Supplemental Methods

Analysis of germline predisposition in MNs

To delineate the landscape of germline predispositions in myeloid neoplasms (MNs), we performed whole-genome or targeted-capture sequencing of buccal smear samples derived from 1,039 Japanese patients with MNs as germline controls. We examined variants in 23 genes previously implicated in germline predispositions (*DDX41*, *CHEK2*, *TP53*, *GATA2*, *SBDS*, *RUNX1*, *SAMD9/SAMD9L*, *CEBPA*, *ETV6*, *ANKRD26*, *RB1*, *FANCL*, *FANCD2*, *FANCE*, *FANCG*, *FANCC*, *FANCF*, *FANCM*, *FANCI*, *FANCA*, *FANCB*, and *BRCA2*).[1] The detected variants were curated based on ACMG criteria as performed in the classification of *DDX41* variants **(Figure 1D–F; supplemental Figure 4)**. Then, we compared the frequencies of pathogenic/likely pathogenic germline variants in these genes.

Definition of *DDX41*-mutated and -wild-type (WT) subjects

Patients with pathogenic and likely pathogenic (P/LP) germline variants and/or somatic mutations in *DDX41* were defined as *DDX41*-mutated ones. Patients with neither of them were defined as wild-type (WT) ones.

Analysis of clonal dynamics during leukemic progression

For the analysis of clonal dynamics, serial samples before and after leukemic progression were available in 6 *DDX41*-mutated and 42 *DDX41*-WT MNs. Based on the changes of VAFs during leukemic progression, somatic mutations were classified as "newly acquired," "persistent with increased/decreased VAF," or "lost" and their proportions were compared across different categories of mutations ("Type-1," "Type-2," "*DDX41,"* and "Others") **(Figure 5C)**. The definitions of "Type-1" and "Type-2" mutations followed those in our previous publication[2].

Previous dataset of *DDX41*-mutated MNs

To delineate the regional distributions of *DDX41* variants, we collated in a meta-analysis ours and previously reported cases of *DDX41*-mutated myeloid neoplasms (MNs) **(Figure 4E)**[3-7].

Comparison of mutation frequencies

To reveal the co-mutation patterns of *DDX41*-mutated MNs, we compared the frequencies of other driver mutations between *DDX41*-mutated and -WT cases among treatment-naïve patients with MNs. Then, to reveal the mutations associated with disease progression, we compared the frequencies of driver mutations between lower-risk and higher-risk MDS, and between higher-risk MDS and sAML. These comparisons were performed within *DDX41*-mutated or -WT MNs **(Figure 5A, B; supplemental Figure 11, 12)**.

Frequencies of *DDX41* mutations in individual disease subtypes

In this study, MDS-RAEB was defined as higher-risk MDS, and the other MDS categories were included in lower-risk MDS. The category of secondary AML (n = 976 cases) included therapy-related AML (n = 43 cases; 4.4%). Scores of the revised/molecular International Prognostic Scoring System (IPSS-R/M) were calculated according to the previous publications[8,9]. Although all patients were classified as either AML, MDS, MDS/MPN, or MPN, the distinction between primary *vs.* secondary AML, and that between lower-risk *vs.* higher-risk MDS were impossible in 304 and 397 of the *DDX41*-WT cases, respectively, due to incomplete clinical data. Because excluding these cases might bias the frequencies of *DDX41* mutations in individual disease subtypes **(Figure 3A, 4A–C; supplemental Figure 6B)**, we performed multiple imputations combined with bootstrap resampling to estimate the frequencies of *DDX41* mutations and their confidence intervals, using the R package, "bootImpute" (https://cran.r-project.org/web/packages/bootImpute/index.html)[10]. Because we observed substantial differences in the frequencies of *DDX41* mutations between Asian and Caucasian populations, the imputations for diagnosis were performed within each population.

Survival analysis

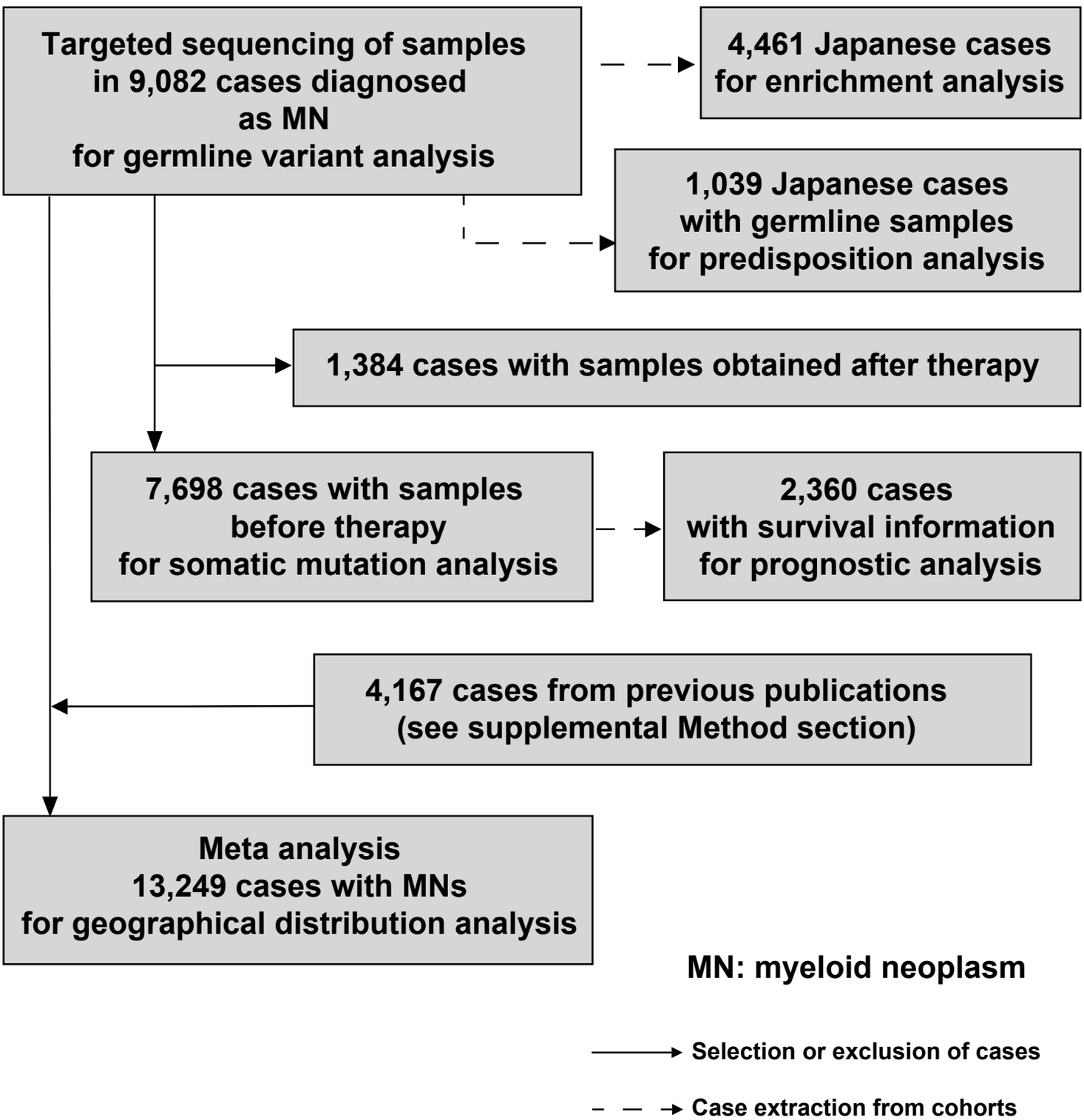
Selection of variables in multivariable analysis was performed according to *P* values ($<5.0\times10^{-2}$) **(supplemental**

Table 7). In the analysis of overall survival and leukemic progression, the observations were censored at hematopoietic stem-cell transplantation (HSCT), unless indicated otherwise **(Figure 6; supplemental Figure 15–17, 19, 20)**. For overall survival analysis in the cohort of patients who underwent HSCT, observations were not censored at HSCT **(supplemental Figure 18)**. We acknowledge the possibility that the smaller numbers of analyzed patients in the *DDX41*-mutant cohorts might result in negative findings when performing outcome analysis. To resolve this issue and avoid confounders, we selected *DDX41*-WT-patients with sample size adjusted to those of mutated cases. In addition, we randomly performed iterations (100 times) of such analyses **(supplemental Figure 15B–E)**. To resolve the same issue for high-risk mutations, we performed the same adjustment as above in the prognostic analyses for *TP53*-WT, single-hit, and multi-hit mutation stratification **(supplemental Figure 20A)**.

Supplemental References

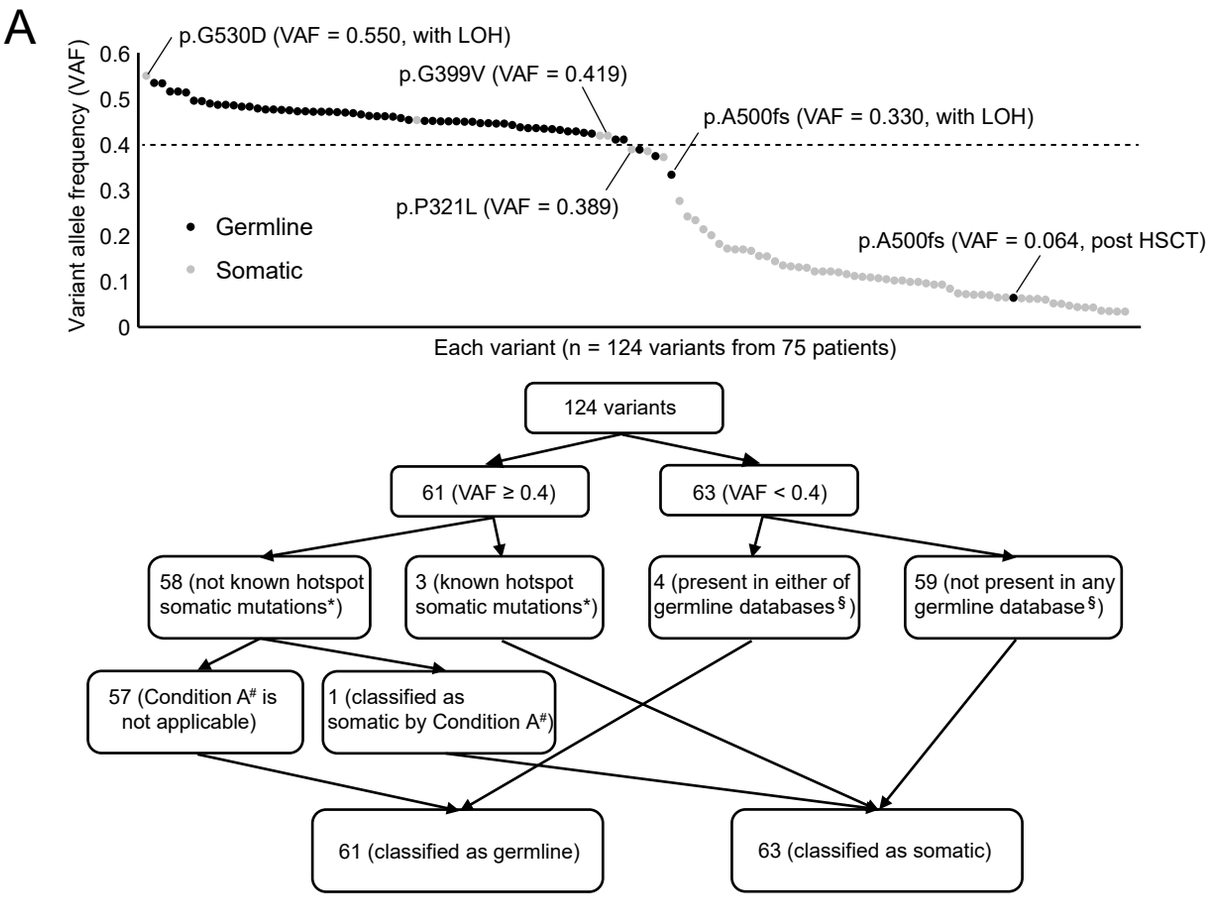
1. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood 2017;130:424-32.
2. Makishima H, Yoshizato T, Yoshida K, et al. Dynamics of clonal evolution in myelodysplastic syndromes. Nat Genet 2017;49:204-12.
3. Polprasert C, Schulze I, Sekeres MA, et al. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. Cancer Cell 2015;27:658-70.
4. Sebert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood 2019;134:1441-4.
5. Choi EJ, Cho YU, Hur EH, et al. Unique ethnic features of DDX41 mutations in patients with idiopathic cytopenia of undetermined significance, myelodysplastic syndrome, or acute myeloid leukemia. Haematologica 2022;107:510-8.
6. Lewinsohn M, Brown AL, Weinel LM, et al. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood 2016;127:1017-23.
7. Quesada AE, Routbort MJ, DiNardo CD, et al. DDX41 mutations in myeloid neoplasms are associated with male gender, TP53 mutations and high-risk disease. Am J Hematol 2019;94:757-66.
8. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120:2454-65.
9. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evid 2022;1.
10. Bartlett JW, Hughes RA. Bootstrap inference for multiple imputation under uncongeniality and misspecification. Stat Methods Med Res 2020;29:3533-46.

