Biological and pathogenic roles of major genes harbored in intrachromosomal amplification of chromosome 21 in childhood acute lymphoblastic leukemia (Review)

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Received September 3, 2025; Accepted April 16, 2026

DOI: 10.3892/ol.2026.15678

Abstract. Chromosomal alterations are key in the study of acute lymphoblastic leukemia (ALL) as they facilitate the establishment of risks, prognosis and treatment. The intrachromosomal amplification of chromosome 21 (iAMP21) can generate a structurally heterogeneous derivative chromosome 21 that can typically replace a normal chromosome 21 and defines a subtype of high-risk childhood ALL (iAMP21-ALL). A region commonly involved in this amplification has been delineated and includes genes such as chromatin assembly factor 1 subunit B, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A, erythroblast transformation-specific-related gene, high mobility group nucleosome binding domain 1 and Runt-related transcription factor 1, but its role in the development of leukemia has not yet been fully elucidated. The Down syndrome critical region on chromosome 21 (ripply transcriptional repressor 3) overlaps with a common amplification region in iAMP21. Therefore, it has been hypothesized that iAMP21-related genes may be associated with Down syndrome susceptibility to ALL. The present review described the biological role of iAMP21-related genes and their relationship with ALL development.

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Key words: acute lymphoblastic leukemia, B-cell precursor, intrachromosomal amplification of chromosome 21, chromosome 21

Contents

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant hematological cancer in children with an globally incidence of ~3 cases per 100,000 individuals per year (1,2). The majority of cases exhibit various chromosomal alterations, which are associated with the survival and evolution of the disease. This is complemented by genomic studies that together have provided key information regarding the diagnosis, prognosis and development of novel therapeutic strategies (1,3). Specifically, 80-85% of ALL cases are B-cell precursor (BCP) ALL (B-ALL/BCP-ALL), with the remaining cases involving T-cells (1).

It has been reported that one of the most common chromosomal abnormalities identified in malignant hematological processes is the presence of an extra chromosome 21, which is identified in ~15% of ALL cases worldwide. Children with regular trisomy 21 are 20, 150 and 400-600 times more likely to develop ALL, acute myeloid leukemia (AML) and acute megakaryoblastic leukemia, respectively. Notably, trisomy 21 is the most common acquired aneuploidy in patients with any type of leukemia (4). Despite being the chromosome with the lowest gene density, chromosome 21 has been reported to contain a notable number of genes associated with the development of leukemia, majority of which have a locus within the Down syndrome (DS) critical region (DSCR) (5).

In 2003, the United Kingdom National Cancer Research Institute Childhood Leukemia Working Party reported a novel cytogenetic abnormality termed the intrachromosomal amplification of chromosome 21 (iAMP21). This rare alteration occurs in only 2-5% of cases of childhood BCP lymphoblastic leukemia, majority of which are older children with a low white blood cell count at diagnosis (3,6,7). iAMP21 was first observed using fluorescence *in situ* hybridization (FISH), when several signals corresponding to the Runt-related transcription factor 1 (*RUNX1*) gene were identified during the analysis of the t(8;21)(q22;q22) translocation in patients with AML. At present, iAMP21 is commonly defined as 'three or more extra copies of *RUNX1* on a single abnormal chromosome 21 (a total of five or more *RUNX1* signals per cell) (Fig. 1) (8,9).

The abnormal chromosome 21 presents a complex structure that comprises multiple regions of gain, amplification, inversion and deletion (8). It has been proposed that the origin of the derivative chromosome may be the result of a series of events including an initial double-strand break, followed by fusion and bridge formation, with the final presence of chromothripsis (Fig. 2) (10,11). As the *RUNX1* gene locus is located within the region primarily responsible for chromosome 21 amplification, an easy and accessible method to identify iAMP21-ALL is to erythroblast transformation-specific (ETS) variant transcription factor 6 *(ETV6)*::*RUNX1* fusion probe mark this gene via FISH (12). Therefore, majority of cases of iAMP21-ALL have been identified by FISH. However, chromosome 21 can also be structurally heterogeneous, which can only be evaluated using chromosome banding analysis (7). The structure of the chromosome is described as an addition, duplication or simply a derivative of chromosome 21 (11). While iAMP21 arises through chromosomal instability, the last chromosome remains stable and is unique for each case (Fig. 1C) (9).

Cytogenetics and whole genome sequencing enabled the identification of iAMP21, which constituted a novel, distinct genetic subgroup within ALL (13,14). Notably, children with iAMP21 do not respond adequately to traditional treatment. Thus, the early detection of chromosome amplification is crucial, as this subgroup requires intensive treatment. (3,6,10,15).

There is debate regarding the relationship between iAMP21 and the development of leukemia. Amplification can be heterogeneous, in particular at the molecular level where there is notable gene destabilization, depending on the structural rearrangement of chromosome 21 (16). Multiple genomic studies have delineated the common region of amplification in iAMP21, which ranges from 1.57 to 20.77 Mb depending on the cohort and methodology employed. Comprehensive array-comparative genomic hybridization and multiplex ligation dependent probe amplification analyses have consistently identified the amplification of genes including chromatin assembly factor 1 subunit B (*CHAF1B*), dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (*DYRK1A*), ETS-related gene (*ERG*), high mobility group nucleosome binding domain 1 (*HMGN1*) and *RUNX1*, with ripply transcriptional repressor 3 (*RIPPLY3*/DSCR6) recently identified as the most highly upregulated gene within the minimal 1.57 Mb region that overlaps with the DSCR. These genes are differentially expressed in iAMP21-ALL compared with non-iAMP21-ALL and represent candidates for coordinated involvement in leukemogenesis (1,10,11,15-18). Ofverholm *et al* (19) characterized the genomic and transcriptional landscape of iAMP21, and identified differentially expressed genes, including *DYRK1A*, *CHAF1B* and SON, which had a notable association with iAMP21-ALL. Due to the large size of the region involved in amplification and the deregulation of several genes, including *RUNX1, DYRK1A, CHAF-1* and *ERG*, a coordinated action of these genes has been hypothesized to occur for the development of iAMP21-ALL (16).

