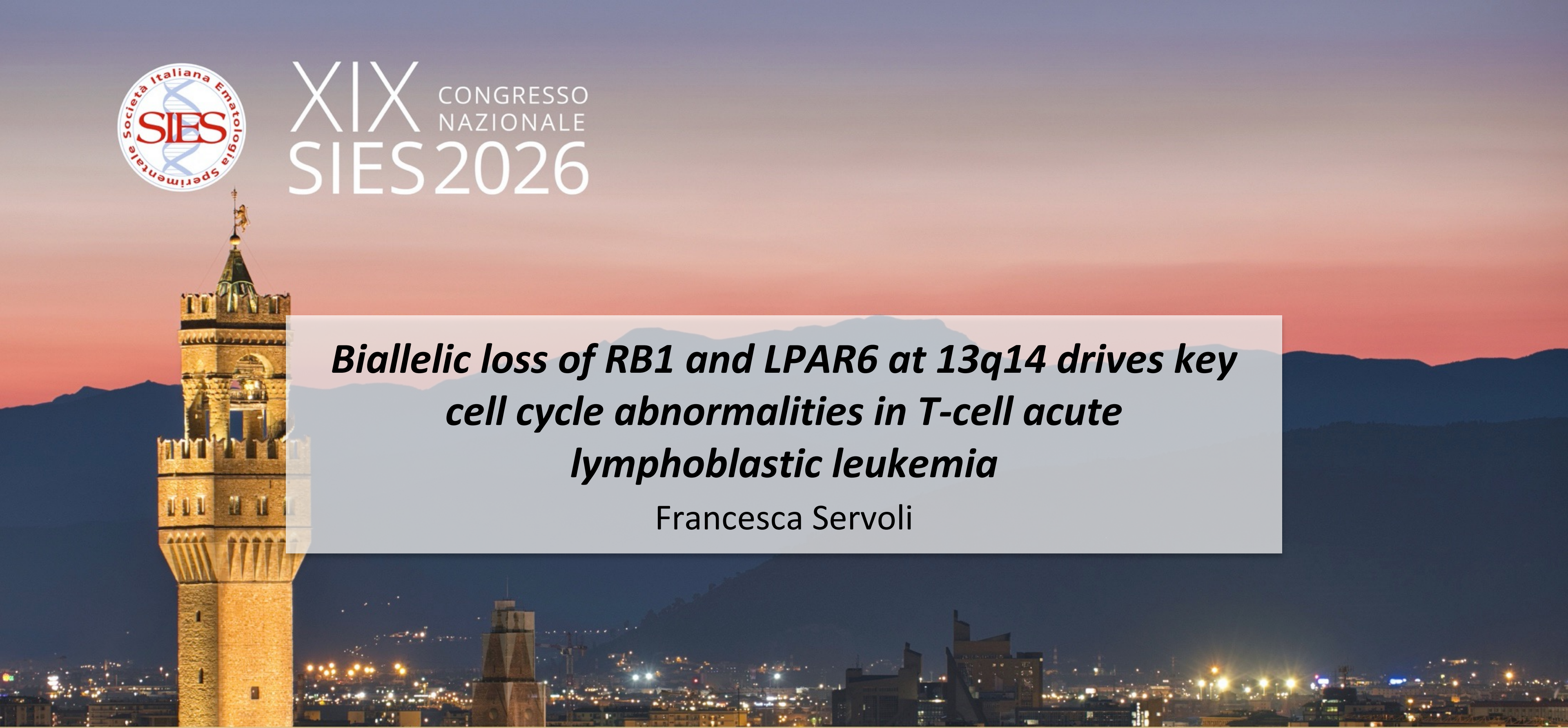


XIX CONGRESSO NAZIONALE
SIES 2026

Biallelic loss of RB1 and LPAR6 at 13q14 drives key cell cycle abnormalities in T-cell acute lymphoblastic leukemia

Francesca Servoli

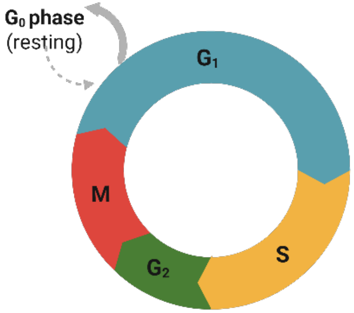
Firenze | **4-6 marzo 2026**
Palazzo degli Affari

