KMT2A partner genes in infant acute lymphoblastic leukemia have prognostic significance and correlate with age, white blood cell count, sex, and central nervous system involvement: a Children's Oncology Group P9407 trial study

KMT2A translocations, the commonest abnormalities in acute lymphoblastic leukemia (ALL) in <1-year-old infants, are associated with poor outcomes,[1-5] yet the prognostic significance of *KMT2A*-rearranged (*KMT2A*-R) *versus* *KMT2A*-germline (*KMT2A*-G) status and *KMT2A* partner genes is poorly understood in the context of demographic and clinical covariates. We investigated these variables in the Children's Oncology Group (COG) P9407 trial for newly diagnosed infant ALL (*clinicaltrials gov. Identifier: NCT00002756*). This trial, designed to reduce early relapses by induction intensification, enrolled 221 infants (209 treatment-eligible) from June 1996-June 2006, and was amended in cohorts 2 and 3 for toxicities and hematopoietic stem cell transplantation lacking benefit.[3] Specimens were collected under Pediatric Oncology Group (POG) 9900 or COG AALL03B1 with separate consent and individual Institutional Review Board approvals.[3]

Of 209 (199 treatment-eligible) cases analyzed, 157 (75.1%) (148/199 treatment-eligible; 74.4%) were *KMT2A*-R, and the rest were *KMT2A*-G. Partner genes in 5'-*KMT2A*-partner-3' fusions were assigned to five categories similar to Interfant-99/Interfant-06[2,4] and COG AALL0631[5]: *AFF1* (n=78, 49.7%; 73/78 treatment-eligible); *MLLT1* (n=33, 21.0%; 31/33 treatment-eligible); *MLLT3* (n=14, 8.9%; 13/14 treatment-eligible); 'other' (n=20, 12.7%; all treatment-eligible); 'unknown' (n=12, 7.6%; 11/12 treatment eligible). 'Other' included all non-*AFF1*/non-*MLLT1*/non-*MLLT3* partner genes: *EPS15* (n=4), *MLLT10* (n=1), *ACER1* (n=1), *ACTN4* (n=1), non-*AFF1*/non-*MLLT1*/non-*MLLT3* not further classified (n=13). 'Unknown' included non-*AFF1* not further classified (n=5; 4/5 treatment-eligible) and *KMT2A*-R not further classified (n=7; all treatment-eligible). COG P9407 used leukemia classification methods of the trial era including karyotype, fluorescence *in situ* hybridization, Southern blot and/or conventional polymerase chain reaction (PCR), and panhandle PCR analyses for unknown partner genes.[6] While advanced genomics may detect covert rearrangements and improve partner gene assignments,[7,8] the 75.1% *KMT2A*-R in this study is comparable to 79%, 74%, and 70% in other large infant ALL clinical trials.[2,4,5]

Limitations notwithstanding, breakpoint heterogeneity and partner gene diversity were uncovered: one case had a 5'-*KMT2A* exon 9-*AFF1* exon 11-3' transcript outside the usual *AFF1* exon 3-6 breakpoint region.[9] Another had the partner genes *ACTN4* and *RYR1*, both from 19q13.2, in 5'-*KMT2A*-partner-3' and 5'-partner-*KMT2A*-3' fusions, suggesting a new unbalanced t(11;19). *ACTN4* and *RYR1* have not occurred as partner genes in *KMT2A*-R infant ALL, but *ACTN4* was reported in separate cases of treatment-related ALL and treatment-related MDS.[10] *ACER1* from 19p13.3 was reported in one case of infant ALL.[11]

Five-year event-free survival (EFS) was: *MLLT1*, 25±9%; *AFF1*, 34±7%; 'other', 40±14%; *MLLT3*, 68±17%; *KMT2A*-G, 69±9% (log-rank test; P<0.0001) (Figure 1A). After treatment modifications ameliorated excessive toxicities, in cohort 3 5-year EFS was: *MLLT1*, 15±10%; *AFF1*, 33±10%; 'other', 39±15%; *MLLT3*, 73±27%; *KMT2A*-G, 70±13% (P=0.0004) (*Online Supplementary Figure S1A*), suggesting consistent impact of genetic subtypes.

