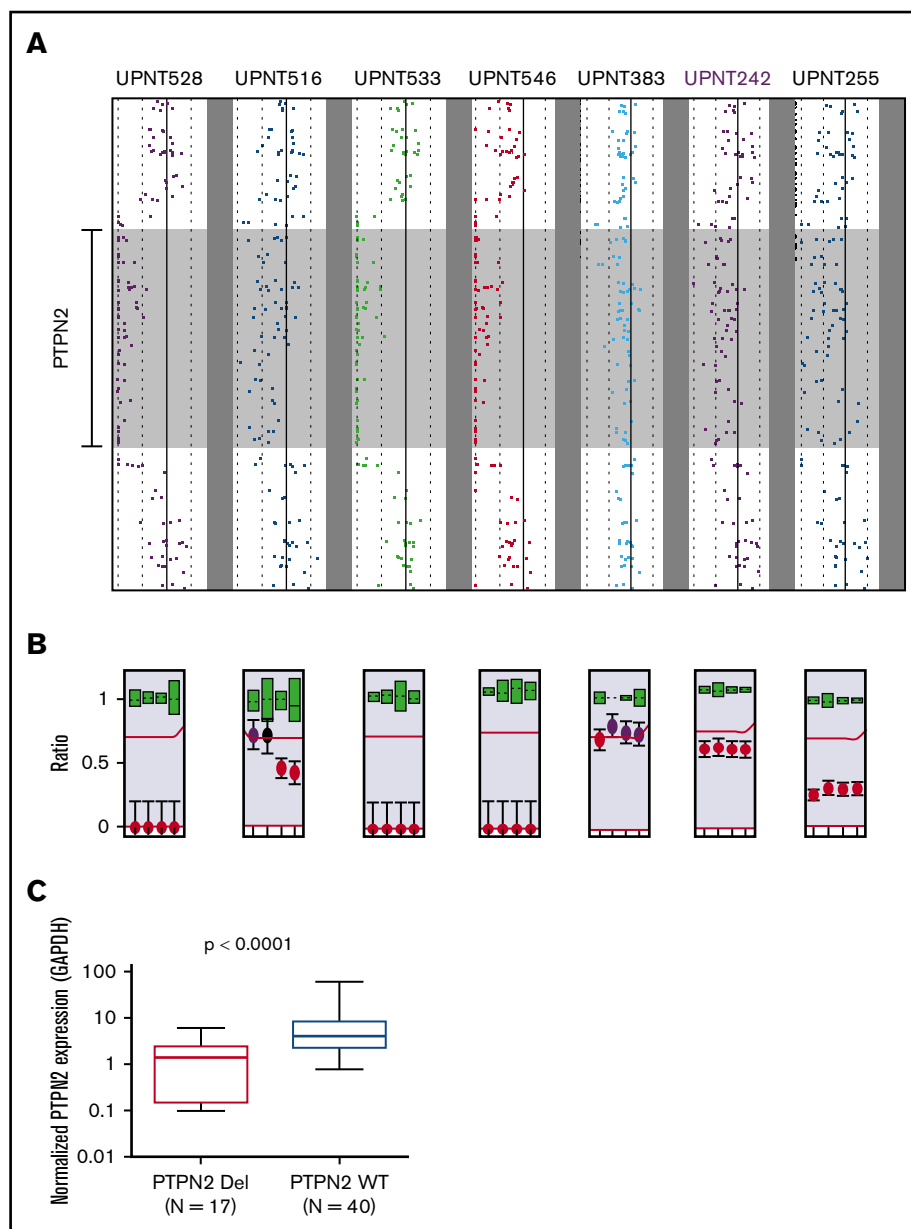


Figure 1. PTPN2 alterations. (A) PTPN2 deletions as identified by array CGH. Seven patients harboring deletions of the entire PTPN2 locus are represented. (B) Corresponding MLPA analyses. Patients UPNT516, UPNT383, UPNT242, and UPNT255 show monoallelic deletion of PTPN2, whereas patients UPNT528, UPNT533, and UPNT546 demonstrate biallelic deletions. (C) Quantitative real-time reverse transcription-polymerase chain reaction analysis of PTPN2 expression in T-ALL cases with (Del) or without (WT) PTPN2 deletion. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