Supplemental Figure 1

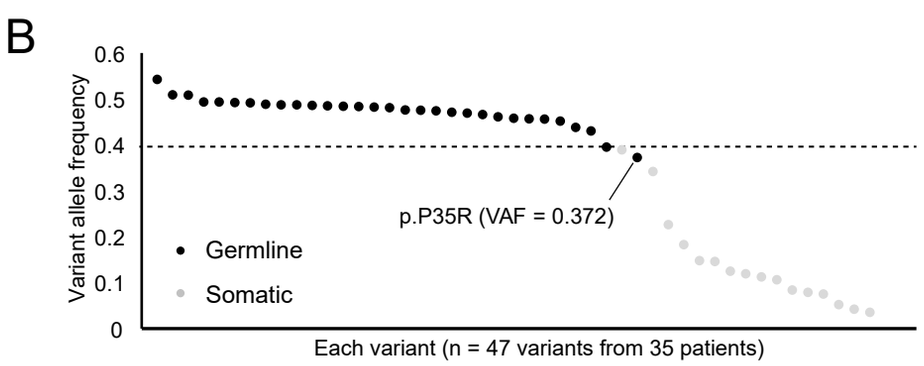


Supplemental Figure 1. Study design, cases numbers, and the corresponding analyses.
A flow diagram shows cohort information on availability of clinical parameters and selection of the cases for each analysis.

Supplemental Figure 2



Condition A: If two variants are classified as germline in a sample, further validation with germline control samples or serial samples is required. *p.R525H, p.G530D, and p.G530S, § gnomAD database (v. 2.1.1) downloaded for *DDX41* on 4/30/2020, and germline variants previously confirmed by inhouse germline samples (p.P35R, p.S363del, p.V445del, and p.L553del).

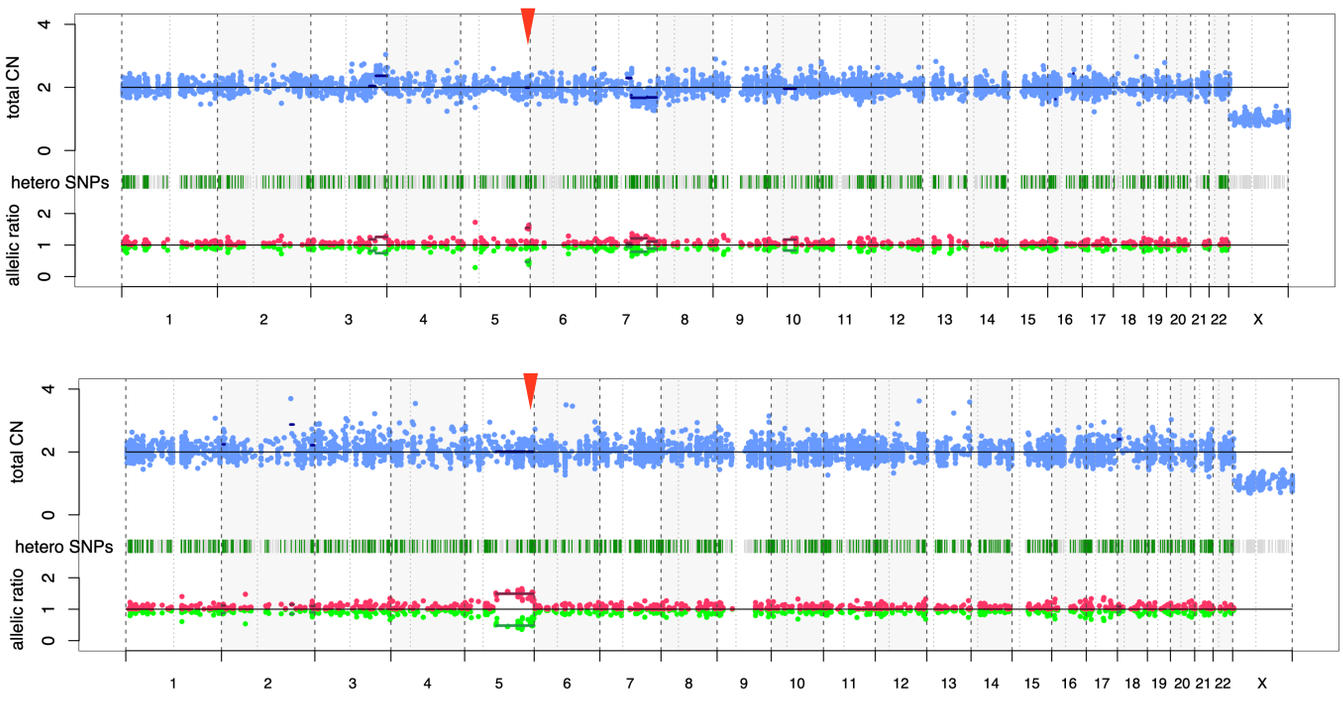


		Confirmation#	
		Germline	**Somatic**
Prediction**	**Germline**	**31**	**0**
	Somatic	**0**	**16**

** Germline and somatic origins are predicted according to the criteria establised in the panel **A**.
# Germline and somatic origins are confirmed using germline control samples.

Supplemental Figure 2. Criteria for discriminating germline and somatic *DDX41* variants.
A The criteria used for classifying *DDX41* variants into germline and somatic variants was established based on the confirmed germline and somatic variants in training samples. **B** The criteria established in the training set (**A**) was validated in independent validation samples. VAF; Variant allele frequency, LOH; loss of heterozygosity, HSCT; hematopoietic stem cell transplantation.

Supplemental Figure 3



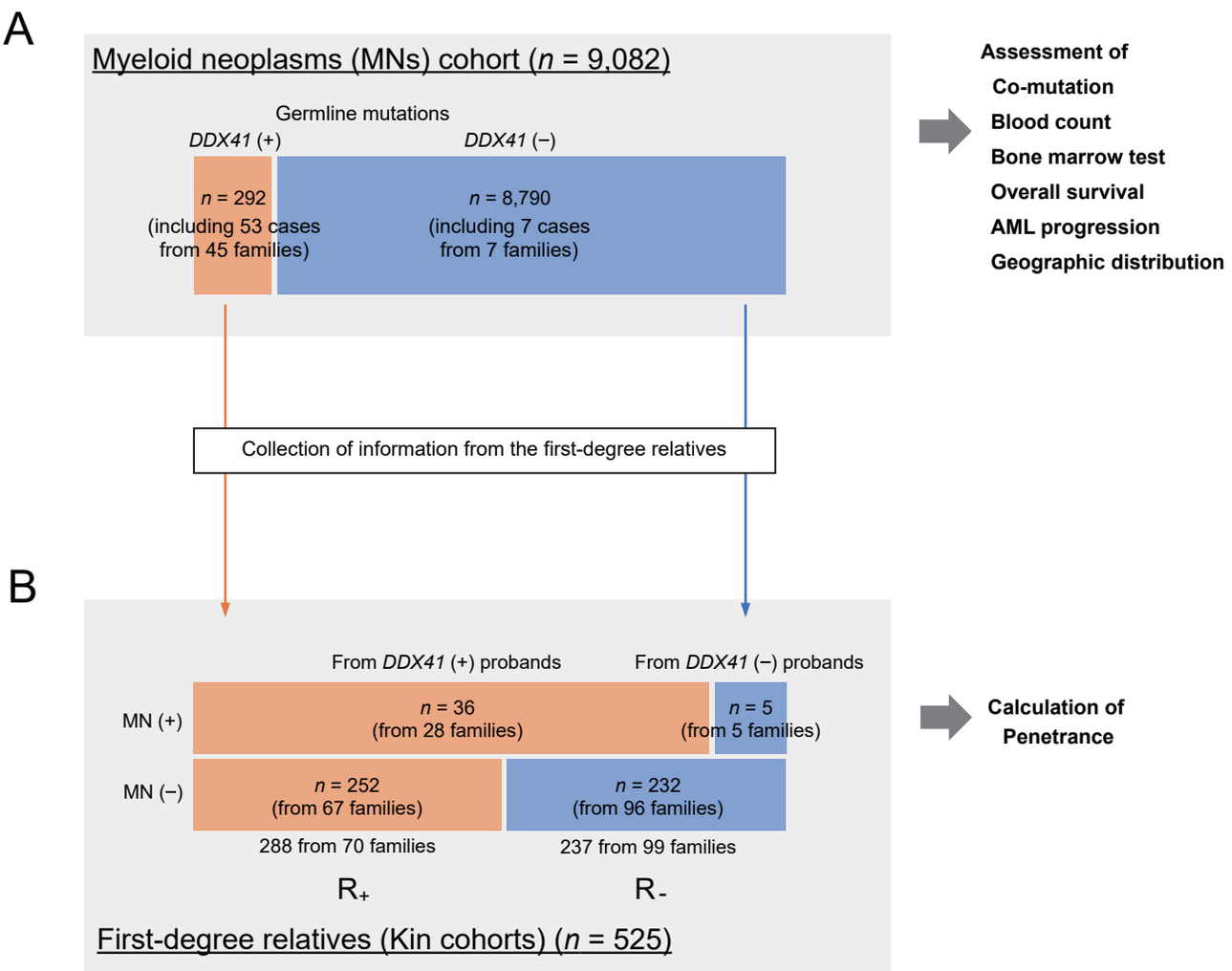
Supplemental Figure 3. Uniparental disomy at the *DDX41* locus.
Copy-number profiles assessed by the sequence-based CNACS algorithm (Yoshizato *et al. Blood* 2017) in representative cases with somatic *DDX41* mutations and 5q uni-parental disomy (Red triangles). Blue dots indicate total copy numbers (total CN), while red and green ones indicate allele-specific copy numbers on heterozygous single nucleotide polymorphisms (SNPs).

Supplemental Figure 4

Gene	MDS (n =430)	AML (n =409)	MDS/MPN (n =45)	MPN (n =155)	Total (n =1,039)
DDX41	21	14	1	0	36
TP53	2	1	0	0	3
SBDS	0	2	0	0	2
GATA2	2	0	0	0	2
RUNX1	0	1	0	0	1
CHEK2	1	0	0	0	1
SAMD9	0	0	0	0	0
SAMD9L	0	0	0	0	0
CEBPA	0	0	0	0	0
ETV6	0	0	0	0	0
ANKRD26	0	0	0	0	0
RB1	0	0	0	0	0
FANCL	0	0	0	0	0
FANCD2	0	0	0	0	0
FANCE	0	0	0	0	0
FANCG	0	0	0	0	0
FANCC	0	0	0	0	0
FANCF	0	0	0	0	0
FANCM	0	0	0	0	0
FANCI	0	0	0	0	0
FANCA	0	0	0	0	0
FANCB	0	0	0	0	0
BRCA2	0	0	0	0	0

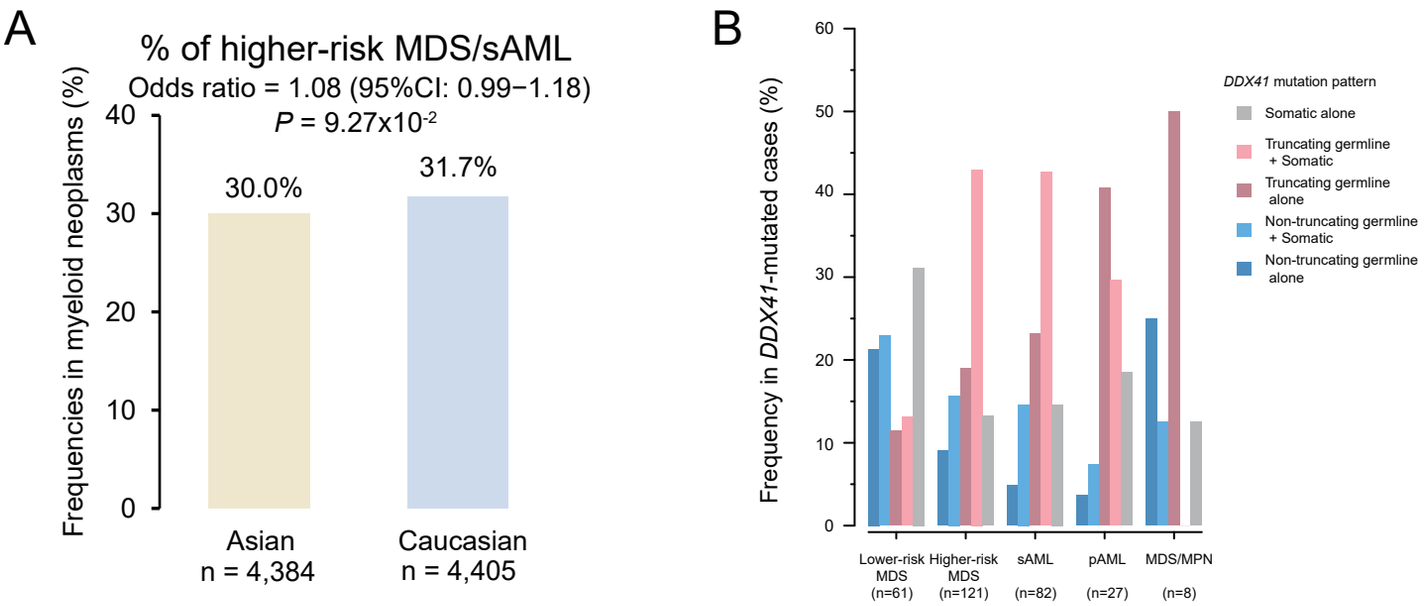
Supplemental Figure 4. Germline predisposition in Japanese cases with MNs.
Frequencies of pathogenic variants in 23 genes previously implicated in germline predisposition of MNs (also shown in **Figure 1E**). In the underlined genes, only homozygous/compound heterozygous cases were counted.