Nothing to disclose

T-cell acute lymphoblastic leukemia/lymphoma

- T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) is an aggressive hematological tumor, representing 15% of pediatric and 25% of adult ALL cases
- T-ALL/LBL develops through multiple events that disrupt key cellular processes:

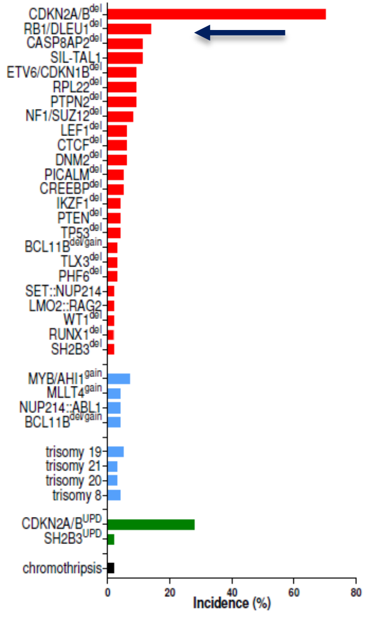
- self-renewal
- T-cell differentiation
- proliferation
- survival
- cell cycle regulation



Cell cycle dysregulation occurs in 70% of T-ALL/LBL

9p21/*CDKN2AB* (28%)
12p13/*CDKN1B* (9%)
12p13/*CCND2* (3%)
13q14/*RB1* (14%)

13q14 deletions are the second most common deletions in adult T-ALL



Balducci E et al., *Blood*, 2024

AIM

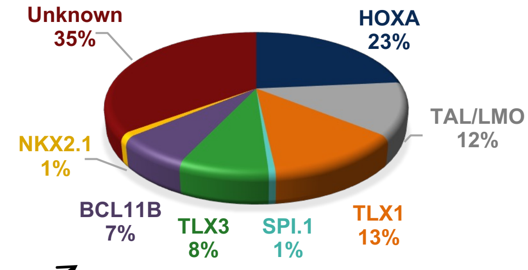
The study examined biallelic deletions in the 13q14 genomic region of T-ALL/LBL cases to clarify the genomic background

MATERIALS AND METHODS

SNPa to study CNV
319 T-ALL/LBLs:

Adults/Children: 252/67
Males/Females: 241/78
Typical/Immature: 172/146

- **Genomics**:
  - Multiplex CI-FISH
  - Custom Target NGS
  - WGS



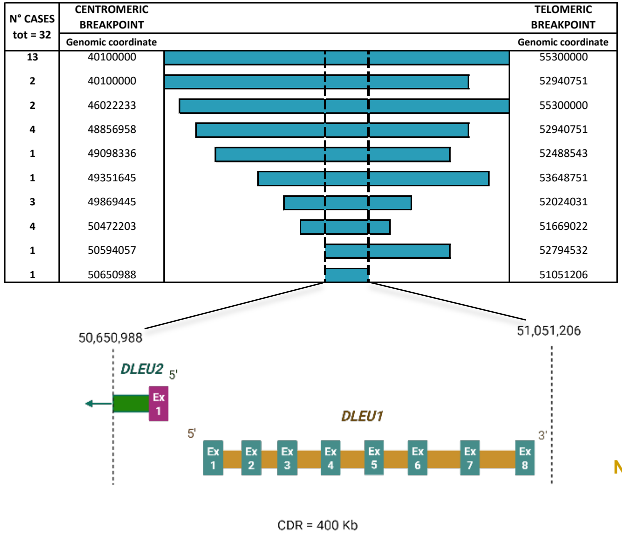
- **Transcriptomics:**
  - Whole Transcriptomic Expression array (WTEa)
  - RT-qPCR