The present review describes the biological role of the primary genes associated with iAMP21-ALL and their relationship with disease development.

2. *CHAF1B*

The *CHAF1B*, also termed CAF1, MPP7, chromatin assembly factor I (CAF-I), CAF1A, CAF1P60, CAF-IP60 or MPHOSPH7, is part of CAF-I and is required for the assembly of histone octamers onto newly replicated DNA. This subunit is typically located in the nucleus and relocated into the cytoplasm during mitosis. *CHAF1B* is differentially phosphorylated in a cell cycle-dependent manner. Furthermore, *CHAF1B* is a member of the WD-repeat histone regulator 1 family, may also be involved in DNA repair (20) and is located within the DSCR of chromosome 21 (21q22.12-q22.13; Fig. 3) (21,22).

Remodeling the chromatin structure after replication is a key process in maintaining gene regulation (23) and epigenetic information, and the regulation of the alteration of chromatin states. Consisting of three subunits, CAF1 participates in nucleosome assembly at the beginning of the S phase of the cell cycle. CAF1 acts as a histone chaperone and interacts with the Proliferating Cell Nuclear Antigen (PCNA). Furthermore, *CHAF1B* serves a key role in epigenetic silencing, as well as in the replication of centromeric heterochromatin by interacting with the heterochromatin protein. It is well established that CAF1 is key to forming tetramers of histones H3 and H4 at the replication fork, as well as nucleosomes, during the S phase (24). The participation of *CHAF1B* in these processes is key to the cell cycle and any impairment in its function affects normal cell division. *CHAF1B* was found to be altered in various cancer types such as high-grade gliomas, melanomas, endometrial, renal, cervical and prostate cancer, likely due to its key role in chromatin replication (21,23-25). Furthermore, another key function of *CHAF1B* is in DNA repair during interphase through the ATP-dependent nucleotide excision mechanism and under the action of PCNA (21).

CHAF1B is highly expressed in the bone marrow and testes (19) and typically serves a role in hematopoiesis. However, the upregulation of *CHAF1B* can lead to leukemia. When *CHAF1B* binds specifically to chromatin, it can have a pro-leukemic effect by affecting the binding of transcription factors such as CCAAT/enhancer-binding protein α (CEPBA), which are key to blood cell differentiation, particularly in the myeloid lineage (24). The process of leukemogenesis is promoted when the expression levels of different transcription factors, such as friend leukemia integration 1 (FLI1), CCAAT/enhancer-binding protein β and *RUNX1*, are suppressed due to the upregulation of *CHAF1B*. An increase in DNA methyltransferase activity leads to hypermethylation

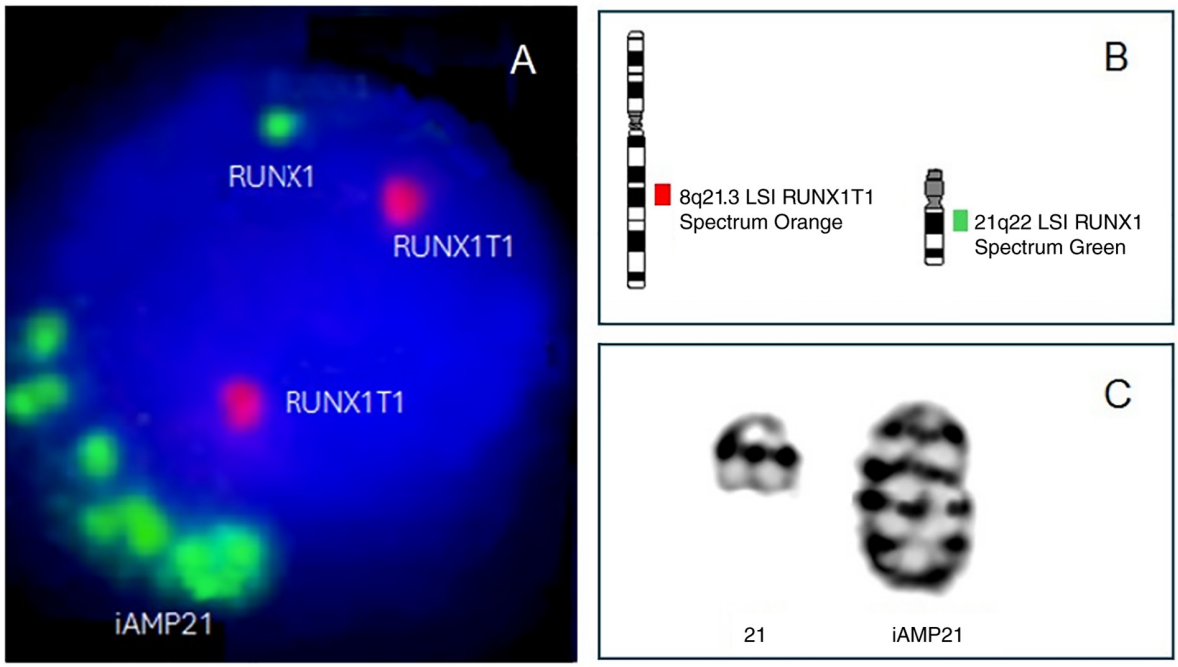

Figure 1. A case of ALL with iAMP21. (A) Interphase cell hybridized with *RUNX1* (Spectrum Green)/*RUNX1T1* (Spectrum Orange) FISH Probe Kit for translocation (8;21)(q21.3;q22) (Vysis, Inc.; Abbott Pharmaceutical Co. Ltd.) presenting amplification of the *RUNX1* signal associated with iAMP21. Image of the Hemato-oncology Laboratory, Hospital for Children Maternal and Child Institute of the State of Mexico (B) Schematic showing the location of each probe. (C) An example of structurally abnormal chromosome 21 with iAMP21. Image of the Hemato-oncology Laboratory, Hospital for Children Maternal and Child Institute of the State of Mexico. ALL, acute lymphoblastic leukemia; intrachromosomal amplification of chromosome 21; *RUNX1*, Runt-related transcription factor 1; *RUNX1T1*, *RUNX1* partner transcriptional co-repressor 1; LSI, locus-specific identifier.

of the FLI1 promoter and a notable reduction in its expression, and *RUNX1* indicated no change in expression despite amplification of the gene, possibly as an effect of *CHAF1B* upregulation (21). Furthermore, *CHAF1B* is upregulated in several solid tumors and has been associated with increased tumor grade and aggressiveness (25). Various neoplasms, including melanomas, endometrial tumors, prostate cancer and gliomas, have been associated with *CHAF1B* upregulation. However, the mechanisms underlying this association are not fully understood (23-25). Specifically, there is controversy regarding the association of tumorigenesis with *CHAF1B* upregulation and it has been hypothesized that this may simply be due to the high proliferation of abnormal cells (23). Notably, it has been observed that *CHAF1B* is highly expressed in patients with DS and acute megakaryocytic leukemia.

