Genomic Determinants of Outcome in Acute Lymphoblastic Leukemia

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ABSTRACT

PURPOSE Although cure rates for childhood acute lymphoblastic leukemia (ALL) exceed 90%, ALL remains a leading cause of cancer death in children. Half of relapses arise in children initially classified with standard-risk (SR) disease.

MATERIALS AND METHODS To identify genomic determinants of relapse in children with SR ALL, we performed genome and transcriptome sequencing of diagnostic and remission samples of children with SR (n = 1,381) or high-risk B-ALL with favorable cytogenetic features (n = 115) enrolled on Children's Oncology Group trials. We used a case-control study design analyzing 439 patients who relapsed and 1,057 who remained in complete remission for at least 5 years.

RESULTS Genomic subtype was associated with relapse, which occurred in approximately 50% of cases of *PAX5*-altered ALL (odds ratio [OR], 3.31 [95% CI, 2.17 to 5.03]; $P = 3.18 \times 10^{-8}$). Within high-hyperdiploid ALL, gain of chromosome 10 with disomy of chromosome 7 was associated with favorable outcome (OR, 0.27 [95% CI, 0.17 to 0.42]; $P = 8.02 \times 10^{-10}$; St Jude Children's Research Hospital validation cohort: OR, 0.22 [95% CI, 0.05 to 0.80]; $P = .009$), and disomy of chromosomes 10 and 17 with gain of chromosome 6 was associated with relapse (OR, 7.16 [95% CI, 2.63 to 21.51]; $P = 2.19 \times 10^{-5}$; validation cohort: OR, 21.32 [95% CI, 3.62 to 119.30]; $P = .0004$). Genomic alterations were associated with relapse in a subtype-dependent manner, including alterations of *INO80* in *ETV6::RUNX1* ALL, *IKZF1*, and *CREBBP* in high-hyperdiploid ALL and *FHIT* in *BCR::ABL1*-like ALL. Genomic alterations were also associated with the presence of minimal residual disease, including *NRAS* and *CREBBP* in high-hyperdiploid ALL.

CONCLUSION Genetic subtype, patterns of aneuploidy, and secondary genomic alterations determine risk of relapse in childhood ALL. Comprehensive genomic analysis is required for optimal risk stratification.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

B-progenitor acute lymphoblastic leukemia (B-ALL) is the commonest childhood tumor and a leading cause of cancer death in children.[1] Determining the optimal intensity of therapy for newly diagnosed patients with ALL is of high priority to maximize cure and minimize toxicity. Genomic profiling of B-ALL has identified multiple subtypes and genomic alterations increasingly used for therapy allocation.[2] However, many studies have been enriched for patients with high-risk (HR) features (age >10 years or a WBC > 50,000/μL)[3,4] while neglecting standard-risk (SR) ALL, which accounts for approximately half of relapsed cases.[5] National Cancer Institute (NCI) SR ALL (age 1-9 years and WBC <50,000/μL) comprises 65% of B-ALL, and over half have somatic genomic lesions associated with cure rates exceeding 95%, such as *ETV6::RUNX1* or hyperdiploidy with double trisomy (DT) of chromosomes 4 and 10.[6] In this Molecular Profiling to Predict Responses to Therapy (MP2PRT) study, we thus examined 1,496 children with predominantly SR B-ALL enrolled across four Children's Oncology Group (COG) clinical trials and performed integrated genomic analysis (Data Supplement, Fig S1, online only) to identify predictors of relapse and end of induction minimal residual disease (EOI MRD).

CONTEXT

Key Objective
How will the reported data advance therapy for childhood acute lymphoblastic leukemia (ALL)?

Knowledge Generated
The study team has identified new genomic predictors of relapse for pediatric patients with standard-risk (SR) ALL using a weighted case-control study design. Using this approach, 50% of children with PAX5alt rearrangements relapsed, and those with SR ALL who also had IKZF1^{plus} had higher rates of relapse.

Relevance *(S. Lentzsch)*
The study contributes to the de-intensification strategies which can minimize the toxicity without increasing the risk of relapse in SR ALL by refining the current risk predictors. Future studies should validate these findings.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

MATERIALS AND METHODS

Patients and Specimen Characteristics

To enrich for cases that relapsed, we used an approximately 1:2 case-control design to select cases representing patients who experienced relapse (n = 439, 29.3%) up to the data cutoff date of March 31, 2021. Controls were chosen to represent individuals in complete continuous remission (CCR) for more than 5 years (Data Supplement, Fig S2). The cases and controls were matched for the presence of MRD (Supplementary Methods). Primary leukemia samples were obtained before starting treatment and paired with nontumor blood or bone marrow available at the end of induction. Patients or their guardians consented to the classification protocols for specimen banking, AALL03B1 and AALL08B1, as well as the clinical trials listed below, which were institutional review board–approved at each institution.

The study group consisted primarily of 1,381 patients enrolled on COG trials of NCI SR B-ALL (AALL0331[7,8] and AALL0932[9,10]), with either favorable (n = 776) or neutral (n = 605) cytogenetic features (Supplementary Methods, Data Supplement, Tables S1-S3 and Figs S1and S2). This included 439 patients (405 SR, 34 HR) who relapsed and 1,057 (976 SR, 81 HR) who remained in CCR for more than 5 years (Data Supplement, Table S4 and Supplementary Methods). In total, 115 patients with NCI HR B-ALL with favorable cytogenetic features (AALL0232[11,12] and AALL1131[13]) were also included. All patients were in complete remission at the end of the first month of therapy. Cytogenetic profiles and outcome were also assessed in patients treated on St Jude Total Therapy 15 and 16 studies.[27,28]

Assay Methods and Statistical Analysis

In total, 1,462 samples had both whole genome sequencing (WGS) and whole transcriptome sequencing (WTS), 31 WGS only, and three WTS only (Supplementary Methods) with adequate quality (Data Supplement, Fig S3). For most analyses, we treated relapse as a binary outcome and used logistic regression or Fisher's exact test to perform association tests. Due to the 1:2 case-control design, a weighting methodology was used for accurate depiction of Kaplan-Meier survival plots (Supplementary Methods).

RESULTS

Associations Between B-ALL Subtype and Outcome

The most common genetic subtypes, defined by cytogenetics and genomic features (Data Supplement, Tables S5-S8 and Figs S3-S6),[14-16] were *ETV6::RUNX1* (n = 557, 37.2%) and hyperdiploidy with gain of at least five chromosomes (n = 514, 34.4%; Fig 1A, Data Supplement, Tables S4, S7, and S9). Due to the study design, the relapse frequency was higher in favorable-risk subtypes than in previously reported studies without enrichment for patients who experienced relapse (*ETV6::RUNX1,* 23.2%; hyperdiploid, 23.5%, Fig 1B, Data Supplement, Table S10).