La Starza R et al. *J Mol Diagn* , 2020; Bardelli V et al. *J Mol Diagn*, 2025

RESULTS

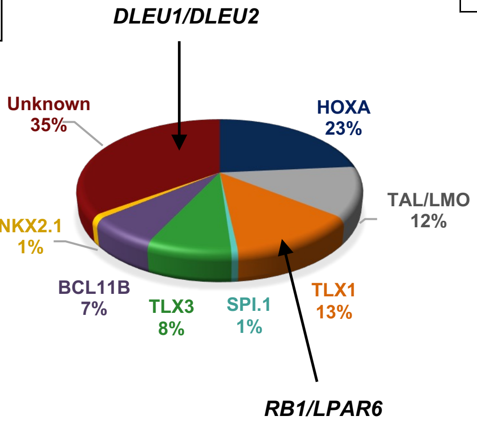
Molecular cytogenetics identified two types of 13q14 deletion (50/319; 16%)

1) Monoallelic deleletion: *DLEU1/DLEU2* (32/50)

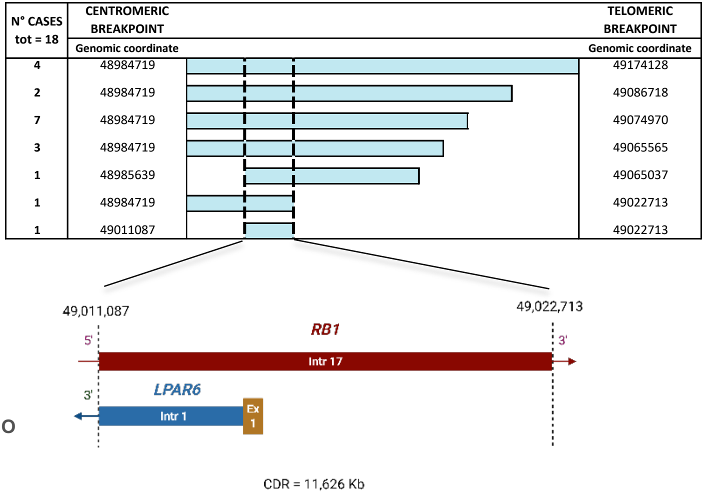


N° CASES tot = 32	CENTROMERIC BREAKPOINT Genomic coordinate	TELOMERIC BREAKPOINT Genomic coordinate
13	40100000	55300000
2	40100000	52940751
2	46022233	55300000
4	48856958	52940751
1	49098336	52488543
1	49351645	53648751
3	49869445	52024031
4	50472203	51669022
1	50594057	52794532
1	50650988	51051206

- ○ <u>Phenotype</u>: **immature T-ALL** (22/32; 69%)
- ○ <u>Genetic category</u>: **unknown** (20/32; 63%)



2) Focal biallelic deletion: *RB1/LPAR6* (18/50)

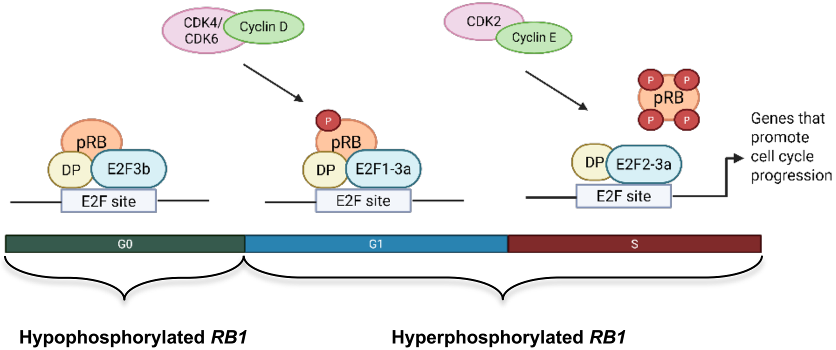


N° CASES tot = 18	CENTROMERIC BREAKPOINT Genomic coordinate	TELOMERIC BREAKPOINT Genomic coordinate
4	48984719	49174128
2	48984719	49086718
7	48984719	49074970
3	48984719	49065565
1	48985639	49065037
1	48984719	49022713
1	49011087	49022713

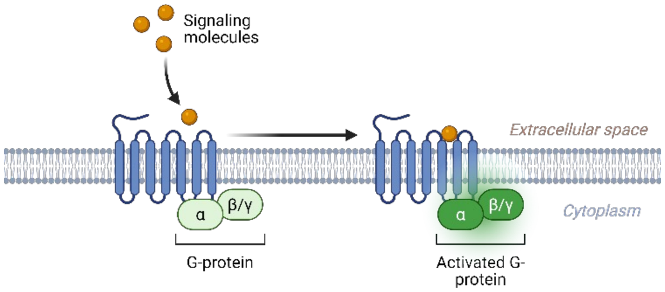
- ○ <u>Phenotype</u>: **cortical T-ALL** (14/18; 77%)
- ○ <u>Genetic category</u>: ***TLX1*** (11/18; 61%)