Supplemental Figure 5



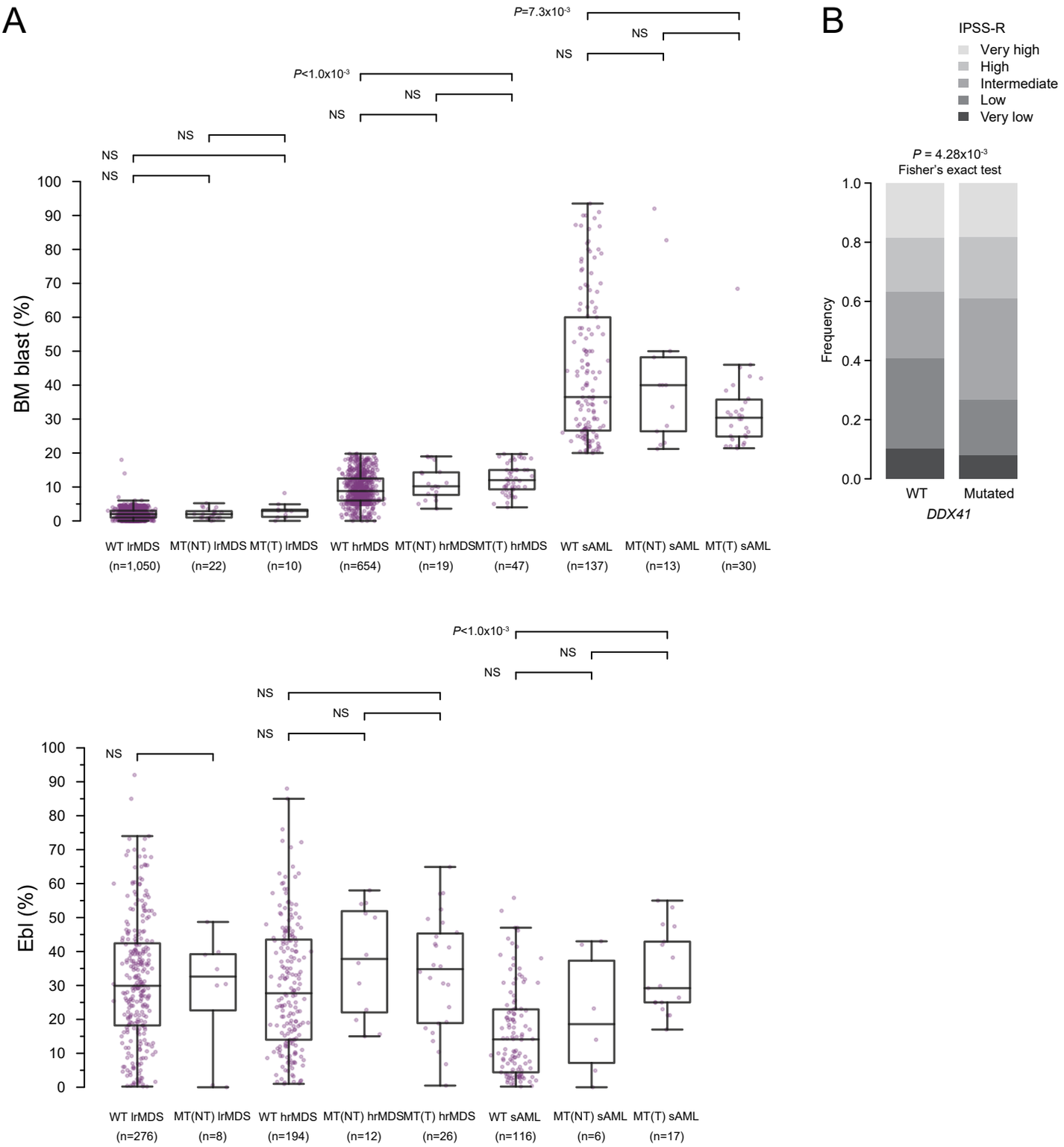
Supplemental Figure 5. Family history and genotype in patients and their first-degree relatives enrolled in this study.
Cases with myeloid neoplasms (MNs) (**A**: MNs cohort) were analyzed for assessment of various genetic and clinical parameters as indicated. After MN cases were subdivided into those with (orange) and without (blue) germline *DDX41* mutations, information related to ages at disease onset and death was collected from their first-degree relatives (parents, siblings, and children) (**B**: Kin cohorts). The kin cohorts were used for calculating the cumulative incidence of disease (R) in the first-degree relatives of MN cases with (R_+) and without (R_-) germline *DDX41* mutations. Penetrance was calculated by $2R_+ - R_-$ as previously reported (Struewing *et al. N Eng J Med* 1997).

Supplemental Figure 6



Supplemental Figure 6. Frequency of *DDX41*-associated-disease phenotypes and disease-specific frequencies of *DDX41* variants.
A Similar frequencies of most prevalent disease subtypes associated with *DDX41* mutations (higher-risk MDS and sAML) between Asian and Caucasian patients enrolled in this study. **B** Frequencies of cases with various allelic status of *DDX41* mutations in each disease subtype.

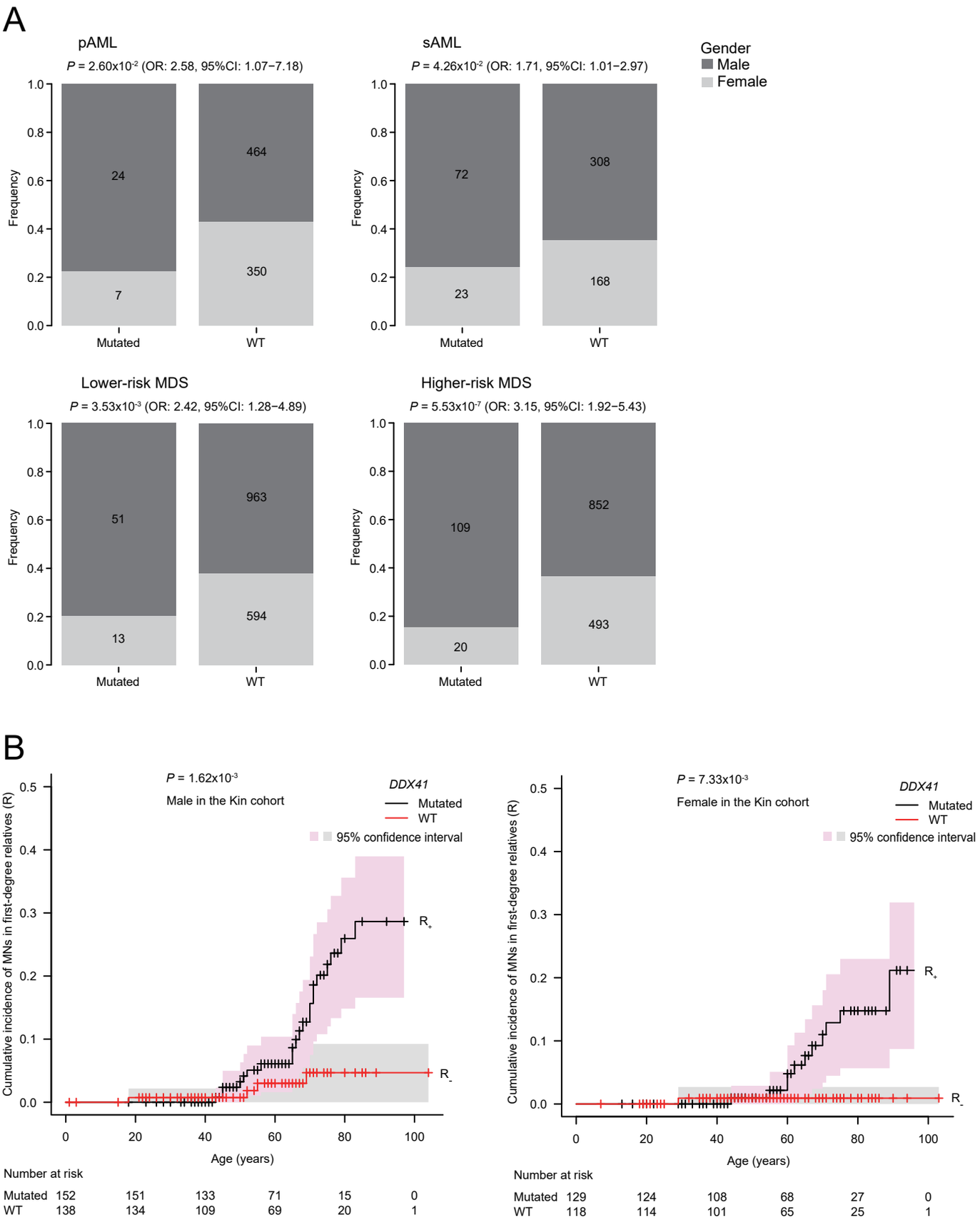
Supplemental Figure 7



Supplemental Figure 7. Bone marrow cell counts of MN patients depending on the type and state of *DDX41* alleles, and IPSS-R in *DDX41*-WT and mutated patients.

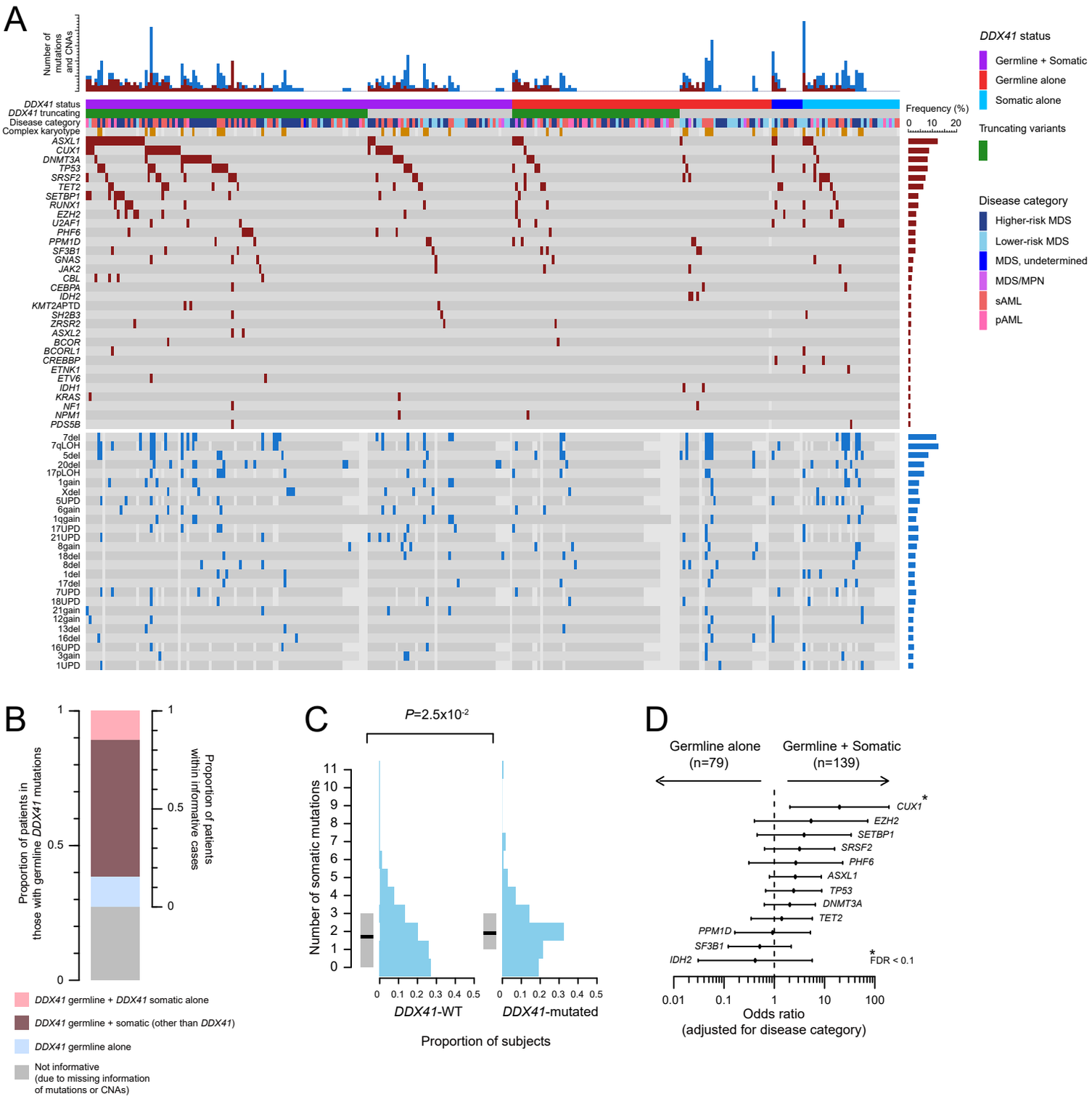
A Percentages of bone marrow (BM) blasts (Upper panel) and erythroblasts (Ebl) (Lower panel) were compared among patients with wild-type (WT) *DDX41*, and non-truncating (NT) and truncating (T) *DDX41* mutations (MT) in the disease subtypes as indicated: lower-risk (lr) MDS, higher-risk (hr) MDS, and secondary (s) AML. **B** Ratio of *DDX41*-unmutated and mutated patients with categories of the Revised international prognostic scoring system (IPSS-R). NS, not significant.

