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TO THE EDITOR:

CREBBP alterations are associated with a poor prognosis in de novo AML

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The *cyclic adenosine monophosphate response element-binding protein* (*CREBBP*) gene is located on chromosome 16p13 and encodes a histone acetyltransferase having the same name that is involved in transcriptional regulation and cell cycle control.[1,2] The translocation t(8;16)(p11;p13)[*KAT6A::CREBBP*] results in the disruption of *CREBBP* as well as its fusion to *KAT6A*, another gene important in transcription control. This fusion is sufficient for leukemogenesis and leads to a rare but well described type of acute myeloid leukemia (AML) with consistent biologic characteristics and a distinct gene expression profile.[3-8] Although generally associated with inferior outcomes among adults, including a recent adjustment made by the European LeukemiaNet toward the adverse-risk group, there are variable reports regarding the prognostic significance of this fusion among pediatric patients.[4,7,9] This prognostic variability is partially related to the high association of *KAT6A::CREBBP* with congenital leukemia as well as the phenomenon of spontaneous regression in a majority of these patients.[4,10-17] Because of the poor outcomes associated with this alteration on North American protocols, patients aged >90 days with *KAT6A::CREBBP* have been reclassified as high risk in the active Phase 3 Children's Oncology Group (COG) trial for de novo AML, AAML1831 (NCT04293562). Little is known about the prognostic significance of *CREBBP* sequence variants, including pathogenic single nucleotide variants (SNVs) and insertion/deletions (indels). In this letter, we report the prevalence and prognostic significance of all alterations involving *CREBBP* in pediatric patients with AML and their impact on co-occurring lesions, specifically t(8;21)[*RUNX1::RUNX1T1*].

CREBBP variant status was determined in a total of 2216 patients enrolled in 4 successive COG trials for de novo pediatric AML (NCT00003790, NCT00070174, NCT01407757, and NCT01371981) and associated with comprehensive clinical and cytogenetic information. Fusions involving *CREBBP* were prospectively obtained via conventional cytogenetics and retrospectively confirmed via RNA sequencing. Indels and SNVs were retrospectively interrogated via next generation sequencing[18] and their pathogenicities were established in accordance with American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines. For patients with transcriptome data available, unsupervised clustering was done and their results were compared with those of patients without *CREBBP* alterations. The research was approved by the appropriate review boards and conducted in accordance with the Declaration of Helsinki. The Kaplan-Meier method was used to determine overall survival (OS) and event-free survival (EFS). The significance of predictor variables was tested using the log-rank statistic. The significance of observed difference in proportions was analyzed using Fisher exact test, and observed differences in medians were analyzed using the Kruskal-Wallis test. The Cox proportional hazards model was used to estimate a hazard ratio for EFS in a multivariable analysis.

