# B-cell precursor acute lymphoblastic leukemia with *IGH*::*CEBP* rearrangement: what have we learnt over the years?

CCAAT-enhancer binding protein (*CEBP*) members have been implicated in B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) through translocation with the *IGH* locus. While the translocation of *IGH* with partner genes has a prognostic relevance,[1,2] the low incidence of *IGH*::*CEBP* translocations has limited comprehensive analysis. Here, we review all reported cases of *IGH*::*CEBP* in BCP-ALL up to 2025 to investigate correlations with genetics, clinical and demographic characteristics. We report new *IGH*::*CEBP* cases, correlate their gene expression profile to the major BCP-ALL subtypes, and explore the interplay between *CEBP* members and the affected pathways. This study was conducted in accordance with the ethical standards of the country in which it was performed.

A total of 151 cases, including six new cases, of BCP-ALL with *IGH*::*CEBP* translocations at initial diagnosis have been reported (*Online Supplementary Figures S1* and *S2*). Most involve *IGH*::*CEBPD* (N=96), followed by *IGH*::*CEBPA* (N=25), *IGH*::*CEBPE* (N=17), and *IGH*::*CEBPB* (N=13) (Figure 1A). Although the male:female ratio overall was 1:1.01 (males: 50.3%), there were more female cases with *IGH*::*CEBPA*, *IGH*::*CEBPB*, and *IGH*::*CEBPE* compared to *IGH*::*CEBPD* (1:1.6, males: 38%) (Figure 1B). The median age at diagnosis was 15 years (range, 2-76 years). However, patients with *IGH*::*CEBPD* rearrangements were younger (median: 13 years, Mann–Whitney U test, $P<0.001$) (Figure 1C). In contrast, *IGH*::*CEBPA* patients had a median age at diagnosis of 28 years, *IGH*::*CEBPB* cases 26.3 years, and *IGH*::*CEBPE* cases 16 years (Figure 1C). The median white blood cell count of these cases was $16.1x10^9$/L (range, 1-$190x10^9$/L). Very limited survival data were available for these patients. However, among 69 patients for whom information was available, 14 patients had been reported to have died while 55 remained alive at the time of reporting (*Online Supplementary Table S1*). As expected, a higher proportion of adults had died (8/21, 38%) compared with children (6/48, 13%, $P<0.01$). The proportion of both adults and children who had died showed some evidence of correlation by *CEBP* gene (Figure 1D) but the small number of patients and the heterogeneity in treatment eras and protocols make it impossible to draw any firm conclusions. There was a strong association between Down syndrome (DS) and *IGH*::*CEPBD* with 42% (N=40/96) of *IGH*::*CEBPD* cases co-occurring with DS, which is higher than the overall rate of DS in ALL cohorts of <5%.[3] This percentage increased to 50% (N=48/96) when including individuals with somatic gain of chromosome 21 (+21). The DS-associated cases were found in individuals under 24 years of age, potentially explaining the observed enrichment of younger patients in the *IGH*::*CEBPD* subgroup. In contrast, other *IGH*::*CEBP* members showed lower prevalence in DS-ALL patients and patients with +21, accounting for 12% (N=3/25) in *IGH*::*CEBPA* and 18% (N=3/17) in *IGH*::*CEBPE*. These findings suggest a possible unique role for *CEBPD* in the leukemogenesis of DS-associated BCP-ALL. Further investigation is required to elucidate the mechanisms by which *CEBPD* contributes to leukemic transformation in the context of DS.

