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Genomic and clinical characterization of early T-cell precursor lymphoblastic lymphoma

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Key Points

- Like T lymphoblastic leukemia, a subset of T lymphoblastic lymphomas shows an early T-cell phenotype.
- Early T-cell phenotype T lymphoblastic lymphomas show recurrent genomic changes distinct from other cases of T lymphoblastic lymphoma.

Early T-cell precursor phenotype acute lymphoblastic leukemia (ETP-ALL) is a subtype of T-ALL with a unique immunophenotype and genetic abnormalities distinct from conventional T-ALL. A subset of T lymphoblastic lymphoma (T-LLy) also demonstrates the early T-cell precursor immunophenotype and may be a counterpart of ETP-ALL. Unlike ETP-ALL, the incidence, clinical features, and genomic features of ETP-LLy are unknown. We reviewed the immunophenotyping data of 218 T-LLy patients who enrolled in the Children's Oncology Group AALL0434 clinical trial and identified 9 cases (4%) exhibiting a definitive ETP immunophenotype. We performed single-nucleotide polymorphism array profiling on 9 ETP-LLy and 15 non-ETP T-LLy cases. Compared with non-ETP T-LLy, ETP-LLy showed less frequent deletion of 9p (*CKDN2A/B*), more frequent deletion of 12p (*ETV6*) and 1p (*RPL22*), and more frequent absence of biallelic T-cell receptor γ deletions. Recurrent abnormalities previously described in ETP-ALL such as deletions of 5q and 13q and gain of 6q were not observed in ETP-LLy cases. There were no failures of therapy among the ETP-LLy subtype with a 4-year event-free survival of 100%. Overall, ETP-LLy does not exhibit unifying genetic alterations but shows some distinct genomic features from non-ETP T-LLy suggesting that ETP-LLy may be a distinct entity from non-ETP T-LLy.

Introduction

T-cell lymphoblastic lymphoma (T-LLy) is an aggressive neoplasm of immature T-cell precursors and represents 25% to 30% of childhood non-Hodgkin lymphoma.¹ It is classified as an overlapping entity with T-cell acute lymphoblastic leukemia (T-ALL) in the 2017 World Health Organization classification because they share morphologic and immunophenotypic features and are treated with similar strategies.² Despite these similarities, clinical and molecular differences have been established suggesting potential

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The SNP array data have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE168884 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE168884>).

The full-text version of this article contains a data supplement.

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pathogenetic differences. T-LLy and T-ALL share many clinical features, often presenting with an extramedullary mass in the mediastinum and/or lymph nodes. T-ALL by definition displays primary bone marrow involvement (defined as >25% bone marrow blasts).² Genomic and gene expression studies have shown that T-LLy and T-ALL have different transcriptional and genetic characteristics.³⁻⁵ For example, genes involved in chemotactic responses and angiogenesis are differentially expressed⁵ and a copy number gain on chromosome 22q including the *PIM3* oncogene is specifically found in T-ALL. However, the genomic abnormalities of T-LLy are not well-characterized because of the lack of fresh or frozen samples required for most genomic studies.

Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a subtype of T-ALL that shows an early T-cell precursor immunophenotype (CD1a⁻, CD8⁻, CD5⁻ or weakly positive, CD34/myeloid antigen positive).^{2,6} Initial reports suggested that ETP-ALL was a high risk T-ALL subset with poor survival, but outcomes are comparable to non-ETP T-ALL in more recent studies.⁷⁻⁹ ETP-ALL demonstrates genetic abnormalities distinct from conventional T-ALL including less frequent deletions of *CDKN2A/B* and more frequent absence of biallelic T-cell receptor (TCR) γ deletion (ABD).¹⁰⁻¹³ ETP-ALL also exhibits some genetic abnormalities also observed in acute myeloid leukemia with less frequent *NOTCH1* mutations; frequent mutations in *FLT3*, *DNMT3A*, *RAS*, and *IDH* genes; and 5q and 13q deletions.^{14,15} The World Health Organization 2017 classification of ALL included ETP-ALL as a provisional entity.² A subset of T-LLy with an ETP immunophenotype has been described, suggesting that there may be an early T-cell precursor lymphoblastic lymphoma (ETP-LLy) counterpart of ETP-ALL.¹⁶ Unlike ETP-ALL, the incidence, clinical features, and genomic features of ETP-LLy are unknown.

In the present study, we sought to assess the incidence of ETP-LLy among a large cohort of T-LLy patients treated on the Children's Oncology Group (COG) AALL0434 trial,^{17,18} and to compare the copy number profiles of ETP-LLy and non-ETP T-LLy using DNA isolated from archival formalin-fixed, paraffin-embedded (FFPE) samples. Our study provides an initial understanding of the genetic landscape of ETP-LLy and indicates that the underlying pathogenic mechanisms of ETP-LLy may differ from non-ETP T-LLy.

Methods

COG AALL0434 was a phase 3 trial developed for children, adolescents, and young adults 1 to 30.99 years old with T-ALL and T-LLy. AALL0434 was approved by the National Cancer Institute, Cancer Therapy Evaluation Program, Food and Drug Administration, and the Pediatric Central institutional review board, and by institutional review boards at each participating center. In accordance with the Declaration of Helsinki, informed consent/assent was obtained before study entry. The details and results of AALL0434 have been reported previously.¹⁸⁻²¹

Central pathology review of immunophenotyping data, including flow cytometry and immunohistochemistry, was performed for all T-LLy patients enrolled in AALL0434 to identify ETP cases according to the definition published by Costain-Smith et al.⁶ Cases were considered ETP if they were CD1a⁻, CD8⁻, CD5⁻ or weak, and expressed at least 1 of the following stem/myeloid markers: CD34, CD13, CD33, CD117. Non-ETP T-LLy cases selected for comparison were required to express CD1a, CD5, and CD8. Clinical parameters

including patient age, sex, and Murphy stage were extracted, and cytogenetic data were reviewed when available. The institutional review board of the University of Utah approved this study, and use of COG specimens was approved under study number ANHL17B1-Q.