patients vs 41% within the PTPN2 wild-type group, was also observed ($P < .0001$) (Figure 2; supplemental Table 8). Moreover, PTPN2 deletions and WT1 mutations were significantly associated, because 26% of PTPN2-deleted adults presented with WT1 mutations vs 10% among PTPN2 wild-type T-ALL ($P = .047$) (Figure 2; supplemental Table 8). Conversely, none of the analyzed pathways was mutually exclusive from PTPN2 deletions except PTEN deletions/mutations.

Prognostic impact of PTPN2 deletions in adult and pediatric patients

Among the entire cohort, the median age of PTPN2-deleted patients was 27.4 years, significantly older than wild-type patients (Table 1; supplemental Figure 4). There was no statistically significant difference regarding the main other clinical characteristics analyzed.

Despite this, the treatment response differed between the 2 groups because the corticosenitivity rate was higher among PTPN2-deleted (25/32, 78%) than wild-type patients (217/388 [56%]; Table 1). Complete remission and minimal residual disease (MRD) rates were not significantly different (Table 1).

In adults, we observed no significant differences in either 5-year CIR (deleted PTPN2, 32%; 95% confidence interval [CI], 16% to 59% vs wild-type PTPN2, 30%; 95% CI, 24% to 37%; $P = .988$) or 5-year OS (deleted PTPN2, 62%; 95% CI, 36% to 80% vs wild-type PTPN2, 66%; 95% CI, 59% to 73%; $P = .843$) (Figure 3A,C).

In contrast, we noted a trend in better survival in the pediatric population. Indeed, 5-year CIR was 8% (95% CI, 1% to 43%) among PTPN2-deleted pediatric patients vs 26% (95% CI, 20% to 33%; $P = .177$), and 5-year OS was 92% (95% CI, 54% to 99%)