The COG uses ≤90 days to define high-risk *KMT2A*-R infant ALL.[5] Our microarray studies had revealed *AFF1* case separation at ~90 days, with elevated expression of B-cell maturation genes in older *versus* interleukin, HSP, and HLA genes in younger infants,[12] providing biological grounds for this cut-off. Consistently, in ≤90-day-old *versus* >90-day-old infants, 5-year EFS was worse among *KMT2A*-R overall (6±4% *vs.* 47±6%; P<0.0001); *AFF1* (5±5% *vs.* 46±9%; P<0.0001); and *MLLT1* (0% *vs.* 37±12%; P=0.0008) (Figure 1B). Using National Cancer Institute risk groups of white blood cell (WBC) count <50x10^9/L *versus* ≥50x10^9/L,[13] 5-year EFS was 76±7% *versus* 33±5% (P<0.0001) in treatment-eligible overall (Table 1); 67±10% *versus* 29±5% (P=0.0002) in all *KMT2A*-R; 67±22% *versus* 15±8% in *MLLT1* (P=0.029); and 88±9% *versus* 52±14% in *KMT2A*-G (P=0.013) (Figure 1C).

Using Interfant-99 risk groups,[2] 5-year EFS was: high-risk (*KMT2A*-R with age <6 months and WBC count >300x10^9/L), 24±9%; intermediate-risk (IR) (*KMT2A*-R without these features), 41±6%; low-risk (LR) (*KMT2A*-G), 69±9% (overall P<0.0001; high-risk *vs.* IR; P=0.047) (*Online Supplementary Figure S1B*), suggesting better *KMT2A*-R separation when analyzed by partner gene, age ≤/>90 days, or WBC count </≥50x10^9/L (Figure 1A-C).