Unstained slides leftover from central pathology review were used for DNA isolation. An hematoxylin and eosin stain was reviewed on each case to verify at least 80% tumor cells in sections. FFPE tissue from 10 slides per case was scraped into tubes, and DNA was isolated using the RecoverAll Total Nucleic Acid Isolation kit (Ambion/Applied Biosystems, Austin, TX) and quantitated with the PicoGreen assay (Invitrogen).

Genomic microarray hybridization was performed using OncoScan FFPE molecular inversion probe single-nucleotide polymorphism assay (MIP SNP, Affymetrix/ThermoFisher, Santa Clara, CA). The MIP SNP array was performed as previously described.^{22,23} Analysis was performed using Nexus copy number software version (version 8.0; BioDiscovery, El Segundo, CA) and Chromosome Analysis Suite (version 3.3; Applied Biosystems, Santa Clara, CA). Data that passed quality control criteria of the array (MAPD value < 0.6) were analyzed using Nexus Copy Number software and Chromosome Analysis Suite with NCBI build 37.0 of the human genome. The SNP-TuScan segmentation algorithm and default settings for significance and number of probes per segment were used. Minimal threshold setting of log2ratio for absence of biallelic ABD was -1.5 and a minimum of 5 probes per segment were required to determine the presence of ABD. Both number and size of copy number aberrations (CNAs) were used to measure the level of genomic instability in non-ETP T-LLy and ETP-LLy.⁶ The SNP array data have been deposited in NCBI's Gene Expression Omnibus²⁴ and are accessible through GEO Series accession number GSE168884 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE168884>).

Pairwise comparisons were made using the Fisher's exact test, and continuous variable were compared using the *t* test. Two-tailed *P* values are reported and were considered significant when *P* < .05. Survival analysis was performed using Kaplan-Meier curves.

Results

A total of 24 patient samples were analyzed. Nine ETP-LLy cases were identified using the criteria previously presented, and 15 non-ETP-LLy cases were randomly selected for comparison from among the remaining cases with non-ETP phenotypes and adequate tissue.

The clinical characteristics of the T-LLy patients are shown in supplemental Table 1. The mean age was 10.7 years (range, 1-23) with a male:female ratio of 2.0 for all 24 patients in the study. Patients were classified as Murphy stage 2 (*n* = 1), 3 (*n* = 9), or 4 (*n* = 9); staging data were not available on 5 patients.

A subset of T-LLy shows an ETP phenotype

A total of 9/218 T-LLy cases (4%) showed a definitive ETP phenotype as defined in the methods section (complete immunophenotyping data in supplemental Table 2). An additional 15 non-ETP cases were selected for comparison. There were no differences between ETP and non-ETP cases in age (10.3 vs 10.9, *P* = .8), male:female ratio (1.25 vs 2.75, *P* = .4), or stage (*P* = .35). In addition to the defined differences in immunophenotype, fewer ETP cases expressed CD2 (3/9 vs 13/15, *P* = .021) or CD4 (0/9 vs 14/15, *P* < .0001) than non-ETP cases.

Similarities and differences in the genetics lesions between ETP-LLy and non-ETP T-LLy

MIP SNP array was performed on the 24 cases (9 ETP-LLy and 15 non-ETP T-LLy) and identified CNAs and copy-neutral loss-of-heterozygosity (CN-LOH) (Figure 1). CNAs and/or CN-LOH were identified in 8 of 9 ETP-LLy cases and in 15/15 non-ETP T-LLy cases. The genetic lesions found by MIP SNP array for all 24 cases, along with cytogenetic results available in a subset of cases, are listed in Table 1. Genetic lesions observed in 2 or more ETP and/or non-ETP T-LLy cases were considered recurrent abnormalities and are summarized in Table 2. ETP-LLy cases showed significantly less frequent 9p deletion/CN-LOH than non-ETP T-LLy (4/9, 44% vs 14/15, 93%, $P = .015$; Figure 2A). All of the 9p deletion/CN-LOH lesions except case 21 include both *CDKN2A* and *CDKN2B* genes (Figure 2B; Table 1). The 9p deletion in case 21 (chr9: 21901262-21971430, hg19) includes exons 2-3 of the *CDKN2A* gene (NM_058195) but not the *CDKN2B* gene. Deletions of 12p including the *ETV6* gene were only observed in ETP-LLy (3/9, 33% in ETP-LLy vs 0/15, 0% in non-ETP T-LLy, $P = .042$; Figure 2C-D). The minimal common deleted region on 12p (chr12: 9c512c809-25c551,025, hg19; Figure 2D; Table 1) contains the *ETV6* gene. Deletions of 1p including the *RPL22* gene were only observed in ETP-LLy (4/9, 44% in ETP-LLy vs 0/15, 0% in non-ETP T-LLy, $P = .012$; Figure 2E-F). The minimal common deleted region on 1p (chr1: 3c921c449-7c050c061, hg19) seen in case 23 includes the *RPL22* gene (Figure 2F; Table 1).

Deletions of the TCR gene regions are a normal part of TCR rearrangement and can be detected by SNP array in a clonal population. ABD

at 7p14.1 is more frequent in ETP-LLy compared with non-ETP T-LLy (8/9, 88.9% in ETP-LLy vs 5/15, 33.3% in non-ETP T-LLy, $P = .013$).

Focal *PHF6* deletions on Xq and gain of *NUP214-ABL1* fusion on 9q were observed together in 2 cases, 1 non-ETP T-LLy case (case 11) and 1 ETP-LLy case (case 23) (Tables 1 and 2). Two non-ETP T-LLy cases (cases 14 and 15) were noted to have *CHIC2* deletions. *CHIC2* deletions result in *FIP1L1-PDGFR*A fusion and up-regulated tyrosine kinase activity. They have been described in chronic eosinophilia as well as T/myeloid proliferations that can present as acute myeloid leukemia, T-LLy, or both, which are often associated with eosinophilia.² Neither of the cases showed increased eosinophils in the blood (0.7 and 0.2 k/ μ L, respectively) or lymphoma tissue; however, the bone marrow pathology report for case 14 did note 17% eosinophils in the aspirate smear, whereas case 15 had 6%. A myeloid leukemia component was not reported in either case.

