

Dual *JAK1* and *JAK2* Mutations in Philadelphia Chromosome–Like ALL: A Case Report and the Impact of Implementing NGS in a Resource-Limited Setting

David Garrido¹, Gabriela Jaramillo-Koupermann², Gabriela Galvez², Anahis Rebolledo¹, María del Carmen Trujillo¹

¹Servicio de Hematología, Hospital de Especialidades Eugenio Espejo, Quito, Ecuador

²Servicio de Biología Molecular, Hospital de Especialidades Eugenio Espejo, Quito, Ecuador

Corresponding Author: David Garrido, Servicio de Hematología, Hospital de Especialidades Eugenio Espejo, Quito, Ecuador
E-mail: david0labinmuno@gmail.com

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Editorial

Philadelphia chromosome–like acute lymphoblastic leukemia (Ph-like ALL) represents a biologically high-risk subtype of B-progenitor ALL characterized by a gene expression profile resembling *BCR:ABL1*-positive disease despite the absence of the canonical fusion. This leukemia is characterized by convergent activation of kinase and cytokine receptor signaling pathways, most prominently ABL-class fusions, CRLF2 dysregulation, and alterations that drive constitutive JAK/STAT signaling. Such lesions frequently co-occur with cooperating variants, including *IKZF1* deletions, which contribute to treatment resistance and increased relapse risk¹.

Epidemiologically, Ph-like ALL spans the age spectrum, with prevalence increasing from childhood into adolescence and adulthood. Clinically, it is associated with higher leukocyte counts at presentation, increased persistence of measurable residual disease (MRD) following induction, and inferior event-free survival compared with non-Ph-like ALL, supporting its classification as an adverse-risk subtype².

Within this spectrum, activation of the JAK/STAT axis is particularly relevant in adolescents and adults, where CRLF2 overexpression or rearrangement

frequently coincides with activating *JAK* mutations. Hotspot variants at *JAK2* codon 683 refine biological risk stratification and provide a mechanistic rationale for considering JAK-directed strategies in clinical trials and risk-adapted therapeutic pathways³.

From a translational standpoint, timely recognition is actionable: contemporary diagnostic workflows integrate rapid immunophenotypic or expression-based screening with confirmatory cytogenetic testing and targeted or RNA sequencing to identify the driver lesion. These findings are increasingly linked to precision interventions, such as early ABL tyrosine kinase inhibitors or investigational JAK inhibitors for JAK/EPOR/CRLF2 alterations, embedded within MRD-driven therapy modification⁴.

Although conventional cytogenetics, standard PCR assays, and targeted fusion testing remain essential components of the initial diagnostic evaluation, they may fail to identify cryptic kinase pathway alterations and heterogeneous Ph like ALL signatures, underscoring the complementary role of targeted NGS or RNA-based approaches in contemporary risk stratification.

We report the case of a 16-year-old female patient who presented to the emergency department with

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asthenia, dyspnea, marked pallor, tachycardia, and mucocutaneous bleeding. Physical examination was otherwise unremarkable, without clinically evident lymphadenopathy, hepatomegaly, or splenomegaly. Initial blood tests showed leukocytosis (white blood cell count $11.02 \times 10^9/L$), severe neutropenia (absolute neutrophil count $0.30 \times 10^9/L$), lymphocytosis ($10.44 \times 10^9/L$), profound anemia (hemoglobin 4.0 g/dL), and severe thrombocytopenia (platelet count $3.0 \times 10^9/L$).

Bone marrow flow cytometry showed a blast population accounting for 97.7% of total cellularity, with an immunophenotype consistent with common B-cell precursor ALL: CD45 dim, CD19 positive, cytoplasmic CD79a positive, CD34 high, CD10 high, partial CD20 expression, CD66c positive, homogeneous CD38 expression, CD58 positive, nuclear TdT positive, CD22 positive, CD24 high, and CD81 high. The blasts were negative for surface CD3, cytoplasmic CD3, CD7, cytoplasmic myeloperoxidase, CD33, cytoplasmic IgM, surface IgM, CD117, surface kappa, surface lambda, CD9, CD13, CD21, CD15, CD65, CD123, and NG2.

Somatic profiling identified activating kinase pathway alterations, including *JAK2* c.2047A>G (*p.Arg683Gly*) at a variant allele frequency (VAF) of 29.4%, and *JAK1* c.2347C>T (*p.Leu783Phe*) at a VAF of 13.3% (Figure 1). The *JAK2* *p.Arg683Gly* variant is a recognized activating hotspot within the pseudokinase domain, associated with constitutive JAK/STAT signaling and characteristic of Ph-like ALL⁵. Targeted somatic DNA profiling was performed using an institutional 87-gene NGS panel that included key lymphoid and kinase signaling genes such as *JAK1*, *JAK2*, *JAK3*, *IKZF1*, *KRAS*, *NRAS*, *FLT3*, *SH2B3*, and *TP53*. Genomic DNA was enriched using a hybridization-based protocol with Twist Bioscience probes and sequenced on the PacBio Onso short read sequencing system using sequencing by binding technology. Reads were aligned to the GRCh38 reference genome, and variants were interpreted using curated databases and bioinformatic predictors.