Cytogenetic aberrations, such as trisomy 6 or deletions of chromosome 6, have been observed in a subset of ALL cases.[4,5] In *IGH*::*CEBPA* cases, we identified two instances of trisomy 6 and two instances with chromosome 6 deletion, distributed among *IGH*::*CEBPD* and *IGH*::*CEBPE* cases (*Online Supplementary Figure S1*). The gain of chromosome 6 in one *IGH*::*CEBPA* case was associated with high hyperdiploidy (HeH), a feature that has been linked to a favorable prognosis in ALL.[4] However, deletions of 6q21, which includes several known tumor-suppressor genes, could contribute to malignant transformation.[5] In addition, chromosome 8 abnormalities were identified in 14 *IGH*::*CEBP* cases. Of these, six showed gains of chromosome 8 (2 were associated with HeH, 2 with low hyperdiploidy [HeL], 1 with high hypodiploidy, and 1 with normal diploidy), another six had complete deletion of chromosome 8, and two exhibited either an isochromosome, i(8)(q10), or isodicentric chromosome, idic(8)(p11). These alterations were distributed across *IGH*::*CEBPA* (N=3), *IGH*::*CEBPB* (N=4), and *IGH*::*CEBPD* (N=7) cases (*Online Supplementary Figure S1*). The majority (N=10/14) occurred in adults, consistent with reported cases of chromosome 8q24 aberrations being more frequent in adult ALL.[6] Somatic gain of chromosome 14 or trisomy 14 is relatively common in hyperdiploid BCP-ALL. In our cohort, trisomy 14 was noted in seven cases, primarily associated with *IGH*::*CEBPD* and occurring in the context of a HeL karyotype (N=6/7) (*Online Supplementary Figure S1*). These findings highlight the need for further investigation to elucidate the biological and clinical implications of these chromosomal alterations in *IGH*::*CEBP*-driven BCP-ALL.

*BCR*::*ABL1* was identified in 7% of *IGH*::*CEBP* cases (N=10/151). This was most prominent in *IGH*::*CEBPD*, occurring in 8% of cases (N=8/96) (*Online Supplementary Figure S1*). Interestingly, all these cases were exclusive to non-DS patients under 15 years of age, a frequency higher than the reported percentage (3-5%) for *BCR*::*ABL1* in pediatric ALL.[7] The coexistence of *BCR*::*ABL1* and *IGH*::*CEBP* rearrangements

remains largely unknown. *BCR*::*ABL1* leads to persistently enhanced tyrosine kinase activity, whereas *CEBP* rearrangements result in aberrant overexpression of transcription factors critical for hematopoietic differentiation. Together, these alterations may synergistically disrupt normal B-cell development and function, contributing to the initiation and progression of BCP-ALL.

We analyzed the transcriptome of seven patients with *IGH*::*CEBP* rearrangements from a larger cohort of 188 BCP-ALL cases, including 182 cases from EGAS00001001795[8] and six newly collected cases. Molecular subtyping was conducted based on gene expression profiling.[9] In total, eight distinct molecular subtypes of BCP-ALL were identified and visualized using uniform manifold approximation and projection (Figure 2A). The *IGH*::*CEBP* cases were distributed across two clusters, including one associated with a hyperdiploid expression profile. This cluster included cases with HeL, HeH, and tetraploid karyotypes. Although five *IGH*::*CEBP* cases clustered with the HeH group, they lacked classical HeH karyotypes. Notably, two of these cases were associated with DS, and an additional case with +21. Most cases clustering within the HeH-defined group harbored additional chromosome 21q material, which was significantly enriched compared to cases outside this group (86% *vs*. 35%, $P$=3.08×10$^{-13}$). This increase in chromosome 21 dosage appeared to underlie the observed co-clustering rather than hyperdiploidy. To further visualize transcriptional differences, we performed hierarchical clustering based on the top 300 differentially expressed genes identified between the *IGH*::*CEBP* cases, which were classified as hyperdiploid, and *IGH*::*CEBPA*. As expected, the two *IGH*::*CEBPA* cases formed a separate cluster, while the remaining five cases of *IGH*::*CEBPB* (N=1), *IGH*::*CEBPD* (N=3), and *IGH*::*CEBPE* (N=1) clustered together, reflecting the differential expression used in the gene set (Figure 2B). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the differentially expressed genes identified significant enrichment in pathways related to cancer and