RB1/LPAR6 $^{\text{bDEL}}$

- ***RB1*** is located at 13q14 and encodes the tumor suppressor pRB, which regulates cell growth and the G1/S cell cycle transition



- ***LPAR6***, within intron 17 of *RB1*, is a gene belonging to the LPAR family of G protein-coupled receptors
  - Oncogene: hepatocellular carcinoma, prostate, and pancreatic cancers
  - Tumor suppressor: breast and colorectal cancers

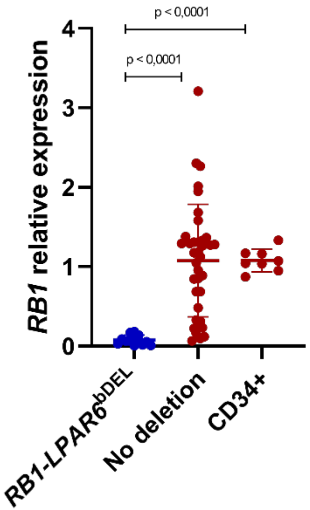


RESULTS

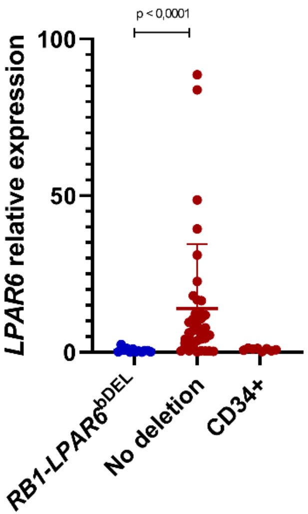
RB1/LPAR6^{bDEL} T-ALL/LBL: significant downregulation of both *RB1* and *LPAR6*

RT-qPCR:

***RB1* expression**

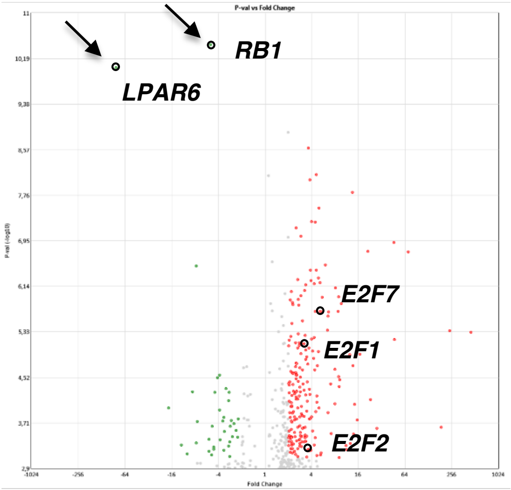


***LPAR6* expression**



WTEa:

253 DEGs
216 up-regulated
37 down-regulated

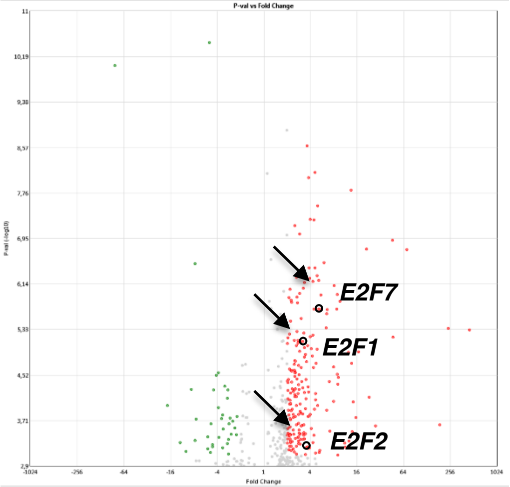


RESULTS

RB1/LPAR6$^{\text{bDEL}}$ T-ALL/LBL: significant upregulation of E2F transcription factors

WTEa:

