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TO THE EDITOR:

RUNX1 mutations in pediatric acute myeloid leukemia are associated with distinct genetic features and an inferior prognosis

Genki Yamato,[1-3] Norio Shiba,[3,4] Kenichi Yoshida,[5] Yusuke Hara,[2,3] Yuichi Shiraishi,[6] Kentaro Ohki,[7] Jun Okubo,[1] Myoung-ja Park,[1] Manabu Sotomatsu,[1] Hirokazu Arakawa,[2] Nobutaka Kiyokawa,[7] Daisuke Tomizawa,[8] Souichi Adachi,[9] Takashi Taga,[10] Keizo Horibe,[3] Satoru Miyano,[6,11] Seishi Ogawa,[5,12] and Yasuhide Hayashi[1,3,13]

[1]Department of Hematology/Oncology, Gunma Children's Medical Center, Gunma, Japan; [2]Department of Pediatrics, Graduate School of Medicine, Gunma University, Gunma, Japan; [3]Clinical Research Center, National Hospital Organization Nagoya Medical Center, Aichi, Japan; [4]Department of Pediatrics, Yokohama City University Hospital, Kanagawa, Japan; [5]Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [6]Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [7]Department of Pediatric Hematology and Oncology Research, National Research Institute for Child Health and Development, Tokyo, Japan; [8]Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan; [9]Department of Human Health Science, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [10]Department of Pediatrics, Shiga University of Medical Science, Shiga, Japan; [11]Laboratory of Sequence Analysis, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [12]Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institute, Stockholm, Sweden; and [13]Japanese Red Cross Gunma Blood Center, Gunma, Japan

Acute myeloid leukemia (AML) is a complicated disease characterized by the uncontrolled proliferation of hematopoietic precursors and the loss of differentiation ability caused by various genetic alterations. Recent advances in massively parallel sequencing technologies have identified several gene mutations associated with the pathogenesis of AML, including mutations in *NPM1*, *DNMT3A*, *IDH1/2*, and *TET2*.[1-6] However, the rarity of some of mutations, such as *DNMT3A*, *IDH1/2*, and *TET2*, in pediatric AML[7,8] necessitates exploring additional biomarkers to stratify pediatric patients with AML. Remarkably, the 2017 European LeukemiaNet recommendations incorporated *RUNX1* mutations to the group of markers, suggesting adverse risks in adult AML.[9] However, the low frequency of *RUNX1* mutations renders the prognosis of pediatric patients with AML uncertain.[10-12] Thus, this study aims to investigate *RUNX1* mutations and their correlation with other gene aberrations to elucidate the prognostic impact in 503 pediatric patients with de novo AML.

In this retrospective cohort study, we recruited patients with de novo AML (age, <18 years) who participated in either the AML99 clinical trial of the Japanese Childhood AML Cooperative Study (January 2000 to December 2002) or the AML-05 clinical trial of the Japanese Pediatric Leukemia/Lymphoma Study Group (November 2006 to December 2010).[13,14] Overall, we enrolled 503 patients with available leukemic samples in this study comprising 134 of 280 from the AML99 trial and 369 of 485 from the AML-05 trial (supplemental Table 1, available on the *Blood* Web site). We observed no significant differences in the overall survival (OS) between the available and unavailable samples in the AML99 or AML-05 trial (supplemental