Supplemental Figure 8



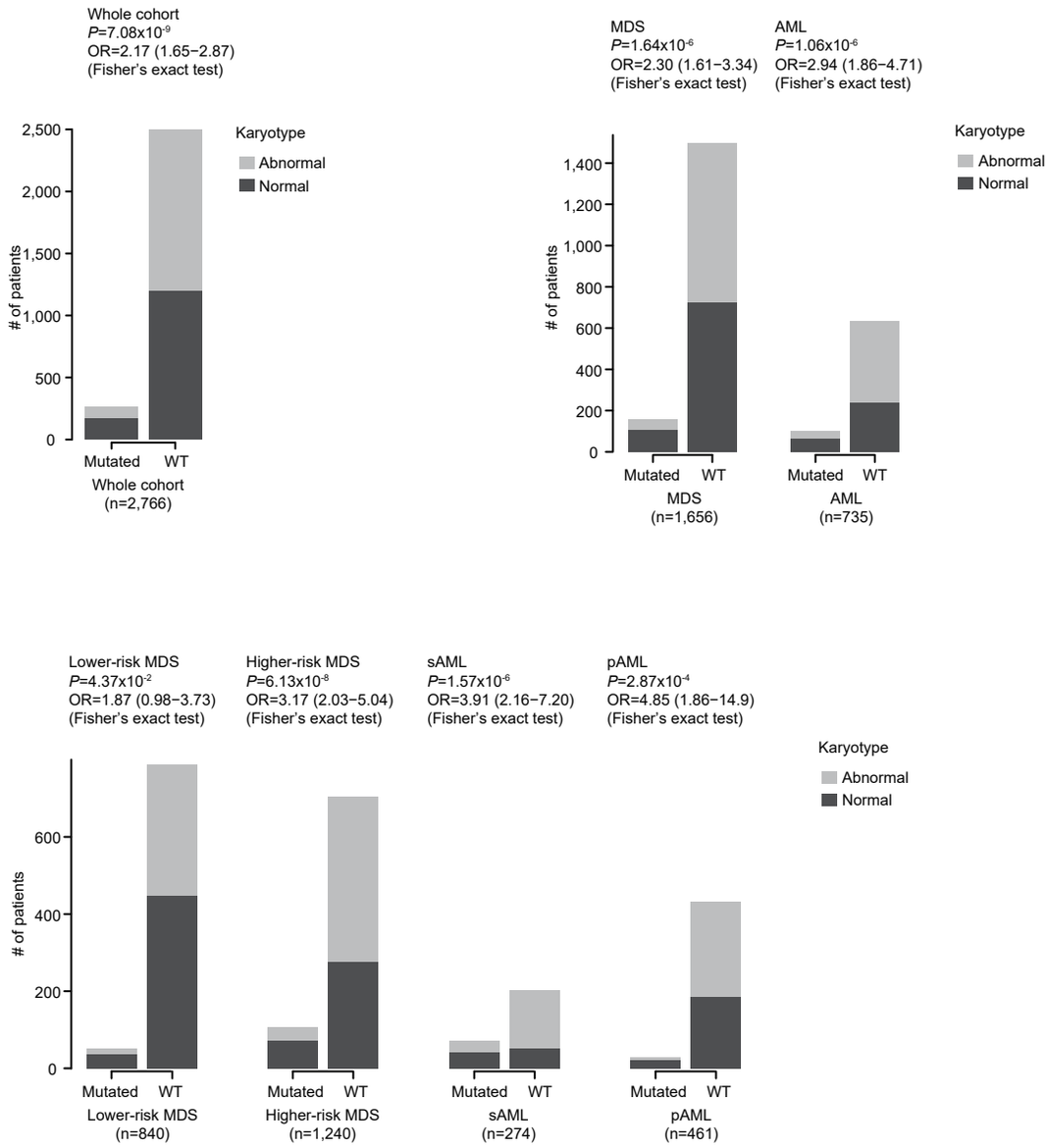
Supplemental Figure 8. Male dominancy in *DDX41*-mutated patients.
A Odds ratios of male *vs.* female patients between *DDX41*-mutated and wild-type (WT) patients and corresponding *P* values were calcurated by Fisher's exact test in each disease subtype. **B** Cumulative incidence of myeloid neoplasms (MNs) calculated by Fine-Gray test of ages at disease onset and death in the first-degree relatives of MN cases with (red) or without (black) P/LP germline *DDX41* variants (Left; male, Right; female).

Supplemental Figure 9



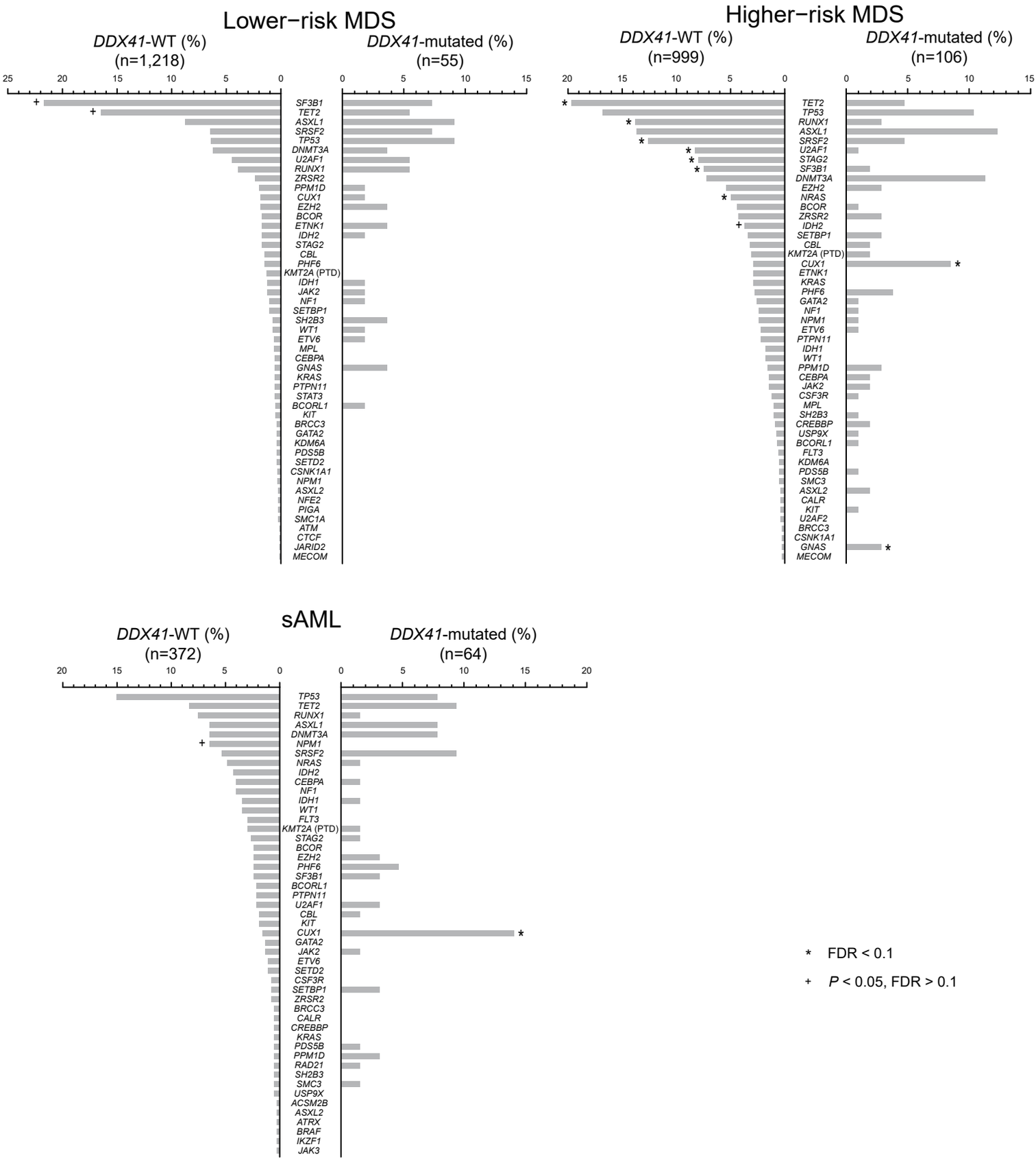
Supplemental Figure 9. Landscape of somatic alterations in *DDX41*-mutated patients.
A Profiles of somatic mutations and copy number alterations (CNAs) in *DDX41*-mutated myeloid neoplasms (MNs) (n=294). Cases are ordered according to *DDX41* mutation status and disease categories as indicated by colors. Somatic mutations and CNAs are shown in dark red and blue, respectively. Dark and light grays indicate negative results for somatic mutations/CNAs and uninformative results, respectively. The top bar plot shows the number of somatic mutations and CNAs in each case. The right-sided bars demonstrate frequencies of mutations and CNAs for each genetic alteration. **B** Among MN patients with germline *DDX41* variants, proportions of those with somatic *DDX41* mutations, with somatic driver mutations in the genes other than *DDX41*, and without any somatic driver mutations are shown. **C** Distributions of the number of somatic driver mutations in *DDX41*-mutated and -WT MNs. Somatic *DDX41* mutations are included in the analysis as driver mutations. Black bars indicate the mean number of somatic mutations. Gray rectangles show the intervals between the 1st and 3rd quantiles. Statistical significance was tested by two-sided Wilcoxon test. **D** Comparison of frequencies of mutations between MNs with *DDX41* germline and somatic mutations and those with germline mutation(s) alone. Odds ratios were calculated in multivariate logistic regressions adjusted for disease categories. Error bars indicate 95% confidence intervals. Statistical significance was examined by two-sided Wald test.

Supplemental Figure 10



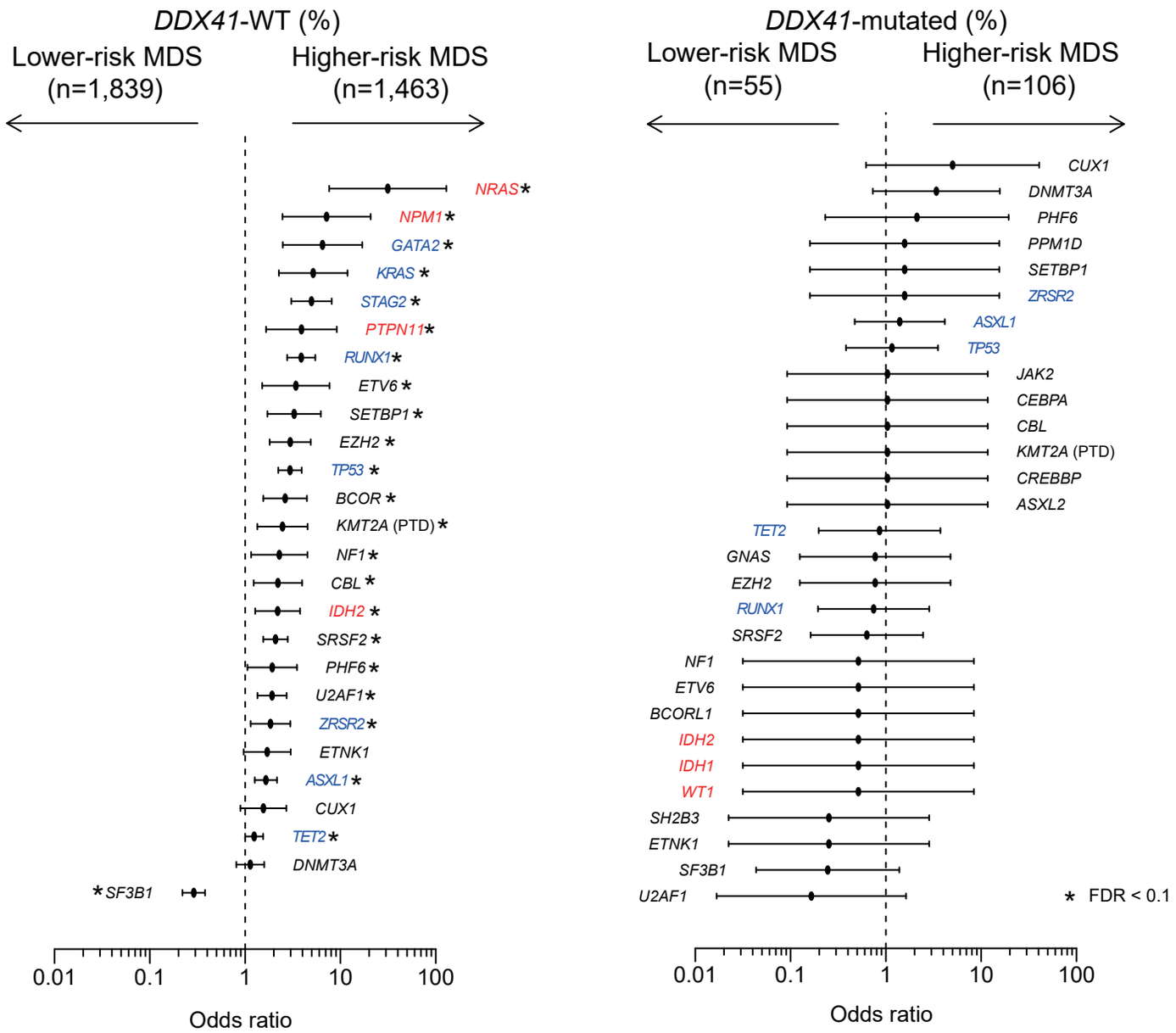
Supplemental Figure 10. Freuent normal karyotype in *DDX41*-mutated patients.
Odds ratios of normal *vs.* abnormal karyotypes between *DDX41*-mutated and wild-type (WT) patients and corresponding *P* values were calcurated by Fisher's exact test in each disease subtype.