A previous study conducted in mice confirmed the key role of *CHAF1B* in hematopoiesis and cell viability through the conditional elimination of *CHAF1B* in interferon-sensitive cells. The results also demonstrated that *CHAF1B* upregulation increases hematopoietic stem and progenitor cell proliferation. After confirming the association between *CHAF1B* upregulation and leukemia development, researchers suggested that targeting the CAF1-dependent pathway in the nucleosome assembly process could represent an innovative treatment approach (23).

CHAF1B is key to DNA replication-coupled nucleosome assembly. Therefore, its loss or reduced activity may lead to a decrease in the proliferation of leukemic cells. Li *et al* (23) identified that *CHAF1B* serves a key role in silencing genes involved in myeloid cell differentiation. The study reported that reducing the dose of *CHAF1B* induced the differentiation of human AML cells and murine mixed lineage leukemia-ALL fused gene from chromosome 9 cells, and the same conclusion was reached when studying the transcriptome of cells that overexpressed or deleted the gene. Since *CHAF1B* shares a genomic locus with CEPBA, FLI1 and *RUNX1*, it interacts with these transcription factors at the chromatin level. These transcription factors are key regulators of hematopoietic differentiation and any increase in the dose of *CHAF1B* influences the silencing of these genes key to leukemic cell differentiation (23).

The overall summary of the physiological roles of the main genes involved in the common region of chromosome 21, which is affected in iAMP21, is presented in Table I, as well as the genetic alterations associated with the development of hematological malignancies.

3. *DYRK1A*

DYRK1A, also termed MNB, DYRK, HP86, MNBH, MRD7 or DYRK1, encodes a member of the DYRK family (20). *DYRK1A* is a member of a conserved family of CMGC kinases, named from the first letter of each family member, including cyclin-dependent kinases (CDK), mitogen-activated protein kinases, glycogen synthase kinase 3 and CDK-like kinases (26). They are structurally characterized by the presence of a protein kinase domain, a leucine zipper motif and a series of 13 highly conserved histidine repeats (20). The DYRK family consists of five members divided into two classes, with the first class including *DYRK1A* and *DYRK1B*, and the second class including *DYRK2, DYRK3* and *DYRK4*. Of these five variants, only *DYRK1A* (21q22.13; Fig. 3) is located on