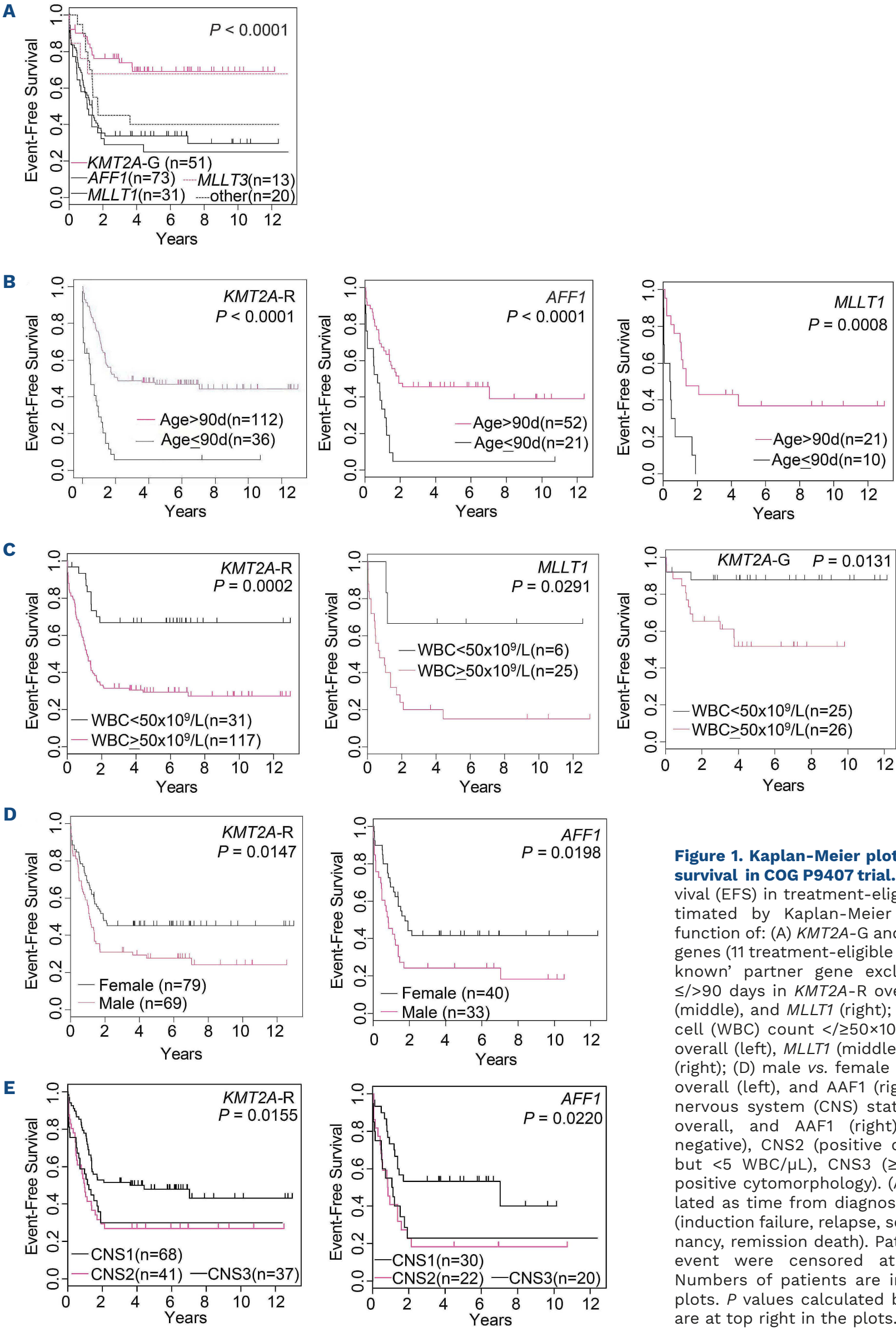

Figure 1. Kaplan-Meier plots of event-free survival in COG P9407 trial. Event-free survival (EFS) in treatment-eligible infants estimated by Kaplan-Meier method as a function of: (A) *KMT2A*-G and *KMT2A* partner genes (11 treatment-eligible in category 'unknown' partner gene excluded); (B) age ≤/>90 days in *KMT2A*-R overall (left), AAF1 (middle), and *MLLT1* (right); (C) white blood cell (WBC) count </≥50×10^9/L in *KMT2A*-R overall (left), *MLLT1* (middle), and *KMT2A*-G (right); (D) male *vs.* female sex in *KMT2A*-R overall (left), and AAF1 (right); (E) central nervous system (CNS) status in *KMT2A*-R overall, and AAF1 (right). CNS1 (CNS-negative), CNS2 (positive cytomorphology but <5 WBC/μL), CNS3 (≥5 WBC/μL and positive cytomorphology). (A-E) EFS calculated as time from diagnosis to first event (induction failure, relapse, secondary malignancy, remission death). Patients having no event were censored at last contact. Numbers of patients are indicated in the plots. *P* values calculated by log-rank test are at top right in the plots.

Male sex adversely affected 5-year EFS in *KMT2A*-R overall (28±6% *vs.* 45±7%, girls; *P*=0.0147) and *AFF1* (24±9% *vs.* 42±10%, girls; *P*=0.0198) (Figure 1D). Five-year EFS for CNS1, CNS2, and CNS3 was 54±6%, 41±8%, and 33±10% (*P*=0.025) in treatment-eligible overall (Table 1); 48±7%, 27±8%, and 30±9% (*P*=0.0155) in all *KMT2A*-R; and 53±12%, 18±10%, and 23±12% (*P*=0.022) in *AFF1* (Figure 1E).

