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Research Article

Genomic Landscape of Relapsed Pediatric B-Cell Acute Lymphoblastic Leukemia

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Abstract

Background: Relapse remains the leading cause of leukemia-related death in children with B-cell acute lymphoblastic leukemia (B-ALL), and matched diagnosis-relapse sequencing studies over the past fifteen years have reframed relapse as the outgrowth of a genetically distinct, therapy-selected clone rather than a resurgence of the original tumor.

Objective: To synthesize the published genomic literature on clonal evolution, relapse-driver mutations, and relapse risk stratification in pediatric B-ALL, focusing on chemoresistance genes such as NT5C2 and PRPS1, glucocorticoid pathway alterations in NR3C1 and CREBBP, and structural lesions such as IKZF1 deletion.

Methods: Narrative review of peer-reviewed genomic-profiling studies of pediatric B-ALL diagnosis-relapse cohorts, clonal tracking and xenograft studies, and genomic risk-stratification and targeted-therapy reports identified through literature search.

Findings: Relapse clones are frequently detectable as minor subclones at diagnosis; thiopurine resistance is recurrently driven by NT5C2 and PRPS1 mutations; glucocorticoid resistance is linked to CREBBP and NR3C1 disruption; and IKZF1 deletion, IKZF1plus, and Ph-like kinase signatures mark relapse risk that is increasingly actionable with targeted agents.

Conclusions: Relapse genomics has matured from descriptive clonal-evolution studies into candidate diagnosis-time risk scores and druggable-lesion strategies, but most of this evidence remains retrospective and now requires prospective validation.

Keywords: B-cell ALL; relapse; clonal evolution; NT5C2; IKZF1

1. Introduction

Modern therapy cures roughly nine of ten children with B-cell acute lymphoblastic leukemia (B-ALL), yet relapse remains the disease's most stubborn failure mode and, in aggregate, still kills more children than any other malignancy of childhood [1]. The paradox is now understood at the level of the genome rather than the clinic chart: relapse is, in most cases, not a re-emergence of the diagnostic tumor but the outgrowth of a genetically distinct, therapy-selected clone that was present, often at low abundance, before treatment ever began [2]. That single observation, first made through matched diagnosis-relapse copy-number and sequencing studies, reframed relapse from a treatment failure into a problem of clonal selection, and it has driven fifteen years of work identifying which mutations chemotherapy selects for, which lesions predict that selection before it happens, and which of the resulting targets can be drugged.

This review traces that arc. It starts with what whole-genome and whole-exome sequencing of matched diagnosis-relapse pairs revealed about clonal architecture, moves through the specific chemoresistance mutations relapse selects for — mutations in NT5C2 and PRPS1 that blunt thiopurine activity, and disruptions of CREBBP and NR3C1 that blunt glucocorticoid signaling — and then to the structural lesions, chiefly IKZF1 deletion, that mark high relapse risk from the moment of diagnosis. It closes with how these findings are being translated into risk-directed therapy, from minimal-residual-disease-integrated genomic risk classifiers to kinase inhibitors for Ph-like ALL and MEK inhibitors for RAS-mutant relapse. Throughout, the goal is synthesis of published, verifiable genomic studies rather than a new primary analysis; no original patient cohort is presented here.

2. Clonal architecture at diagnosis versus relapse

The founding experiment of this field compared copy-number lesions in paired diagnosis and relapse samples and found that a meaningful fraction of relapse-specific deletions were undetectable at diagnosis by standard methods, implying that relapse frequently arose from an ancestral clone that diverged from the diagnostic dominant clone before diagnosis rather than descending linearly from it [2]. Genome-wide copy-number profiling of matched pairs reinforced the same picture from a different angle, showing that relapse samples routinely carried structural lesions absent from the paired diagnostic sample, evidence of ongoing clonal evolution under therapy rather than static persistence of the original leukemia [3]. The same conclusion emerged in ETV6-RUNX1-rearranged ALL, where backtracking of relapse-specific alterations into diagnostic and even prenatal blood spots showed relapse clones branching from a common preleukemic ancestor well upstream of the clinically apparent diagnosis [4].