We identified 52 (2.3%) patients with a pathogenic alteration involving *CREBBP*, which is slightly higher than the incidence in publicly available adult AML databases (1.1%).[19,20] This higher incidence is largely driven by fusions involving *CREBBP* (*CREBBP*/fus), which made up 31% (n = 16) of our cohort (compared with 12.5% in the adult database). The remaining 36 patients (69%) in our cohort had a *CREBBP* mutation (*CREBBP*/mut; supplemental Table 1, available on the *Blood* website). Eighteen of these were due to an indel (*CREBBP*/indel), including 15 leading to frameshift mutations and 3 leading to deleterious inframe insertions or deletions (Figure 1A). The other 18 were due to a SNV (*CREBBP*/SNV), including 17 deleterious missense or nonsense mutations and 1 splice-site mutation (Figure 1A). A single patient had 2 pathogenic missense mutations. Patients with *CREBBP*/fus were younger than patients with *CREBBP*/indel or *CREBBP*/SNV (median ages of 2.6 vs 8.7 vs 7.4 years, respectively; *P* = .056), including 4 patients with a *CREBBP*/fus diagnosed in the first 90 days of life. There was a higher prevalence of *RUNX1::RUNX1T1* in patients with *CREBBP*/indel (n = 8) than in patients with *CREBBP*/SNV (n = 1) (44.4% vs 5.6%, respectively; *P* = .018; Figure 1A). In contrast, there was no association between *CREBBP*/SNV and a specific cytogenetic abnormality. There was a similar prevalence of cooccurring contemporarily defined high-risk lesions among patients with CREBBP/indel (n = 4; *CBFA2T3*::*GLIS2*, *KMT2A*::*AFF1*, *MLLT10*::*PICALM*, and *NUP98*::*HOXA9*) and those with *CREBBP*/SNV (n = 5; *CBFA2T3*::*GLIS2*, *FUS*::*ERG*, *NUP98*::*KDM5A*, *ETV6*::*MNX1*, and high allelic ratio *FLT3*-ITD). There was a paucity of cooccurring genomic mutations in patients with *CREBBP*/fus (Figure 1A). In contrast, genomic mutations most frequently cooccurring in patients with CREBBP/mut included mutations in RAS (25%), *KIT* (13.9%), and *WT1* (11.1%). The frequency of these mutations were the same between patients with *CREBBP*/SNV and patients with *CREBBP*/indel and had a similar distribution to that of patients without *CREBBP* mutations. Transcriptome data were analyzed, and, consistent with previous reports, unsupervised clustering showed tight clustering of *CREBBP*/fus as well as a similar but distinct gene expression profile to that of *KMT2A* rearrangements.[3,4] *CREBBP*/indel clustered together, which was likely driven by the cooccurrence of *RUNX1::RUNX1T1*, given its strong gene expression profile.[21] In contrast, *CREBBP*/SNV did not show a specific clustering pattern (Figure 1B).

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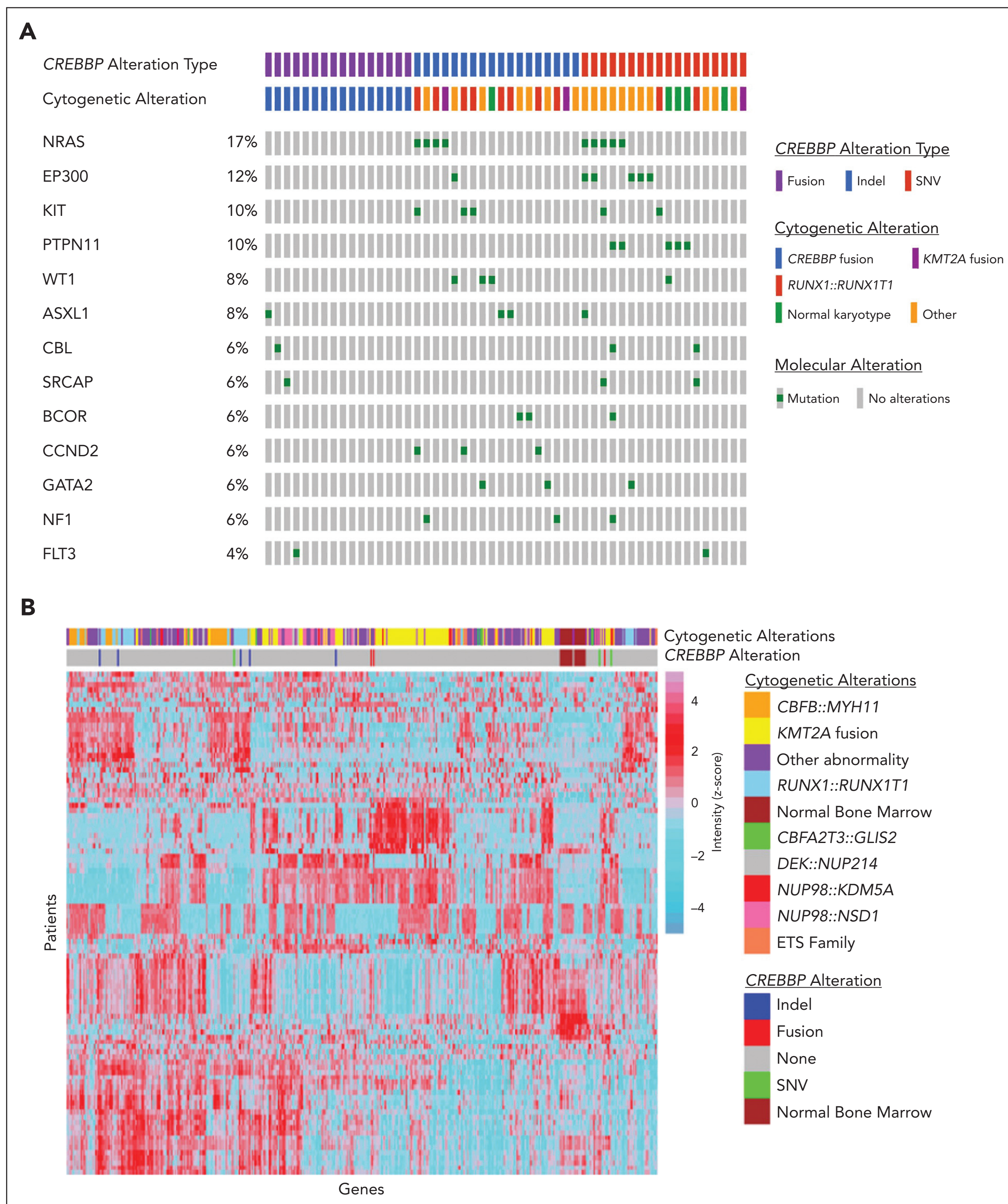