The impact of *KMT2A*-R *versus KMT2A*-G, partner genes, and demographic and clinical covariates was further studied using multivariable Cox regression models. After adjusting for sex, age, WBC, and central nervous system (CNS) disease at diagnosis, *AFF1* (hazard ratio [HR]=2.51; *P*=0.0032), *MLLT1* (HR=3.30; *P*=0.0007), 'other' (HR=2.50; *P*=0.021), and 'unknown' (HR=2.81; *P*=0.048) partner genes were significant for high risk, and *MLLT3* had similar risk (HR=1.04; *P*=0.95) compared to *KMT2A*-G as reference. Age ≤90 days (HR=2.58; *P*<0.0001), WBC count ≥50x10^9/L (HR=2.70; *P*=0.0027), and male sex (HR=1.59; *P*=0.023) were associated with significantly higher risk (Table 1).

Separate multivariable analysis of *KMT2A*-R subtypes without *KMT2A*-G (*Online Supplementary Table S1*) revealed similar effects of age, WBC count, sex, and CNS disease, with all except CNS disease independently impacting outcome. Using *AFF1* as reference, *MLLT3* had lower observed risk (HR=0.41; *P*=0.15), and *MLLT1* had higher observed risk (HR=1.34; *P*=0.27), but *KMT2A*-R subtypes did not reach significance. We also explored a model containing age as a continuous variable; age proved to be significant, and effects of all other covariates were similar to both models described above (*Online Supplementary Table S1*). Another model controlling for cohort 3 after therapy adjustments did not show an effect of treatment; *KMT2A* partner genes, age, WBC count, and sex retained independent impact on prognosis (*Online Supplementary Table S1*).

We then asked whether demographic or clinical covariates differed by genetic subtype. Age distribution differed among *AFF1*, *MLLT1*, *MLLT3*, 'other', and *KMT2A*-G (*P*<0.0001) (Figure 2A). Age ≤90 days was more common in *KMT2A*-R overall (40/157; 25.5%) than *KMT2A*-G (6/52; 11.5%) (*P*=0.036). Nineteen of 20 'other' (i.e., all non-*AFF1*/non-*MLLT1*/non-*MLLT3*) (95%) occurred in >90-day-

Table 1. Univariate and multivariable analyses of prognostic factors.

	Univariate analysis				Cox regression model	
	Patients N, %	Events N	5-year EFS, % (SE)	*P***	Estimated hazard ratios#	*P*##
Sex				0.093		
Male	102 (51.3)	61	39.3 (6.1)		1.59 (1.07-2.37)	0.023
Female	97 (48.7)	47	51.3 (6.3)		Reference	
Age at diagnosis (days)				<0.0001		
≤ 90	42 (21.1)	35	14.8 (6.8)		2.58 (1.61-4.15)	<0.0001
> 90	157 (78.9)	73	53.2 (5.0)		Reference	
WBC count at diagnosis				<0.0001		
<50x10^9/L	56 (28.1)	13	76.1 (7.0)		Reference	
≥50x10^9/L	143 (71.9)	95	33.3 (5.1)		2.70 (1.41-5.16)	0.0027
KMT2A status/partner gene				<0.0001		
KMT2A-G	51 (25.6)	15	69.1 (8.8)		Reference	
KMT2A-R	148 (74.4)	93	37.0 (4.8)			
AFF1	73 (36.7)	49	33.8 (6.9)		2.51 (1.36-4.62)	0.0032
MLLT1	31 (15.6)	23	24.9 (8.8)		3.30 (1.66-6.57)	0.0007
MLLT3	13 (6.5)	4	67.7(17.2)		1.04 (0.29-3.68)	0.95
Other partner gene	20 (10.1)	12	40.0(13.9)		2.50 (1.15-5.41)	0.021
Unknown partner gene	11 (5.5)	5	54.6 (15.0)		2.81 (1.01-7.83)	0.048
CNS status				0.025		0.95
CNS1	99 (49.7)	46	53.5 (6.2)		Reference	
CNS2	56 (28.1)	33	41.1 (8.4)		1.08 (0.66-1.77)	0.77
CNS3	42 (21.1)	27	33.2 (9.6)		1.01 (0.59- 1.72)	0.97
Unknown	2 (1.0)	2	0.0 (-)			