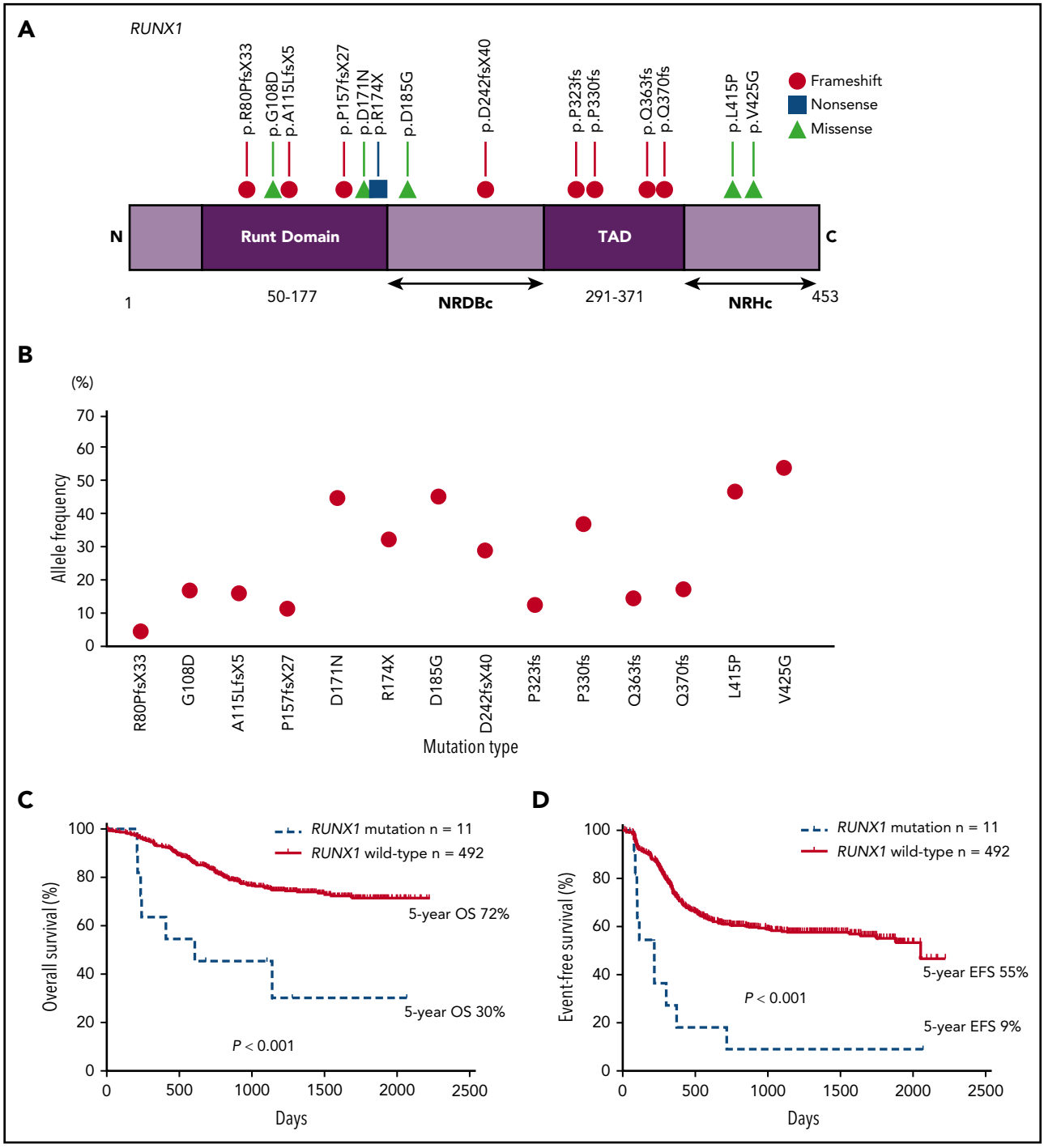

Figure 1. A gene diagram and prognostic impact in pediatric AML patients with *RUNX1* mutations. (A) A gene diagram depicting *RUNX1* mutations in pediatric patients with AML (NCBI reference sequence; NM_001001890). (B) A VAF of 14 *RUNX1* mutations. (C) A comparison of the OS and (D) EFS between patients with and without *RUNX1* mutations. NRDBc, the C-terminal negative regulatory region for DNA binding; NRHc, the C-terminal negative regulatory region for heterodimerization; TAD, transcription activation domain.

Tables 2 and 3). Patients with Down syndrome and acute promyelocytic leukemia were excluded. Details of these protocols are available elsewhere.[13-15] This study was approved by the institutional review board of Gunma Children's Medical Center and was conducted in accordance with the Declaration of Helsinki guidelines.

We extracted genomic DNA from leukemic samples using the ALLPrep DNA/RNA Mini kit (Qiagen, Hilden, Germany). In addition, targeted deep sequencing of *RUNX1* was performed in 503 pediatric patients with de novo AML using the next-generation sequencing (details of the study methodology, additional molecular and cytogenetic analyses, and statistical analyses are described in supplemental Methods).