Table 1: Clonal relationship between diagnosis and relapse across matched-pair sequencing studies of pediatric B-ALL [2,5,7,4].

Study	Cohort	Method	Key clonal finding
[2]	Matched diagnosis-relapse pairs	Copy-number and targeted sequencing	Relapse-specific lesions undetectable at diagnosis
[5]	20 diagnosis-relapse trios	Whole-exome sequencing	Median 3 subclones; relapse clone minor (median 7%) at diagnosis in 15/20 (75%)
[7]	Diagnostic B-ALL, xenografts	Cellular barcoding, scRNA-seq	Drug-tolerant relapse-fated subclones detectable pre-therapy
[4]	ETV6-RUNX1 diagnosis-relapse pairs	Backtracking into neonatal blood spots	Relapse clone branches from a common preleukemic ancestor

Whole-exome sequencing of twenty matched trios put numbers on that architecture: a median of three genetically distinct subclones was detectable at both diagnosis and relapse, and in fifteen of the twenty cases (75%) the clone that eventually caused relapse was a

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minor subclone at diagnosis, present at a median population frequency of only 7% (range 2-20%) [5]. Mutation burden did not distinguish the clones that expanded from those that were eliminated — rising and falling subclones carried a similar median of eleven mutations each — which argues against a simple model in which the most heavily mutated clone always wins, and instead points to selection acting on specific, functionally relevant lesions rather than on mutation load [5]. A larger series of matched diagnosis-relapse-relapse trios extended this to sequential relapses and confirmed that clonal turnover, gain of new epigenetic-regulator mutations, and occasional reversal of relapse-selected alleles between first and second relapse are all recurrent features rather than exceptions [6].

The most direct demonstration that relapse-fated clones exist before chemotherapy starts comes from functional tracking rather than retrospective sequencing. Using cellular barcoding and xenografting of diagnostic B-ALL samples, a substantial fraction of diagnostic specimens were shown to harbor detectable, drug-tolerant subclones with a distinct metabolic and transcriptional program well before any treatment was given, and these were the clones that dominated at relapse in matched xenograft and patient samples [7]. Put together, these studies converge on the same structural fact: the genome that ultimately kills a relapsing child is usually already present, in miniature, in the diagnostic bone marrow aspirate.

3. Chemoresistance mutations acquired at relapse

If relapse clones exist before treatment, the question becomes which mutations chemotherapy selects them for. The clearest answer concerns the thiopurines 6-mercaptopurine and 6-thioguanine, maintenance-phase drugs whose resistance mechanisms have been mapped almost mutation by mutation. Activating mutations in the 5'-nucleotidase gene NT5C2 were identified in 19% of relapsed T-ALL and 3% of relapsed B-ALL cases in the original discovery cohort, virtually absent at diagnosis, and shown functionally to increase nucleotidase activity and confer resistance to thiopurine chemotherapy in leukemic cells [8]. A parallel study identified relapse-specific NT5C2 mutations converging on the same functional domain in independent B-ALL cohorts, cementing NT5C2 as a genuine relapse driver rather than a passenger [9]. In the twenty-trio deep-sequencing series described above, NT5C2 mutations were present in 9 of 20 relapses (45%), a substantially higher rate than earlier estimates and a reminder that ascertainment depth changes prevalence estimates in this literature [5]. Structural and biochemical work has since shown that the mutations cluster in recurrent hotspots that stimulate the enzyme through an altered oligomeric interface, and that NT5C2-mutant subclones, while chemoresistant, often carry a fitness cost off therapy that can cause them to be outcompeted by NT5C2-wild-type subclones at a subsequent relapse — an elegant example of resistance and relapse being governed by different, sometimes opposing, selective pressures [10,11].