**P value for the log-rank test on the difference between subgroups. #Data are hazard ratio (95% confidence interval). ##Calculated with Wald tests in joint analysis of sex, age, white blood cell (WBC) count, *KMT2A* partner gene category *vs.* *KMT2A*-G, and central nervous system (CNS) status. 'Other' partner gene includes: *EPS15, MLLT10, ACTN4, ACER1*, and non-*AFF1*/non-*MLLT1*/non-*MLLT3* not further classified. 'Unknown' partner gene includes: non-*AFF1* not further classified, and *KMT2A*-R not further classified. CNS status: CNS1, negative; CNS2, positive cytomorphology/and <5 WBC/μL; CNS3, ≥5 WBC/μL/and positive cytomorphology. Analysis does not include CNS status unknown stratum (N=2). CNS: central nervous system; EFS: event-free survival; SE: standard error.

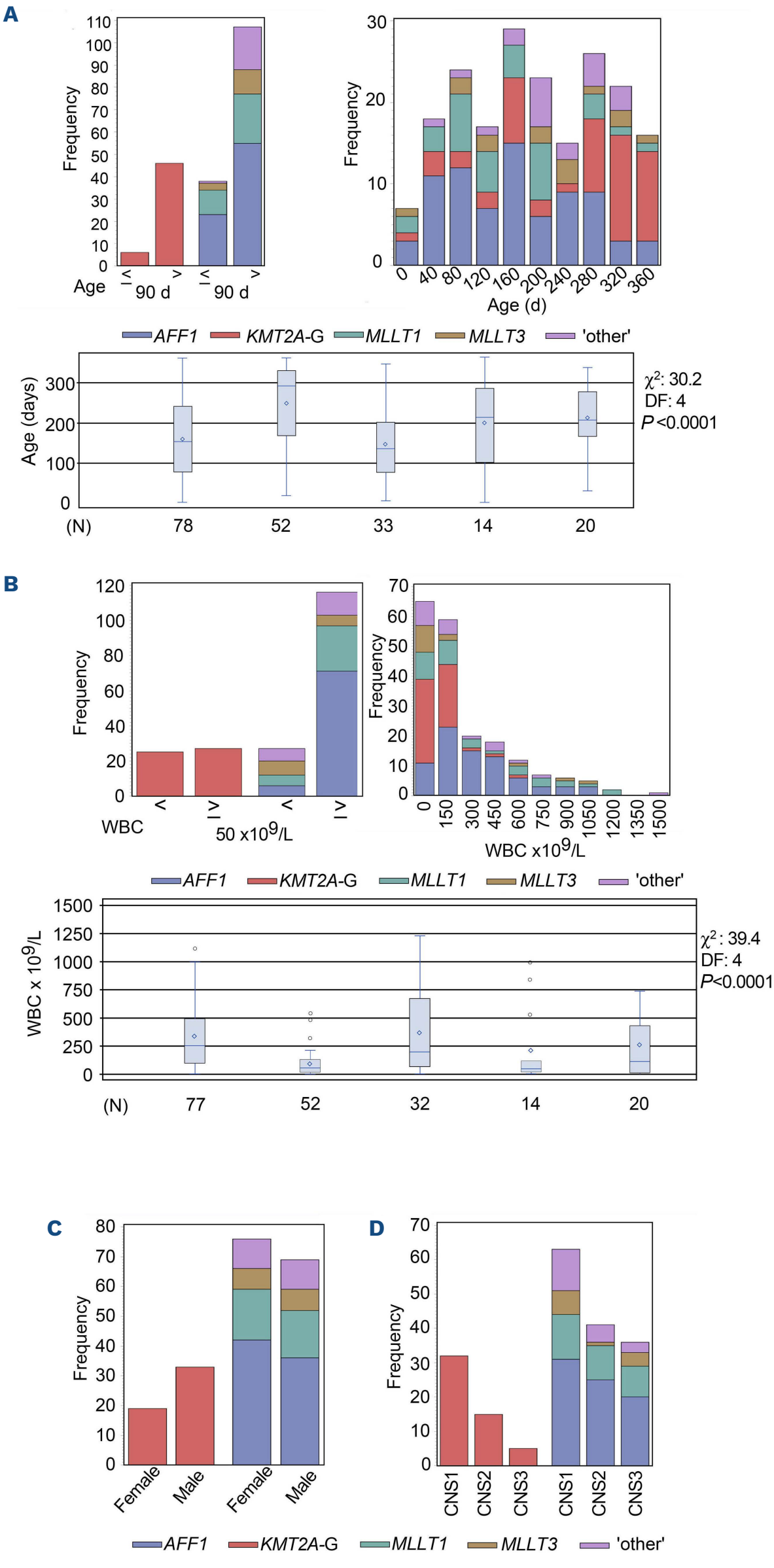

Figure 2. Correlations of demographic and clinical covariates with *KMT2A-G* and *KMT2A* partner genes. Distributions among *KMT2A*-G and *AFF1*, *MLLT1*, *MLLT3*, and 'other' *KMT2A*-R genetic subtypes for all treatment-eligible and treatment-ineligible infants plotted by: (A) age at diagnosis ≤90 days (d) *vs.* >90 d (top left), and age as a continuous variable (top right). Box and whisker plots (bottom) indicate that distribution by age in days as a continuous variable differs among genetic subtypes (χ^2 statistic 30.2; degrees of freedom (DF) 4; P<0.0001). Error bars represent range; horizontal lines, quartiles; and small diamond, the mean. (B) Presenting white blood cell (WBC) count <50x10^9/L *vs.* ≥50x10^9/L (top left), and as a continuous variable (top right). Box and whisker plots (bottom) indicate that WBC distribution as a continuous variable differs among genetic subtypes (χ^2 statistic 39.4; DF 4; P<0.0001). (A, B) Distributions among genetic subtypes were compared by Kruskal-Wallis χ^2 square-test; (C) sex; (D) central nervous system (CNS) status at diagnosis. (A-D) Cases in 'unknown' partner gene category were excluded.