We identified *RUNX1* mutations in 2.8% (14 of 503) of pediatric patients with de novo AML, 64% (9 of 14) of whom had frameshift/nonsense mutations, and 36% (5 of 14) of whom had heterozygous

Table 1. Summary of characteristics of 11 AML patients with *RUNX1* mutations

Pt no.	Sex	Age, y	WBC, ×10⁹/L	FAB	Cytogenetics	Chromosomal aberrations	*FLT3*-ITD	*KMT2A*-PTD	Type of mutation	Nucleotide change Amino acid change*	CR	SCT	Prognosis	VAF, %
1	F	14.3	123.1	M5a	46,XX[20]	–	+	+	Frameshift	c.968_969ins p.P323fs	No	Yes	Death	12.7
2	M	11.8	70.8	M5a	46,XY[20]	–	+	+	Missense	c.G511A p.D171N	No	Yes	Death	45.5
3	F	14.1	16.5	M1	46,XX[20]	–	–	+	Frameshift	c.989dupC p.P330fs	No	No	Death	37.8
4	F	11.8	60.1	M4	46,XX[20]	–	–	+	Frameshift	c.1108dupC p.Q370fs	Yes	Yes	Alive	18.0
5	F	8	25.7	M0	46,XX[20]	–	+	NA	Frameshift	c.238_239insCCAGTGC p.R80PfsX33	Yes	Yes	Death	5.0
6	M	6	25.3	M4	46,XY[20]	*NUP98-NSD1*	–	NA	Frameshift	c.470delC p.P157fsX27	Yes	Yes	Death	11.6
7	M	9.9	38.7	M2	46,XY,t(8;19)(q22;p13) or t(8;19;21)(q22;p13;q22)[20]	*RUNX1-RUNX1T1*	–	–	Missense	c.G323A p.G108D	No	No	Death	17.2
8	M	11	17.1	M2	45,X,-Y,t(8;21)(q22;q22)[20]	*RUNX1-RUNX1T1*	–	NA	Frameshift	c.1087delC p.Q363fs	Yes	No	Alive	15.6
9	F	15.2	69.0	M5b	47,X,-Y,add(3)(q11.2),+6,add(6)(p21)x2,+7,del(8)(q24),der(8)t(1;8)(q11;q24),del(11)(q?),add(17)(p11.2)[7]/48,sl,+22[6]/47,sl,-14,+mar1[2]	Complex karyotype	–	–	Frameshift	c.341_342insCCTCT p.A115LfsX5	No	Yes	Death	16.4
10	M	1.9	16.1	M6a	46,XY,-7,+mar[17]/46,idem, del(6)(q?)[3]	Monosomy 7	–	–	Nonsense	c.C520T p.R174X	No	Yes	Alive	32.0
11	F	2.3	195.1	M0	48,XX,+8,+21[3]/49, sl, del(6)(q?), +19[14]/49,sl,add(6)(q21),+19[3]	Trisomy8	–	–	Frameshift	c.725_731del p.D242fs40	Yes	Yes	Alive	29.8

+, positive; –, negative; CR, complete remission; FAB, French-American-British; ITD, internal tandem duplication; N/A, not available; PTD, partial tandem duplication; Pt no., patient number; SCT, stem cell transplantation; VAF, variant allele frequency; WBC, white blood cell count.

*NCBI reference sequence; NM_001001890.

point mutations that resulted in translational changes (Figure 1A). Figure 1B shows variant allele frequencies (VAFs) of *RUNX1* mutations. Notably, none of the 14 patients with *RUNX1* mutations had thrombocytopenia, history of myelodysplastic syndrome, or family history of AML. Based on previous studies and The Cancer Genome Atlas database (TCGA), 3 point mutations (*G108D*, *D171N*, and *R174X*) in the Runt domain were confirmed as somatic mutations.[16-18] Among 3 missense mutations (*D185G*, *L415P*, and *V425G*) that were not confirmed to be somatic, we detected 2 types (*D185G* and *V425G*) both at diagnosis and complete remission (CR). Despite not being able to assess the remaining 1 type (*L415P*) owing to a lack of samples at CR, it was anticipated as a germ line mutation because VAF was nearly 50% (46.6%).[19] In addition, these 3 mutations were located in the C-terminal negative regulatory region for DNA binding (NRDBc) or the C-terminal negative regulatory region for heterodimerization (NRHc; Figure 1A).[20] Although roles of these domains remain unclear, a study reported that missense mutations in the C-terminal region, including NRDBc and NRHc, are uncommon in pedigrees with familial platelet disorder/AML.[21] As these 3 patients with *RUNX1* mutations reported no episode suggestive of familial platelet disorder/AML, we excluded these 3 mutations from this study. Thus, we finally analyzed only 11 patients with *RUNX1* mutations. Table 1 summarizes the characteristics of the study cohort.