Supplemental Figure 11



Supplemental Figure 11. Co-mutations in *DDX41*-mutated patients.
Comparison of mutation frequencies between *DDX41*-mutated or -WT cases in lower-risk MDS, higher-risk MDS, and sAML. Statistical significance was examined by two-sided Fisher exact test. False discovery rates (FDR) were calculated by Benjamini & Hochberg methods.

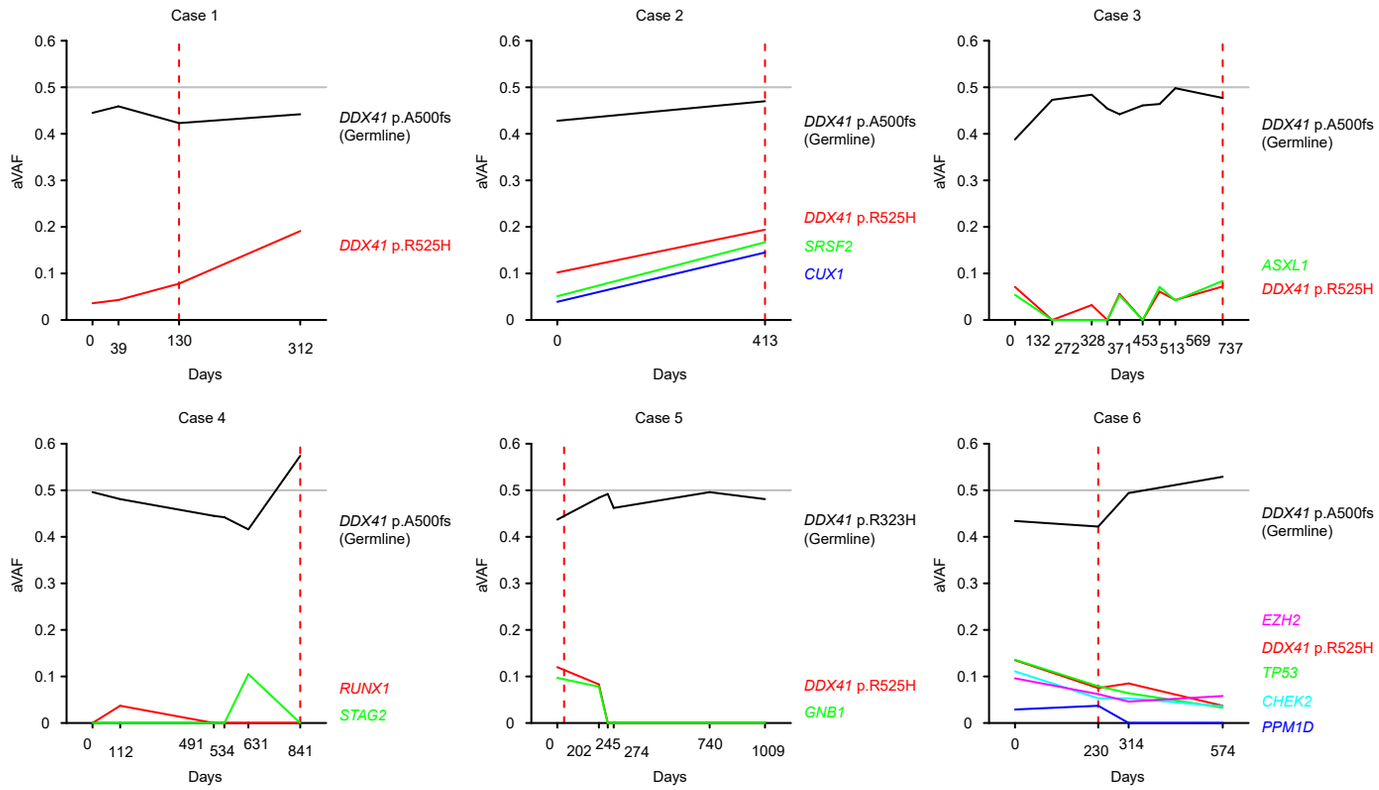
Supplemental Figure 12



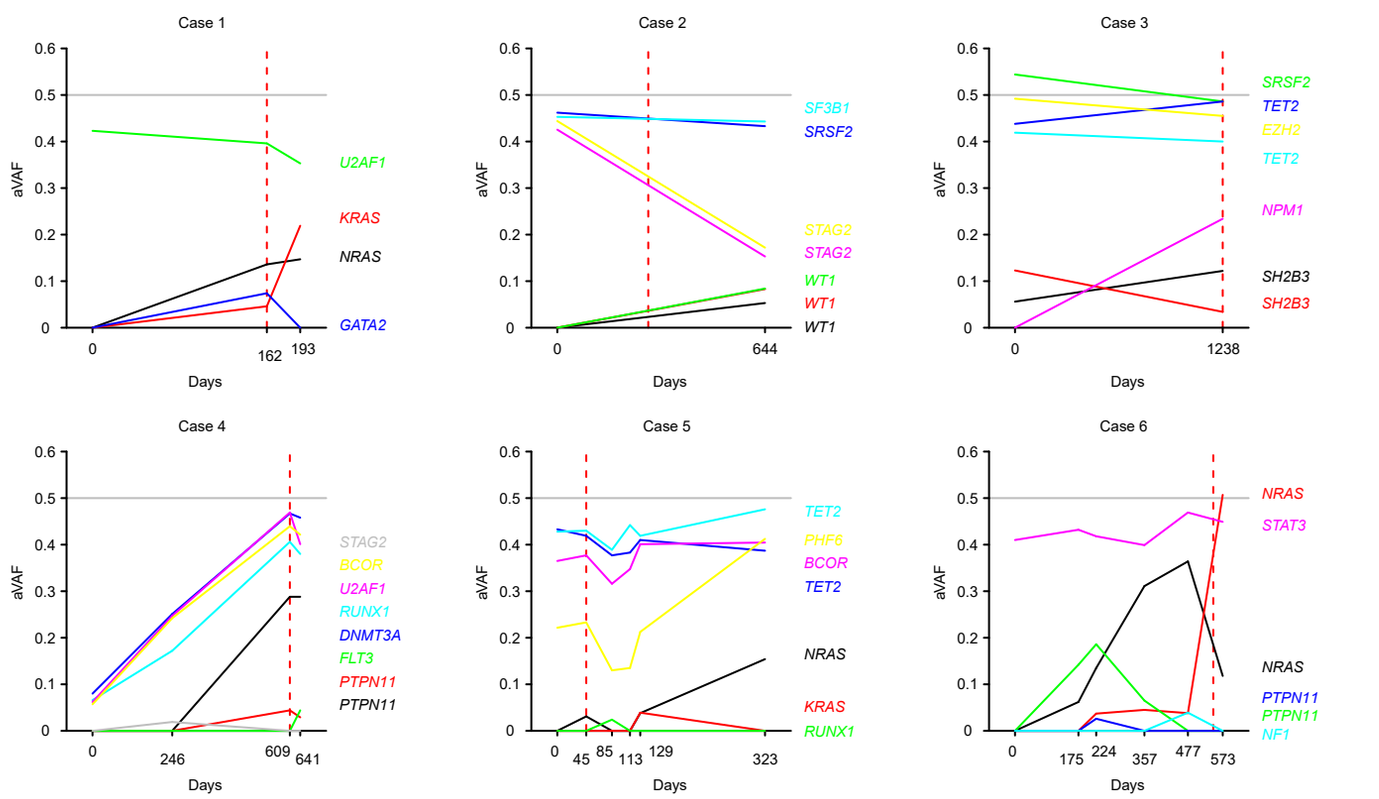
Supplemental Figure 12. Comparison of mutation frequencies between lower-risk and higher-risk MDS.
The frequencies of driver mutations were compared between lower-risk MDS and higher-risk MDS. Odds ratios in *DDX41*-mutated and -WT cases are shown separately, and error bars indicate 95% confidence intervals. Type-1 (*FLT3*, *NRAS*, *WT1*, *NPM1*, *IDH1*, *IDH2*, and *PTPN11*) and Type-2 (*GATA2*, *KRAS*, *TP53*, *RUNX1*, *STAG2*, *ASXL1*, *ZRSR2*, and *TET2*) genes, as defined according to the previous publication (Makishima *et al. Nat Genet* 2017), are indicated by red and blue characters, respectively.

Supplemental Figure 13

DDX41-mutated cases

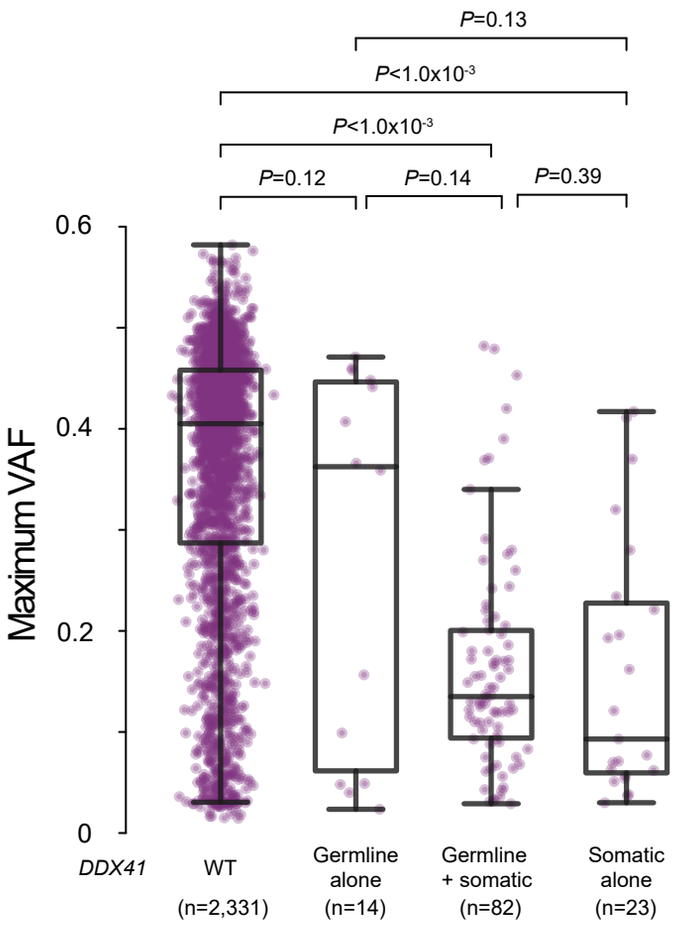


DDX41-WT cases



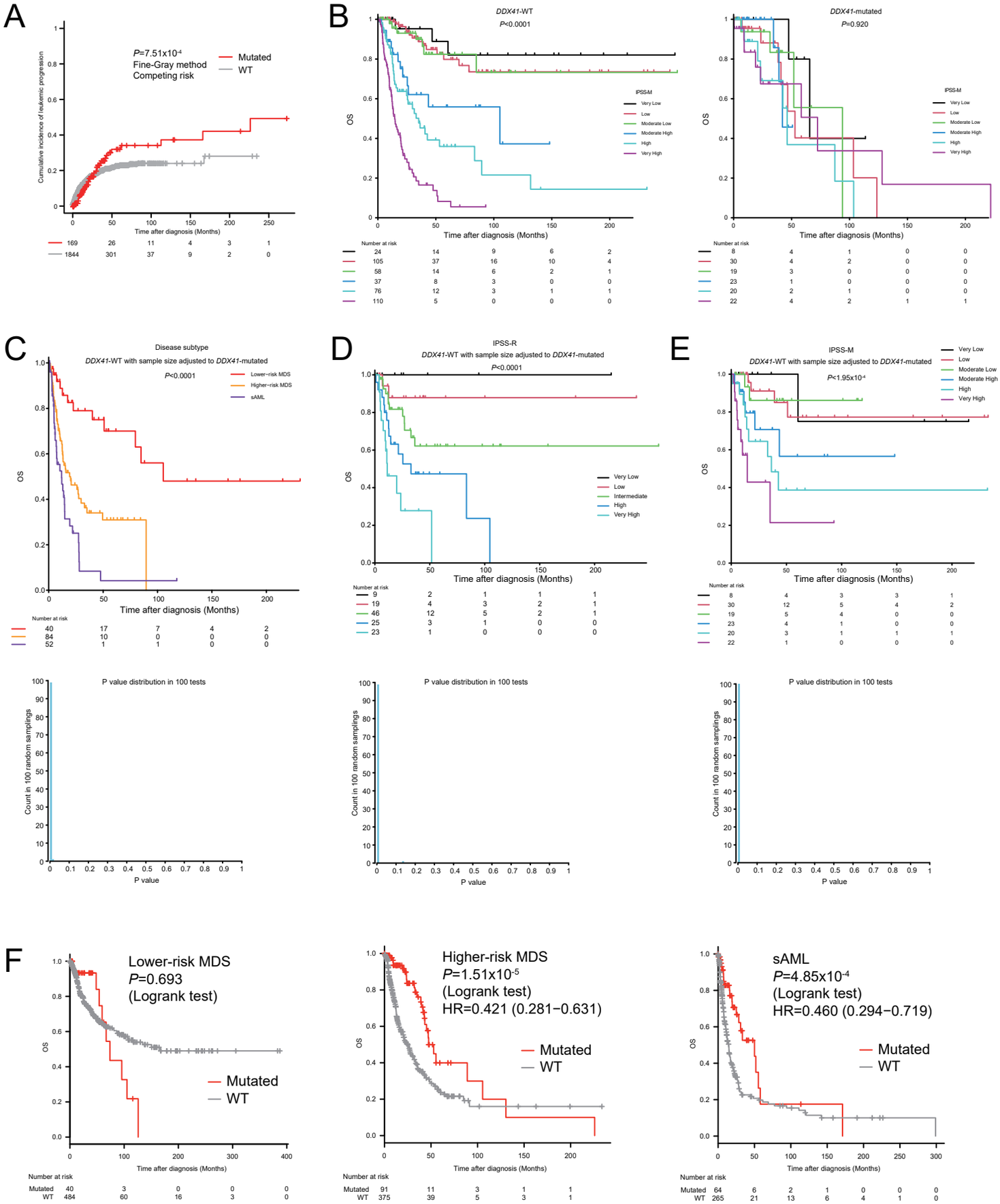
Supplemental Figure 13. Clonal dynamics during leukemic progression in *DDX41*-mutated and -WT patients.
Transition of adjusted variant allelic frequencies (aVAFs) of somatic mutations during leukemic progressions in 6 *DDX41*-mutated and 6 -WT MNs are shown. aVAFs of P/LP germline *DDX41* variants are also shown in black. The times of leukemic progressions are indicated by red dashed lines.