Except for an association between age at diagnosis of 3-5 years and EOI MRD (odds ratio [OR], 0.68 [95% CI, 0.50 to 0.93]; $P = .016$), we did not observe associations between clinical features and relapse or MRD (Fig 1B, Data Supplement, Table S10). Risks of relapse and MRD positivity varied according to subtype. The highest risks of relapse were observed in *TCF3/4::HLF* (compared with *ETV6::RUNX1* ALL, OR, 23.20 [95% CI, 2.42 to 3,091.00]; $P = 3.86 \times 10^{-3}$), *ETV6::RUNX1*-like (OR, 4.01 [95% CI, 2.02 to 8.00]; $P = 9.08 \times 10^{-5}$), *BCR::ABL1*-like (OR, 2.15 [95% CI, 1.05 to 4.29]; $P = 3.72 \times 10^{-2}$), and *PAX5*-altered ALL (PAX5alt; OR, 3.31 [95% CI, 2.17 to 5.03]; $P = 3.18 \times 10^{-8}$; Fig 1B, Data Supplement, Table S10). Patients with B-ALL and Down syndrome were also more likely to relapse (OR, 7.10 [95% CI, 2.80 to 19.91]; $P = 3.45 \times 10^{-5}$). Conversely, hyperdiploid cases with DT of chromosomes

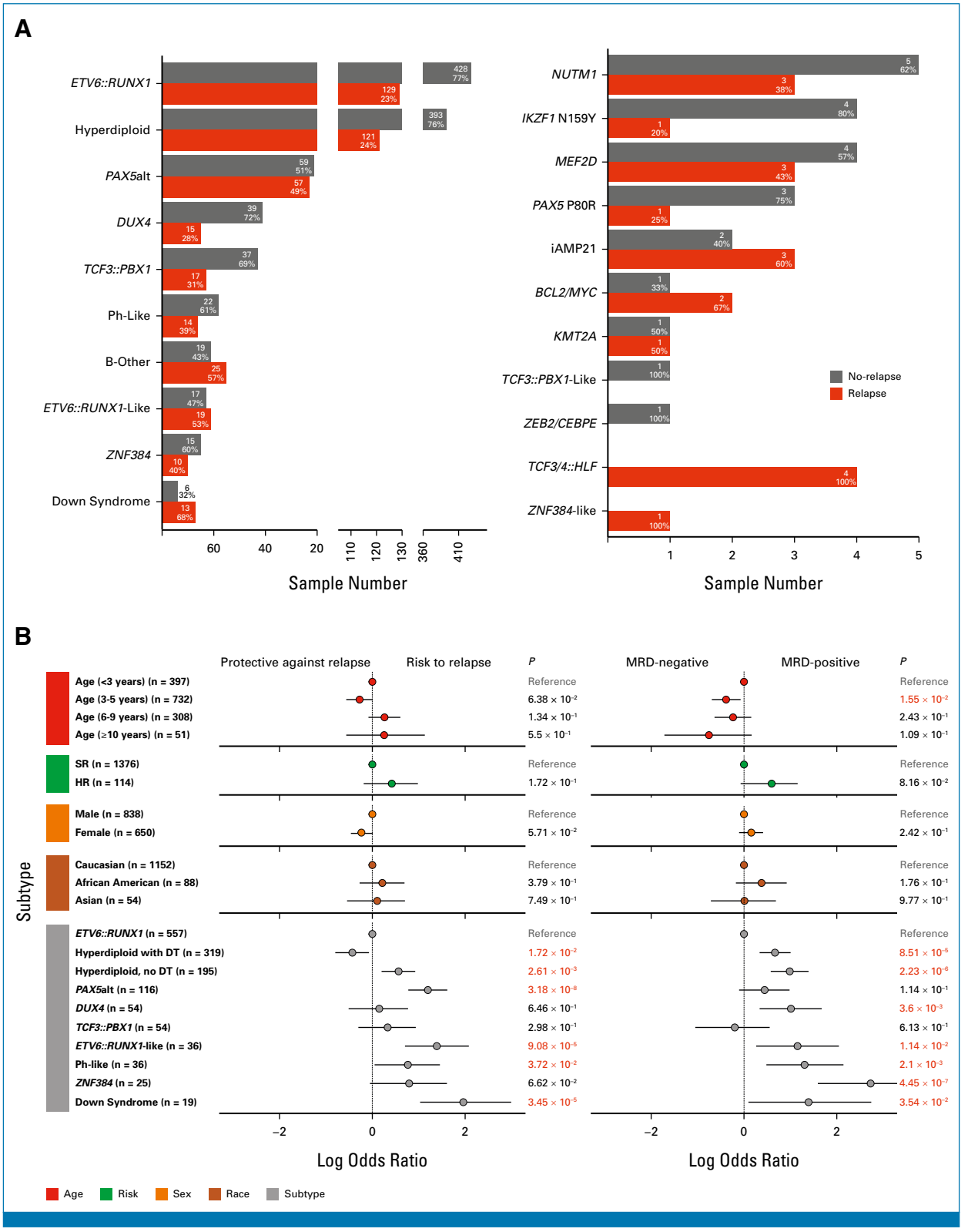

FIG 1. Numbers of subtypes, relapse, and associated clinical features of the 1,496 analyzed MP2PRT study group. (A) Genomic subtypes and frequency relapse for the entire group; (B) Forest plots assessing contributions of clinical features and major genetic subtypes on risk of relapse. The dots represent $\log_2$ odds ratios and the lines represent the lower and upper bound of the 95% CI of the odds ratio. For risk, the reference level is the standard risk; for sex, the reference level is male; for self-identified ancestry, the reference level is Caucasian. DT, double trisomy of chromosomes 4 and 10; for age, the reference level is age <3 years; for subtype, the reference level is *ETV6::RUNX1*. The subtypes with sample size <10 are not shown. MP2PRT, Molecular Profiling to Predict Responses to Therapy; MRD, minimal residual disease.

4 and 10 (319 of 514 hyperdiploid cases [62.0%]) experienced lower rates of relapse than *ETV6::RUNX1* ALL (OR, 0.65 [95% CI, 0.45 to 0.93]; $P = .017$), but hyperdiploidy without DT (195 of 514 cases [38.0%]) had higher relapse rates (OR, 1.76 [95% CI, 1.22 to 2.52]; $P = .003$). Among the patients who relapsed, the time to relapse varied by subtype and was shortest for *TCF3::PBX1* (median time to relapse of 19.2 months, 95% CI, 15.8 to 21.0) and PAX5alt cases (median of 29.0 months, 95% CI, 23.8 to 37.6 months) compared with *ETV6::RUNX1* (median of 42.7 months, 95% CI, 40.1 to 45.7; Data Supplement, Fig S7).

The burden of DNA sequence mutations varied by subtype and relapse status and was highest in *ETV6::RUNX1* and hyperdiploid ALL, and in *ETV6::RUNX1* patients who relapsed versus those who did not (Data Supplement, Fig S4 and Table S11). The nature of genomic alterations at translocation breakpoints was also associated with clinical outcome. Unbalanced *ETV6::RUNX1* translocations with gain of *RUNX1* or *ETV6::RUNX1* were more common in patients who relapsed (OR, 2.01 [95% CI, 1.25 to 3.20]; $P = .002$; Figs 2A-2D). Conversely, in *TCF3::PBX1* ALL, unbalanced translocations resulting in 1q23-1qter gain and 19p13.3-19pter loss were associated with fewer relapses compared with those with balanced translocations (OR, 0.11 [95% CI, 0.01 to 0.50]; $P = .003$; Data Supplement, Fig S8).

