

ETV6:RUNX1-Positive Pediatric Acute Lymphoblastic Leukemia: A Review

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ABSTRACT

The ETV6:RUNX1 (formerly TEL: AML1) fusion gene resulting from the cryptic translocation t(12;21) (p13; q22) represents the most frequent chimeric oncogene in pediatric B-cell precursor acute lymphoblastic leukemia (B-ALL), accounting for approximately 25% of cases. Typically initiating in utero during fetal hematopoiesis, the fusion protein establishes a covert pre-leukemic clone that persists across a variable latency period. Overt leukemogenesis necessitates secondary postnatal genomic events, such as deletions of the un-rearranged ETV6 allele, alterations in B-cell developmental genes (PAX5, EBF1), or mutations in signaling cascades (KRAS, NRAS). Although ETV6:RUNX1-positive ALL confers a distinctly favorable prognosis with long-term survival exceeding 90–95%, up to 10–15% of patients suffer late disease recurrence or treatment toxicity. This comprehensive review examines the molecular architecture of ETV6:RUNX1, its multi-step pathobiology, diagnostic methods, clinical outcomes, risk factors for relapse, and emerging targeted/de-escalation therapeutic strategies.

Introduction and Background

Acute lymphoblastic leukemia (ALL) is the most prevalent childhood malignancy, representing roughly 75–80% of pediatric leukemias [1,2]. Advances in cytogenetics and molecular profiling have transformed pediatric B-ALL from a single clinical entity into a molecularly heterogeneous spectrum of disease subtypes defined by distinct recurrent chromosomal rearrangements and gene mutations [1,3].

Among these subtypes, the translocation t(12;21) (p13;q22) yielding the ETV6:RUNX1 fusion gene is the most common structural genetic alteration, detected in 20–25% of pediatric B-ALL cases [1-4]. The frequency of ETV6:RUNX1 peaks in children between 2 and 5 years of age, matching the peak incidence of pediatric B-ALL worldwide [1,5]. Clinically, ETV6:RUNX1-positive ALL is widely associated with favorable baseline biological features, including low white blood cell (WBC) counts at presentation, age between 1 and 9 years, CD10+ B-lineage immunophenotype, and high sensitivity to conventional multi-agent chemotherapy regimens [2,5].

Molecular Structure and Pathogenesis

Molecular Architecture of the Fusion Protein

The t(12;21) (p13;q22) translocation fuses the 5' non-coding and amino-terminal coding regions of the ETV6 (ETS variant 6)

gene on chromosome 12p13 to nearly the entire coding sequence of the RUNX1 (Runt-related transcription factor 1) gene on chromosome 21q22 [1,4].

- **ETV6:** Encodes an ETS-family transcription factor possessing a point-pointed (PNT) protein-protein interaction domain and a C-terminal DNA-binding domain.
- **RUNX1:** Encodes the alpha subunit of the Core Binding Factor (CBF) complex, containing the conserved Runt domain essential for DNA binding and heterodimerization with CBF β .

In the chimeric ETV6:RUNX1 protein, the PNT dimerization domain of ETV6 is joined to the DNA-binding and transactivation/repression domains of RUNX1 [1,4]. As a result, the fusion protein acts as a dominant-negative repressor of wild-type RUNX1 target genes. It alters normal transcriptional programs by recruiting corepressors such as N-CoR, SMRT, mSin3A, and histone deacetylases (HDACs) to native RUNX1 regulatory binding sites [1,4].

Prenatal Origin and Pre-Leukemic State

A hallmark of ETV6:RUNX1 biology is its initiation during human intrauterine development [1,5]. Backtracking studies on archived neonatal blood spots (Guthrie cards) from children who later developed ALL confirmed that the clonal ETV6:RUNX1 genomic breakpoint sequence is present at birth

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[1,5]. Furthermore, concordance studies in monozygotic twins sharing a placenta demonstrated intra-placental metastasis of ETV6:RUNX1-positive pre-leukemic stem cells [1,5].

Retrospective screening reveals that ETV6:RUNX1 fusion sequences occur in utero in up to 1–5% of healthy newborns—a frequency far exceeding the incidence of clinical ALL [1,4,5]. This discrepancy highlights that while ETV6:RUNX1 functions as a primary initiating “first hit,” it is insufficient on its own to induce overt clinical leukemia [1,5].

The “Two-Hit” Model and Secondary Genetic Alterations

Transformation from a silent pre-leukemic clone to overt acute leukemia requires the accumulation of secondary postnatal genetic driver mutations (“second hits”) [1,5]. The latency period between the in-utero translocation and clinical presentation ranges from months to over a decade [1,5].