Previous SNP array analysis showed significantly more CNAs in ETP-ALL compared with non-ETP T-ALL, suggesting a higher genomic instability in ETP-ALL.⁶ In our study, ETP-LLy cases showed a trend but not significantly more or larger CNAs than the non-ETP T-LLy cases (Table 3).

Correlation between cytogenetic and MIP SNP array studies

Chromosome and/or fluorescence in situ hybridization (FISH) results are available for 7 cases including 5 non-ETP T-LLy and 2 ETP-LLy cases (Table 1). MIP SNP array detected unbalanced rearrangements observed by chromosome or FISH studies including the

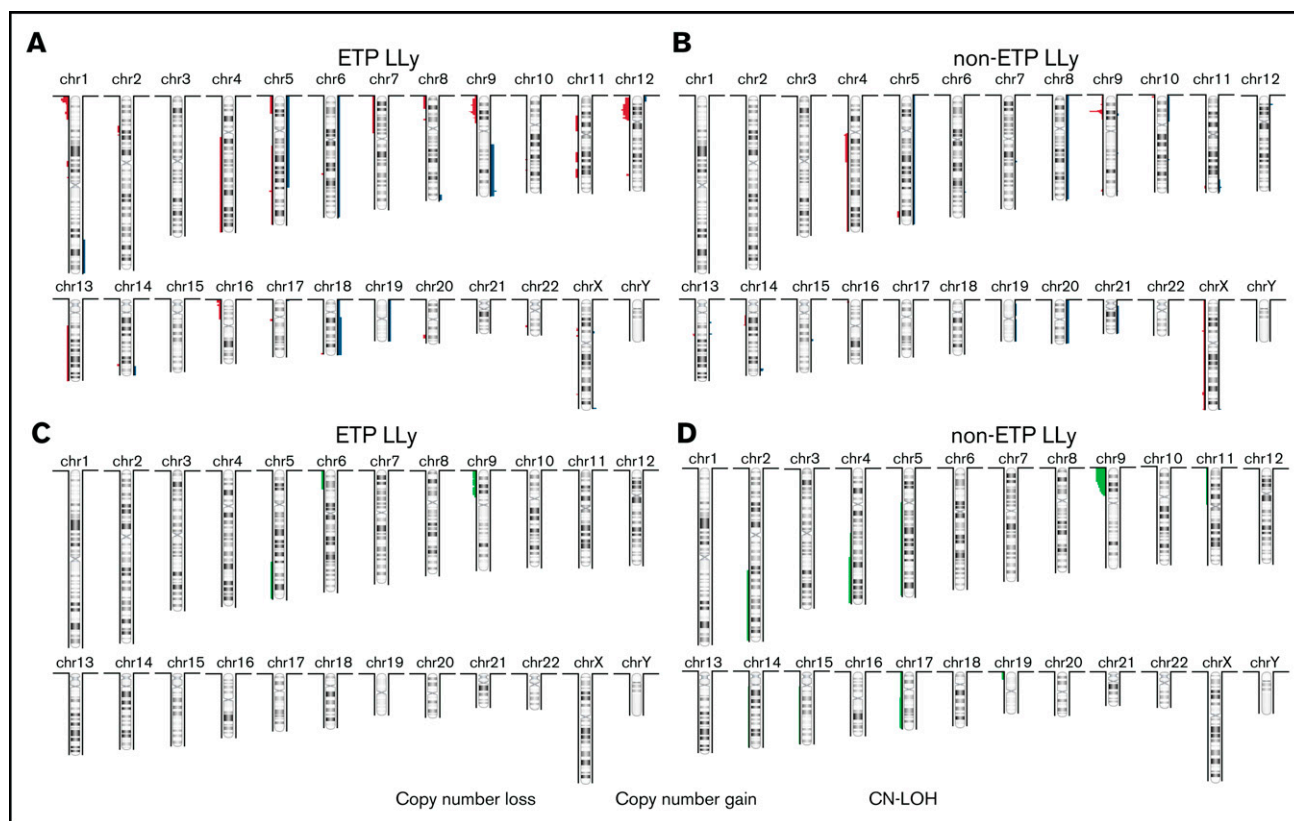


Figure 1. Summary of copy number aberrations (CNAs). (A-B) and copy-neutral loss-of-heterozygosity (CN-LOH) (C-D) in ETP-LLy (A,C) and non-ETP T-LLy (B,D). In panels A and B, losses are to the left and gains are to the right, and the amplitude reflects the incidence.

Table 1. Complete list of copy number abnormalities and loss of heterozygosity by SNP array for each case