A striking finding was the high relapse rate of PAX5alt ALL (57 of 116 cases [49%], Figs 1 and 3). *PAX5* encodes a transcription factor required for normal B-cell development that is mutated in B-ALL. Distinct *PAX5* alterations define two B-ALL subtypes: PAX5 P80R[14,17,18] and PAX5alt ALL that harbors diverse *PAX5* rearrangements, intragenic amplification, and sequence mutations.[14,19,20] The type of *PAX5* alteration was associated with relapse risk in PAX5alt ALL (Fig 3). Drivers of PAX5alt ALL reported in studies enriched for HR B-ALL, *PAX5::ETV6* and PAX5 R38H/R140H,[14] were not observed, suggesting their association with HR features.

Conversely, PAX5alt cases in this study exhibited a high frequency of *PAX5::NOL4L* and *PAX5::ZCCHC7* fusions, and focal internal tandem *PAX5* amplifications[14] that always involved *PAX5* exon 5, encoding part of the DNA-binding paired domain (Fig 3B, Data Supplement, Fig S9 and Table S12). Compared with cases without *PAX5* alterations, those cases with *PAX5* amplification in combination with other structural *PAX5* variants had the worst relapse-free survival (four of five cases relapsed, OR, 13.00 [95% CI, 1.25 to 255.49]; $P = .03$, weighted Cox regression test $P = .02$), followed by those with *PAX5* amplification and *PAX5* rearrangement (three of four cases relapsed, OR, 10.11 [95% CI, 0.90 to 204.62]; $P = .06$, weighted Cox regression test $P = .04$, Fig 3C, Data Supplement, Fig S10). Thus, biallelic alterations of *PAX5* were associated with worst outcomes in cases with PAX5 amplification. In addition, *PAX5* amplification was significantly enriched in PAX5alt MRD-positive patients. Specifically, *PAX5* amplification was present in 34.9% of 43 MRD-positive patients versus 11.0% of 73 MRD-negative patients (OR, 4.29 [95% CI, 1.51 to 13.14]; $P = .0032$). Thus, genomic subtype and the type of driver alterations in PAX5alt ALL are important determinants of relapse in SR B-ALL.

Genome-Wide Analysis of Determinants of Relapse and MRD

Risk of relapse conferred by genomic alterations varies by B-ALL subtype, such as *IKZF1* in *BCR::ABL1* and *BCR::ABL1*-like ALL,[4,21,22] and *TP53* mutation in low-hypodiploid ALL.[23] Accordingly, we identified somatic genomic alterations present in at least 3% of samples and further stratified these by subtype (Data Supplement, Fig S5 and Table S13).

Genome-wide analysis using all samples identified associations between any type of somatic alterations in 1,986 genes and relapse, with 452 remaining significant after adjusting for subtype (FDR <0.2, Data Supplement, Fig S11 and Table S14A). Thus, B-ALL subtypes/primary somatic alterations explain a large portion of the associations with relapse. Conversely, additional secondary alterations contributed to the risk of relapse. *CDKN2A/CDKN2B* deletions were frequent in PAX5alt B-ALL (73% of cases), and the association of homozygous deletions with relapse (OR, 1.87 [95% CI, 1.43 to 2.45]; $P = 7.03 \times 10^{-6}$ for *CDKN2A*, OR, 1.92 [95% CI, 1.45 to 2.54]; $P = 8.06 \times 10^{-7}$ for *CDKN2B*, using the full study group without adjustment for subtype) was moderated by adjustment for subtype (OR, 1.48 [95% CI, 1.08 to 2.01]; $P = .015$ for *CDKN2A*, OR, 1.50 [95% CI, 1.08 to 2.07]; $P = .016$ for *CDKN2B*). However, homozygous *CDKN2A* deletion was associated with relapse in non-PAX5alt cases (OR, 1.43 [95% CI, 1.02 to 2.00]; $P = .036$), and PAX5alt B-ALL was associated with relapse in cases lacking homozygous *CDKN2A* deletion (OR, 2.24 [95% CI, 1.04 to 4.67]; $P = .043$). Thus, PAX5alt is associated with relapse irrespective of *CDKN2A* status due to the presence of other types of alterations. Also, chromosome 9p23.1 alterations including homozygous deletion of *CDKN2A/CDKN2B* and the flanking genes *IFNA7* and *MTAP* were associated with increased risk of relapse but a reduced risk of being MRD-positive at the end of induction (Data Supplement, Figs S12 and S13).

For common (No. > 10) subtypes, 881 genes were associated with relapse, many of which were attributable to large genomic alterations (Data Supplement, Table S14B). For example, 542 of 751 relapse-associated genes in *ETV6::RUNX1* ALL reflected associations of deletion of chromosome 11 with CCR (OR, 0.06, [95% CI, 0.0004 to 0.41]; $P = .0007$; Fig 2E) and chromosome 15 deletions that were associated with relapse (OR, 3.38 [95% CI, 1.78 to 6.39]; $P = .0002$; Data Supplement, Table S15). The maximal region of chromosome 11q deletion was 47 Mb and encompassed seven leukemia driver genes, including *KMT2A*.

Genome-wide analysis of individual types of genomic alteration (Data Supplement, Table S14C) showed that homozygous deletions of *PAX5* and *CDKN2A/CDKN2B* were significant for relapse (Data Supplement, Table S16). Logistic