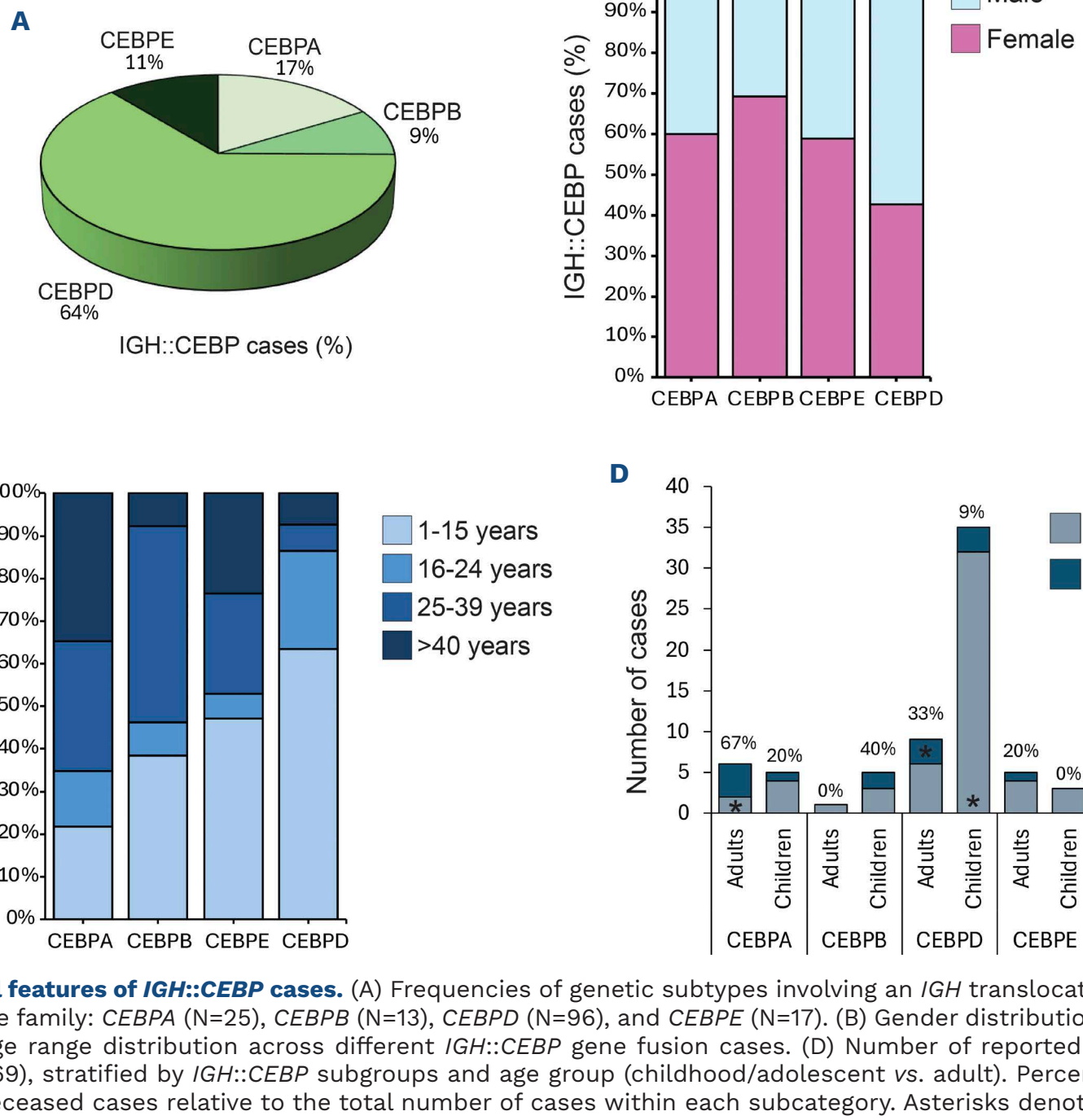



**Figure 1. Clinical features of *IGH*::*CEBP* cases.** (A) Frequencies of genetic subtypes involving an *IGH* translocation with a member of the *CEBP* gene family: *CEBPA* (N=25), *CEBPB* (N=13), *CEBPD* (N=96), and *CEBPE* (N=17). (B) Gender distribution across *IGH*::*CEBP* subtypes. (C) Age range distribution across different *IGH*::*CEBP* gene fusion cases. (D) Number of reported cases with known vital status (N=69), stratified by *IGH*::*CEBP* subgroups and age group (childhood/adolescent *vs*. adult). Percentages indicate the proportion of deceased cases relative to the total number of cases within each subcategory. Asterisks denote cases associated with Down syndrome. See *Online Supplementary Table S1* for further details.