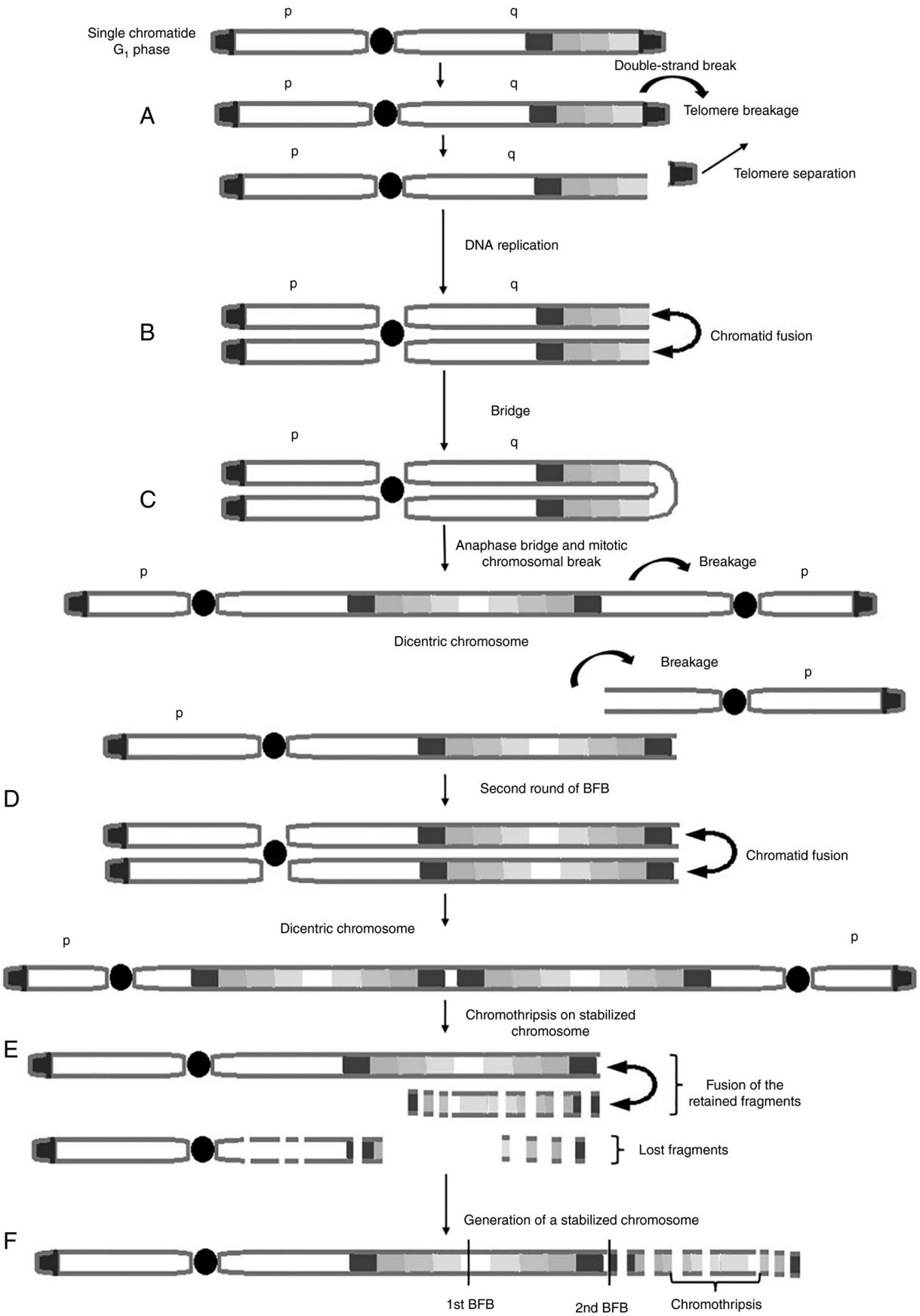

Figure 2. BFB mechanism in the formation of intrachromosomal amplification of chromosome 21. (A) Double-strand break in an unreplicated chromosome with telomere loss (red block). (B) Both sister chromatids lack telomeres. (C) These two ends are considered to fuse and form a dicentric chromosome. At anaphase, the two centromeres are pulled apart, forming a bridge between the telophase nuclei. Eventually the bridge is broken, leading to the formation of a large, inverted duplication. (D) After a novel replication cycle, the chromosome once again has an unprotected end and forms a novel dicentric chromosome. (E) Stable chromosome undergoes chromothripsis resulting in a structurally different chromosome. (F) The new chromosome may contain inversions, duplications and loss of genetic material. BFB, Breakage-fusion-bridge.

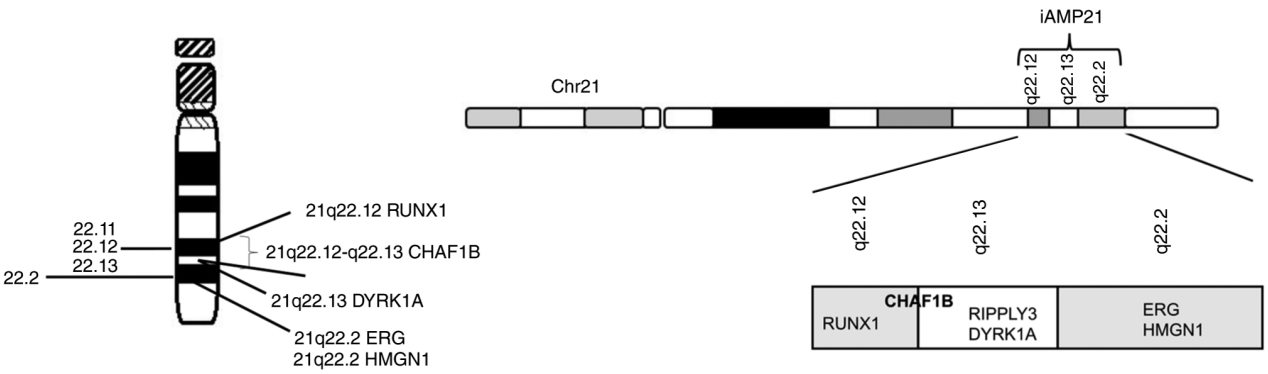

Figure 3. Ideogram of the iAMP21 loci. Chr, chromosome; *RUNX1*, Runt-related transcription factor 1; *ERG*, erythroblast transformation-specific-related gene; *DYRK1A*, dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase; *HMGN1*, high mobility group nucleosome binding domain 1; *RIPPLY3*, ripply transcriptional repressor 3; iAMP21, intrachromosomal amplification of chromosome 21.

chromosome 21, whilst *DYRK1B* is on 19q13.2, *DYRK2* is on 12q15, *DYRK3* is on 1q32.1 and *DYRK4* is on 12p13.32 (22).

DYRK1A increases its activity through autophosphorylation of its activation loop and participates in the phosphorylation of several regulatory proteins, such as STAT3 and FOXO1 (26). *DYRK1A* regulates cell proliferation and brain development by participating in the Notch signaling pathway. It has been hypothesized that *DYRK1A* is associated with learning disabilities in individuals with DS, autism and Alzheimer's disease (26). During transcription, this gene encodes at least 5 isoforms that differ in the 5'-UTR or in the 3'-coding regions and has ubiquitous expression in bone marrow and testes (20).

DYRK1A is a kinase that participates in key biological processes, including chromatin transcription, mRNA splicing, signal transduction, DNA repair, cell cycle control and neuronal function development. *DYRK1A* is dysregulated in various types of malignant neoplasms, including lung and pancreatic cancer, glioblastoma, melanoma and leukemia, as well as in other diseases such as type 1 and type 2 diabetes mellitus and heart disease (26-28). The *DYRK1A* protein appears to serve a key role in the development of these conditions and its modulation may lead to cell cycle dysregulation control (27). A notable development in the current understanding of the role of *DYRK1A* in these processes has been the study of patients with DS, who are at an increased risk of developing various congenital disorders, as well as leukemia, lymphoma and retinoblastoma (26-28). These conditions have been associated with different functions of the *DYRK1A* gene. Therefore, it has been suggested that there is an association between these alterations and the presence of constitutional trisomy 21. However, the role of *DYRK1A* remains to be elucidated, as there are several studies indicating that it has both oncogenic and tumor suppressor functions (27,28).

It has been reported that upregulation of *DYRK1A* deactivates CDK1. This cyclin-dependent kinase serves a role in regulating mitosis and cell cycle inhibition. Furthermore, the protein levels of *DYRK1A* upregulation are positively associated with those of *STAT3*, cellular-mesenchymal-epithelial transition factor (MET) and *EGFR*, as it has been reported that *DYRK1A* small interfering RNA can suppress the levels of *EGFR* and MET receptor tyrosine kinases in lung and pancreatic cancer cells (27).

Children with trisomy 21 who have a GATA-binding factor 1 mutation associated with *DYRK1A* upregulation are at an increased risk of developing acute megakaryoblastic leukemia. *DYRK1A* affects the regulation of transcription factors of the nuclear factor of activated T cells, which are key to megakaryopoiesis (26).