Case no.	Chromosome region	Cytoband	Event	Length (Mb)	Cytogenetic study
1	chr9:204c738-36c232,413	p24.3-p13.3	CN-LOH	36.03	NA
	chr9:21c778,976-22c081,850	p21.3	Homozygous deletion	0.30	
	chr9:133c510,616-133c730,353	q34.12	Deletion	0.22	
	chr11:192c764-51c575,951	p15.5-p11.12	CN-LOH	51.38	
	chr14:22c922,369-36c982,350	q11.2-q13.3	Deletion	14.06	
	chr17:37c291,349-80c263,427	q12-q25.3	CN-LOH	42.97	
2	chr9:204c738-23c386,738	p24.3-p21.3	CN-LOH	23.18	NA
	chr9:21c856,470-22c176,560	p21.3	Homozygous deletion	0.32	
	chr10:0-36c046,475	p15.3-p11.21	Gain	36.05	
	chr10:89c617,344-90c167,065	q23.31	High copy gain, CN = 4	0.55	
	chr14:98c086,294-99c793,689	q32.2	Gain	1.71	
	chrX:0-155c270,560	p22.33-q28	Deletion	155.27	
3	chr9:204c738-27c123,260	p24.3-p21.2	CN-LOH	26.92	46,XY,t ^{1,14} (³² P;q11.2)[6]/46XY[9] (TAL1-TCR fusion)
	chr9:21c331,119-22c549,702	p21.3	Homozygous deletion	1.22	
4	chr5:38c139-180c698,312	p15.33-q35.3	Gain	180.66	NA
	chr9:19c277,320-21c853,221	p22.1-p21.3	Deletion	2.58	
	chr9:21c856,470-22c004,153	p21.3	Homozygous deletion	0.15	
	chr9:22c004,669-23c897,432	p21.3	Deletion	1.89	
	chr20:69c094-15c687,866	p13-p12.1	Gain	15.62	
	chr20:15c691,240-15c792,451	p12.1	Gain	0.10	
	chr20:15c795,175-62c912,463	p12.1-q13.33	Gain	47.12	
5	chr6:135c483,742-135c754,471	q23.3	High copy gain, CN = 4	0.27	47,XY,t11,19(q23;p13.3), +der(19)t11,19[5]/46,XY[21]; FISH positive for MLL rearrangement in 7.5% cells
	chr9:204c738-39c184,065	p24.3-p13.1	CN-LOH	38.98	
	chr10:607c980-718c912	p15.3	Deletion	0.11	
	chr11:118c411,424-134c938,847	q23.3-q25	Gain	16.53	
	chr13:32c929,387-32c952,164	q13.1	Gain	0.02	
	chr19:6c585c298-23c460,785	p13.3-p12	Gain	16.88	
	chr19:28c462,580-59c093,239	q11-q13.43	Gain	30.63	
	chrX:154c979,673-155c219,364	q28	Gain	0.24	
6	chr5:48c877,508-180c915,260	q11.1-q35.3	CN-LOH	132.04	NA
	chr9:204c738-21c951,040	p24.3-p21.3	Deletion	21.75	
	chr9:21c953,099-25c029,497	p21.3	Homozygous deletion	3.08	
	chr9:25c049,865-27c722,059	p21.3-p21.2	Gain	2.67	
	chr13:48c984,722-49c065,037	q14.2	Homozygous deletion	0.08	
	chr14:36c649,246-36c949,593	q13.3	Deletion	0.30	
	chrX:154c979,673-155c219,364	q28	Deletion	0.24	
7	chr4:52c657,621-191c154,276	q11-q35.2	Deletion	138.50	FISH positive for nullisomy of CDKN2A (9p21) gene in 88% cells; karyotype NA
	chr8:0-146c364,022	p23.3-q24.3	Gain	146.36	
	chr9:11c311,712-13c036,747	p23	Deletion	1.73	
	chr9:21c242,161-21c813,718	p21.3	Deletion	0.57	
	chr9:21c816,528-22c655,723	p21.3	Homozygous deletion	0.84	
	chr9:22c669,166-23c694,188	p21.3	Deletion	1.03	
	chr13:19c084,823-115c103,150	q11-q34	Gain	96.02	

The last column includes karyotype and/or FISH data when available. Cases 1-15 are non-ETP T-LLy; cases 16-24 are ETP-LLy. NA, not available.

Table 1. (continued)

Case no.	Chromosome region	Cytoband	Event	Length (Mb)	Cytogenetic study
	chr15:22c752,399-102c397,317	q11.2-q26.3	CN-LOH	79.64	
	chr17:0-81c195,210	p13.3-q25.3	CN-LOH	81.20	
	chr19:247c232-10c976,405	p13.3-p13.2	CN-LOH	10.73	
	chr21:9c648c315-48c097,610	p11.2-q22.3	Gain	38.45	
8	chr4:126c144,980-191c154,276	q28.1-q35.2	CN-LOH	65.01	FISH negative for BCR-ABL, karyotype NA
	chr9:204c738-33c282,392	p24.3-p13.3	CN-LOH	33.08	
	chr9:21c901,263-21c993,964	p21.3	Homozygous deletion	0.09	
	chr16:3c892c461-4c518c754	p13.3	Deletion	0.63	
9	chr9:62c209-19c471,279	p24.3-p22.1	CN-LOH	19.41	NA
	chr9:19c628,633-32c741,593	p22.1-p21.1	Deletion	13.11	
	chr11:127c117,212-129c553,078	q24.2-q24.3	Deletion	2.44	
10	chr9:204c738-36c489,161	p24.3-p13.2	CN-LOH	36.28	NA
	chr9:21c827,992-22c008,313	p21.3	Homozygous deletion	0.18	
11	chr2:144c545,138-243c052,331	q22.3-q37.3	CN-LOH	98.51	NA
	chr2:213c584,595-214c009,831	q34	Deletion	0.43	
	chr9:21c901,263-21c993,468	p21.3	Homozygous deletion	0.09	
	chr9:21c993,964-22c098,619	p21.3	Deletion	0.10	
	chr9:133c719,421-134c094,802	q34.12-q34.13	Gain	0.38	
	chr13:48c984,722-49c065,037	q14.2	Homozygous deletion	0.08	
	chr13:50c652,628-51c516,305	q14.2-q14.3	Deletion	0.86	
	chrX:130c973,820-134c581,228	q26.2-q26.3	Deletion	3.61	
12	chr9:131c468,740-133c828,128	q34.11-q34.12	Deletion	2.36	NA
13	chr5:162c623,390-170c762,448	q34-q35.1	Deletion	8.14	NA
	chr9:20c678,439-21c987,472	p21.3	Deletion	1.31	
	chr9:21c988,896-22c207,037	p21.3	Homozygous deletion	0.22	
	chr11:114c990,423-118c489,708	q23.3	CN-LOH	3.50	
	chr14:22c187,584-107c282,024	q11.2-q32.33	CN-LOH	85.09	
14	chr4:54c296,381-55c130,682	q12	Deletion	0.83	Normal karyotype
	chr9:204c738-39c184,065	p24.3-p13.1	CN-LOH	38.98	
	chr9:21c928,654-22c114,495	p21.3	Deletion	0.19	
	chrX:44c810,604-44c896,206	p11.3	Homozygous deletion	0.09	
15	chr4:54c324,930-55c102,425	q12	Deletion	0.78	NA
	chr4:55c105,182-64c560,949	q12-q13.1	Deletion	9.46	
	chr4:64c573,303-83c148,663	q13.1-q21.22	Deletion	18.58	
	chr4:83c164,184-93c288,641	q21.22-q22.1	Deletion	10.12	
	chr4:92c607,449-191c154,276	q22.1-q35.2	CN-LOH	98.55	
	chr6:135c293,365-135c754,471	q23.3	High copy gain, CN = 4	0.46	
	chr7:92c245,458-92c471,899	q21.2	High copy gain, CN = 4 – 5	0.23	
	chr9:204c738-39c184,065	p24.3-p13.1	CN-LOH	38.98	
	chr9:21c965,073-22c014,524	p21.3	Homozygous deletion	0.05	
	chr9:80c446,364-80c704,731	q21.2	High copy gain, CN = 4 – 5	0.26	
	chr11:128c157,643-128c615,486	q24.3	Gain	0.46	
	chr12:11c795,269-12c059,452	p13.2	Gain	0.26	
	chr13:48c885,423-49c262,256	q14.2	Gain	0.38	
	chr14:98c100,176-100c100,128	q32.2	Gain	2.00	
	chr15:56c642,839-58c955,123	q21.3	Gain	2.31	