BCR: ABL1 was not detected using an institutional RT qPCR fusion transcript panel for recurrent leukemia-associated translocations. Conventional karyotyping

and FISH were not available at our institution at the time of diagnosis.

To the best of our knowledge, concurrent activating lesions in both *JAK1* and *JAK2* have been infrequently described in Ph-like ALL, particularly in adolescents and young adults. The joint presence of these variants in this patient further supports classification within the JAK/EPOR/CRLF2 signaling cluster. These molecular findings did not lead to the immediate use of a JAK inhibitor, as this strategy was not part of the approved frontline treatment protocol in our setting. Instead, the identification of concurrent *JAK1* and *JAK2* alterations supported high-risk reassessment, multidisciplinary leukemia board discussion, and stringent MRD-based monitoring during frontline therapy according to the GATLA protocol.

This case underscores the clinical significance of systematic genomic profiling in ALL, particularly in adolescents and young adults, in whom Ph-like phenotypes may be underrecognized. Institutional preparation to identify these alterations through integrated molecular testing and multidisciplinary leukemia board discussion is essential to ensure the timely implementation of genotype-directed management. As molecular subtyping continues to refine the biological taxonomy of ALL, collaborative reporting of real-world cases, especially those with uncommon constellations such as dual *JAK1* and *JAK2* mutations, remains critical to improving translational understanding and optimizing treatment outcomes across diverse resource contexts.

Within our hematology service, this case represents the first formally documented diagnosis of Ph like ALL following the implementation of next generation sequencing in the upfront diagnostic workup of acute leukemias in July 2025. Before the incorporation of targeted genomic profiling, patients with similar clinical and immunophenotypic features may have been classified according to conventional risk criteria alone, without recognition of cryptic kinase pathway alterations. This institutional experience illustrates how the stepwise adoption of NGS can refine diagnostic classification, improve risk stratification, and support multidisciplinary decision making in real world settings with limited resources.

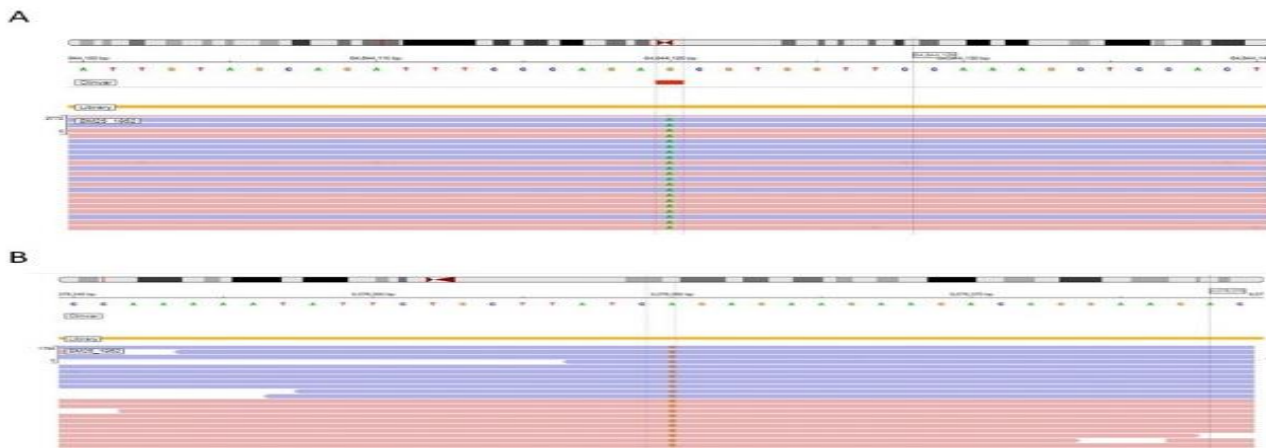


Figure 1. Integrated Genome Viewer confirmation of JAK pathway variants detected by targeted next generation sequencing at diagnosis.

Somatic DNA profiling was performed using an institutional targeted next generation sequencing panel for hematologic malignancies. Genomic DNA was enriched through a hybridization-based protocol using Twist Bioscience probes and sequenced on the PacBio Onso short read sequencing system using sequencing by binding technology. A. *JAK2* NM_004972.3:c.2047A>G, p.Arg683Gly, in exon 16 within the JH2 pseudokinase domain. The alternate base is seen at the dashed vertical guide with concordant reads on both strands; variant allele frequency 29.4%. B. *JAK1* NM_002227.4:c.2347C>T, p.Leu783Phe, in the JH2 pseudokinase domain. The alternate base is shown on the same guide; variant allele frequency 13.3%.

CONFLICT OF INTEREST

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