The secondary genomic lesions in ETV6:RUNX1 ALL are predominantly copy number alterations (CNAs) caused by aberrant RAG-mediated somatic recombination or oxidative stress [1,5]:

- **Loss of wild-type ETV6:** Deletion of the second, un-rearranged ETV6 allele on chromosome 12p occurs in up to 70% of cases, eliminating its tumor-suppressive activity [1,5].
- **B-cell lineage transcription factor alterations:** Recurrent deletions in genes critical for B-cell differentiation, including PAX5, EBF1, IKZF1, and TCF3 [1,5].
- **Cell cycle deregulation:** Deletions involving the CDKN2A/CDKN2B locus at 9p21 [1,5].
- **Gain/Loss of Chromosomes:** Extra copies of chromosome 21, der(21)t(12;21), or deletions of 6q, 9p, 11q, and 13q [1,2,5].
- **Kinase and Ras Pathway Mutations:** Somatic point mutations in KRAS, NRAS, FLT3, or PTPN11 that drive proliferation [3,5].

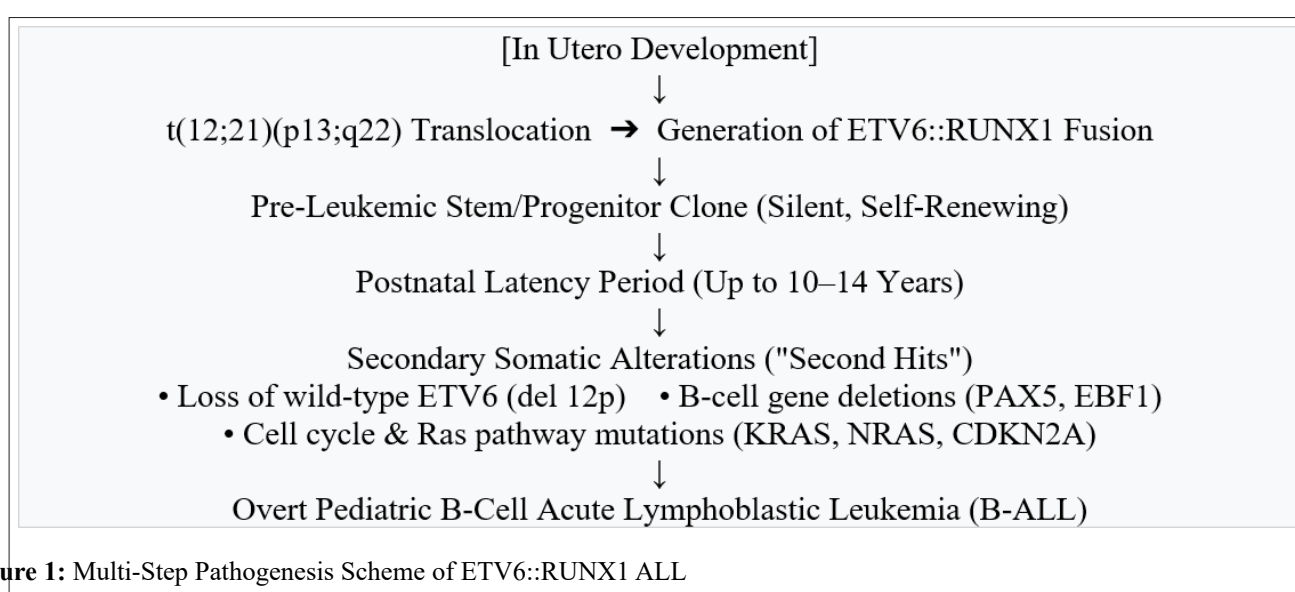


Figure 1: Multi-Step Pathogenesis Scheme of ETV6::RUNX1 ALL

Diagnostic Methods

Because t(12;21) (p13;q22) is cytogenetically cryptic and cannot be identified by conventional G-banded karyotyping, specialized molecular diagnostic tools are required [2,5]:

Diagnostic Method	Sensitivity	Clinical / Diagnostic Role
Fluorescence In Situ Hybridization (FISH)	10^{-2}	Standard diagnostic gold standard for detecting t(12;21) fusion signals and accompanying ETV6 deletions [2,5].
Reverse Transcription PCR (RT-PCR)	$10^{-4} - 10^{-5}$	Rapid confirmation of the ETV6:RUNX1 transcript at initial presentation [2,5].
Quantitative Real-Time PCR (qRT-PCR)	10^{-5}	Standard tool for minimal residual disease (MRD) monitoring during and after induction therapy [2,5].
Multiplex Ligation-Dependent Probe Amplification (MLPA)	Variable	Screening for associated secondary gene deletions (ETV6, PAX5, CDKN2A/B, IKZF1) [1,5].
Next-Generation Sequencing (RNA-Seq / WES)	High	Comprehensive profiling of fusion variants, secondary driver mutations, and clonal evolution ([3,5].