Supplemental Figure 14



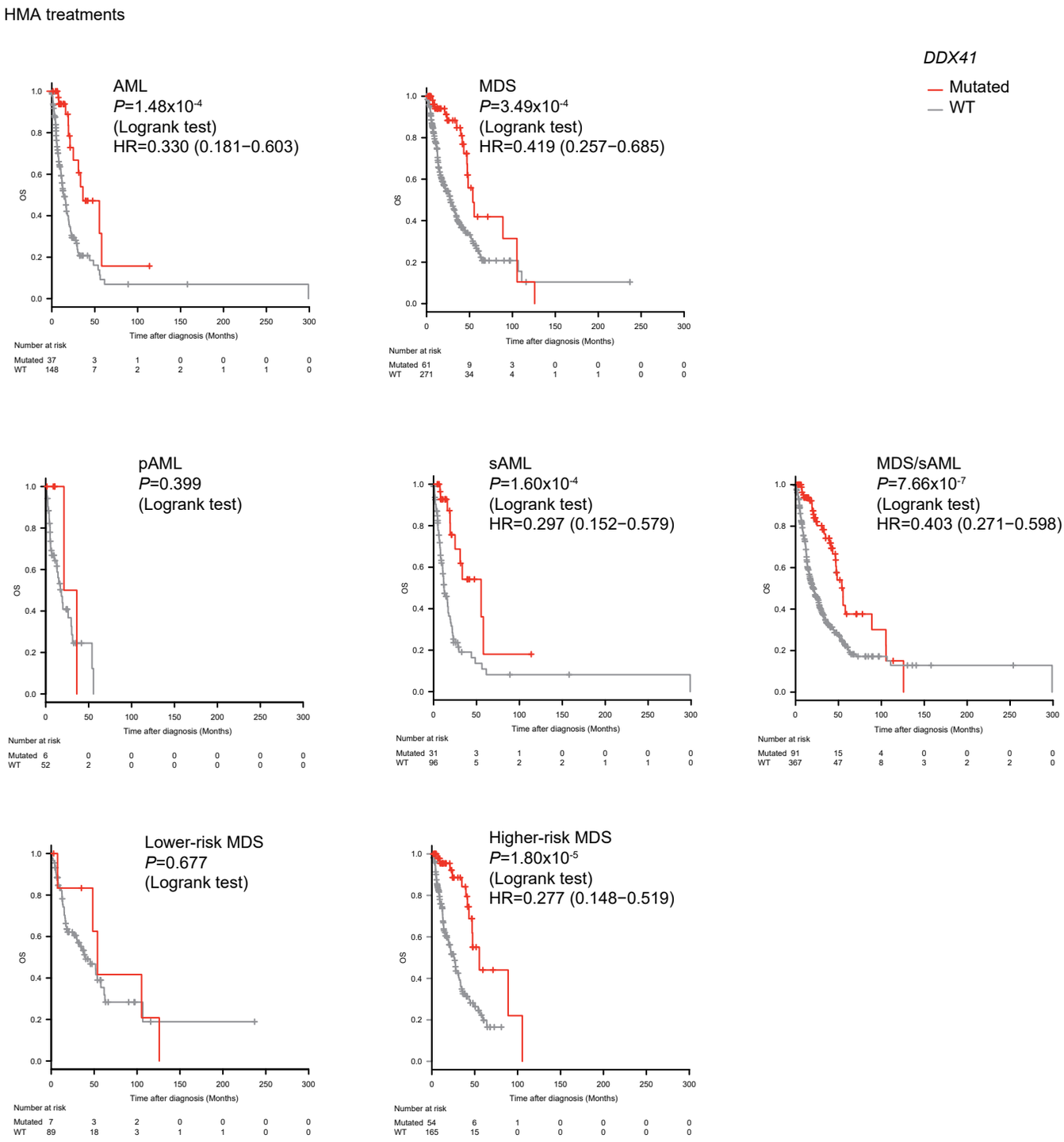
Supplemental Figure 14. Distributions of maximum variant allele frequency of somatic mutations.
Maximum VAF values for individual patients (adjusted by CNAs) of somatic mutations in driver genes including *DDX41* are shown. Box plots indicate the median, first, and third quartiles (Q1 and Q3) and whiskers extend to the furthest value between Q1 – 1.5 × the interquartile range (IQR) and Q3 + 1.5 × IQR. Purple dots represent individual patients. Differences between groups (*DDX41* WT, germline mutation alone, germline and somatic mutations (two-hit), and somatic mutation(s) alone) were examined by two-sided Wilcoxon test. *P* values were not adjuested for multiple testing.

Supplemental Figure 15



Supplemental Figure 15. Impacts of *DDX41* mutations on leukemic evolution and overall survival (OS).
A Cumulative incidence of leukemic progression in *DDX41*-mutated and -unmutated myeloid neoplasms (MNs) was estimated by Fine-Gray method with non-leukemic death as a competing risk. **B** Kaplan-Meier curves of overall survivals (OS) for *DDX41*-mutated or -WT MNs were shown in each IPSS-M category. **C−E** Kaplan-Meier curves of OS for randomely selected WT MNs with adjusted sample size to mutated ones (upper panels) and the distribution of P-values calculated by logrank tests of the adjusted WT MNs randomely selected 100 times (lower panels). **C, D, E** show the results of analysis for disease subtype, IPSS-R, and IPSS-M, respectively. **F** Kaplan-Meier curves of OS for *DDX41*-mutated or -WT MNs were shown in each disease subtype. Statistical significance was tested by two-sided Log-rank test. The observations were censored at hematopoietic stem-cell transplantation.

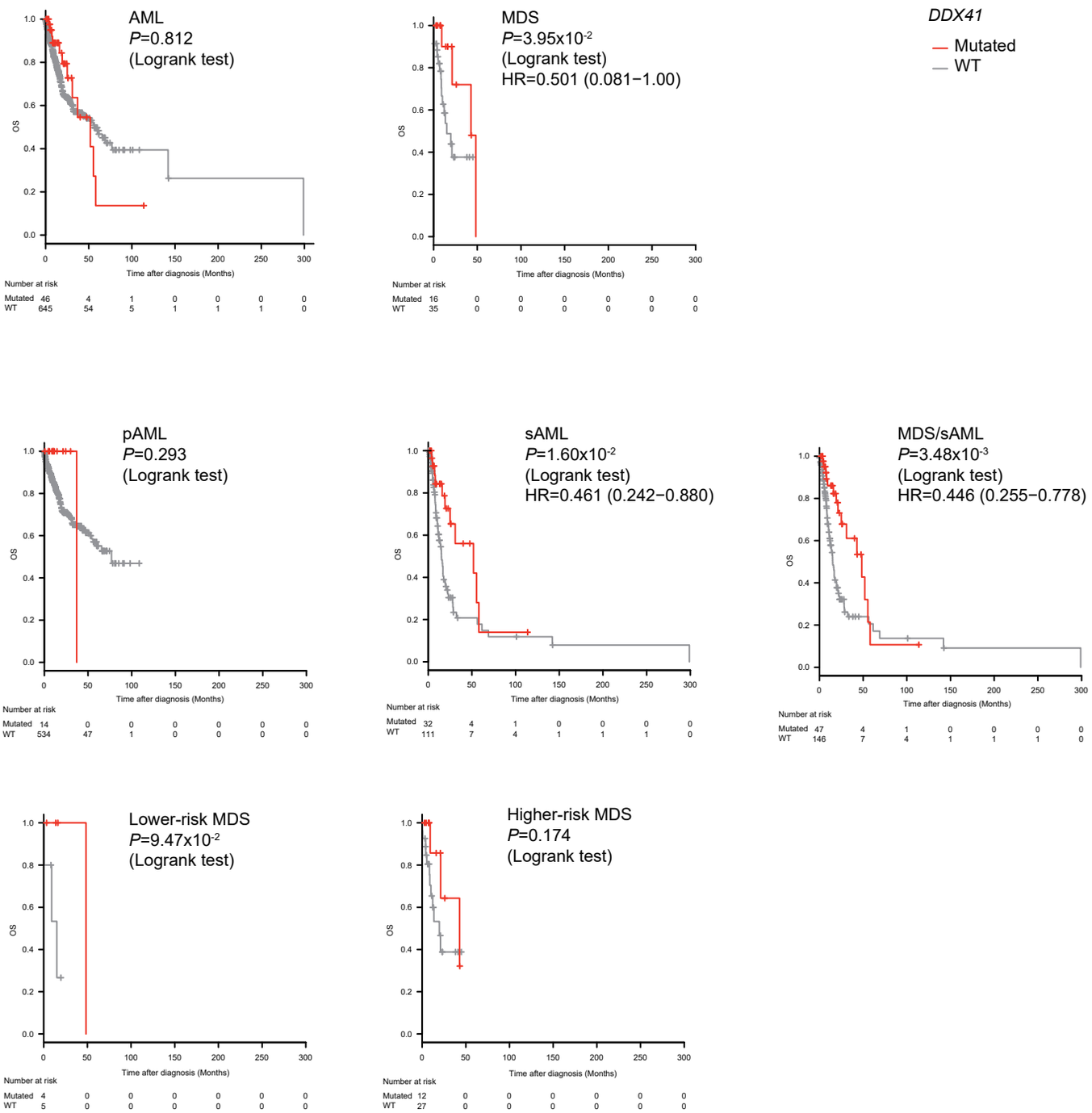
Supplemental Figure 16



Supplemental Figure 16. Prognostic impacts of *DDX41* mutations in the cohort with hypomethylating agent (HMA) treatment. Kaplan-Meier curves of overall survivals (OS) for *DDX41*-mutated or -WT myeloid neoplasms (MNs) with hypomethylating agent (HMA) treatment were shown in each disease subtype. Statistical significance was tested by two-sided Log-rank test. Hazard ratios and 95% confidence intervals were calculated by Cox proportional hazard regression. The observations were censored at hematopoietic stem-cell transplantation.