Figure 1. Molecular and transcriptome profiles based on *CREBBP* status. (A) Cytomolecular status and cooccurring mutational profile of patients based on *CREBBP* alterations, (B) Unsupervised clustering was performed across the entire transcriptome patient data set (n = 1079). Variance stabilizing transformation was performed (R function, vst), and scaled values were used to calculate the variance for each gene across all samples (R function, var). The genes were sorted based on variance, and the top 100 genes with highest variance were clustered (R function, ward.D2) and presented visually in a heatmap generated using pheatmap function in R.

Evaluation of outcomes based on the type of alteration demonstrated a similar EFS between patients with *CREBBP*/fus and patients with *CREBBP*/mut (5-year EFS was 33.3% vs 22.2%, respectively; *P* = .801; Figure 2A). Patients with *CREBBP*/mut had a significantly worse EFS compared with patients without (5-year EFS was 22.2% vs 45.2%, respectively; *P* = .005; Figure 2A), and this inferior EFS is similar to that of patients with contemporarily defined high-risk but without *CREBBP*/mut

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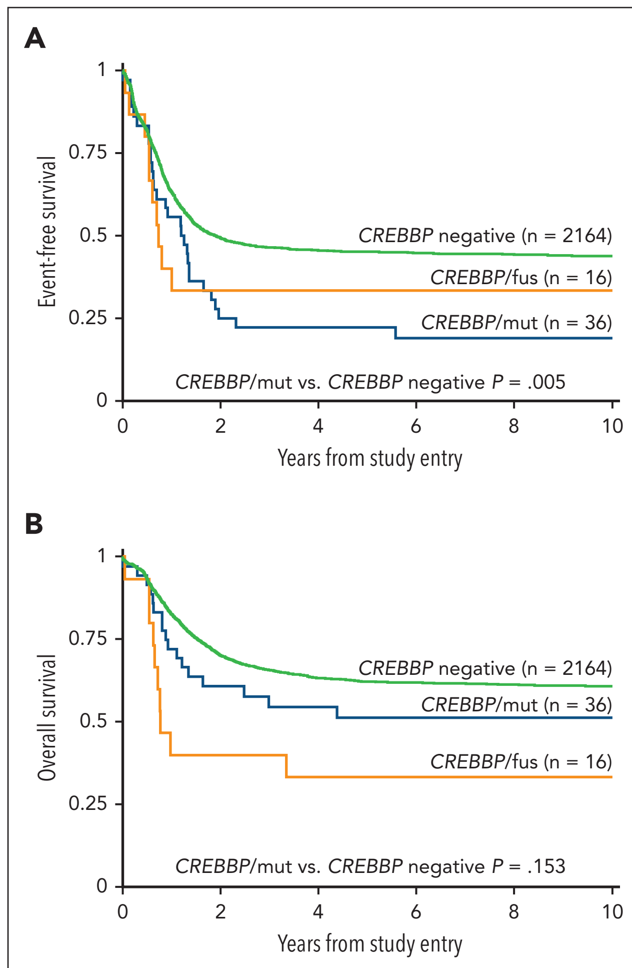