In the normal process of lymphopoiesis, *DYRK1A* phosphorylates cyclin D3, marking this protein for degradation. This inactivates lymphocytes and promotes their differentiation. Bhansali *et al* (28) studied both B-ALL cell lines and patient samples, including those with poor prognosis such as those associated with the Philadelphia chromosome, and reported that *DYRK1A* was overexpressed.

The association between the development of leukemia and the involvement of *DYRK1A* is well established. Analysis of a human pediatric ALL database revealed *DYRK1A* amplification or mRNA upregulation in 10.83% of all cases. Autoimmune diseases and malignant B-cell neoplasms can develop when B-cell activating factor (BAFF) becomes dysregulated, and the survival of both mature and immature T2 B cells depends directly on BAFF. Notable reductions in both cell types have been associated with *DYRK1A* deficiency, as *DYRK1A* acts as a key mediator in the BAFF signaling pathway. It facilitates B-cell survival and the activation of the non-canonical NF-kB pathway. When this process is dysregulated, it contributes to the development of B-ALL. It has been suggested that the integration of a *DYRK1A* inhibitor in the treatment of ALL may improve outcomes (29).

Therapeutic targets for *DYRK1A* have been evaluated in B-ALL cell lines treated with ETH 1610, a potent inhibitor of *DYRK1A*, which demonstrated a dose-dependent decrease in cell number. The effects were most notable in trisomy 21 or hyperdiploid cells. In patients with DS and B-ALL, synergy is observed between EHT 1610 and multiple chemotherapeutic agents, such dexamethasone, cytarabine and methotrexate (26).

4. *ERG*

The *ERG* gene encodes a member of the ETS family of transcriptions factors; it is also termed p55, *ERG*-3 or LMPHM14. These transcription factors serve a role in regulating processes such as embryonic development, cell proliferation and differentiation, angiogenesis, inflammation and apoptosis. The *ERG*

Table I. Physiological roles and genetic alterations in hematological malignancies of key genes located in the commonly affected region of chromosome 21 in iAMP21.

Function	*CHAF1B*	*DYRK1A*	*ERG*	*HMGN1*	*RUNX1*	*RIPPLY3*
Physiological roles	Encodes p60 required for chromatin assembly, regulates DNA transcription, repair and replication; regulation of gene expression; normal hematopoiesis	Phosphorylates diverse regulatory proteins; regulation of cell proliferation, differentiation and growth; DNA damage repair	Regulator of cell proliferation, differentiation and apoptosis; regulates hematopoiesis, differentiation and maturation of megakaryocytic cells	Binds nucleosomal DNA; associated with transcriptionally active chromatin; modulates gene expression; DNA damage repair	Transcription factor key in hematopoiesis and embryonic development; cell division and proliferation regulator	Transcriptional repressor that regulates the transcriptional activity of TBX1 and STAT3; involved in negative regulation of transcription by RNA polymerase II
Genetic alterations and roles in hematological malignancies	Genomic instability that increases the risk of mutations associated with cancer; upregulation promotes leukemia by suppressing the expression levels of TFs in myeloid differentiation, including *RUNX1*	Dysregulation is associated with leukemia by disruption of cell cycle control; it has both oncogenic and tumor suppressor functions; upregulation deactivates CDK1, which positively regulates mitosis and inhibits the cell cycle	Involved in CTs, resulting in different fusion gene products such as FUS::ERG in AML; elevated *ERG* and c-Myc expression levels are necessary for pre-B cells clonal expansion and leukemia development; *ERG* deletions can be identified in 3-7% of BCP ALL cases	Methylase activity of *HMGN1* is associated with increased transcriptional activation and development of leukemia; is associated with increased chromatin accessibility, expression, and histone H3K27 acetylation of 1 oci necessary for HSCS and leukemia	CTs associated with several types of leukemia (>50 affect *RUNX1*: t(12;21) in pediatric ALL; *RUNX1* can act as a tumor promoter or suppressor in hematological malignancies; somatic mutations are observed in AML, ALL and MDS	Upregulated in the iAMP21 cases studied; no associations with hematological malignancies have been reported yet

TFs, transcription factors; CTs, chromosome translocations; CDK1, cyclin-dependent kinase 1; AML, acute myeloid leukemia; BCP, B-cell precursor; ALL, acute lymphoblastic leukemia; HSCS, hematopoietic stem cells; MDS, myelodysplastic syndrome; *RUNX1*, Runt-related transcription factor 1; H3K27, lysine 27 on histone H3; *ERG*, erythroblast transformation-specific-related gene; FUS, fused in sarcoma; TBX1, T-box transcription factor 1; *CHAF1B*, chromatin assembly factor 1 subunit B; *DYRK1A*, dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase; *HMGN1*, high mobility group nucleosome binding domain 1; *RIPPLY3*, ripply transcriptional repressor 3; iAMP21, intrachromosomal amplification of chromosome 21.

gene encodes a protein with a DNA-binding ETS domain and a pointed domain that exhibits nuclear activity and associates with chimeric oncoproteins. *ERG* not only serves a key role in hematopoietic process regulation through platelet adhesion and vascular cell remodeling but also contributes to the differentiation and maturation of megakaryocytic cells. AML that involves a chromosomal translocation (16;21) (p11;q22) is associated with poor prognosis and resistance to treatment. This type of leukemia involves the *FUS::ERG* gene fusion. Other *ERG* fusions include *TMPSMR2::ERG* and *NDRG1::ERG* in prostate cancer, as well as *EWS::ERG* in Ewing's sarcoma. It has been reported that the *ERG* gene has several alternative promoters that generate >24 variants via alternative splicing. However, the function of these variants has not yet been fully established (20). *ERG* (21q22.2) is a key transcription factor that is extensively expressed in multiple tissues (whole blood, brain, cortex, spinal cord, heart, kidney) (Fig. 3) (22).