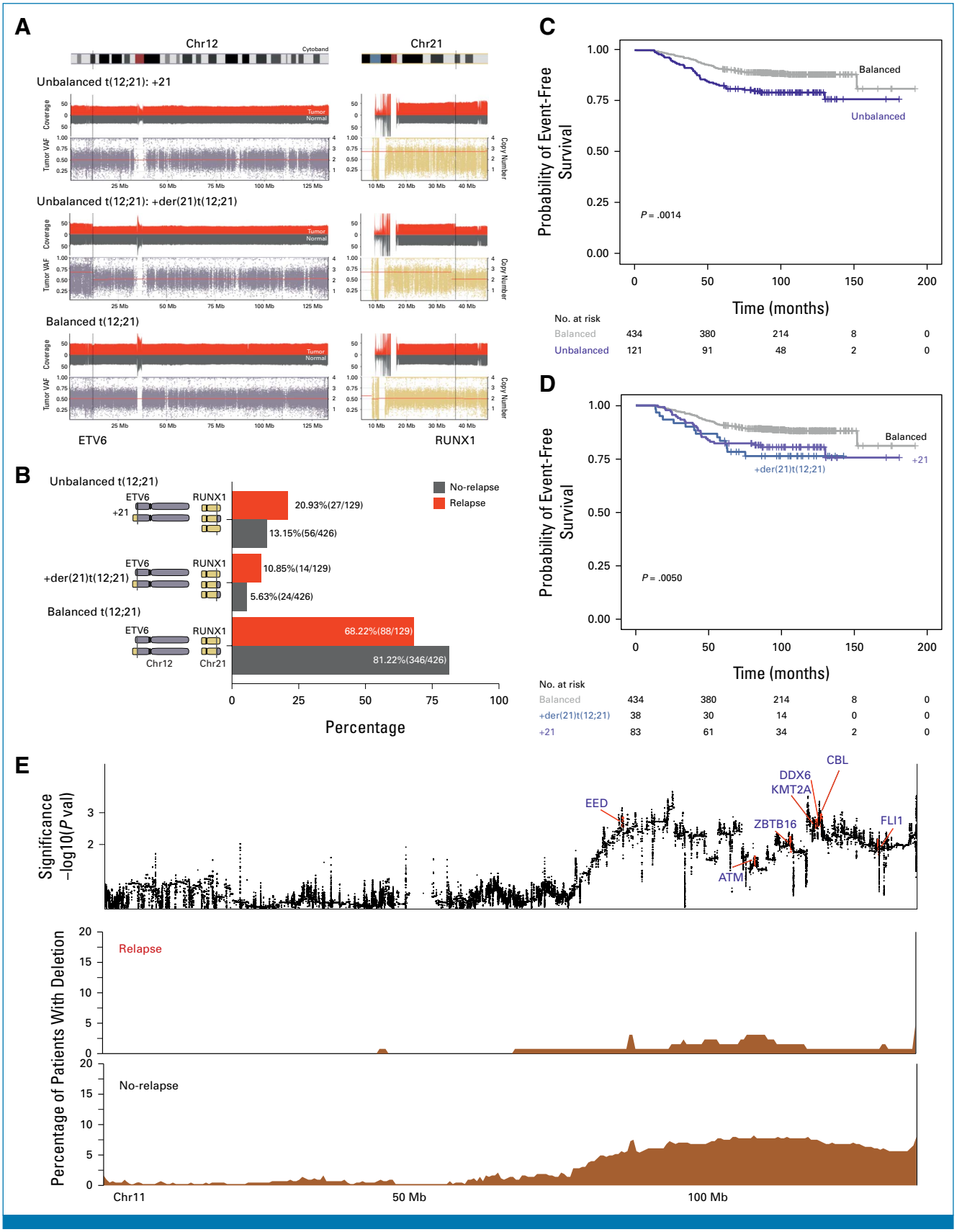

FIG 2. Associations of unbalanced translocations with poor outcome and 11q deletions with favorable outcome in *ETV6::RUNX1* ALL. (A) Coverage profiles and variant allele frequency distribution on chr12 and chr21 for representative cases. For each case, WGS coverage for matched tumor/normal samples is shown in the top track and variant allele frequency is shown in the bottom. The red line represents the $\log_2$ ratio of the segments. (B) Comparison of percentage of patients with balanced and unbalanced (continued on following page)

FIG 2. (Continued). *ETV6::RUNX1* translocations. Unbalanced *ETV6::RUNX1* translocation was more prevalent in relapse samples ($P = .0027$). (C) Weighted Kaplan-Meier (KM) curves of cases with unbalanced versus balanced *ETV6::RUNX1* translocations. Cases with unbalanced translocations had inferior outcome compared with those with balanced translocation. (D) Weighted KM curves with unbalanced cases subclassified into +21 and +der(21)t(12;21) groups. (E) Top, significance of chr11q deletion enrichment in nonrelapsed patients on the basis of associations between CNV (log_2 ratio) and the relapse status. Putative leukemia driver genes are highlighted in blue. Bottom, percentage of cases with deletion in relapse or no-relapse of *ETV6::RUNX1*. Window size is 500 Kbp. CNV, copy number variations; WGS, whole genome sequencing.

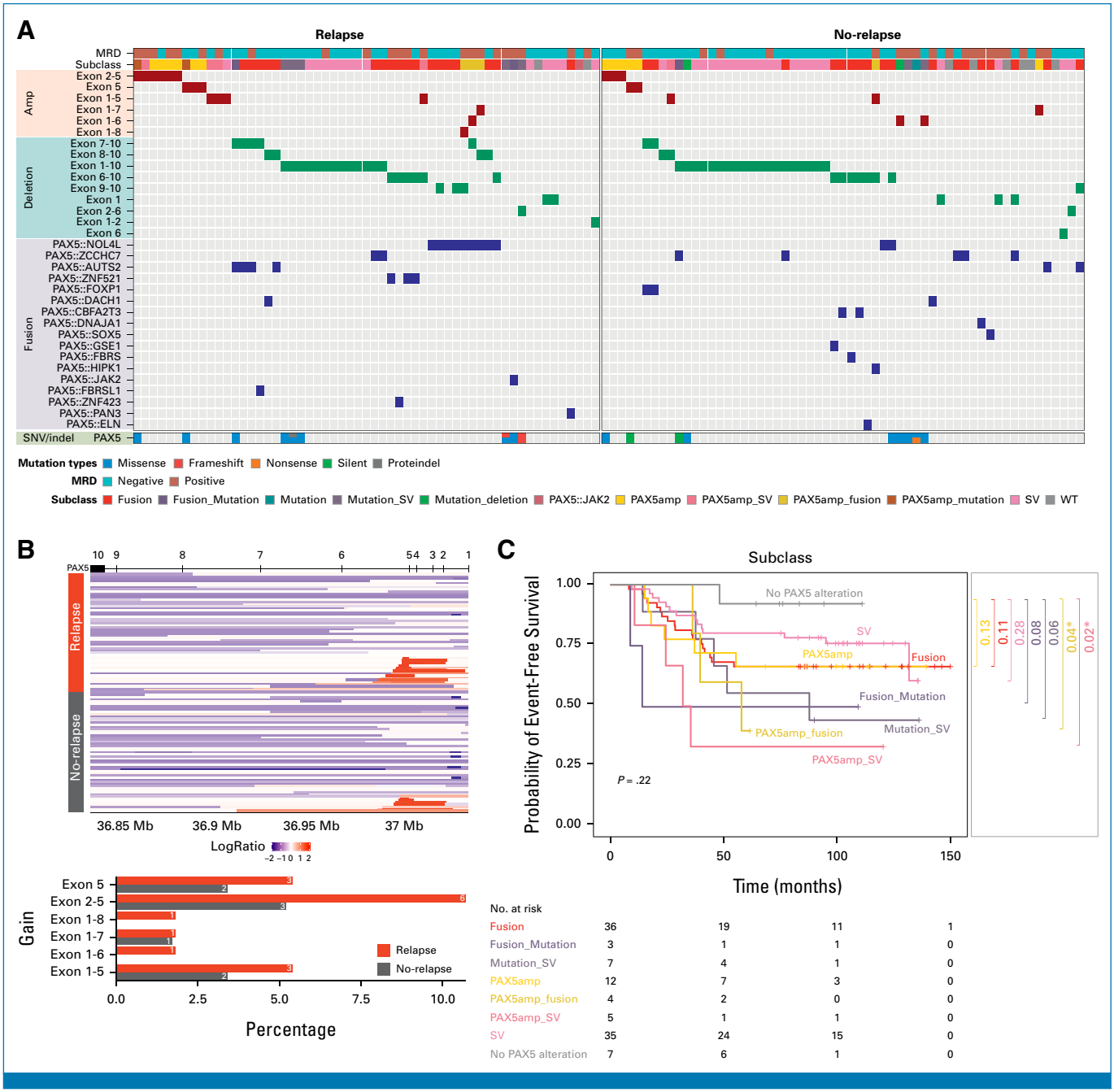

FIG 3. PAX5alt genomic alterations and associations with relapse. (A) Oncoprint of PAX5alt lesions in the MP2PRT study group. (B) CNV segmentation plot and percentage of samples with PAX5 gains. (C) Weighted Kaplan-Meier curves for groups classified on the basis of granular combination types of SNV/indel, SV, and CNV. Significance values from weighted Cox regression test results are shown on the right. *$P < .05$. CNV, copy number variations; MP2PRT, Molecular Profiling to Predict Responses to Therapy; SNV, single nucleotide variations; SV, structural variations; WT, wild-type.

regression considering *PAX5* and *CDKN2A* status in the model showed that each gene was associated with relapse ($P = .0023$ for *CDKN2A* homozygous deletion and $P = .012$ for *PAX5* homozygous deletion). Similar analysis within each subtype identified additional associations with outcome (Data Supplement, Tables S14D).