The last column includes karyotype and/or FISH data when available. Cases 1-15 are non-ETP T-LLy; cases 16-24 are ETP-LLy. NA, not available.

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Table 1. (continued)

Case no.	Chromosome region	Cytoband	Event	Length (Mb)	Cytogenetic study
16	chr11:79c517,863-93c209,472	q14.1-q21	Deletion	13.69	46,XX,t7,12(p13;p13), ?add17(p11.2)[16]/46,XX[11]
17	chr1:202c643,208-249c212,878	q32.1-q44	Gain	46.57	51,XY,+5,del5(q31),+6, +del9(p13),?inv9(p24q21)x2, der(11)t1,11(q32;q?230,+18, +19[9]; FISH positive for 9p21 homozygous deletion in 89% cells; negative for MLL rearrangement and BCR-ABL fusion.
	chr5:38c139-128c975,230	p15.33-q23.3	Gain	128.94	
	chr5:128c846,774-180c698,312	q23.3-q35.3	CN-LOH	51.85	
	chr6:204c909-31c553,468	p25.3-p21.33	Gain	31.35	
	chr6:31c555,130-32c162,418	p21.33-p21.32	Gain	0.61	
	chr6:32c167,778-170c913,051	p21.32-q27	Gain	138.75	
	chr8:138c891,978-146c292,734	q24.23-q24.3	Gain	7.40	
	chr9:0-12c042,349	p24.3-p23	CN-LOH	12.04	
	chr9:12c054,659-13c345,642	p23	Homozygous deletion	1.29	
	chr9:13c354,725-21c585,658	p23-p21.3	CN-LOH	8.23	
	chr9:21c604,067-24c075,082	p21.3	Homozygous deletion	2.47	
	chr9:24c044,951-38c802,685	p21.3-p13.1	CN-LOH	14.76	
	chr9:68c170,421-141c054,761	q13-q34.3	Gain	72.88	
	chr14:95c161,449-107c282,024	q32.13-q32.33	Gain	12.12	
	chr18:0-78c077,248	p11.32-q23	Gain	78.08	
	chr19:0-59c128,983	p13.3-q13.43	Gain	59.13	
18	Normal female				NA
19	chr1:754c192-8c788c907	p36.33-p36.23	Deletion	8.03	NA
	chr1:91c967,341-99c114,927	p22.2-p21.3	Deletion	7.15	
	chr8:172c417-17c835,685	p23.3-p22	Deletion	17.66	
	chr10:89c432,286-90c306,376	q23.2-q23.31	Deletion	0.87	
	chr11:28c057,957-49c688,837	p14.1-p11.12	Deletion	21.63	
	chr12:189c400-25c551,025	p13.33-p12.1	Deletion	25.36	
	chr12:27c498,107-32c164,030	p11.23-p11.21	Deletion	4.67	
	chr17:400c959-1c461c125	p13.3	Gain	1.06	
	chrX:41c201,762-41c531,564	p11.4	Homozygous deletion	0.33	
	chrX:42c869,649-44c344,324	p11.3	Homozygous deletion	1.47	
	chrX:45c481,094-48c206,911	p11.3-p11.23	Gain	2.73	
	chrX:50c817,478-52c695,241	p11.22	Homozygous deletion	1.88	
	chrX:154c979,673-155c219,364	q28	Gain	0.24	
20	chr6:108c974,746-110c936,144	q21	Deletion	1.96	NA
	chr12:189c400-29c877,262	p13.33-p11.22	Deletion	29.69	
21	chr9:148c341-21c900,510	p24.3-p21.3	CN-LOH	21.75	NA
	chr9:21c900,511-21c971,583	p21.3	Homozygous deletion	0.07	
	chr9:21c971,584-34c406,287	p21.3-p13.3	CN-LOH	12.43	
22	chr1:754c192-33c899,167	p36.33-p35.1	Deletion	33.14	NA
	chr4:58c592,202-190c915,650	q12-q35.2	Deletion	132.32	
	chr5:38c139-24c037,074	p15.33-p14.2	Deletion	24.00	
	chr5:70c306,678-180c698,312	q13.2-q35.3	Deletion	110.39	
	chr7:41c421-52c432,938	p22.3-p12.1	Deletion	52.39	
	chr9:4c304c915-21c255,150	p24.2-p21.3	Deletion	16.95	
	chr9:21c265,500-25c891,012	p21.3-p21.2	Homozygous deletion	4.63	

The last column includes karyotype and/or FISH data when available. Cases 1-15 are non-ETP T-LLy; cases 16-24 are ETP-LLy. NA, not available.