It has been reported that *ERG* and *c-Myc* work in conjunction in a regulatory network in ALL, which is triggered by the fusion of breakpoint cluster region (*BCR)::ABL1* genes. This association regulates the expression levels of genes involved in ribosome formation and RNA polymerase I subunit regulation. Clonal expansion of pre-B cells and subsequent development of leukemia require increased expression levels of *ERG* and c-Myc in B-ALL cells with the *BCR::ABL* fusion. By contrast, in human *BCR::ABL1* B-ALL cell lines, reduction of *ERG* or *c-Myc* levels limited the expansion of leukemia cells and delayed the development of leukemia in transplanted mice. It has also been suggested that *ERG* and *c-Myc* are co-expressed in other B-ALL subtypes, in addition to B-ALL with *BCR::ABL* gene fusion (30).

ERG (ETS transcription factor) gene deletions can be identified in 3-7% of cases of pediatric BCP-ALLs (31,32). *ERG* gene deletions occurs almost exclusively in other B-ALL subtypes, a heterogeneous subset comprising 20-25% of pediatric BCP-ALL cases, defined by the absence of cytogenetic alterations identified by chromosome banding analysis. Previous studies have reported that the negative prognostic impact is reduced when simultaneous deletions occur in *ERG* and Ikaros family zinc finger 1 (31,33).

The processes of hematopoietic differentiation, megakaryopoiesis and the development of megakaryoblastic leukemia in patients with DS are all associated with the direct involvement of *ERG* (32). As aforementioned, *ERG* is frequently upregulated in prostate carcinoma. This rarely occurs in acute leukemia because another type of damage is more prevalent (33). However, cases of AML with poor prognosis have been described as they show upregulation of the gene (33). Although it has been suggested that B lymphoid cell development may be regulated when *ERG* is enhanced, its association with ALL development remains to be elucidated. Notably, there are a few reported cases in which *ERG* is deleted, suggesting that *ERG* deregulation is a notable but secondary event in leukemogenesis (31,32). However, if it is identified during the initial phases of leukemogenesis, it may manifest as a clonal event. Previous studies have demonstrated that dysregulation can be complex and affect both alleles in majority of cases of *ERG* deletion. Therefore, the concept of a single gene alteration may not be applicable and the idea of a single-copy gene being inactivated (haploinsufficiency) may not fully explain the biological impact (31,32).

ERG, along with other transcription factors such as double homeobox 4 (DUX4), may be deregulated and exhibit differential gene expression, constituting a specific subtype of B-cell progenitor ALL. The genomic alterations described for *ERG*, which present atypical gene expression manifested as the upregulation or downregulation of normal transcripts or the production of chimeric transcripts, are associated with different mechanisms. These can include shorter transcripts, have different splicing patterns, start translation from unusual codons or be hybrid genes that produce transcripts with both coding and non-coding functions. An example of this is the expression of the novel *ERG* coding transcript, *ERG* isoform 1 (*ERG*alt) (33). By contrast, clonal or subclonal deletions of *ERG* are also observed in majority of cases and *ERG* deregulation by DUX4 is similar to the deregulation of other ETS genes in solid tumors such prostate cancer and Ewing's sarcoma (32,33).

As in myeloid cells, *ERG* expression is preferential and strong in both B lymphocytes and immature T cells. Identifying emerging markers in different signaling pathways will be key to designing novel therapeutic alternatives in the future. Certain pathways associated with *ERG* upregulation, such as the Wnt/β-catenin, p53 and PI3K/AKT/PTEN pathways, are associated with hyperactive or defective kinases or altered kinase expression levels, as is the case with casein kinase 2 (CK2), leading to resistance to kinase inhibitors. CK2 upregulation has been observed in hematological malignancies such as acute and chronic leukemias, including T-cell ALL (T-ALL), B-ALL and AML, and has been associated with poor clinical outcomes (34). Furthermore, an increase in *ERG* expression has been associated with poor relapse-free survival in patients with T-ALL. By contrast, low *ERG* expression has been associated with high white blood cell counts and poor relapse-free survival rates in pediatric patients with B-ALL. The expression levels of CK2, Myc and *ERG* in pediatric patients with ALL have not been fully studied. Therefore, it is proposed that characterizing these genes could lead to the identification of novel disease markers and/or therapeutic targets in this type of leukemia (34).

5. *HMGN1*

HMGN1 (21q22.2; Fig 3) (22), also termed HMG14, is a nucleosome remodeling protein. *HMGN1* is expressed in nearly all cell and tissue types in the body; however it is particularly notable in the bone marrow and lymph nodes (20). The main function of *HMGN1* is to act as a nucleosome-binding protein, which regulates chromatin structure and function. This facilitates access of regulatory factors to DNA, thereby affecting gene expression, development and the cellular response to damage (20). *HMGN1* exhibits notable demethylating activity, which increases transcriptional activity and could be associated with the development of leukemia (5).

HMGN1 upregulation suppresses the trimethylation of lysine 27 on histone H3 (H3K27). Furthermore, it simultaneously promotes the proliferation of B cells and B-ALL cells *in vitro* and *in vivo*, respectively (35). *HMGN1* amplification and H3K27 acetylation are both epigenetic

mechanisms that promote chromatin opening. This process can affect hematopoietic stem cells (HSCs), which impacts myeloid differentiation and leads to leukemia. The upregulation of *HMGN1*, in conjunction with the presence of the fusion oncoprotein AML-ETO9a, can produce a cellular environment that promotes genomic instability and the dysregulation of signaling pathways that are key to the development of myeloid cells and the onset of leukemia. The factors that modulate chromatin accessibility in HSCs and leukemia stem cells (LSCs) are key to gene expression. This allows HSCs to differentiate into blood cells and maintain homeostasis. However, in LSCs, dysregulation of these factors promotes uncontrolled cell proliferation, which is a hallmark of leukemia. By modifying chromatin structure and increasing histone acetylation, *HMGN1* promotes blast immaturity and the persistence of LSCs. Furthermore, its ability to decompress chromatin allows transcription factors and coactivators, such as the histone acetyltransferase (HAT) CREB-binding protein (CBP)7p300, to bind more easily. This makes it a potential therapeutic alternative for AML (4).