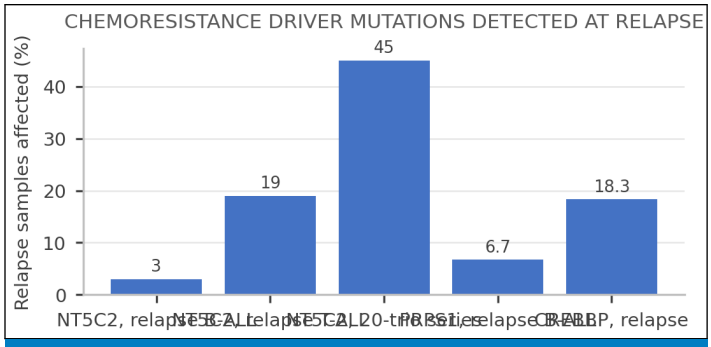

Figure 1: Frequency of chemoresistance driver mutations detected at relapse across independent pediatric ALL cohorts: NT5C2 in 3% of relapsed B-ALL versus 19% of relapsed T-ALL in the discovery cohort [8], rising to 45% (9 of 20) in a deep-sequencing trio series [5]; PRPS1 in 6.7% (24 of 358) of relapsed B-ALL [12]; and CREBBP mutations in 18.3% of relapse samples [16]; values come from different cohorts and sequencing depths and are not a head-to-head comparison.

A second, mechanistically distinct route to thiopurine resistance runs through the purine synthesis enzyme PRPS1. Negative-feedback-defective PRPS1 mutations were found in 24 of 358 relapsed childhood B-ALL cases

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(6.7%), nearly always acquired at relapse, and shown to drive resistance by increasing de novo purine synthesis, which competitively suppresses thiopurine activation while also creating a specific vulnerability to purine synthesis inhibitors as a rational combination strategy [12]. Epigenetic regulators are recurrently hit alongside these metabolic genes: relapse-acquired mutations in SETD2 and other chromatin modifiers were identified in matched diagnosis-relapse pairs, expanding the relapse-driver landscape beyond direct drug-metabolizing enzymes into the broader chromatin machinery that shapes how leukemic cells respond to genotoxic stress [6]. TP53 mutations, though uncommon at diagnosis, are markedly enriched at relapse and disproportionately represented in hypodiploid ALL, where they mark both intrinsic chemoresistance and a genome already prone to further mutation acquisition [13]. RAS pathway mutations, chiefly in NRAS and KRAS, are also prevalent and recurrently subclonal at relapse, and — unlike most relapse drivers — they open an immediate therapeutic option, since RAS-mutant relapse clones show selective sensitivity to MEK inhibition in preclinical models [14,15].

4. Glucocorticoid pathway alterations

Glucocorticoids are a backbone of every pediatric ALL regimen, and resistance to them is one of the strongest single predictors of relapse, which has made the glucocorticoid signaling pathway a natural place to look for relapse-driver mutations. Sequencing of 300 genes across matched diagnosis-relapse pairs identified CREBBP mutations, predominantly truncating or catalytic-domain substitutions in the histone acetyltransferase domain, in 18.3% of relapse samples; functionally, these mutations impaired histone acetylation at a panel of CREBBP target genes that includes glucocorticoid-responsive loci, providing a direct mechanistic link between an epigenetic lesion and steroid resistance [16]. Because CREBBP acetylates and coactivates the glucocorticoid receptor itself, its loss blunts the transcriptional response to dexamethasone and prednisolone independent of any change at the receptor gene.

The receptor gene can also be hit directly. In a cohort of pediatric T-lineage ALL, recurrent NR3C1 (glucocorticoid receptor) deletions were found in 4% of diagnostic samples and inactivating point mutations in a further 3%, together identifying a discrete group of patients with intrinsic steroid resistance detectable before treatment starts, disproportionately enriched among early T-cell precursor cases [17]. While that series was T-lineage rather than B-lineage, the biology generalizes: NR3C1 haploinsufficiency reduces glucocorticoid receptor dosage below the threshold needed for an adequate apoptotic response, and the same class of lesion — focal deletion or loss-of-function mutation of a single glucocorticoid-pathway gene — recurs across B- and T-ALL relapse genomics as a mechanism that is mutationally simple but clinically potent. Taken with CREBBP, these findings mean that a meaningful share of relapse in glucocorticoid-treated ALL can now be attributed to a specific, sequenceable lesion in the pathway the drug itself depends on, rather than to a diffuse, unexplained "steroid resistance" phenotype.