Table 1. (continued)

Case no.	Chromosome region	Cytoband	Event	Length (Mb)	Cytogenetic study
	chr12:9c512c809-30c667,228	p13.31-p11.22	Deletion	21.15	
	chr13:36c912,708-115c103,150	q13.3-q34	Deletion	78.19	
	chr16:83c887-27c690,168	p13.3-p12.1	Deletion	27.61	
	chr18:26c057,437-78c007,784	q12.1-q23	Gain	51.95	
23	tetraploidy				NA
	chr1:3c921c449-7c050c061	p36.32-p36.31	Deletion, CN = 2	3.13	
	chr1:23c103,620-24c108,104	p36.12-p36.11	Deletion, CN = 2	1.00	
	chr1:114c594,372-115c470,556	p13.2	Deletion, CN = 2	0.88	
	chr2:54c374,691-55c005,224	p16.2-p16.1	Deletion, CN = 2	0.63	
	chr5:133c415,731-134c917,467	q31.1	Deletion, CN = 2	1.50	
	chr6:0-26c382,744	p25.3-p22.2	CN-LOH, CN = 4	26.38	
	chr8:33c078,287-33c503,454	p12	Deletion, CN = 2	0.43	
	chr9:30c001,529-30c721,717	p21.1	Deletion, CN = 2	0.72	
	chr9:133c618,461-134c097,558	q34.12-q34.13	High copy gain, CN = 6	0.48	
	chr10:104c369,298-104c562,842	q24.32	Deletion, CN = 2	0.19	
	chr11:103c091,553-114c475,360	q22.3-q23.2	Deletion, CN = 2	11.38	
	chr12:17c200,436-18c268,880	p12.3	Deletion, CN = 2	1.07	
	chr12:110c067,819-111c370,885	q24.11	Deletion, CN = 2	1.30	
	chr12:111c370,885-111c911,916	q24.11-q24.12	Homozygous deletion, CN = 0	0.54	
	chr12:111c911,916-112c035,561	q24.12	Deletion, CN = 2	0.12	
	chr14:91c600,426-94c111,212	q32.11-q32.12	Deletion, CN = 2	2.51	
	chr16:0-2c210c796	p13.3	Deletion, CN = 2	2.21	
	chr16:7c299c668-8c301c002	p13.3-p13.2	Deletion, CN = 2	1.00	
	chr17:27c957,832-29c631,473	q11.2	Deletion, CN = 2	1.67	
	chr17:29c631,473-29c897,502	q11.2	Homozygous deletion, CN = 0	0.27	
	chr17:29c897,502-30c692,775	q11.2	Deletion, CN = 2	0.80	
	chr18:76c375,122-77c458,776	q23	Deletion, CN = 2	1.08	
	chr20:49c176,050-53c504,956	q13.13-q13.2	Deletion, CN = 2	4.33	
	chr22:37c543,717-39c369,251	q12.3-q13.1	Deletion, CN = 2	1.83	
	chrX:133c432,498-134c242,874	q26.2-q26.3	Deletion, CN = 2	0.81	
24	chr1:754c192-9c617c682	p36.33-p36.22	Deletion	8.86	NA
	chr2:42c280,854-50c636,065	p21-p16.3	Deletion	8.36	
	chr9:204c738-38c495,131	p24.3-p13.1	Deletion	38.29	
	chr9:68c170,421-141c054,761	q13-q34.3	Gain	72.88	
	chr12:189c400-6c771c877	p13.33-p13.31	Gain	6.58	
	chrX:154c979,673-155c219,364	q28	Gain	0.24	

The last column includes karyotype and/or FISH data when available. Cases 1-15 are non-ETP T-LLy; cases 16-24 are ETP-LLy. NA, not available.

unbalanced *KMT2A* (*MLL*) rearrangement in case 5, *CDKN2A* deletion in case 7, and complex numerical and structural rearrangements in case 17. In case 5, the breakpoints of CNAs on chromosomes 11 and 19 are located at the *KMT2A* and *MLL1* genes supporting the translocation involving the *KMT2A* and *MLL1*. This translocation is associated with acute leukemia including T-ALL.²⁵

Balanced rearrangements including translocation between chromosomes 1 and 14 resulting in *TAL1-TCR α* fusion in case 3 and balanced translocation between chromosomes 7 and 12 in case 16 were not detected by MIP SNP array as expected. MIP SNP array

detected additional CNAs and CN-LOH in all cases with chromosome and/or FISH results (cases 3, 5, 7, 8, 14, 16, and 17). In addition, MIP array was able to detect CNAs and CN-LOH in 15 of 17 cases without chromosomal analysis or FISH results.

Comparison of patient outcome

Patient outcomes were assessed after a median follow-up of 6.3 years (range, 0.7-8.4 years). Patients with ETP-LLy had an excellent outcome with no failures or treatment related deaths leading to a 4-year event-free survival (EFS) of 100%. This is in comparison with 1

relapse and 2 remission deaths in the 15 non-ETP Lly patients in this small cohort leading to a 4-year EFS of 79%. EFS and overall survival were not different between ETP and non-ETP T-Lly in our cohort (supplemental Figure 1). However, these findings must be interpreted with appropriate caution because of the small number of patients, the missing stage data in 5 patients, and the selection of patients based on availability of immunophenotyping data and unstained slides.

Discussion

Patel et al first reported ETP-Lly having an incidence of 4% with an additional 7% that showed ETP features but were incompletely immunophenotyped.¹⁶ In the present study, we have confirmed 4% incidence of pediatric ETP-Lly in a separate cohort and further assessed the immunophenotypic and genomic characteristics of this subtype. ETP-Lly patients were not different in terms of age or sex, but the lymphomas were less likely to express CD2 and CD4 than non-ETP T-Lly. Lack of CD4 in ETP-ALL has been described and proposed as part of an alternative immunophenotypic definition.⁹

In our study, ETP-Lly showed less frequent 9p deletions including the *CDKN2A/CDKN2B* genes and more frequent 12p deletions including the *ETV6* gene compared with non-ETP T-Lly. Similar findings have been reported in ETP-ALL.^{10-12,14,15,26} Deletions of 9p were identified in 93% (14/15 cases) in non-ETP T-Lly cases in our cohort, which is higher than 33% frequency (3/9 cases) reported previously in a smaller cohort of T-Lly⁴ but closer to the 75% (12/16) recently reported in T-Lly²⁷ and the 75% to 83% frequency reported previously in T-ALL.^{10,11,14} The higher incidence of 9p deletion in our selected non-ETP patients thus may not be representative, and the true incidence should be assessed in future studies of larger cohorts.