Competition between histone H1 and nucleosome-binding proteins belonging to the HMGN family promotes chromatin decondensation, increased accessibility and locally enhanced transcription. HMGN interacts with nucleosomes, regardless of the DNA sequence, through the recognition of histones H2A and H2B7 by a specific nucleosome-binding domain. It has a specific location on regulatory marks in active promoters, enabling it to influence the organization of nucleosomes, DNase hypersensitivity patterns and post-translational histone marks. As *HMGN1* controls access to functional elements in chromatin, it can influence myeloid differentiation by increasing gene expression, which blocks differentiation and promotes the accumulation of leukemic stem cells, alongside H3K27 acetylation and AML oncogenes. *HMGN1* could be a therapeutic target with the inhibition of HAT, as it is dependent on CBP and p300 (4). In cases of ALL with an extra chromosome 21, iAMP21 or DS, an increase of gene expression in the amplification of DSCR, including *HMGN1*, has been identified. This was particularly observed in cases with a deletion in the Xp22p22 or Yp11p11 region that generates the purinergic receptor P2Y, G-protein coupled, 8*::*cytokine receptor-like factor 2 (*CRLF2*) fusion and causes *CRLF2* upregulation and activation of the Janus kinase-STAT pathway, a common process in B-ALL. This fusion is most prevalent in patients with ALL and DS, followed by those with iAMP21, and it is rare in patients (only 5-16%) with ALL without an extra chromosome 21 (36).

In general, it is well established that the upregulation of *HMGN1* reduces chromatin compaction and modulates epigenomic control globally (5).

6. *RUNX1*

RUNX1, also termed *AML1*, *CBFA2*, *EVI-1*, *AMLCR1*, *PEBP2aB*, *CBF2α*, *AML1-EVI-1* or *PEBP2α*, is extensively expressed in the appendix, bone marrow and 24 other tissues (20).

RUNX1 (21q22.12; Fig. 3) (22) forms a complex with its associated protein, core binding factor β, which is key to efficient DNA binding and complex stability. As a member of the Runt-related transcription factor family, *RUNX1* serves a key role in various biological processes, including hematopoietic stem cell differentiation and normal development. However, it is also involved in the progression of cancer types, such as leukemia (20). Various alterations to this gene have been identified, including mutations, upregulation and increased copy number. Translocations have been particularly well documented and are associated with different types of leukemia (37). *RUNX1* has been associated with >50 different translocations. In hematological malignancies, the most notable are the t(12;21) translocation involving the *ETV6::RUNX1* fusion gene, which is identified in pediatric ALL, and the t(8;21) and t(3;21) translocations involving the *AML1::MTG8* and *RUNX1::MECOM* fusion genes, respectively, which are identified in AML. The latter fusion results in the upregulation of the EVI1 factor, which acts as an oncogene (38).

The mammalian RUNX family of transcription factors comprises three members: i) *RUNX1*; ii) *RUNX2*; and iii) *RUNX3*. These proteins serve key roles in a variety of biological processes, such as cell differentiation, proliferation, apoptosis and embryonic development. Each exhibits distinct tissue expression patterns and functions. For instance, *RUNX1* is involved in hematopoiesis, *RUNX2* in osteogenesis and *RUNX3* in neurogenesis and lymphopoiesis (39). The diversity of RUNX transcripts is due to the presence of two different promoters for each of the three RUNX genes (*RUNX1*, *RUNX2* and *RUNX3*), which result in alternative splicing and the formation of different N-terminal amino acid sequences in the resulting isoforms. These transcripts produce various mRNA molecules that serve specific roles in regulating gene expression and cell differentiation in different tissues and developmental stages (38).

Previous studies have reported that *RUNX1* is frequently involved in the progression of acute leukemia and serves a key role in other types of cancer like pancreatic adenocarcinoma, uterine endometrioid carcinoma, lung adenocarcinoma and colorectal adenocarcinoma (39,40). Depending on its expression level, *RUNX1* can act as a tumor promoter or suppressor in hematological malignancies (40). Mutations in this gene are relatively frequent and its study is of key importance in hematological malignancies. For example, *RUNX1* proteins have been found to fuse with other genes in patients with AML. *RUNX1-ETO* fusion is found in 10-20% of these cases. In children with ALL, *TEL-RUNX1* fusion is found in 20-25% of cases (41).

Germline mutations in *RUNX1* cause familial platelet disorder with associated myeloid malignancies. In particular, somatic mutations of the gene are observed in different types of leukemia such as AML, ALL, myelodysplastic syndromes and chronic myelomonocytic leukemia. Due to the involvement of *RUNX1* in these processes, it is considered a key element for the development of potential therapeutic strategies (38,42). Whether due to germline or somatic alterations, the inactivation of *RUNX1* is considered a determining factor in the development of hematological neoplasms (41).

Furthermore, transcriptomic studies have reported that *RUNX1* in particular is differentially expressed in patients with shorter survival times. Both increased and decreased

levels of *RUNX1* gene expression have been described in different types of leukemia, as well as in different neoplasms (37). Somatic mutations in the *RUNX1* gene are commonly observed in hematological malignancies (39), including AML and myelodysplastic syndromes. These mutations often worsen the prognosis and are associated with a poor response to standard chemotherapy (37). It has been suggested that *RUNX1* works with other transcription factors to promote leukemia development. This is evident in its interaction with Notch1, a key element in signaling pathways that regulates cell development. By behaving as an oncogene, Notch1 promotes the growth and survival of cancer cells, particularly in acute T cell lymphoblastic leukemia. This association in turn promotes the expression levels of various proto-oncogenes, including Notch3, Myc and DTX1, and contributes to chromatin reprogramming, generating abnormal gene expression, which is key in cell development and malignancy (37).