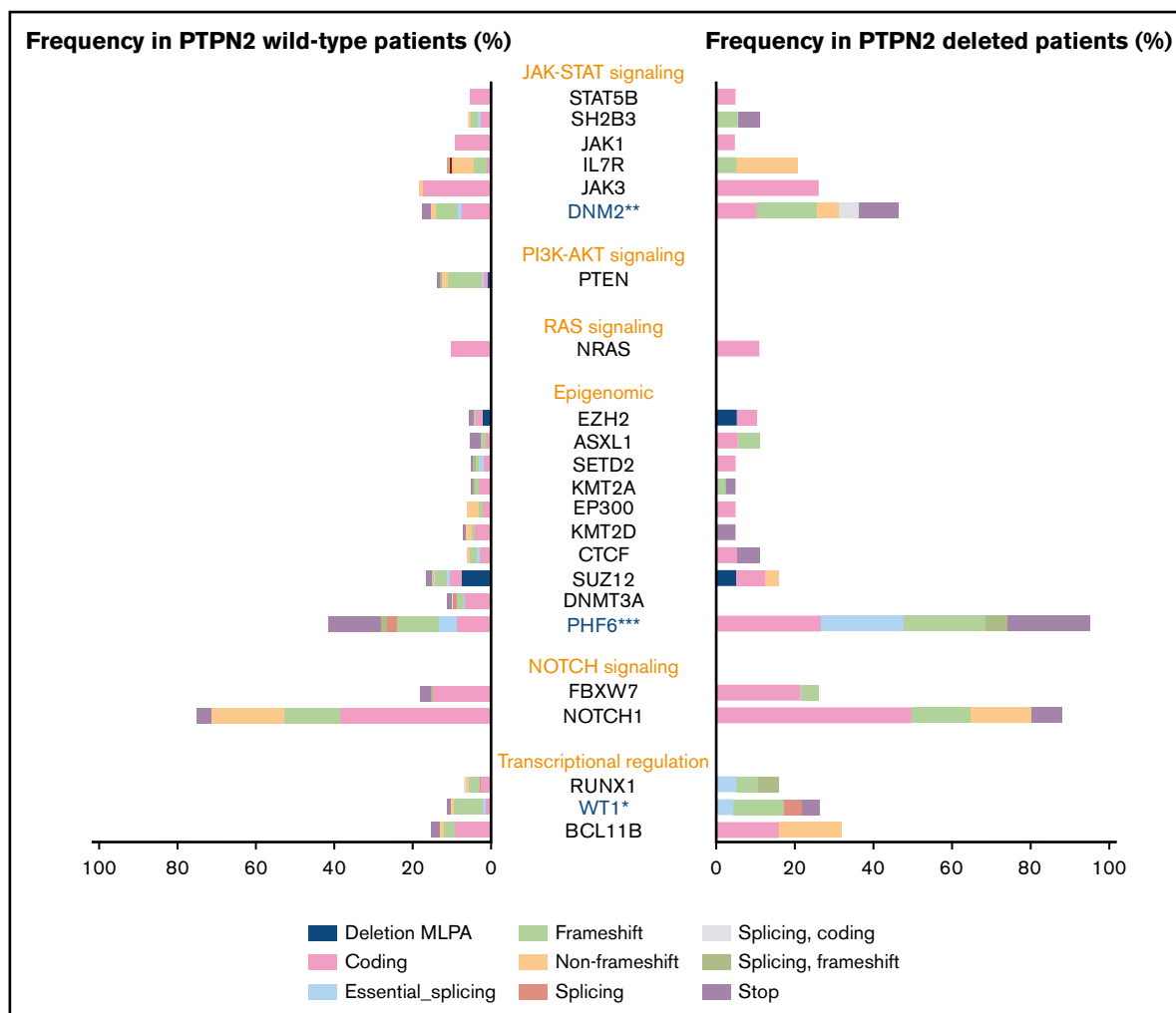


Figure 2. Genetic profile of PTPN2-deleted adult T-ALL. Comparison of the mutational genotypes and large deletions of adult PTPN2-deleted (N = 19) and wild-type adult T-ALLs (N = 175), with a focus on alterations found in at least 5% of the whole cohort. Percentage frequencies in each group are indicated. Mutations are color coded according to type, as depicted. Genes are grouped by functional categories. * $P < .05$; ** $P = .004$; *** $P < .0001$.

among PTPN2-deleted cases vs 78% (95% CI, 71% to 83%; $P = .234$) (Figure 3B,D). Altogether, these data suggest that PTPN2 deletions are not associated with poor outcome in either adult or pediatric T-ALL.

Discussion

This study provided a comprehensive analysis of PTPN2 deletions in a fully characterized cohort of 430 T-ALL patients. The previously described 8% incidence of deletions of the entire PTPN2 locus was confirmed,^{7,8,24} but we observed that deletion rates are similar in the adult and pediatric populations, in contrast to a previous study reporting a higher prevalence of PTPN2 alterations in adults.²⁴ This discrepancy is likely explained by the larger size of the adult cohort reported here.

The equilibrium between protein tyrosine kinases and protein tyrosine phosphatases is essential for normal cellular signaling, and this balance is often disrupted in cancer.²⁶ PTPN2 is a phosphatase whose loss sensitizes the leukemic cells to cytokine stimulation, thus supporting T-ALL proliferation through the activation of

multiple cytokine receptor pathways, such as JAK-STAT.^{7,8,19} In line with this, we report a significant association between PTPN2 deletions and mutations in the IL7R/JAK-STAT signaling pathway, especially DNM2. DNM2 is a GTPase involved in clathrin-dependent endocytosis.²⁷ The role of DNM2 loss-of-function mutations in T-ALL has recently been deciphered²⁸ with DNM2 mutations impairing IL7R endocytosis and increasing cell surface receptor expression. As such, DNM2 mutations enhance interleukin-7 signaling and could have an additive effect to PTPN2 deletions in promoting T-ALL progression.