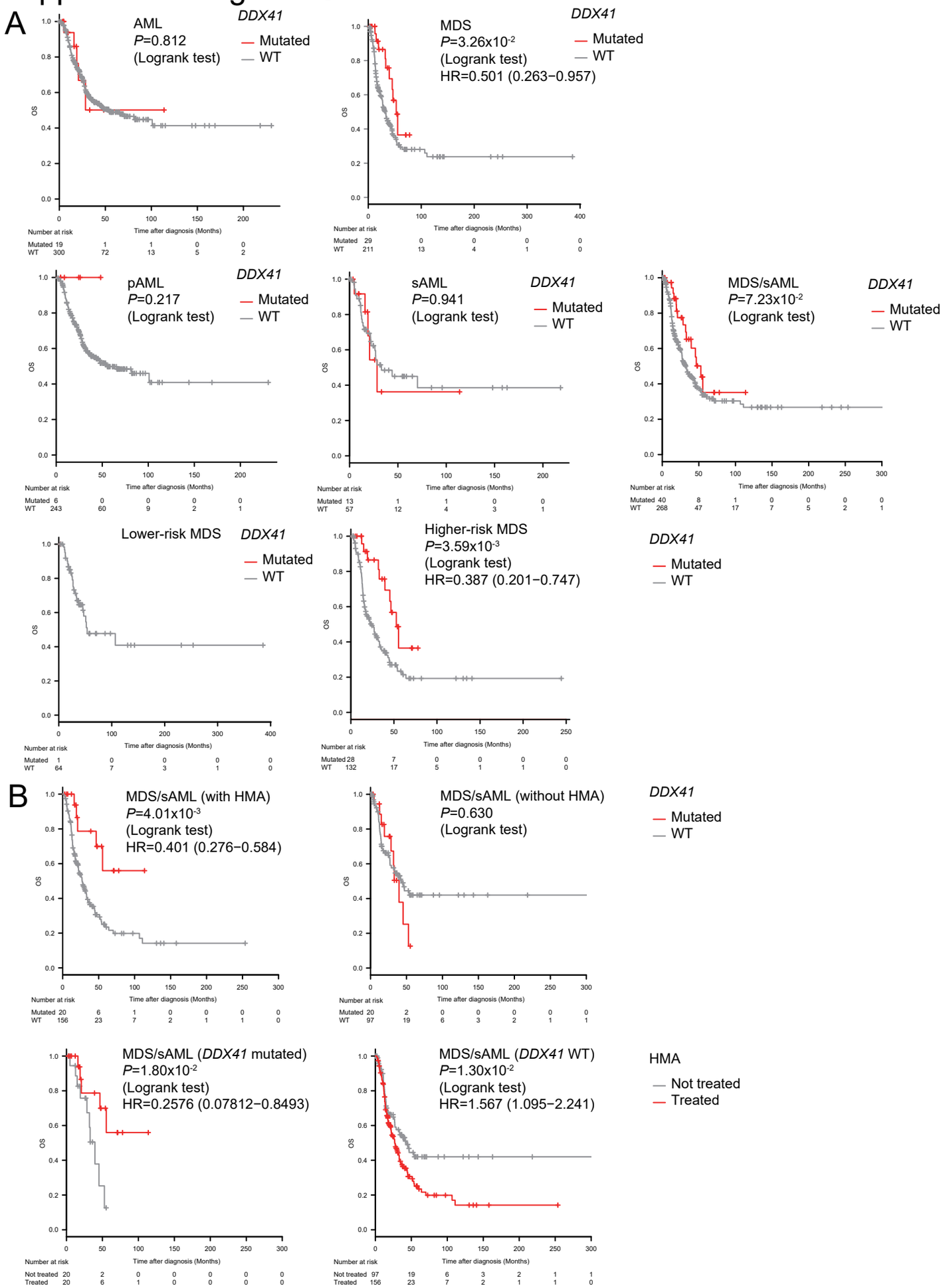
Supplemental Figure 17

Chemotherapy



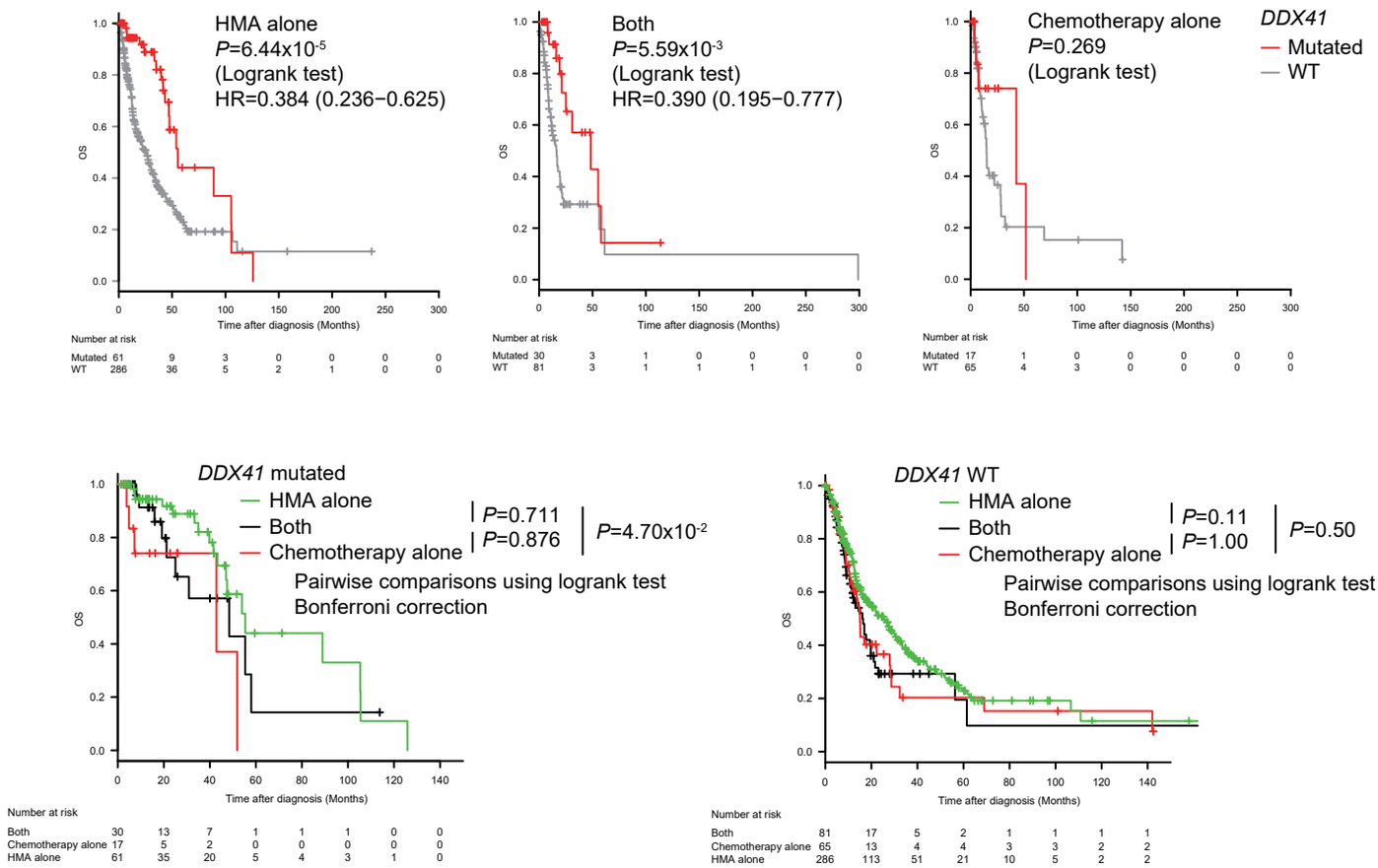
Supplemental Figure 17. Prognostic impacts of *DDX41* mutations in the cohort with chemotherapy.
Kaplan-Meier curves of overall survivals (OS) for *DDX41*-mutated or -WT myeloid neoplasms (MNs) with chemotherapy were shown in each disease subtype. Statistical significance was tested by two-sided Log-rank test. Hazard ratios and 95% confidence intervals were calculated by Cox proportional hazard regression. The observations were censored at hematopoietic stem-cell transplantation.

Supplemental Figure 18



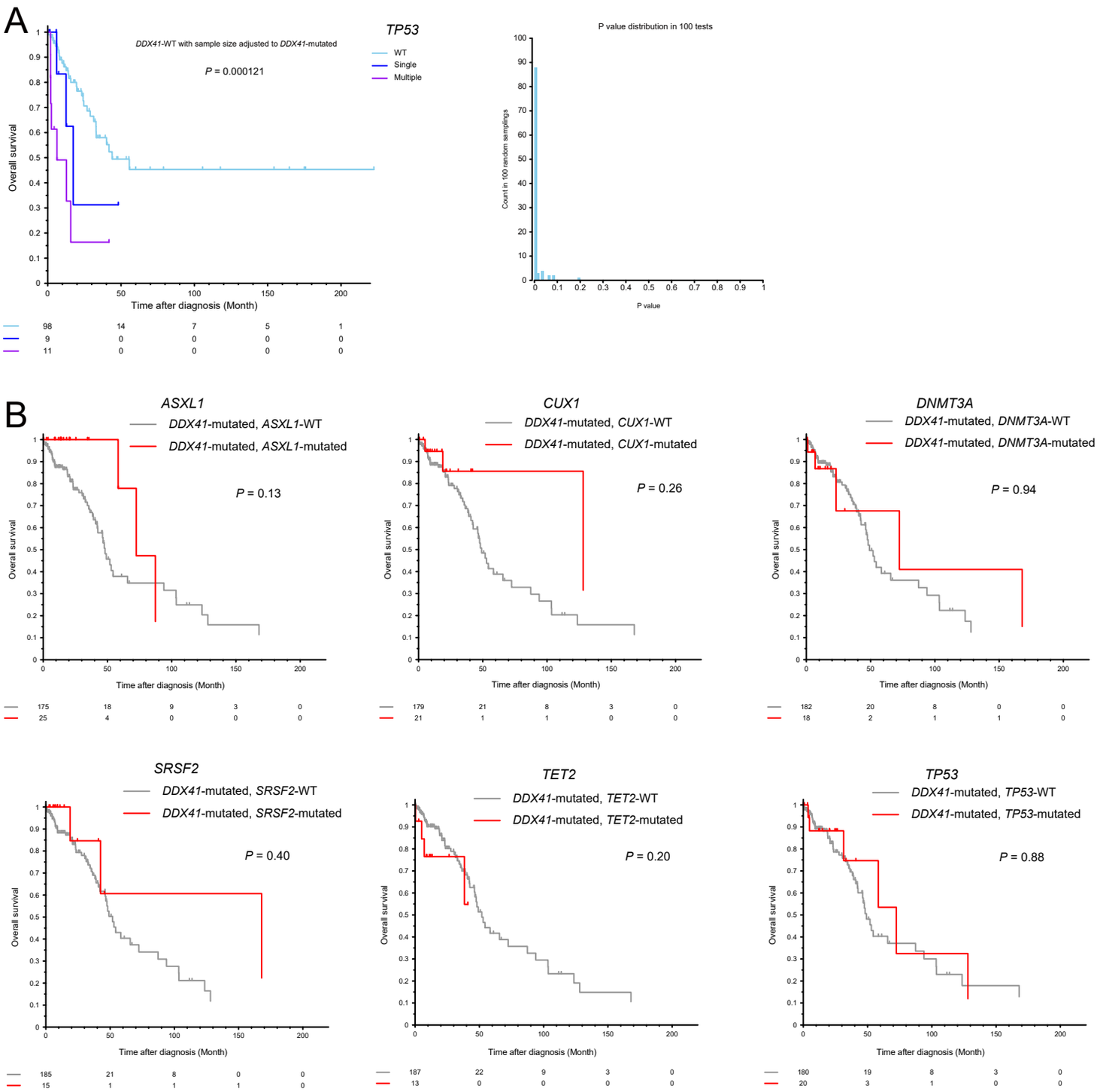
Supplemental Figure 18. Prognostic impacts of *DDX41* mutations in the cohort with hematopoietic stem cell transplantation (HSCT). **A**, **B** Kaplan-Meier curves of overall survivals (OS) for *DDX41*-mutated or -WT myeloid neoplasms (MNs) with HSCT were shown in each disease subtype (**A**) and with and without an additional hypomethylating agent (HMA) treatment (**B**). Statistical significance was tested by two-sided Log-rank test. Hazard ratios and 95% confidence intervals were calculated by Cox proportional hazard regression. The observations were not censored at HSCT.

Supplemental Figure 19



Supplemental Figure 19. Prognostic impacts of *DDX41* mutations in the cohort with hypomethylating agent treatment and chemotherapy. Kaplan-Meier curves of overall survivals (OS) for *DDX41*-mutated or -WT MDS/sAML were shown in the cohorts with hypomethylating agent (HMA) treatment alone, both HMA treatment and chemotherapy, and chemotherapy alone. Statistical significance was tested by two-sided Log-rank test. Hazard ratios and 95% confidence intervals were calculated by Cox proportional hazard regression. The observations were censored at HSCT.

Supplemental Figure 20



Supplemental Figure 20. Prognostic impacts of co-mutations on *DDX41*-mutated MDS and AML.
A Kaplan-Meier curves of overall survival stratified by *TP53* mutation status are shown for selected *DDX41*-WT MNs with adjusted sample size to mutated ones (left), and the distribution of P-values calculated by logrank tests was drawn for such adjusted WT MNs randomely selected 100 times (right). **B** Kaplan-Meier curves of overall survivals for *DDX41*-mutated MDS and AML were shown in those with and without each co-mutation. Results of 6 most frequently co-mutated genes are shown. Co-mutated genes were indicated on the top of each panel. Statistical significance was tested by two-sided Log-rank test. The observations were censored at HSCT.

Supplemental Table 1. Disease phenotypes in cases with and without survival data

Variables	With survival data	Without survival data	Total	P-value*
Diagnostic or treatment-naïve cases (%)	2,360 (30.7%)	5,338 (69.3%)	7,698 (100%)	
Diagnosis				<0.0001
Myelodysplastic syndromes	908	2,887	3,795	
Acute myeloid leukemia	1,059	1,321	2,380	
Myelodysplastic myeloproliferative neoplasms	94	522	616	
Myeloproliferative neoplasms	299	608	907	

*Fisher's exact test

Supplemental Table 2. Genes common to all the different RNA baits and amplicon libraries.

ASXL1	*EZH2*	*NF1*	*SRSF2*
BCOR	*FLT3*	*NPM1*	*STAG2*
CALR	*GATA1*	*NRAS*	*TET2*
CBL	*GATA2*	*PHF6*	*TP53*
CEBPA	*IDH1*	*PPM1D*	*U2AF1*
CSF3R	*IDH2*	*PTPN11*	*WT1*
CUX1	*JAK2*	*RAD21*	*ZRSR2*
DDX41	*KIT*	*RUNX1*	
DNMT3A	*KRAS*	*SETBP1*	
ETV6	*MPL*	*SF3B1*	

Supplemental Table 3. Characteristics of MN patients with *DDX41* mutation (NM_016222).