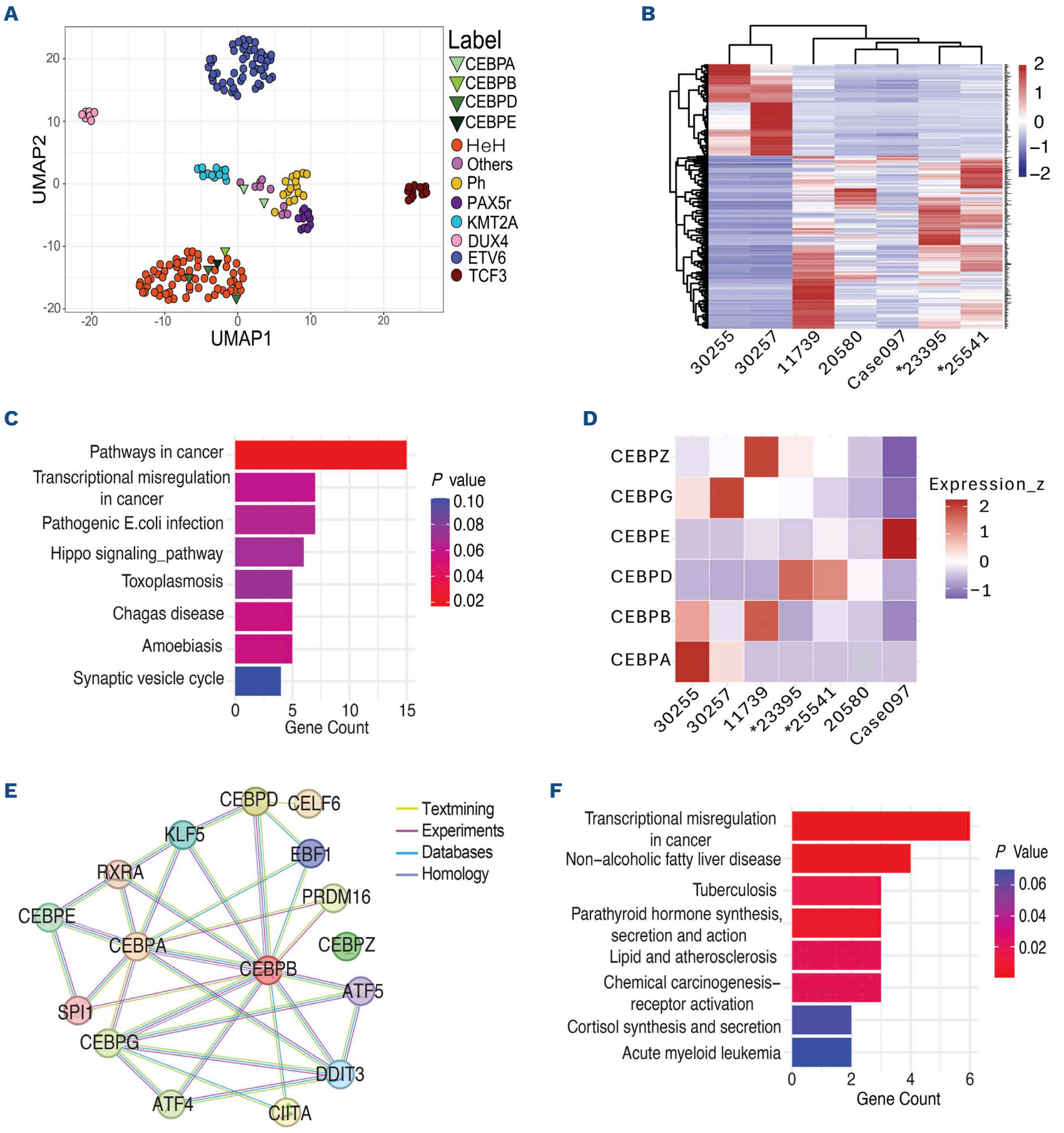



**Figure 2. Transcriptomic and genomics of *IGH*::*CEBP* cases.** (A) RNA sequencing for six *IGH*::*CEBP* cases was performed at Eurofins Genomics (Ebersburg, Germany) using a TruSeq Stranded mRNA Library Prep Kit (Illumina) on diagnostic samples, and molecular subtyping was conducted based on gene expression profiling with reference to Li *et al*. (2018).[9] Raw sequencing data from the available 182 cases reported in Lilljebjorn *et al*. (2016)[8] were processed to generate gene-level count matrices. Counts were log-transformed using the variance-stabilizing transformation implemented in DESeq2. Batch correction between the cohort of Lilljebjorn *et al*. and newly generated cases was performed using permuted surrogate variable analysis (pSVA). Gene expression normalization and downstream analyses were conducted using limma/voom, and differential gene expression analysis was performed with the limma package. Generalized principal component analysis confirmed the absence of batch-specific clustering following pSVA correction. The gene expression of 188 cases of B-cell precursor acute lymphoblastic leukemia visualized by uniform manifold approximation and projection (UMAP), showed the *IGH*::*CEBP* cases (N=7, green) distributed across different clusters. *IGH*::*CEBPA* cases were clustered separately from the other *IGH*::*CEBP* cases. The average silhouette score was used to generate this two-dimensional UMAP, using the R package UMAP with default settings, except for the following parameters: n_neighbors = 10, spread = 5, and min_dist = 0.15. Clusters and *CEBP* cases are shown in different colors. (B) Hierarchical clustering of the *IGH*::*CEBP* cases was performed using significantly differentially expressed genes identified by DESeq2 (Wald test on raw integer read counts; Benjamini-Hochberg adjusted *P* value [*P*adj] <0.001) between the *CEBP* cases, which were all clustered as high hyperdiploidy and CEBPA

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cases. Clustering