Across this study group, no subtype-adjusted associations with MRD were observed for analyses combining different alteration types (Data Supplement, Table S14A). Within common subtypes, the majority of 810 gene-level associations with MRD (FDR < 0.2, Data Supplement, Table S14B) were observed in the *PAX5*alt group, most of which (702 of 797 genes) were due to deletions of chromosomes 9 (OR, 0.18 [95% CI, 0.05 to 0.52]; $P = .001$) and 20 (OR, 0.22 [95% CI, 0.06 to 0.65]; $P = .006$, Data Supplement, Table S15) that accompany the formation of structural variants of *PAX5*, such as unbalanced rearrangements.

We also performed analyses focusing on 381 putative leukemia driver genes.[16] Sixteen were associated with relapse without adjustment for subtype and 10 with MRD. After subtype adjustment, seven were associated with relapse and none with MRD (Fig 4, Data Supplement, Table S17). Several of these associations were subtype-dependent. *CREBBP* alterations, most commonly sequence mutations, were associated with relapse (OR, 2.22 [95% CI, 1.45 to 3.40]; $P = .0003$) in hyperdiploid ALL and with elevated MRD in hyperdiploid ALL without DT (OR, 3.11 [95% CI, 1.53 to 6.49]; $P = .0002$, Data Supplement, Tables S16 and S17). Alterations of *NRAS* were associated with elevated MRD (OR, 2.32 [95% CI, 1.54 to 3.51]; $P = 4.9 \times 10^{-5}$, Data Supplement, Table S17), but were not associated with relapse (OR, 0.79 [95% CI, 0.52 to 1.21]; $P = .28$). Deletions and sequence mutations of *INO80* were associated with relapse in *ETV6::RUNX1* B-ALL (Fig 4); deletions occurred in 19 (14.7%) of 129 cases that relapsed compared with 31 (7.24%) of 428 controls (OR, 2.23 [95% CI, 1.20 to 4.04]; $P = .01$); 22 (17.05%) *ETV6::RUNX1* cases that relapsed had *INO80* sequence mutations compared with 43 (10.05%) of 428 controls (OR, 1.85 [95% CI, 1.05 to 3.19]; $P = .03$, Data Supplement, Fig S14).

IKZF1 Alterations and Outcome in Standard-Risk B-ALL

IKZF1 (IKAROS) alterations were associated with increased relapse risk after adjusting for subtypes (OR, 1.80 [95% CI, 1.34 to 2.40]; $P = .00008$) and were significant within multiple subtypes (PAX5alt, *DUX4*-r, and *ETV6::RUNX1*-like, Data Supplement, Table S18), particularly hyperdiploid ALL (OR, 3.23 [95% CI, 2.00 to 5.20]; $P = 2.14 \times 10^{-6}$). The most common *IKZF1* alterations were deletions involving the whole gene (n = 69, 42.9%), followed by exon 4-7 (encoding the dominant-negative isoform IK6, n = 33, 20.5%) and exon 4-8 deletions that result in loss of function (n = 17, 10.6%; Figs 5A and 5B, Data Supplement, Table S19). Mutations in the C-terminal zinc fingers that mediate IKAROS dimerization were almost exclusively observed in diagnostic cases that experienced relapse (Fig 5C). Dominant-negative *IKZF1* deletions were associated with relapse: 64.7% of cases with dominant-negative deletions relapsed compared with 26.3% of cases without *IKZF1* deletions (OR, 5.11 [95% CI, 2.39 to 11.46]; $P = 4.39 \times 10^{-6}$; Fig 5D). Moreover, dominant-negative *IKZF1* deletions or sequence mutations were associated with the worst relapse rates compared with patients with other *IKZF1* deletions or no *IKZF1* deletion (62% relapsed *v* 28.2% of cases lacking dominant-negative alterations, OR, 4.15 [95% CI, 2.24 to 7.86]; $P = 1.56 \times 10^{-6}$; Data Supplement, Fig S15).

The composite IKZF1^{plus} genotype (*IKZF1* deletion/mutations with homozygous *CDKN2A/CDKN2B* deletion, and/or *PAX5* deletion, and/or *CRLF2* rearrangement in the absence of *DUX4* rearrangment) has been reported to be associated with inferior outcome compared with *IKZF1* alterations alone in B-ALL.[24] However, IKZF1^{plus} status is commonly identified using the multiplex ligation probe amplification (MLPA) assay, which does not detect all *DUX4* and *CRLF2* rearrangements. We analyzed MLPA-equivalent and genomically faithful definitions of IKZF1^{plus} (Supplementary Methods; Data Supplement, Fig S16). Approximately 5% of the study group studied were IKZF1^{plus}, and the results of MLPA-equivalent and genomically faithful approaches were similar (MLPA-equivalent: n = 73, relapse = 44 [60.3%], no-relapse = 29 [39.7%]; genomically faithful: n = 62, relapse = 39 [62.9%], no-relapse = 23 [38.1%]). *ETV6::RUNX1*-like and *BCR::ABL1*-like cases had the highest proportion of IKZF1^{plus} cases among the B-ALL subtypes (Data Supplement, Table S20). Patients with *IKZF1* deletion not fulfilling criteria for IKZF1^{plus} had event-free survival (EFS) intermediate between IKZF1^{plus} cases and those lacking *IKZF1* deletion (Fig 5E, Data Supplement, S17A). IKZF1^{plus} cases consistently had inferior outcome compared with non-IKZF1^{plus} cases using both classifications (OR, 3.94 [95% CI, 2.38 to 6.64]; $P = 1.97 \times 10^{-8}$, Fig 5F, Data Supplement, Fig S17B).