In our study, 1p deletions including the *RPL22* gene were frequent in ETP-Lly (44%) but not seen in non-ETP T-Lly. The *RPL22* gene

encodes a component of the RNA-binding 60S ribosomal subunit. Autosomal dominant germline mutations in multiple ribosomal protein family members result in impaired ribosome biogenesis and function, termed ribosomopathies, and bone marrow failure syndrome such as Diamond-Blackfan syndrome with subsequent risk of development MDS and AML.²⁸ Somatic mutations in the ribosomal proteins *RPM5* and *RPL10* are reported in ~10% of pediatric T-ALL patients.²⁹ *RPL22* is a component of the TCR signaling pathway and is essential during T-cell development.³⁰ *RPL22* haploinsufficiency has been reported in 10% T-ALL, but this study did not specify the immunophenotype of the patients so it is not known if some of the patients had ETP-ALL.³¹ Our study is the first to specifically associate *RPL22* gene deletion with ETP-Lly, and may provide novel insights in the pathogenesis of ETP-Lly. Additional studies are needed to determine if *RPL22* gene deletion is also characteristic of ETP-ALL.

ABD characterizes early thymocyte precursors before V(D)J recombination and is associated with early treatment failure in both pediatric T-ALL and T-Lly,^{3,32} although a more recent study showed no difference in outcomes.⁹ We noted more frequent ABD in ETP-Lly, similar to previous studies in ETP-ALL.^{9,10,13}

Other recurrent CNAs observed in both ETP-ALL and non-ETP T-ALL include 6q gains involving the *MYB* gene, 13q deletions including the *RB1* genes.^{11,14,33,34} The 6q gain, 13q deletion, and *CHIC2* deletions are each present in 2 non-ETP T-Lly cases but not in ETP-Lly patients in our study. The 4q deletion involving *CHIC2* resulting in fusion between *FIP1L1* and *PDGFRα* is previously reported in T-ALL, but this abnormality was not present in the in ETP-ALL patients.¹⁴ Additional independent studies are needed to confirm if these abnormalities are limited in non-ETP T-ALL or can be present in both subtypes. Multiple complex rearrangements suggesting chromothripsis previously reported in ETP-ALL were not seen in ETP-Lly samples in this study. ETP-Lly cases may exhibit less genomic instability than ETP-ALL,⁶ but this was not directly assessed in our study. Such differences may correspond to the

Table 2. Recurrent CNAs and CN-LOHs in T-Lly with the incidence in ETP and non-ETP cases along with the genomic coordinates

Chromosome	Cases	Incidence in ETP-Lly	Incidence in Non-ETP T-Lly	P value (ETP vs non ETP)	Minimal common region	Start genomic coordinates	Stop genomic coordinates	Affected genes
Recurrent gains								
6	5, 15	0/9	2/15	.511	6q23.3	135c483,742	135c754,471	MYB
9	11, 23	1/9	1/15	1.000	9q34.12q34.13	133c719,421	134c094,802	NUP14-ABL1
Recurrent losses								
1	19, 22, 23, 24	4/9	0/15	.012*	1p36.32p36.31	3c921c449	7c050c061	RPL11
12	19, 20, 22	3/9	0/15	.042*	12p12.3	17c200,436	18c268,880	RERGL
13	6, 11	0/9	2/15	.511	13q14.2	48c984,722	49c065,037	RB1
4	14, 15	0/9	2/15	.511	4q12	54c324,930	55c102,425	FIP1L1, CHIC, PDGFRα
X	11, 23	1/9	1/15	1.000	Xq26.2q26.3	130c973,820	134c242,874	PHF6
Recurrent LOHs								
4	8, 15	0/9	2/15	.511	4q28.1q35.2	126c144,980	191c154,276	FBXW7
Recurrent losses and/or LOHs								
9	1-11, 13-15, 17, 21, 22, 24	4/9	14/15	.015*	9p21.3	21c901,263	21c993,468	CDKN2A, CDKN2B

Cases 1-15 are non-ETP T-Lly, and cases 16-24 are ETP-Lly.

* $P < .05$.