Kleppe et al have identified NUP214-ABL kinase as a substrate of PTPN2⁷ and have demonstrated in vitro oncogenic synergy between NUP214-ABL expression and PTPN2 downregulation. Our data are consistent with these observations, because we observed a significant association of PTPN2 deletions with the NUP214-ABL fusion protein in T-ALL. In addition, Vicente et al have reported a significant association between epigenetic regulators, including PRC2, WT1, and PHF6, and mutations in the IL7R/JAK-STAT pathway.²⁴ Our data are partly concordant with this observation because we found a strong

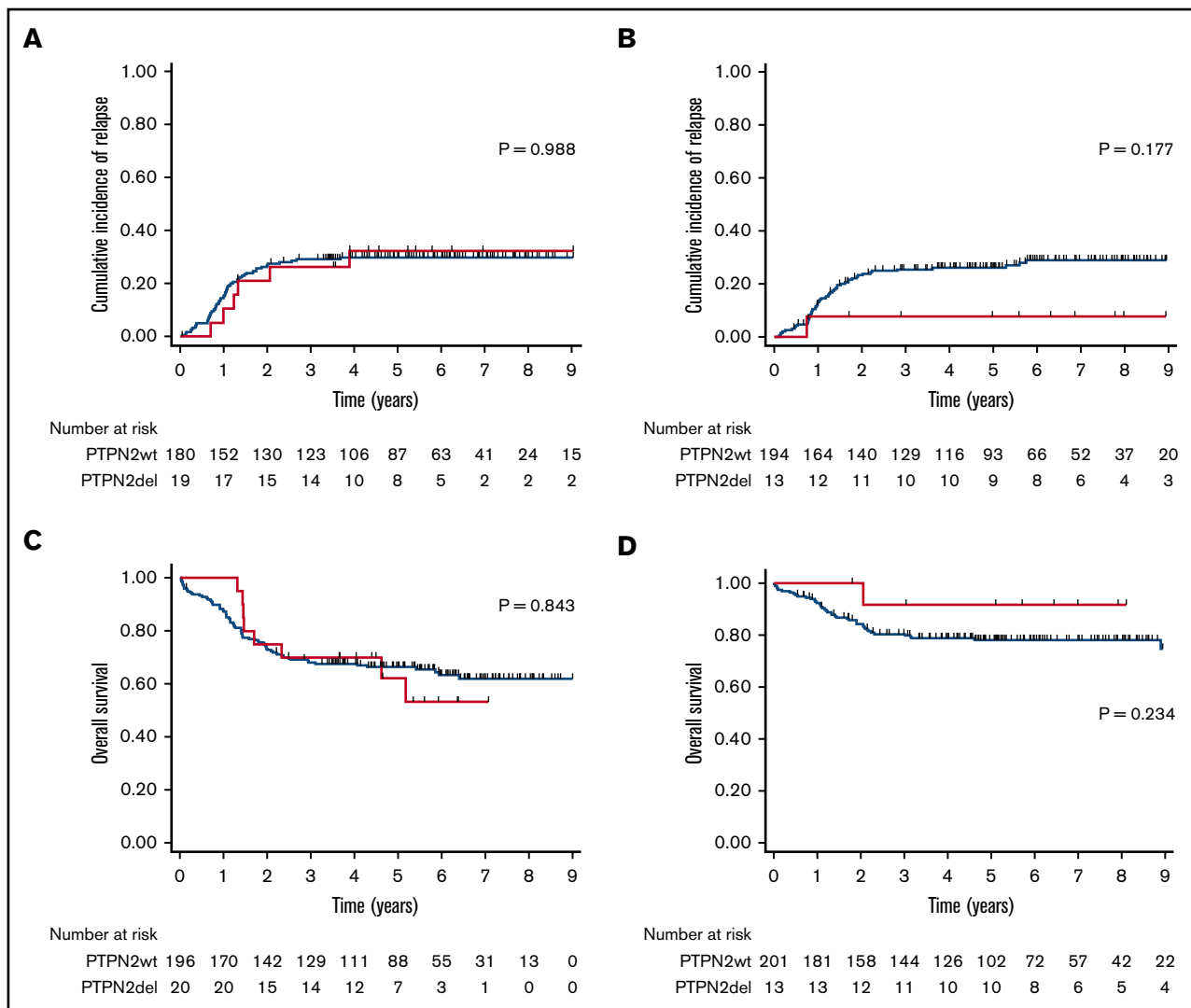


Figure 3. Survival according to PTPN2 status. CIR in the adult (A) and pediatric (B) cohort. OS in the adult (C) and pediatric (D) cohort. Red curves represent PTPN2-deleted T-ALL, and blue curves indicate PTPN2 wild-type patients. *P* values are indicated.

association between PHF6 and PTPN2 mutations and, to a lesser extent, WT1 and PTPN2 mutations, but we did not detect any significant correlation between mutations of the PRC2 complex and PTPN2.

To date, most of PTPN2-deleted T-ALL cases have been identified among TLX1- or TLX3-positive subgroups.^{7-9,24} We confirm the significant association between PTPN2 deletions and TLX1 expression in both the adult and the pediatric cohorts. These findings are also in line with previously described associations between DNM2 and PHF6 alterations and TLX1/TLX3 overexpression.^{9,29}

Interestingly, PTPN2-deleted T-ALL patients show a highly significant association with the $\alpha\beta$ lineage TCR status. This is in contrast to data from Wiede et al, who developed genetic and pharmacologic murine models of PTPN2 inactivation to demonstrate that PTPN2 deficiency promotes $\gamma\delta$ T-cell growth in an LCK- and STAT5-dependent manner.³⁰ One may hypothesize either that PTPN2 deletion may have different consequences depending on the oncogenic context or that murine models have their limits.