Clinical Features and Prognostic Significance

Classical Features

Patients presenting with ETV6:RUNX1-positive ALL typically exhibit favorable baseline demographic and laboratory parameters [2,5,6]:

- Age typically between 1 and 9 years.
- Low initial leukocyte count ($< 50 \times 10^9/L$).

- Common B-precursor immunophenotype (CD10+, CD19+, CD20+/-, TDT+).
- Marked sensitivity to glucocorticoids and L-asparaginase [2,6].

Prognosis and Treatment Response

Overall, ETV6:RUNX1 is associated with an excellent early therapy response and superior long-term survival, with 5-year event-free survival (EFS) and overall survival (OS) rates exceeding 90% and 95%, respectively, on modern risk-adapted regimens [2,6].

However, late relapse occurs in approximately 10–15% of patients, sometimes up to 5 to 10 years following completion of initial chemotherapy [1,2,5]. Relapses may stem from either a re-emerging dormant original pre-leukemic clone that acquires novel secondary mutations, or late evolutionary branches of the original leukemic clone [1,5].

Key Predictors of Disease Relapse

Despite overall high cure rates, specific clinical and molecular features identify sub-populations at increased risk for relapse [3,5]:

- **Persistent Minimal Residual Disease (MRD):** High post-induction or post-consolidation MRD values remain the single strongest independent predictor of disease recurrence [5].
- **Initial High Leukocyte Count:** WBC count $\geq 50 \times 10^9/L$ at presentation [5].
- **Poor Early Response:** Poor prednisone/steroid response at Day 8 or delayed blast clearance [5].

Co-occurring Mutations: Specific secondary genetic mutations (e.g., WHSC1 mutations, TP53 alterations, or high TIMD4 gene expression) have been associated with heightened risk for early relapse [3].

Current Treatment Framework and De-Escalation Strategies

Standard Therapy Protocols

Contemporary treatment for ETV6:RUNX1-positive ALL relies on multi-agent risk-adapted chemotherapy protocols developed by major international cooperative groups, such as AIEOP-BFM, COG, NOPHO, and UKALL [2,6]. Key phases include:

- **Induction:** Glucocorticoids (prednisone or dexamethasone), vincristine, L-asparaginase, $\pm$ anthracyclines (doxorubicin/daunorubicin).
- **Consolidation/Intensification:** High-dose methotrexate, 6-mercaptopurine, and intrathecal therapy for central nervous system prophylaxis.
- **Maintenance:** Oral 6-mercaptopurine and weekly methotrexate for 2–3 years.

Evaluating Therapy Optimization and De-Escalation

Because of the excellent survival outcomes ($\geq 95\%$) in ETV6:RUNX1 B-ALL, attention has turned to reducing treatment-related toxicity, late organ toxicities, and secondary malignancies [6]. Recent cooperative trials have investigated whether chemotherapy de-escalation (e.g., reducing cumulative anthracycline or alkylating agent doses) can be safely executed in low-risk, MRD-negative ETV6:RUNX1 cohorts without compromising event-free survival [6].

Conversely, for patients with high end-induction MRD or late relapse, second-line strategies utilize novel immunotherapies—such as the bispecific T-cell engager (BiTE) blinatumomab, antibody-drug conjugates (inotuzumab ozogamicin), or chimeric antigen receptor (CAR) T-cell therapy—providing targeted salvage options while minimizing long-term chemotherapy toxicities [7–26].

Conclusion

ETV6:RUNX1-positive B-ALL serves as a model for the multi-step pathogenesis of childhood cancer. Originating as a silent pre-leukemic fusion in utero, it requires secondary postnatal genomic alterations to induce overt disease. While current intensive multi-agent chemotherapy regimens achieve cure rates above 90–95%, persistent challenges remain in preventing late relapses and minimizing long-term treatment-related toxicities. Ongoing research focuses on refining MRD-guided risk stratification, exploring safe regimen de-escalation, and incorporating targeted immunotherapies for high-risk or recurrent disease.

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