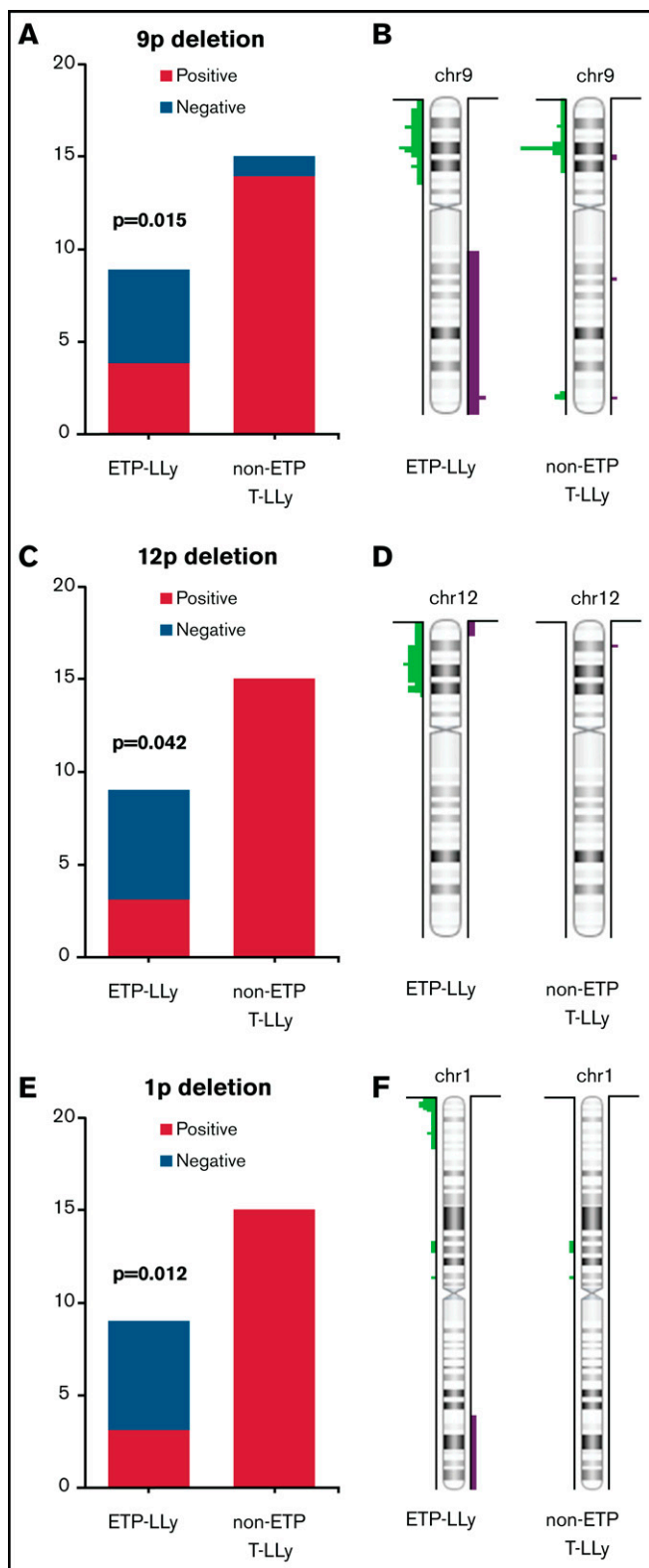


Figure 2. Comparison of frequency and distribution of 9p, 12p, and 1p deletions in ETP-LLy and non-ETP T-LLy. (A,C,E) Frequency, (B,D,F) distribution.

difference in outcome that we observed in this study compared with reports suggesting ETP-ALL was associated with an inferior outcome compared with non-ETP-ALL.⁶

Some recurrent CNAs are seen in both ETP and non-ETP T-LLy cases. Focal *PHF6* deletions on the long arm of chromosome X and *NUP214-ABL1* fusion amplification were observed in non-ETP T-LLy case 11 and ETP-LLy case 23. *PHF6* plays a role in epigenetic regulation of gene expression and was identified as a key tumor suppressor gene in T-ALL. *PHF6* mutation and/or deletion was reported almost exclusively in male T-ALL patients by Van Vlierberghe et al.³⁵ However, the *PHF6* deletion in case 23 (female) is heterozygous, affecting 1 copy of chromosome X. It is possible that the *PHF6* copy on the other chromosome X homolog may be silenced by X-inactivation or carry mutation resulting in loss of function in both copies. Co-occurrence of *PHF6* deletion and *NUP214-ABL1* fusion amplification has not been reported previously, to the best of our knowledge.³⁶ The presence of both abnormalities in 1 ETP-LLy case and 1 non-ETP T-LLy case suggests that these 2 abnormalities may be associated with each other and are not specific for the ETP-LLy subtype.

The 6q CN-LOH, deletion of the *CASP8AP2* gene on chromosome 6 (also known as FLASH deletion), and *PTEN* deletion have been previously reported in T-LLy and T-ALL and shown to have prognostic association.^{3,27} These abnormalities were not observed in our study in either ETP or non-ETP T-LLy.

In comparing MIP SNP array data to cytogenetic and FISH data when available, the MIP SNP array detected all cytogenetic and FISH abnormalities except the balanced translocations. In each case, additional CNAs and CN-LOH were detected by MIP SNP array highlighting that it is a superior test for CNA and LOH detection than conventional chromosome and FISH analysis. In addition, MIP array can be used in LLy patients without access to fresh tissue for chromosomal analysis or when the chromosome analysis fails.

The outcomes for the ETP patients in our cohort were excellent and not significantly different than the outcomes for patients with non-ETP phenotype T-LLy. These findings are in line with recent studies that demonstrated noninferior outcomes of ETP-ALL⁷⁻⁹ but should also be interpreted with appropriate caution because of the small number of patients.

One important limitation of our study may be the classification of ETP-LLy based on immunophenotyping rather than gene expression profiling. The ETP-ALL entity was originally defined by gene expression profiling, and Zuurber et al demonstrated that ETP classification by immunophenotyping likely underestimates the actual incidence relative to gene expression profiling.⁹ In addition, we used a strict definition of ETP/non-ETP and thus excluded near-ETP cases from our assessment.¹⁵

In conclusion, we have established an incidence of ETP-LLy of 4% and demonstrated that ETP-LLy exhibit distinct features from non-ETP T-LLy at the genomic level including less frequent 9p deletion including *CDK2A/B* and more frequent 12p deletion including *ETV6*. We identified *RPL22* deletion on 1p as a recurrent finding in ETP-LLy suggesting ribosomal biogenesis dysfunction may play a role in the pathogenesis of some ETP-LLy. Finally, the MIP SNP array may have clinical utility for assessment of T-LLy specimens, especially when only fixed tissue is available.

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Table 3. Comparison of average number and size of CNAs between non-ETP T-LLy and ETP-LLy

	Average no. of CNAs per case				Total CNAs	Average size of CNAs per case (Mb)
	One copy gain	Two or more copy gain	Heterozygous loss	Biallelic loss		
Non-ETP T-LLy	1.40	0.33	1.93	0.93	4.6	70.30
ETP-LLy	1.89	0.11	4.78	1	7.78	160.66
P value	0.65	0.45	0.13	0.85	0.19	0.23

Mb, megabases of genome involved.

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Authorship

Contribution: X.X., C.N.P., S.L.P., and R.R.M. designed the study, performed the research, and analyzed the data; M.D. performed the statistical analysis; and R.J.H., K.P.D., S.S.W., S.P.H., N.J.W., W.L.C., M.L.L., T.G.G., and C.M.B. designed and supported the AALL0434 clinical trial through the Children's Oncology Group acute lymphoblastic leukemia and non-Hodgkin lymphoma disease committees.

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