Patterns of Aneuploidy Determine the Outcome of Hyperdiploid ALL

High hyperdiploidy, defined by gain of at least five chromosomes, is generally associated with favorable outcome.[15,25] However, a subset of patients with hyperdiploid ALL experience relapse, underscoring the importance of identifying prognostic factors in this group. Within this study, the lack of DT was associated with higher rates of relapse in hyperdiploid ALL than cases with DT (OR, 2.45 [95% CI, 1.59 to 3.80]; $P = 2.59 \times 10^{-5}$), a finding replicated among patients enrolled on St Jude Total Therapy 15 and 16 studies (OR, 6.85 [95% CI, 1.69 to 39.55]; $P = .002$; Data Supplement, Fig S18B). The UK MRC ALL studies reported that trisomy of chromosomes 17 and 18, or one trisomy (17 or 18) without gains of chromosome 5 or 20 was associated with favorable 10-year EFS of 86% (95% CI, 82 to 89)[26]; this observation was replicated in MP2PRT ($P < .0001$) but not ($P > .05$) in the St Jude Total Therapy 15 and 16 studies[27,28] (UK favorable-risk profile 10-year EFS: 96%, 95% CI, 93 to

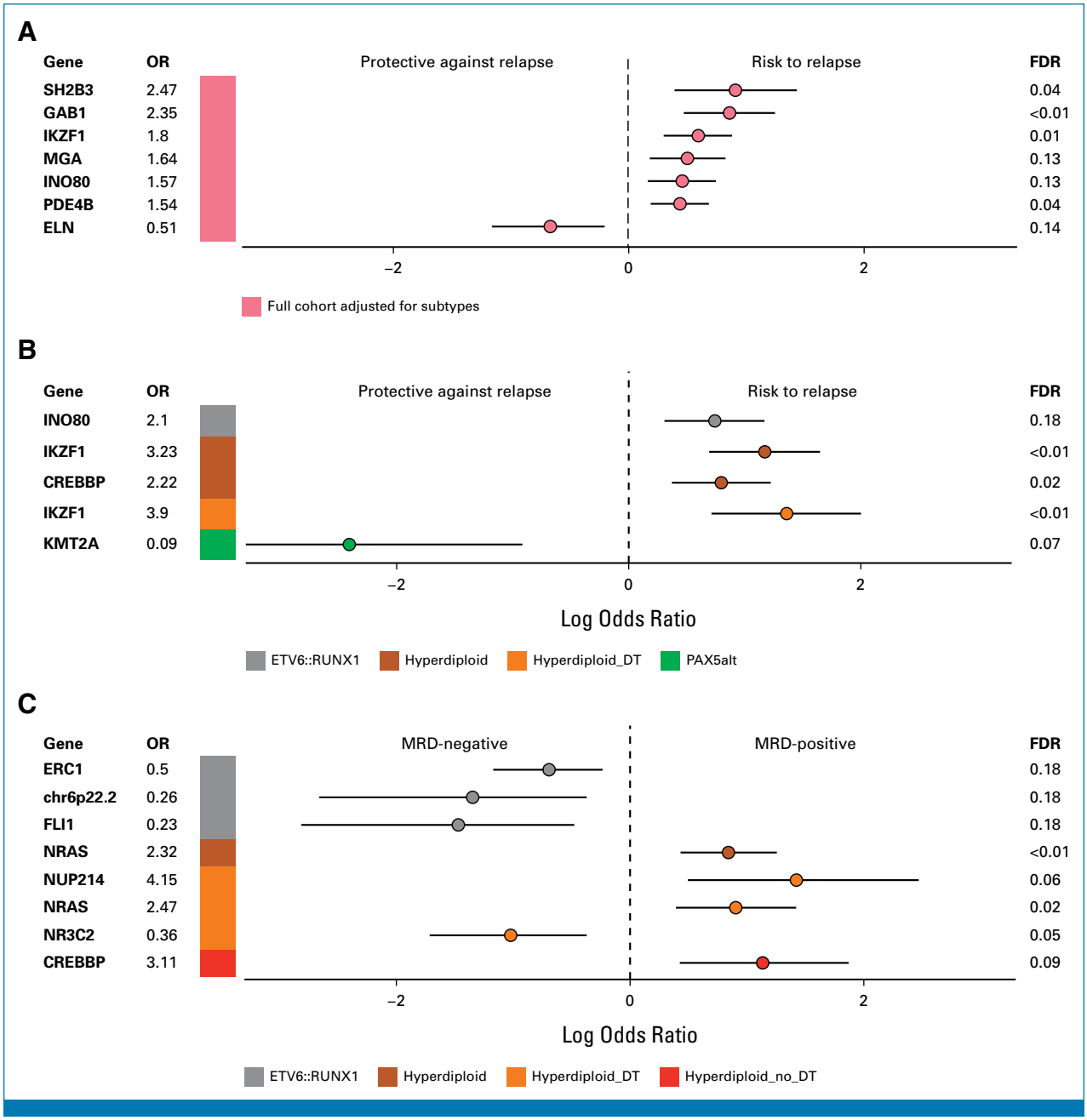

FIG 4. Association of secondary alterations with risk of relapse or MRD positivity for ALL driver genes. (A) Associations with relapse using the full group with adjustment for genomic subtypes. (B) Associations with relapse within each genomic subtype. (C) The association with EOI MRD status (MRD >0.01%) within each subtype. No significant associations with EOI MRD positivity were observed using the full study group adjusting for subtypes. FDR <0.2 and subtypes with sample size >50 were shown. EOI MRD, end of induction minimal residual disease; FDR, false discovery rate; MRD, minimal residual disease; OR, odds ratio.

99; UK poor-risk profile 10-year EFS: 90%, 95% CI, 82 to 99, Data Supplement, Fig S18A).

We thus sought to develop a predictor of outcome considering all possible patterns of aneuploidy. Using a classification and regression tree (CART) analysis considering each individual chromosome alone and in combination, we identified alterations of chromosomes 5, 6, 7, 10, and 17 as predictors of relapse in hyperdiploid ALL. This approach allowed us to classify the cases into distinct groups with varying outcome (Fig 6A). Trisomy of chromosome 10 (10+) with disomy of chromosome 7 (7N) predicted the highest likelihood of remaining in CCR in this study (CCR, 264/307, 86%; 10+,7N *v* non-10+,7N: OR, 0.27 [95% CI, 0.17 to 0.42]; $P = 8.02 \times 10^{-10}$) and the St Jude Total Therapy studies (CCR, 188/193, 97%; 10+,7N *v* non-10+,7N: OR, 0.22 [95% CI, 0.05