Alternatively, these data could suggest that PTPN2 is a candidate for an $\alpha\beta$ lineage differentiation arrest of thymic maturation.

PTEN is the most commonly inactivated phosphatase in T-ALLs, accounting for ~10% to 15% of cases. Its loss of function drives leukemogenesis.³¹ Large deletions and mutations within the exon 7 hot spot are known to impact prognosis.³² Thus, we wondered about the cooccurrence of both PTPN2 and PTEN deletions. Importantly, we observed no PTEN alteration among the patients with PTPN2 deletions. This observation was independent of age, because it was noted in both adult and pediatric patients. We hypothesize that PTEN and PTPN2 pathways could be functionally incompatible, as recently demonstrated for TAL1 and IL7R/JAK-STAT signaling cascades.³³ Functional experiments are needed to understand the mutual exclusion of these 2 phosphatase alterations in T-ALL.

To date, the clinical impact of PTPN2 deletions is unknown. Our study reveals that PTPN2 deletions tend to associate with an improved CIR and OS in the pediatric cohort. Because survival data were only available for 13 PTPN2-deleted pediatric T-ALL, this

study may not be powered to identify a significant difference. On the contrary, we did not observe any survival difference according to PTPN2 deletions within the adult population.

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Authorship

Contribution: M.A. analyzed the data, made the figures, and wrote the paper; M.A., M.S., A.T., M.E.D., N.G., J.M.C., Y.C., C.G., H.D., N.I.,

A.P., E.M., A.B., and N.B. collected and analyzed the clinical data; L.L., A.T., M.L., N.G., J.M.C., and V.A. performed and analyzed the biological annotations; N.B. performed the statistical analyses; N.I., H.D., and A.B. were principal investigators of GRAALL and FRALLE clinical trials; and V.A. designed and supervised the study.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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