In this study, we compared the clinical and molecular characteristics between patients with and without *RUNX1* mutations (supplemental Table 4). No significant differences were observed in age, sex, and white blood cell counts at diagnosis between both groups. In addition, *RUNX1* mutations were associated with the French-American-British M0 morphology ($P = .026$), which corroborates previous pediatric[10,12] and adult[17,22-25] studies. Although 6 of 11 *RUNX1* mutations (55%) were determined in patients with a normal karyotype ($P = .012$), the remaining 5 mutations were detected in 2 patients with *RUNX1-RUNX1T1* and 1 each with monosomy 7, trisomy 8, and complex karyotype (Table 1). Although exclusive correlations between *RUNX1-RUNX1T1* and *RUNX1* mutations have been reported,[22] we observed similar *RUNX1* mutations in patients with *RUNX1-RUNX1T1* to those described in latest studies using next-generation sequencing in adult AML.[17,25] Furthermore, *RUNX1* mutations were associated with *KMT2A*–partial tandem duplication ($P < .001$) and were mutually exclusive with *NPM1* and *CEBPA* mutations; these genetic features of patients with *RUNX1* mutations are consistent with those previously described in adult AML cases.[17,22-25]

Remarkably, *RUNX1* mutations exhibited a high prevalence of non-CR (6 of 11, 55% vs 49 of 492, 10%; $P < .001$). Seven of 11 patients with *RUNX1* mutations died, and 3 of 4 survivors required stem cell transplantation (SCT). Remarkably, the OS and event-free survival (EFS) were significantly poorer in patients with *RUNX1* mutations than in those without *RUNX1* mutations (5-year OS, 30% vs 72%, $P < .001$; 5-year EFS, 9% vs 55%, $P < .001$; Figure 1C-D). Based on the location of mutations, we observed no difference in outcomes in this study, which is consistent with previous adult AML studies.[23,24] We used Cox regression models for univariate and multivariate analyses (supplemental Table 5). Besides *RUNX1* mutations, we used *FLT3*-ITD and some cytogenetic groups, such as t(8;21)(q22;q22)/*RUNX1-RUNX1T1*, inv(16)(p13q22)/*CBFB-MYH11*, 5q deletion, monosomy 7, and t(16;21)(p11;q22)/*FUS-ERG*, as expounding variables in the multivariate analysis; these cytogenetic aberrations were used for risk classification in the AML99 and AML-05 trials.[13,14] In addition, *RUNX1* mutations were significantly associated with inferior OS (univariate [hazard ratio (HR), 4.020; 95% confidence interval (CI), 1.873-8.625; $P < .001$]; multivariate [HR, 2.572; 95% CI, 1.185-5.582; $P = .017$]) and EFS (univariate [HR, 4.351; 95% CI, 2.292-8.259; $P < .001$]; multivariate [HR, 3.678; 95% CI, 1.924-7.030; $P < .001$]).

Furthermore, this study presents clinical features and prognosis of 14 patients, including the 3 excluded ones (supplemental Figure 1; supplemental Tables 6 and 7) because the significance of these 3 variants remains uncertain. Accordingly, both multivariate and univariate analyses revealed that the presence of *RUNX1* mutations correlated with the worse OS and EFS in this study.

In line with adult AML, *RUNX1* mutations in our cohort were associated with adverse outcomes.[17,22-25] Although previous research on pediatric AML could not establish the prognostic impact of *RUNX1* mutations because of the limited number of patients and lack of integrated treatment regimens (supplemental Table 8),[10-12] our study had a considerable sample size that confirmed the prognostic impact of *RUNX1* mutations. Perhaps our research and other recent studies using next-generation sequencing could more precisely reveal the frequency and outcomes of *RUNX1* mutations unlike previous studies using direct sequencing.[10-12,17,22-25] Although this study did not completely confirm mutations as somatic mutations, the fact that patients with *RUNX1* mutations demonstrated a significantly poor prognosis is crucial. Thus, this study suggests that *RUNX1* mutations might be a poor prognostic factor in the risk classification for pediatric AML and clinicians should consider the adaptation of SCT after first CR for patients with *RUNX1* mutations.

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Authorship

Contribution: G.Y., N.S., and Y. Hayashi designed the study and wrote the paper; G.Y., N.S., Y. Hara, K.O., and K.Y. performed the experiments; Y. Hayashi supervised the work; G.Y. and N.S. analyzed the results and constructed the figures; and all authors critically reviewed and revised the manuscript.

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ORCID profile: G.Y., 0000-0003-4000-0753.

Correspondence: Yasuhide Hayashi, Department of Hematology/Oncology, Gunma Children's Medical Center, 779, Shimohakoda, Hokkitsu, Shibukawa, 377-8577 Gunma, Japan; e-mail: hayashiy-tky@umin.ac.jp.

Footnote

The online version of this article contains a data supplement.

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