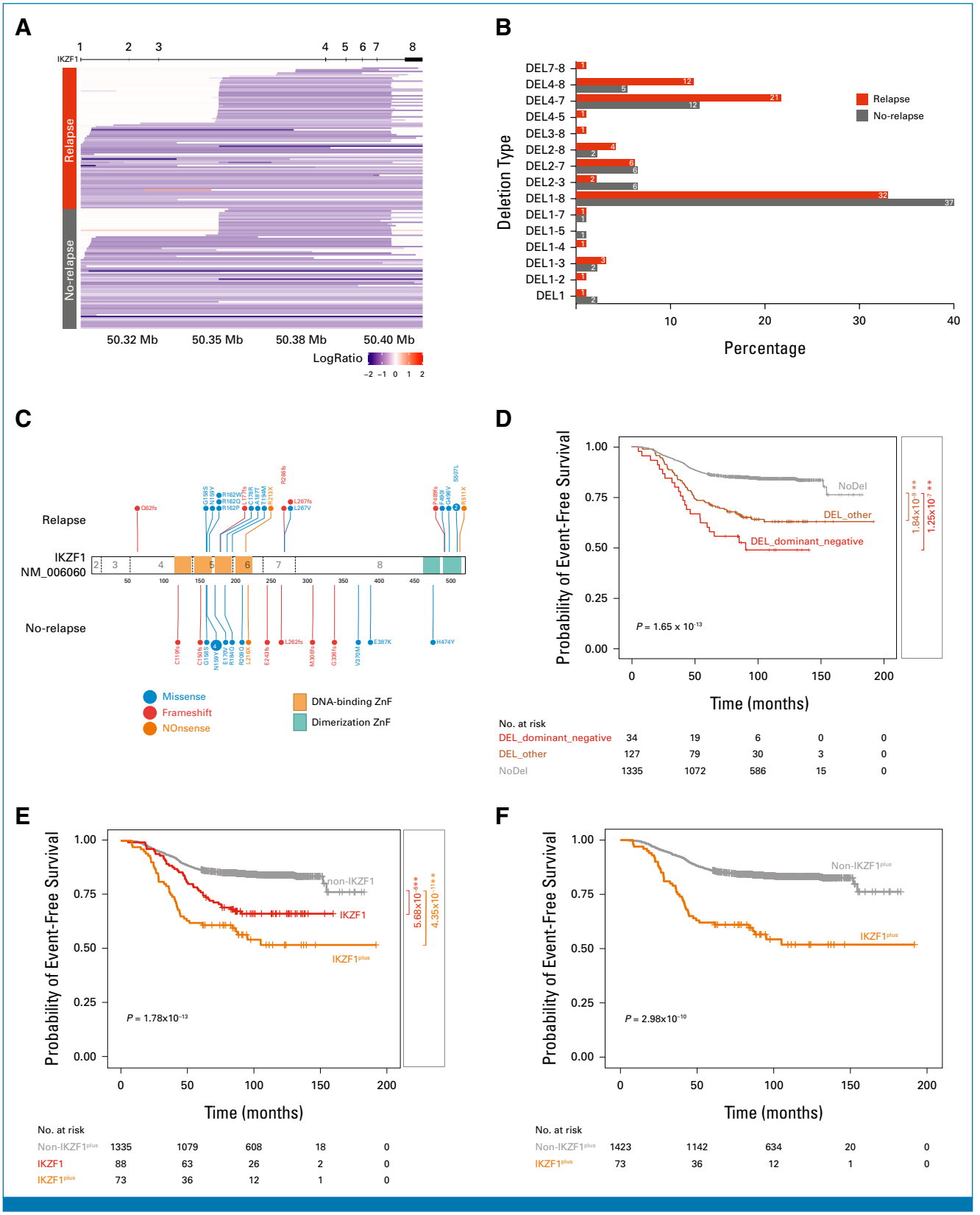

FIG 5. Specific structural somatic variants of *IKZF1* are enriched in patients who relapsed. (A) Regions of somatic deletion of *IKZF1* (blue lines) for each patient, ordered by relapse or no-relapse. Exons are shown on the top. (B) Percentage of samples with *IKZF1* deletions (DEL). Exon 4-7 and 4-8 deletions were enriched in the relapse samples. (C) Somatic IKZF1 (continued on following page)

FIG 5. (Continued). sequence variants in the MP2PRT group. (D) Weighted KM curves for groups classified on the basis of types of exon deletions in each sample. Samples with exon 4-5 or 4-7 deletions were classified as DEL_dominant_negative; samples with other deletions were classified as DEL_other. NoDel are samples without *IKZF1* deletions. The weighted Cox regression test results are shown on the right. (E, F) Weighted KM curves for MLPA-equivalent *IKZF1*^{plus}. **P < .01. MLPA, multiplex ligation probe amplification; MP2PRT, Molecular Profiling to Predict Responses to Therapy.

to 0.80]; P = .009; Figs 6B and 6C). By contrast, disomy of chromosomes 10 and 17 with trisomy of chromosome 6 was associated with increased risk of relapse (MP2PRT: 14 of 20 cases relapsed, OR, 7.16 [95% CI, 2.63 to 21.51]; $P = 2.19 \times 10^{-5}$; St Jude: 4 of 9 cases relapsed, OR, 21.32, [95% CI, 3.62 to 119.30]; P = .0004; Figs 6B and 6C).

Associations of *IKZF1* and *CREBBP* and relapse were evident in high-hyperdiploid ALL. Importantly, these associations remained significant even after stratifying cases according to aneuploidy patterns derived from the CART model (*IKZF1*: OR, 2.98 [95% CI, 1.71 to 5.20]; P = .00006; *CREBBP*: OR, 1.86 [95% CI, 1.12 to 3.08]; P = .012; Data Supplement, Table S21). Notably, these mutations were not significantly enriched in the highest risk strata (10+, 7+, 5+; or 10N, 17N, 6+), but were enriched in other clusters. *IKZF1* alterations were enriched in patients with 10+, 7+, 5N (OR, 34.2 [95% CI, 1.34 to 870.55]; P = .01; Data Supplement, Table S22), 10N, 17+ (OR, 6.17 [95% CI, 1.45 to 31.43]; P = .005), and 10N, 17N, 6N (OR, 4.79 [95% CI, 1.21 to 21.37]; P = .01; Data Supplement, Table S22). Thus, integrated profiling of aneuploidy and sequence mutations refines the risk classification of high-hyperdiploid ALL.

DISCUSSION

Accurately predicting outcome in children diagnosed with SR B-ALL or HR cases with favorable genetics is critical for tailoring treatment intensity to maximize cure and minimize toxicity. However, because of the lack of large studies of uniformly treated ALL analyzed with comprehensive genomic approaches, recent studies refining the genetic taxonomy of B-ALL have not adequately addressed this question. To address this gap, we conducted integrated genomic analysis on a large group of patients using a design that specifically enriched for relapsed cases. Our approach identified multiple genomic alterations associated with treatment outcome, including adverse genetic features in patients otherwise considered to be at very low risk of relapse.

A striking finding was the association of the PAX5alt group with treatment failure, accompanied by variability in the type of *PAX5* alterations and disease risk and outcome.[14] This subtype was common, comprising 7.7% of the group studied or 27.3% of MP2PRT cases/controls lacking hyperdiploidy or *ETV6::RUNX1*, and was strongly associated with poor outcome, with 49% of PAX5alt cases experiencing relapse. The *PAX5* driver alterations in this group differed from previous studies enriched for HR B-ALL, with *PAX5::ETV6* and PAX5 R38/R140 mutations absent in this group.[14] Moreover, we observed combinatorial effects of the type of *PAX5* alterations and outcome, indicating that different PAX5alt driver alterations influence disease biology and outcome, and that genotyping for PAX5alt-defining alterations should be used to refine risk stratification. For example, a child diagnosed with SR B-ALL that has PAX5alt, especially those with PAX5 amplification or biallelic alterations, may require treatment with either high-risk or novel therapies to maximize the chances of cure.

Although generally considered a highly favorable prognostic genetic driver, patients with *ETV6::RUNX1* B-ALL could be further categorized on the basis of translocation-associated alterations. Unbalanced translocations defined by gain of *RUNX1* or an additional copy of *ETV6::RUNX1* identified that a subset of patients were more likely to relapse after 40 months from diagnosis. We previously observed *INO80* alterations in *ETV6::RUNX1*-positive ALL,[16] but that study lacked power to assess associations with outcome in NCI SR patients. Here, we observed both deletions and sequence mutations of this gene predicted outcome. By contrast, patients with *TCF3::PBX1* had a more favorable outcome with an unbalanced t(1;19) than patients with *TCF3::PBX1* ALL and a balanced translocation. Although Down syndrome–associated ALL constituted a small proportion of cases, this group had a much higher incidence of relapse compared with the other common subtypes.