old infants *versus* 88 of 125 (70.4%) with any of these partner genes (*P*=0.026); 55 of 78 (70.5%) *AFF1* (*P*=0.022); and 22 of 33 (66.6%) *MLLT1* (*P*=0.020) (*Online Supplementary Table S2*).

WBC count differed among *AFF1*, *MLLT1*, *MLLT3*, 'other', and *KMT2A*-G (*P*<0.0001) (Figure 2B). WBC count was ≥50x10^9/L in 123 of 155 (79.4%) *KMT2A*-R *versus* 27 of 52 (51.9%) *KMT2A*-G (*P*=0.0003). WBC count was ≥50x10^9/L in higher proportions of *AFF1* (71/77; 92.2%) *versus* any non-*AFF1* partner gene (47/71; 66.2%) (*P*<0.0001); *AFF1 versus MLLT3* (6/14; 42.9%) (*P*<0.0001); *MLLT1* (26/32; 81.3%) *versus MLLT3* (*P*=0.015); and any non-*MLLT3* partner gene (110/129; 85.3%) *versus MLLT3* (*P*=0.0008) (*Online Supplementary Table S2*).

The 45.9% male (n=72)/54.1% (n=85) female *KMT2A*-R differed from 63.5% male (n=33)/36.5% female (n=19) *KMT2A*-G (*P*=0.037). The 46.2% (n=36) male/53.8% (n=42) female *AFF1* did not differ statistically from *KMT2A*-G (*P*=0.073) or any other partner subtypes (Figure 2C; *Online Supplementary Table S2*).

CNS1 occurred in 32 of 52 (61.5%) *KMT2A*-G *versus* 71 of 155 (45.8%) *KMT2A*-R overall (*P*=0.056); 32 of 77 (41.6%) *AFF1* (*P*=0.032); and 13 of 33 (39.4%) *MLLT1* (*P*=0.074). A higher proportion of *KMT2A*-G were CNS1 or CNS2 (47/52; 90.4%) *versus KMT2A*-R overall (117/155; 75.5%) (*P*=0.029); *AFF1* (57/77; 74.0%) (*P*=0.024); and *MLLT1* (23/33; 69.7%) (*P*=0.020) (Figure 2D; *Online Supplementary Table S2*).