was based on row-scaled normalized expression values using Euclidean distance and complete linkage. The two *IGH*::*CEBPA* cases displayed a unique gene expression signature compared to the other *IGH*::*CEBP* cases. Remarkably, the *IGH*::*CEBPD* cases with Down syndrome (DS) clustered together, separate from the *IGH*::*CEBPD* without DS. (C) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the top 300 differentially expressed genes in *IGH*::*CEBP* cases showed enrichment for pathways involved in cancer and transcriptional dysregulation. DAVID v6.8 pathway enrichment was assessed by a modified Fisher exact test (EASE score) with Benjamini–Hochberg false discovery rate (FDR) correction. (D) Heatmap presenting differences in gene expression between *IGH*::*CEBP* cases. Interestingly, *IGH*::*CEBPD* cases with DS showed high expression of *CEBPD* compared to the *IGH*::*CEBPD* case without DS. Moreover, expression of *CEBPG*, which is involved in tight regulation of B-cell development, was high in the two *IGH*::*CEBPA* cases and this could potentially contribute to their distinct expression profile (see panel B). (E) Protein–protein interaction analysis using the STRING database (*https://string-db.org*, version 12.0, June 2025) was performed to investigate the functional interactions among CEBP family members and their associated proteins. A maximum of ten interactors were included, filtered by a high-confidence interaction score (≥0.7). Yellow: textmining; purple: experiments; blue: database; light purple: homology. (F) KEGG pathway analysis of CEBP family members and their associated proteins revealed enrichment in pathways related to transcriptional dysregulation and acute myeloid leukemia. DAVID v6.8 pathway enrichment was assessed by a modified Fisher exact test (EASE score) with Benjamini–Hochberg FDR correction. *Indicates DS-associated B-cell acute lymphoblastic leukemia. Case identities: *CEBPA* (30255-30257), *CEBPB* (11739), *CEBPD* (23395-25541-20580), and *CEBPE* (Case097).