Additional associations of secondary genetic lesions with outcome were dependent on primary driver lesions. Indeed, the overall association of secondary lesions, when corrected for subtype, identified genotype-specific secondary events that may also contribute to improved risk stratification. Homozygous *CDKN2A/CDKN2B* deletion was associated with an increased risk of relapse but reduced risk of elevated EOI MRD, suggesting that patients with *CDKN2A/CDKN2B* deletion, who frequently harbor *PAX5* alterations, could be candidates for therapy intensification or novel approaches, independent of early response.

Given the heterogeneity of genomic alterations targeting *IKZF1*, smaller studies with fewer comprehensive genomic analyses were unable to identify prognostic subsets of ALL according to the type of *IKZF1* alteration.[29] Here, we show that deletions, primarily the exon 4-7 deletion encoding the IK6 isoform, and sequence mutations resulting in dominant-negative IKAROS activity have inferior outcome to others, consistent with mechanistic data.[30,31]

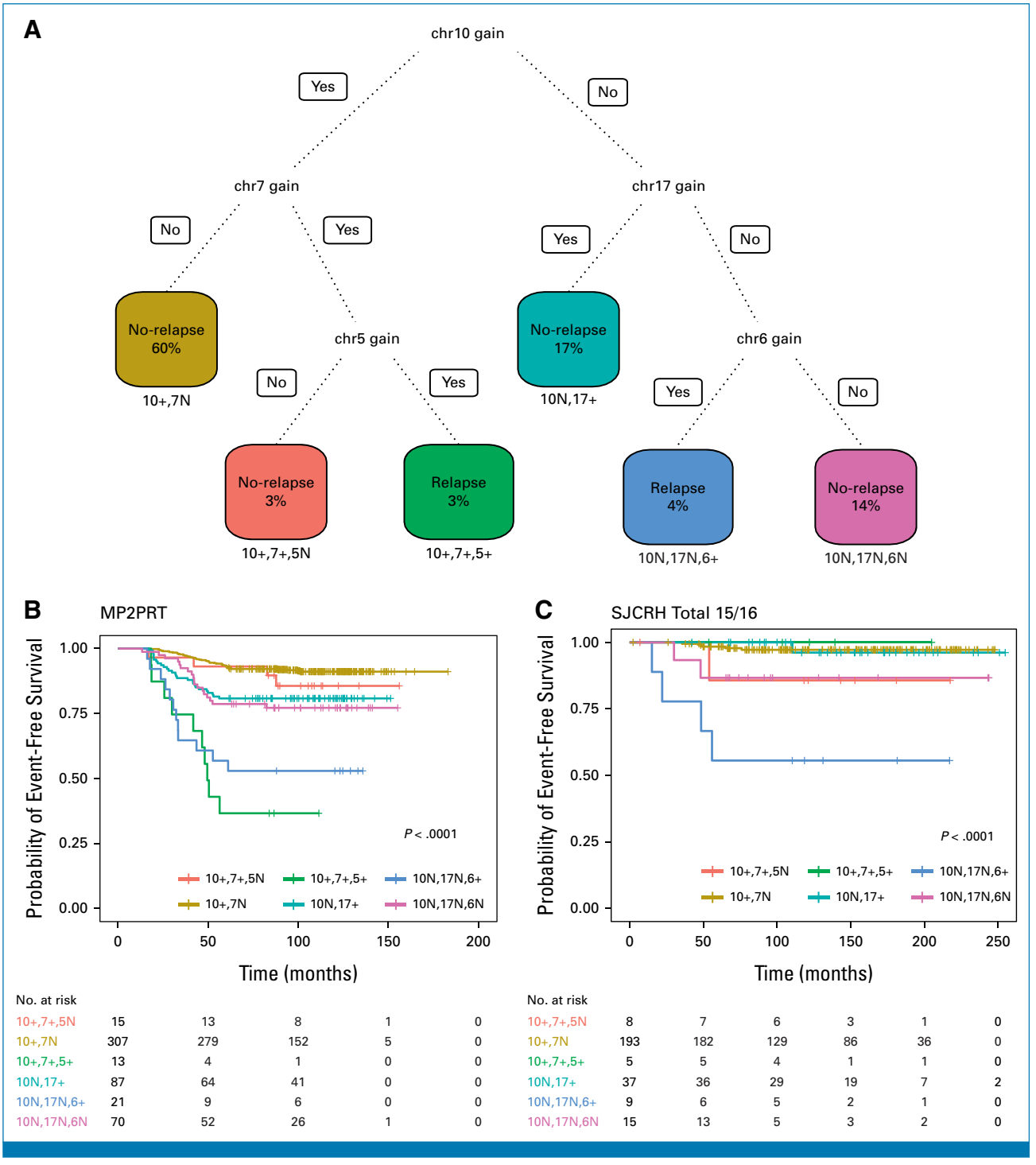

FIG 6. CART classification model using copy number changes to predict risk of relapse for hyperdiploid ALL. (A) CART classification model using copy number changes in hyperdiploid cases. The model was built on the basis of the sample relapse status. The percentage represents the fraction of hyperdiploid patients in each group. (B) Weighted KM curves for hyperdiploid samples in MP2PRT stratified by the classes determined in the CART model. Risk table is shown at the bottom. (C) Weighted KM curves for the hyperdiploid samples in the SJCRH Total 15/16 cohorts stratified by the classes determined by the CART model. Risk table is shown at the bottom. ALL, acute lymphoblastic leukemia; CART, classification and regression tree; MP2PRT, Molecular Profiling to Predict Responses to Therapy; SJCRH, St Jude Children's Research Hospital.

As therapeutic strategies become increasingly tailored to specific genotypic groups, we need to identify certain patients who display the most favorable genetic risk factors to deintensify cytotoxic chemotherapy.[32] Data from COG and other consortia from as early as the 1970s show that many patients may be cured with relatively low-dose systemic

therapy.[32] Refining current risk stratification approaches to identify patients currently considered SR that are curable with less intensive therapy or who require more intensive therapy for cure is a central goal of contemporary management of childhood ALL. Our results suggest several logical ways to achieve this goal: for example, patients with *ETV6::RUNX1* B-ALL could be stratified according to secondary alterations of *INO80D*, chromosome 11q deletions, or unbalanced *ETV6::RUNX1* alterations. Identification of the PAX5alt subtype is critical to accurately assign higher risk to this recently identified group of cases. Our results also indicate that identification of *IKZF1*^{plus} status is important for SR ALL across multiple subtypes and that specific patterns of aneuploidy and secondary mutations modulate risk of relapse in hyperdiploid ALL.

Although many consider childhood ALL a cured disease, we report a large, comprehensively analyzed predominantly NCI SR group enriched for relapse and have identified additional mutational events or patterns of aneuploidy that refine current risk predictors. Validation of these findings in future studies is warranted. As discussions about deintensification of therapy are underway, it is essential to comprehensively genotype newly diagnosed patients with SR ALL to accurately tailor the intensity of therapy to minimize the toxicity without increasing the risk of relapse.

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