5. IKZF1 and other structural drivers of relapse risk

Not every relapse driver is acquired after diagnosis; some are structural lesions already present in the diagnostic clone that mark it for eventual relapse. The paradigm case is IKZF1, encoding the lymphoid transcription factor Ikaros. Focal deletions of IKZF1 were first described as a near-universal feature of BCR-ABL1-positive ALL and BCR-ABL1-like lymphoid blast crisis of chronic myeloid leukemia, establishing Ikaros loss as a cooperating lesion in a specific high-risk genetic subtype [18]. In a broader series of pediatric B-ALL, IKZF1 deletions were identified in a minority of cases at diagnosis but independently predicted inferior event-free survival and a higher cumulative incidence of relapse across treatment protocols, establishing IKZF1 status as a prognostic genetic marker rather than a subtype-restricted curiosity

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[19]. Subsequent work refined this further: the "IKZF1plus" genotype, defined by an IKZF1 deletion co-occurring with deletion of CDKN2A/B, PAX5, or the pseudoautosomal region 1 in the absence of ERG deletion, identifies a subgroup whose relapse risk is concentrated specifically among patients who also have poor early minimal-residual-disease clearance, refining IKZF1 from a single binary marker into a combinatorial genetic-plus-response risk signature [20].

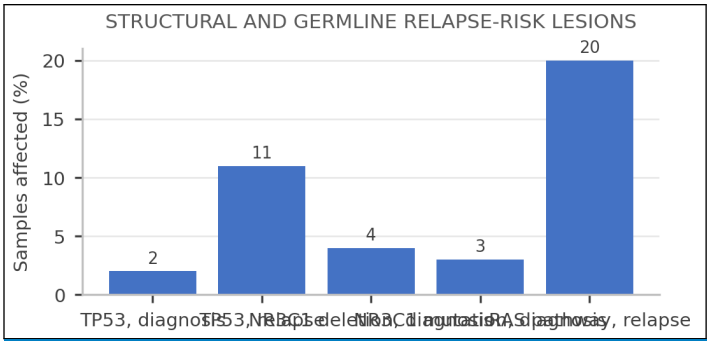

Figure 2: Prevalence of structural and germline relapse-risk lesions reported in pediatric B-ALL genomic studies: TP53 mutation in 11% of relapse versus 2% of diagnosis samples [13]; NR3C1 deletion in 4% and NR3C1 point mutation in 3% of diagnostic T-ALL samples [17]; and RAS-pathway (NRAS/KRAS) mutation in approximately 20% of relapse samples [14,15]; each figure is drawn from a separate cohort and lineage as noted.

IKZF1 deletion also co-travels with the Philadelphia chromosome-like (Ph-like) ALL subtype, a genomically defined group unified by a kinase-activating gene expression signature resembling BCR-ABL1-positive disease despite lacking the BCR-ABL1 fusion itself. Ph-like ALL carries a disproportionate share of relapse and induction failure among B-ALL, and, critically, the kinase lesions that define it — rearrangements and mutations activating ABL-class, JAK-STAT, or other tyrosine kinase signaling — are individually targetable with tyrosine kinase or JAK inhibitors, turning a poor-prognosis genomic subtype into an actionable one [21]. Germline variation contributes an additional, inherited layer to relapse risk: a genome-wide association study of relapse in childhood ALL identified inherited polymorphisms, including variants near genes implicated in purine metabolism, associated with relapse risk independent of the somatic mutations acquired by the leukemic clone, indicating that host genetic background modulates the probability that a given somatic lesion will translate into relapse [22]. A synthesis of the genetic subtypes underlying both diagnosis and relapse risk across B-ALL has been reviewed in detail elsewhere and situates IKZF1, Ph-like signaling, and hypodiploidy as the three structural axes around which most high-relapse-risk genomic subtypes are organized [23].