transcriptional deregulation (Figure 2C). Among the three *IGH*::*CEBPD* cases, two were associated with DS (Figure 2B). In this small set of samples, hierarchical clustering appeared to group the two DS-associated *IGH*::*CEBPD* cases together, while the non-DS case clustered closer to the *IGH*::*CEBPE* case (Figure 2B). DS-associated *IGH*::*CEBPD* cases exhibited higher *CEBPD* expression levels compared to the non-DS case (Figure 2D). Overexpression of *CEPBD* in a DS mouse model was reported to alter B-cell development, resulting in a persistent predominance of pro-B cells, whereas *CEBPD* overexpression in wild-type controls increased B-lineage differentiation.[10] Hence, these findings could suggest that the combination of *CEBPD* overexpression and trisomy 21 may contribute to distinct gene expression patterns in DS-associated *IGH*::*CEBPD*, potentially increasing susceptibility to BCP-ALL. Further investigation is required to elucidate the underlying biological mechanisms, particularly in human cells, and their impacts on B-cell dysregulation.

B-cell development involves tight regulation of CEBP members.[11,12] While CEBPγ and possibly CEBPζ can act as negative regulators of other CEBP proteins – modulating their transcriptional activity through inhibitory interactions[12,13] – their roles in B-cell development or BCP-ALL remain largely unknown. Therefore, we examined the expression of these negative regulators in *IGH*::*CEBP* cases to determine whether they might influence the genomic features observed. Remarkably, *CEBPG* was specifically overexpressed in *IGH*::*CEBPA* cases, while increased expression of *CEBPZ* was observed in both *IGH*::*CEBPB* and DS-associated *CEBPD* cases (Figure 2D). This may suggest a role for these inhibitors in modulating other *CEBP* member activities. The functional protein associations of *CEBP* members were analyzed using the STRING database. This analysis revealed that CEBPα and CEBPβ were central nodes in the network, associated with each other and with other CEBP members, including CEBPγ (for both), CEBPε (for CEBPα), and CEBPδ (for CEBPβ). However, CEBPδ and CEBPε showed no interactions with each other or with CEBPγ (Figure 2E). The top ten interacting proteins with high-confidence interaction scores (≥0.7) were included, encompassing factors involved in lymphoid and myeloid lineage development, such as SPI1, ATF4/5, and DDIT3 (Figure 2E). This network was significantly enriched for KEGG pathways related to transcriptional dysregulation in cancer, carcinogenesis, and acute myeloid leukemia, consistent with the pathway enrichment observed in the *IGH*::*CEBP* cases (Figure 2F). The interaction profile of CEBP members highlights their central role in transcriptional regulation pathways implicated in hematopoietic development and leukemic transformation. This study provides new insights into the molecular and cytogenetic landscape of *IGH*::*CEBP* rearrangements in BCP-ALL. Limited treatment data currently preclude robust prognostic assessment; therefore, an international effort is underway to assemble a larger cohort of *IGH*::*CEBP* cases to address these gaps. Our findings highlight the clinical and biological heterogeneity of *IGH*::*CEBP* fusions and their potential role in B-cell development, particularly in the context of DS and co-occurring genetic alterations. Although no approved therapies directly target *IGH*::*CEBP* fusions, their transcriptional biology suggests that approaches such as proteolysis targeting chimeras (PROTAC) or heterodimer-disrupting peptides may offer promising therapeutic avenues.

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**Contributions**
AA conceived the study, curated data and was involved in the methodology, visualization, validation, investigation and writing the original draft. LJR and AVM conceived the study and were involved in the investigation, acquisition of funding and writing the original draft. LM was involved in validation and acquisition of funding. MB and KTMF conducted the formal analysis. AE was involved in the methodology and validation. CJH and OH supervised the study. All authors revised the manuscript and approved the final version.

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**Data-sharing statement**
The datasets analyzed in the study are from previously published sources. The original datasets are available in the cited publications.

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