In summary, this study demonstrates the impact of *KMT2A* partner genes on prognosis, and partner gene associations and interactions with demographic and clinical covariates. Univariate and multivariable analyses identify *KMT2A*-R subtypes (*AFF1, MLLT1*, 'other') with significantly decreased survival, and survival for *MLLT3* equivalent to *KMT2A*-G, establishing independent prognostic significance of *KMT2A* partner genes compared to *KMT2A*-G. A separate multivariable model excluding *KMT2A*-G revealed non-significantly increased and decreased observed risks *versus AFF1* for *MLLT1* and *MLLT3*, respectively. The study further shows that age, WBC count, sex, and CNS disease are unevenly distributed and, in univariate analyses, partition EFS within genetic subtypes. Moreover, age, WBC count, and sex have independent prognostic significance in all multivariable models tested. Therefore, *KMT2A* partner genes, demographic and clinical covariates, and outcome in infant ALL are interrelated.

MLLT10 and the YEATS-domain-containing proteins MLLT1 and MLLT3 are DOT1L complex members. MLLT3 and AFF1 are Super Elongation Complex (SEC) members.[14] Yet *AFF1, MLLT1,* and 'other' partner genes proved high-risk compared to *KMT2A*-G whereas, similar to pediatric AML,[15] *MLLT3* was favorable.

In contrast, CCG 1953 and Interfant-99 suggested poorer outcomes for all *KMT2A*-R including *MLLT3*,[1,2] and Interfant-06 found higher risk for t(4;11)+t(11;19) together and t(9;11)+'other' together.[4] Survival was worse among *KMT2A*-G with WBC count ≥50x10^9/L in our study, but not WBC count >300x10^9/L in Interfant-99/Interfant-06.[16] In our study male sex adversely impacted EFS in *KMT2A*-R and *AFF1* in univariate analysis, and in multivariable models, whereas Interfant-06 found higher EFS in boys than girls for *KMT2A*-R and *KMT2A*-G together by univariate analysis but no difference by sex in multivariable analysis.[4]

The disproportionate ≤90-day-old infants among *AFF1* and *MLLT1*, and >90-day-old infants among 'other' here, and the 67% of t(11;19), but 31% of t(9;11) in <6-month-old infants in Interfant-99,[2] agree with variable leukemia latencies by partner gene in murine models.[17]

Improved understanding of the spectrum of *KMT2A* partner genes relative to their complex interplay with demographic and clinical covariates is critical to discern high-risk infants. KMT2A fusion proteins involving members of the AF4 (AFF1) and ENL (MLLT1, MLLT3) protein families constitutively activate transcription by forming AEP (AF4/ENL/P-TEFβ) complexes, whereas different KMT2A fusion proteins alter transcription by varied mechanisms.[18] Considering the partner gene heterogeneity and paucity of infant ALL with some 'other' partner genes, advanced genomics classification[7,8] and pooling across trials are essential to discern and validate the prognostic importance of partner genes and demographic and clinical covariates, especially as transcription-targeting agents[18] continue advancing.

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Contributions

CLW, JMH, BMC, NJW, WLC, SPH, ZED and CAF developed the concept. BWR, JAK, MD and CAF developed the methology. BWR, JAK, MD and CAF performed fromal data analysis. BWR, AJC, RCH, NAH, ARB, ECW, NCB, FGB and JP carried out the research. BWR and CAF wrote the original draft. CAF and JAK revised the draft. BWR, JAK, MD, GHR, NJW and SPH reviewed and edited the manuscript. BWR, JAK, MD, KAU and CAF created figures for data visualization. CAF, CLW, MD, GHR and SPH provided funding. CAF supervised the research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Data-sharing statement

Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org.

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