6. Translating relapse genomics into risk-directed therapy

The clinical stakes of this genomic dissection are set by outcome after relapse, which remains far worse than outcome at diagnosis and is highly dependent on both the site and the timing of relapse. A Children's Oncology Group study of relapsed ALL found that survival after relapse varied enormously by these two variables, with early marrow relapse carrying a dramatically worse prognosis than late or isolated extramedullary relapse, a pattern later reviews have consistently reproduced and that remains the backbone of post-relapse risk stratification in most cooperative-group protocols [24]. A comprehensive review of relapsed childhood ALL summarized this landscape and argued that genomic characterization of the relapse clone — rather than treatment intensification alone — was the most promising route to improving the roughly even odds that current relapse regimens still offer many patients [25].

Systematic mutational profiling of large diagnosis-relapse trio cohorts has since moved this argument from aspiration to demonstration. A genomic analysis of relapsed pediatric ALL trios catalogued the recurrent relapse-driver genes described above — NT5C2, PRPS1, CREBBP, NR3C1, TP53 among them — across a large cohort and showed that a substantial share of the genetic lesions found at relapse could already be detected, at low variant allele fraction, in the diagnostic sample using sufficiently sensitive sequencing, raising the prospect of a

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diagnosis-only genomic risk score that flags patients whose leukemia already harbors an incipient relapse-driver clone [26]. Functional work tracking relapse-fated subclones through barcoding and xenotransplantation reinforces the same translational logic from the opposite direction, by showing that these subclones have a definable drug-tolerant, altered-metabolism phenotype that is in principle detectable and potentially targetable before conventional relapse ever occurs [7].

Table 2: Post-relapse outcome and genomically informed therapeutic strategies by relapse feature [24,21,14,20,26].

Relapse feature	Reported association	Source
Early marrow relapse	Substantially worse post-relapse survival than late/isolated extramedullary relapse	[24]
Ph-like kinase lesion	Actionable with tyrosine kinase or JAK inhibitor	[21]
NRAS/KRAS mutation	Selective sensitivity to MEK inhibition	[14]
IKZF1plus genotype	Very-poor prognosis when MRD-high	[20]
Diagnosis-detectable relapse-driver clone	Basis for a diagnosis-only genomic relapse risk score	[26]

Two threads illustrate how far this has already reached the clinic. In Ph-like ALL, kinase-lesion genotyping now routinely triggers consideration of a matched tyrosine kinase or JAK inhibitor added to conventional chemotherapy, converting a genomically defined high-relapse-risk subtype into a group with a specific, mechanism-based intervention [21]. In RAS-pathway-mutant relapse, preclinical sensitivity of NRAS/KRAS-mutant subclones to MEK inhibition has motivated early clinical exploration of MEK inhibitors specifically in the relapse setting, where RAS mutations are both more common and more clinically actionable than they are at diagnosis [14,15]. Neither strategy alone will close the survival gap between diagnosis and relapse outcomes, but together with IKZF1plus- and MRD-integrated risk stratification [20], germline relapse-risk variants [22], and thiopurine-pathway genotyping for NT5C2 and PRPS1 status [8,12], they mark a shift from treating relapse as it happens to anticipating, genomically, which patients are most likely to experience it.

7. Conclusion

Fifteen years of matched diagnosis-relapse sequencing have converted pediatric B-ALL relapse from a clinical event into a legible genomic process. Relapse clones are usually present, in minor form, at diagnosis [5,7]; they are selected during therapy by a now well-characterized set of mutations in NT5C2 and PRPS1 that blunt thiopurine activity [8,12,9], and in CREBBP and NR3C1 that blunt glucocorticoid signaling [16,17]; and their risk is already partly encoded, before any of that selection occurs, in structural lesions such as IKZF1 deletion and Ph-like kinase signatures [19,20,21]. What remains incomplete is prospective validation: most of the risk scores and druggable-lesion strategies described here have been built and tested retrospectively on cohorts assembled after the fact, and the field's next task is to run diagnosis-time genomic risk stratification, and the therapeutic redirections it implies, forward into prospective trials rather than backward into explanatory sequencing of leukemias that have already relapsed.

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