By contrast, most chromosomal translocations lead to gene fusion, which is the initial event in leukemia onset that confers self-renewal properties to HSCs or lymphoid progenitors (40). For example, translocation t(12;21)(p13;q22) is the most common abnormality in childhood ALL with an approximate frequency of 25% and creates the fusion of the *ETV6::RUNX1* genes (43). Although it is associated with a favorable prognosis in majority of cases, it may be associated with late relapses associated with the appearance of additional alterations (44). These additional alterations are predominantly caused by rare genomic rearrangements mediated by aberrant recombination-activating gene (RAG) activity. Jakobczyk *et al* (44) demonstrated that RAG1 transcripts are directly upregulated by *ETV6::RUNX1* from the -1,200 bp RAG1 enhancer and by *RUNX1* from the -80bp RAG1 promoter in human pre-B cells. The study proposed a multistep mechanism, where the translocation usually starts *in utero*. Recent studies have reported that both *RUNX1* and the *ETV6::RUNX1* fusion binds directly to the promoter and enhancers of the RAG1 gene. This causes the upregulation of RAG1, which appears to be a key process in the pathogenesis of childhood B-cell ALL (44,45).

7. *RIPPLY3*

RIPPLY3 (21q22,13; Fig. 3) (22), a transcriptional repressor that acts by repressing the activity of other genes, was among the relevant genes reported to be amplified in iAMP-ALL. Notably, it was the most upregulated gene in all of the iAMP21 cases studied. *RIPPLY3* was identified in 2000; however, it has been infrequently explored in ALL. The reported expression levels suggest a probable association between *RIPPLY3* and iAMP21. However, prior to establishing this association, the role of *RIPPLY3* in the development of neoplastic processes, particularly leukemia, has not been well established (15). The notable similarity in transcriptional signatures suggests that *RIPPLY3* activity serves a key role in the development of iAMP21-ALL. It has been hypothesized that *RIPPLY3* is associated with other neighboring genes, as demonstrated by patients with iAMP21-ALL who have low *RUNX1* amplification (15).

RIPPLY3, also termed DSCR6, has been studied in other types of neoplasms. The role of *RIPPLY3* in cell proliferation suggests that it serves a notable role in regulating proliferation and division, as demonstrated in the thyroid gland, where an association has been observed between the presence of papillary thyroid carcinoma and abnormal development of the thyroid gland (46).

Other previous studies have reported that abnormal methylation patterns in key DNA sequences in the early stages of carcinogenesis can be used to detect certain neoplasms, such as ovarian cancer. A total of 11 candidate DNA methylation markers, including *RIPPLY3*, were identified that exhibited high sensitivity and specificity to distinguish women with ovarian cancer from those without it (47,48).

Lastly, it should be noted that at the time of diagnosis or confirmation, patients receive standard treatment, which is mainly based on the use of steroids, such as prednisone, dexamethasone or methylprednisolone, either on their own or in combination with systemic chemotherapy or intrathecal therapy. During induction therapy, four drugs are used: i) Steroids; ii) vincristine; iii) L-asparaginase; and iv) anthracyclines (49,50). At this stage, any changes and modifications are made based on patient response. This is mainly due to the genetic heterogeneity of patients and provides a unique leukemia profile. These malignancies are characterized by a combination of chromosomal abnormalities, oncogenic mutations and epigenetic deregulation (51). As is the case with the presence of iAMP21, which is associated with a poor prognosis. Children presenting with iAMP21-ALL tend to be older (with an average age of 9 years), have a common or pre-B immunophenotype and have low platelet and white blood cell counts. Treatment should therefore be intensified in these cases to reduce the risk of relapse (52,53).

It is key to consider that the presence or absence of specific sentinel genetic lesions in leukemic blasts serves a key role in determining prognosis and in the stratification of ALL therapy (53). Data from the UK ALL trial demonstrated that patients with iAMP21-ALL had a 10-year event-free survival of only 15%. However, the overall survival was markedly higher at 71%, indicating that these patients responded well to more intensive post-relapse therapy (54). Other studies reported a 5-year event-free survival of 26% and 5-year overall survival of 69% for 28 patients with iAMP21, and the Austrian and German ALL Berlin-Frankfurt-Munster (ALL-BFM) reported a 6-year EFS of 38% and overall survival of 66% for 29 iAMP21 patients (52).

To facilitate the development of possible targets for novel therapies and reduce the toxicity of current high-risk treatments, studies that investigate the role of these genes on chromosome 21 and decipher the genomic complexity of the iAMP21 chromosome should be carried out in the future. The aim is to have more options in addition to early stem cell transplantation and to implement methodologies that allow the molecular profile to be broadened.

8. Discussion

iAMP21 defines a biologically distinct subtype of childhood BCP-ALL, characterized by poor prognosis under standard treatment protocols but improved outcomes with intensified therapy. Despite the structural heterogeneity of the derivative

chromosome 21, the common amplified region encompasses functionally related genes involved in chromatin assembly (*CHAF1B*), cell cycle regulation (*DYRK1A*), transcriptional control (*ERG* and *RUNX1*) and epigenetic modulation (*HMGN1*), suggesting that leukemogenesis in iAMP21-ALL results from the coordinated dysregulation of these pathways rather than a single oncogenic driver. Recent identification of *RIPPLY3* as the most upregulated gene within the minimal common region opens novel research avenues, although its precise role in leukemic transformation remains to be elucidated.

Further functional characterization of genes within the amplified region, validation in prospective clinical cohorts and integration of cytogenetic, genomic and transcriptomic data are key to refining risk stratification and identifying therapeutic vulnerabilities specific to iAMP21-ALL. Comprehensive genetic evaluation including FISH or microarray analysis alongside targeted gene panels for *CHAF1B*, *DYRK1A*, *ERG*, *HMGN1*, *RUNX1* and *RIPPLY3* should be incorporated into diagnostic algorithms for pediatric BCP-ALL, particularly in cases with adverse prognostic features or suboptimal treatment responses. Further understanding of the molecular mechanisms converging in iAMP21 may potentially guide the development of biology-driven therapeutic strategies tailored to the unique genetic landscape of this high-risk ALL subtype in the future.

Acknowledgements

Not applicable.

Funding

The present review was funded by the Department of Science, Humanities, Technology and Innovation (Secihti) scholarship (CVU: 633121).

Availability of data and materials

Not applicable.

Authors' contributions

CEUG and ASC conceived the present review, and wrote, reviewed and edited the manuscript. JAV and HMZ wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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