Figure 2. Correlation of clinical outcomes with *CREBBP* status. (A) EFS based on *CREBBP* status, (B) OS based on *CREBBP* status.

(5-year EFS is 25.2%; *P* = .929). Furthermore, this poor EFS was maintained in patients with *CREBBP*/indel with cooccurring *RUNX1::RUNX1T1*, which was significantly worse than that of patients with *RUNX1::RUNX1T1* but without *CREBBP*/indel (5-year EFS was 12.5% vs 67.7%, respectively; *P* = .001). When patients with cooccurring high-risk lesions were excluded from the analysis, the remaining patients with *CREBBP*/mut (n = 27) who would otherwise be considered low-risk maintained their poor EFS (5-year EFS was 29.6%). We performed a Cox regression analysis and found *CREBBP*/mut was an independent predictor of an inferior EFS in the presence of contemporarily defined cooccurring low- or high-risk cytomolecular alterations (hazard ratio, 1.71; 95% confidence interval, 1.18-2.47; *P* = .005; supplemental Table 2). Despite their poor EFS, patients with *CREBBP*/mut had a comparable OS with those without *CREBBP* disruptions (5-year OS was 51.4% vs 62.4%, respectively; *P* = .153, Figure 2B), demonstrating that these patients could successfully be salvaged following relapse. In contrast, patients with *CREBBP*/fus had an inferior OS (5-year OS was 33.3%; *P* = .002). Strikingly, all patients with *CREBBP*/fus that experienced a relapse ultimately died from their disease. Of the 5 long-term survivors with *CREBBP*/fus, 2 were diagnosed within the first 90 days of life and might have ultimately benefited from spontaneous regression.

We report the prevalence of *CREBBP*/fus in a large cohort of patients with pediatric AML with an incidence similar to that reported in a prior analysis.[4] This is also the first report, to our knowledge, to comprehensively report the prevalence of *CREBBP*/mut in pediatric AML. Furthermore, we show that these patients have a poor EFS, regardless of the alteration type. This was especially notable in those patients with *CREBBP*/indel with a cooccurring *RUNX1::RUNX1T1*. The favorable EFS typically conferred by *RUNX1::RUNX1T1* was abrogated by the cooccurrence of *CREBBP*/indel. Finally, the presence of a *CREBBP/mut* maintained independent prognostic significance for an inferior EFS, within the context of a Cox regression analysis.

Translocations between *CREBBP* and *KAT6A* in patients aged >90 days are considered as high risk in the active COG phase 3 trial. Survival of patients with relapsed *CREBBP*/fus AML is dismal and warrants novel interventions. Histone deacetylase inhibitors have shown preclinical promise in *CREBBP* mutated tumors, and further studies in AML are warranted.[22,23] Given the comparably poor EFS and high salvage rates associated with *CREBBP*/mut AML, intensification of upfront treatment, including hematopoietic stem cell transplant, should be considered in this population.

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Authorship

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Footnotes

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