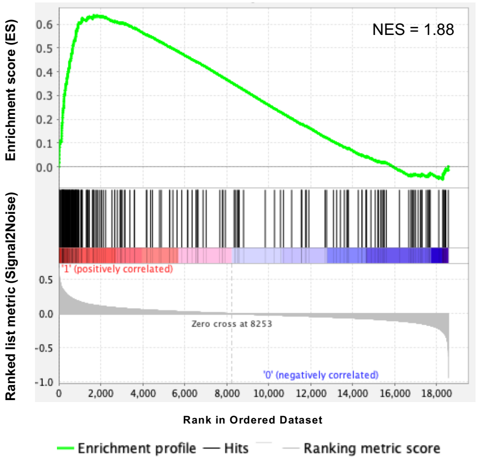
253 DEGs
216 up-regulated
37 down-regulated



Up-regulated DEGS: 23 *E2F1* targets

- Cell cycle regulation: *E2F1, E2F2, E2F7, CDKN2C, CCNE2, CHEK1, CDCA7*
- DNA synthesis, replication, and repair: *CDT1, MCM2, MCM3, MCM4, MCM6, PCNA, RPA3, RRM1, TYMS, BARD1, FEN1, MSH6, UHRF1*
- Wnt signaling pathway: *FZD1, HMGA1*
- Apoptosis: *TP73*

GSEA of *E2F1* TARGET GENES

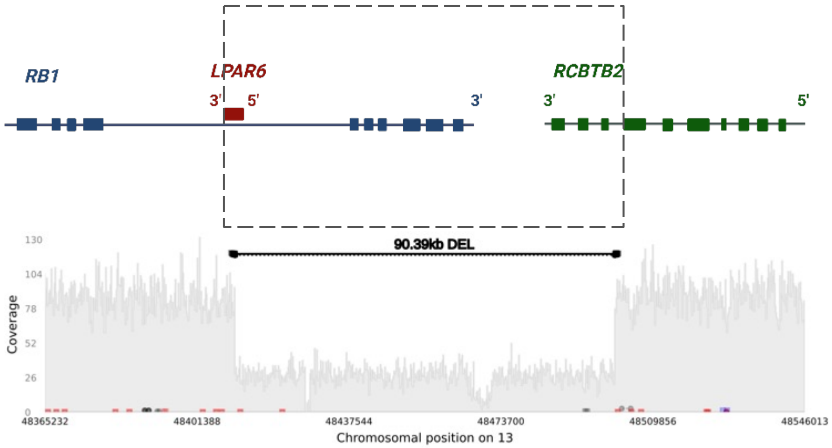


RESULTS

WGS studies

Sample	Gen. Cat.	Phenotype	Fusion
UPN_TALL_034	*TLX1*	CORTICAL	YES
UPN_TALL_044	*TLX1*	CORTICAL	YES
UPN_TALL_037	*TLX1*	CORTICAL	YES
UPN_TALL_041	*TLX3*	MATURE	YES
UPN_TALL_035	*TLX1*	CORTICAL	NO
UPN_TALL_040	*TLX1*	CORTICAL	NO
UPN_TALL_050	*HOXA*	ETP-ALL	NO

RCBTB2::LPAR6




Article

The genomic basis of childhood T-lineage acute lymphoblastic leukaemia

Petri Pölönen et al. *Nature*, 2024

Cohort: 1335 children

13 cases with ***RCBTB2::LPAR6*** (RNA-seq)

- All typical T-ALL
- *TLX1* (55%)

CONCLUSION

- *RB1-LPAR6*$^{\text{bDEL}}$ cases are associated with cortical *TLX1*-positive T-ALL
- *RB1-LPAR6*$^{\text{bDEL}}$ cases mimic the effect of pRB phosphorylation, leading to the accumulation of E2F1, E2F2, and E2F3 and consequently promoting entry into the S phase and cell proliferation
- *LPAR6* inactivation resembles that observed in normal CD34-positive cells. Its leukemogenic role in this leukemia subset has not yet been determined

PERSPECTIVES

- Drug Response Profiling (DRP) are currently underway to determine whether there is sensitivity to specific classes of drugs in *RB1-LPAR6* $^{\text{bDEL}}$ cases

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Biallelic loss of RB1 and LPAR6 at 13q14 drives key cell cycle abnormalities in T-cell acute lymphoblastic leukemia

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