Age (years), Sex	Diagnosis	Country	Sporadic/Familial	P/LP germline *DDX41* variants	Somatic *DDX41* mutations	Cooccurring mutations
80,M	Higher-risk MDS	Germany	Sporadic	p.Q41*	p.R525H	*BCOR, CUX1, TET2*
71,M	pAML	Japan	Sporadic	p.K102fs	p.I520F	*ASXL1, ATM, RUNX1, SETBP1*
94,M	sAML	Japan	Sporadic	p.R591Q	-	*CEBPA, IDH1, NRAS*
73,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*PPM1D*
84,M	sAML	Japan	Sporadic	-	p.K494E	*PDS5B*
61,F	pAML	United States	Sporadic	p.R369*	p.R525H	*CBL, CUX1*
70,M	pAML	United States	Sporadic	p.D140fs	-	-
65,M	sAML	United States	Sporadic	c.1302+3G>T	p.R525H	-
69,M	sAML	United States	Sporadic	-	p.R525H	-
76,M	Lower-risk MDS	United States	Sporadic	p.D140fs	-	-
64,M	sAML	United States	Sporadic	p.M1I	-	*CALR, SF3B1*
63,F	pAML	United States	Sporadic	p.D140fs	-	*DNMT3A*
65,F	pAML	United States	Sporadic	p.M1I	-	-
72,M	Lower-risk MDS	United States	Sporadic	p.Q52fs	p.A225D	-
78,M	Higher-risk MDS	United States	Sporadic	p.E122*	p.R525H	*DNMT3A, NOTCH1, PHF6, TET2*
60,F	Higher-risk MDS	United States	Sporadic	p.R323C	-	-
65,M	MDS/MPN	United States	Sporadic	p.D140fs	-	-
62,M	Lower-risk MDS	United States	Sporadic	p.P206L	p.R525H	*CUX1, SRSF2*
66,M	sAML	United States	Sporadic	p.D140fs	-	-
82,M	Lower-risk MDS	United States	Sporadic	-	p.R525H, p.P179L	-
47,M	Lower-risk MDS	United States	Sporadic	p.L390R	p.P321L	*GNAS, JAK2*
66,M	Higher-risk MDS	United States	Familial	p.F183I	p.R525H	-
80,M	sAML	United States	Sporadic	p.M316fs	-	*SF3B1, TET2*
61,M	Higher-risk MDS	United States	Sporadic	p.R339C	-	-
44,F	pAML	United States	Sporadic	p.A500fs	-	-
65,M	pAML	United States	Sporadic	p.Q410H	-	-
86,M	sAML	United States	Sporadic	p.Q90*	-	-
61,M	Higher-risk MDS	United States	Sporadic	p.Y516C	-	-
69,M	Lower-risk MDS	United States	Sporadic	p.I396T	p.D407delinsLD	-
62,F	Higher-risk MDS	United States	Sporadic	p.M1L	-	-
87,F	Lower-risk MDS	United States	Sporadic	p.V445del	-	-
NA,NA	Higher-risk MDS	United States	Sporadic	p.D140fs	p.R525H	*PRPF8, SF3B1, TET2*
47,M	pAML	United States	Sporadic	p.Q41*	-	*CEBPA, CUX1*
78,F	sAML	United States	Sporadic	c.434+1G>A	-	-
50,M	Higher-risk MDS	United States	Sporadic	p.D140fs	p.M378I	-
68,M	Higher-risk MDS	Germany	Sporadic	-	p.R525H	*CREBBP, SRSF2*
71,F	Lower-risk MDS	Germany	Sporadic	p.P38fs	-	*RUNX1, SF3B1*
79,M	Lower-risk MDS	Germany	Sporadic	p.Y516C	p.T227M	*PPM1D*
68,M	Higher-risk MDS	Germany	Sporadic	p.Y340N	p.R525H	*CUX1, SETBP1*
72,M	Lower-risk MDS	Germany	Sporadic	-	p.R525H, p.P179H	*TET2*
62,F	Higher-risk MDS	Germany	Sporadic	p.I240V	-	*TP53*
82,M	Lower-risk MDS	Germany	Sporadic	p.A270V	p.T227A	*SF3B1*
68,F	Lower-risk MDS	Germany	Sporadic	p.E278D	-	*ASXL1*
59,M	sAML	United States	Sporadic	p.D140fs	-	-
55,M	pAML	United States	Sporadic	p.K381*	-	-
74,M	Higher-risk MDS	United States	Sporadic	p.M1I	-	-
71,M	Higher-risk MDS	United States	Sporadic	-	p.A225D	-
65,M	Higher-risk MDS	United States	Sporadic	p.D140fs	p.R525H	-
68,M	Higher-risk MDS	United States	Sporadic	-	p.R525H	-
70,M	Lower-risk MDS	United States	Sporadic	p.I396T	p.R525H	*GATA2, JAK2, NF1, PTPN11, SF3B1, WT1*
87,M	pAML	United States	Sporadic	p.T529fs	-	*RUNX1*
78,M	Lower-risk MDS	United States	Sporadic	-	p.E256K	-
78,M	Lower-risk MDS	United States	Sporadic	-	p.P321L	-
75,M	Lower-risk MDS	United States	Sporadic	p.LP237-238FT	-	*CUX1, GATA2*
49,F	MDS/MPN	United States	Sporadic	p.G578R	p.G524R	-
28,M	pAML	United States	Sporadic	-	p.T360I	-
63,M	Lower-risk MDS	United States	Sporadic	-	p.R525H	-
62,M	MDS/MPN	United States	Sporadic	-	p.K482R	-

61,M	Lower-risk MDS	United States	Sporadic	-	p.C294fs	-
90,M	Higher-risk MDS	United States	Sporadic	p.D140fs	-	-
90,M	Higher-risk MDS	United States	Sporadic	p.D140fs	p.R525H	-
73,M	Higher-risk MDS	United States	Sporadic	p.D140fs	p.R525H	-
62,M	sAML	United States	Sporadic	p.M1I	-	-
69,M	Higher-risk MDS	United States	Sporadic	-	p.R525H, p.R323H	-
73,F	sAML	Japan	Sporadic	p.A500fs	p.R525H	*TP53*
65,M	pAML	Japan	Sporadic	-	p.R525H	*ASXL1*
69,M	pAML	Japan	Sporadic	p.A500fs	-	*TP53*
56,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*PHF6*
82,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, TP53*
77,M	Lower-risk MDS	Japan	Sporadic	-	p.R42G	*ETNK1*
73,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	*GNAS*
78,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*DNMT3A*
79,M	Lower-risk MDS	Japan	Sporadic	p.E256K	p.R525H	*RUNX1*
73,M	Higher-risk MDS	Japan	Sporadic	p.E7*	-	*JAK2, TET2*
72,M	sAML	Japan	Sporadic	p.S363del	p.R525H	*DNMT3A, RUNX1, STAG2*
15,M	Lower-risk MDS	Japan	Sporadic	p.H203L	-	-
73,M	Lower-risk MDS	Japan	Sporadic	-	p.R525H	*ASXL1, SH2B3*
74,F	Lower-risk MDS	Japan	Sporadic	-	p.A376V	*CUX1, GNAS, SRSF2, TP53*
68,M	Higher-risk MDS	Japan	Sporadic	p.S363del	-	-
71,M	Higher-risk MDS	Japan	Sporadic	p.S363del	p.R525H	*TP53*
67,M	Higher-risk MDS	Japan	Sporadic	p.C281Y	p.G399V	*ASXL1, CUX1*
75,F	Lower-risk MDS	Japan	Sporadic	p.S363del	-	*IDH2, NF1, SF3B1*
16,F	Higher-risk MDS	Japan	Sporadic	-	p.F183S	*GATA2*
64,F	pAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, CUX1, SETBP1, SRSF2*
77,M	Higher-risk MDS	Japan	Sporadic	p.S363del	p.R525H	*SRSF2*
68,F	Lower-risk MDS	Japan	Sporadic	p.I240V	-	-
83,F	Lower-risk MDS	Japan	Sporadic	p.A500fs	p.Q208E	-
66,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	-
77,M	Lower-risk MDS	Japan	Sporadic	p.Y259C	p.G530S	*TET2*
69,M	Higher-risk MDS	Japan	Sporadic	p.S363del	p.R525H	*ASXL1*
75,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1*
80,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*TP53*
74,M	sAML	Japan	Sporadic	-	p.G530D	*U2AF1*
78,M	sAML	Japan	Sporadic	p.S363del	p.D344E	-
80,M	sAML	Japan	Sporadic	c.1303-1G>A	p.R525H	*ASXL1, SRSF2*
79,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.E345D	*ASXL1, SETBP1*
70,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*CUX1, SRSF2*
74,M	sAML	Japan	Sporadic	p.F183S	p.R525H	*CUX1*
69,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*PPM1D, TP53*
NA,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, CUX1, KRAS, SETBP1*
65,M	pAML	Japan	Sporadic	p.E7*	p.G530D	-
69,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.L548H	*PHF6*
78,M	sAML	Japan	Sporadic	c.645-2A>G	p.R525H	*CUX1, SF3B1, TET2*
70,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1*
75,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*CUX1, DNMT3A*
50,F	Lower-risk MDS	Japan	Sporadic	-	p.Q429H	*ETNK1, MPL, TP53*
58,M	sAML	Japan	Sporadic	p.E256K	p.T377N	*ASXL1, CUX1, PHF6*
53,M	sAML	Japan	Sporadic	p.S363del	p.L87F	*CALR, CEBPA, RUNX1*
63,M	sAML	Japan	Sporadic	p.A500fs	-	-
43,M	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.T227M	-
63,M	sAML	Japan	Sporadic	p.K187R	p.T227A	*SETBP1, SRSF2, STAG2*
55,F	Lower-risk MDS	Japan	Sporadic	p.L553del	-	-
60,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	-	-
53,F	sAML	Japan	Sporadic	p.A500fs	-	-
61,M	sAML	Japan	Sporadic	-	p.Q370*, p.T232A	*ASXL1, EZH2, PHF6*
65,M	sAML	Japan	Sporadic	p.A500fs	-	*DNMT3A*
61,M	Lower-risk MDS	Japan	Sporadic	p.S363del	-	-
53,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	-
54,F	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	-

63,F	sAML	Japan	Sporadic	p.A500fs	-	*DNMT3A, FLT3, TET2, WT1*
59,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	*KDM6A*
65,M	Higher-risk MDS	Japan	Sporadic	c.298+1G>T	p.T232A	*ASXL1, EZH2, JAK2, PRPF8*
50,M	Higher-risk MDS	Japan	Sporadic	p.L553del	-	*BCOR*
59,M	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	-
56,M	Higher-risk MDS	Japan	Sporadic	c.571+2T>G	-	-
52,M	sAML	Japan	Sporadic	p.A500fs	-	*NF1*
40,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*SRSF2*
59,M	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	*JAK2*
62,M	sAML	Japan	Sporadic	-	p.P561H	*CEBPA, DNMT3A, FLT3, SRSF2*
50,F	Higher-risk MDS	Japan	Sporadic	-	p.P499S	*EP300, FLT3, IRF1*
62,M	Lower-risk MDS	Japan	Sporadic	p.R219H	-	*ASXL1, ASXL2, CDKN2A, GATA2, GNB1, SETD2, U2AF2*
36,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	-	-
38,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	p.A225V	*MPL, U2AF1*
60,F	Lower-risk MDS	Japan	Sporadic	p.S363del	-	-
59,F	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	-
61,M	sAML	Japan	Sporadic	p.A500fs	-	*ASXL1*
53,M	MDS/MPN	Japan	Sporadic	p.Y259C	-	-
42,M	Higher-risk MDS	Japan	Sporadic	p.R124fs	-	-
62,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	-	*TP53*
65,M	sAML	Japan	Sporadic	p.Y259C	-	*TP53*
60,M	Higher-risk MDS	Japan	Sporadic	-	p.R525H	*ASXL1*
70,F	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
59,M	sAML	Japan	Familial	p.S363del	p.R525H	-
65,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, EZH2, RUNX1*
38,M	pAML	Japan	Sporadic	-	p.G356D	*DNMT3A*
57,M	Higher-risk MDS	Japan	Sporadic	p.E7*	p.R525H	*ASXL1, TP53*
28,M	Lower-risk MDS	Japan	Sporadic	-	p.F183S	-
57,M	Higher-risk MDS	Italy	Sporadic	p.I207T	-	-
51,M	sAML	Italy	Sporadic	p.G218D	-	-
74,M	MDS/MPN	Italy	Sporadic	p.V445del	-	*IDH2, JAK2, SRSF2*
62,M	Higher-risk MDS	Italy	Sporadic	p.G19*	p.A488T	*DNMT3A*
58,M	Higher-risk MDS	Italy	Sporadic	p.Q48*	-	-
81,M	Lower-risk MDS	Italy	Sporadic	p.M1I	p.P321L	-
NA,M	Lower-risk MDS	Italy	Sporadic	p.H160P	p.P321L	*SRSF2*
59,F	Lower-risk MDS	Italy	Sporadic	p.R267W	-	*DNMT3A, IDH1, SRSF2*
48,M	sAML	Italy	Sporadic	p.G218D	-	-
67,M	Higher-risk MDS	Italy	Sporadic	p.M1I	p.T232A	*CBL, TP53*
68,M	Lower-risk MDS	Italy	Sporadic	p.G218D	p.P265L	*SH2B3*
NA,M	Higher-risk MDS	Italy	Sporadic	-	p.G530D	*CSF3R*
NA,M	sAML	Italy	Sporadic	-	p.A447T, p.R525H, c.645-1G>A	*TET2*
72,M	Higher-risk MDS	Japan	Sporadic	p.E256K	-	*PPM1D*
NA,NA	sAML	Netherland	Sporadic	c.435-1G2A>1A2C	p.R525H	-
NA,NA	sAML	Netherland	Sporadic	p.M1I	p.R525H	-
72,M	Higher-risk MDS	Thailand	Sporadic	p.S21fs	-	*DNMT3A, KIT, NPM1*
64,M	sAML	Thailand	Sporadic	p.S21fs	p.R525H	*PHF6*
64,M	Higher-risk MDS	Thailand	Sporadic	p.V234fs	-	*DNMT3A*
68,F	Higher-risk MDS	Thailand	Sporadic	-	p.R525H	-
65,M	Higher-risk MDS	Thailand	Sporadic	p.R339H	p.K494T	*TET2, ZRSR2*
77,M	Higher-risk MDS	Thailand	Sporadic	-	p.F438L	-
69,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
53,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	-
83,M	Higher-risk MDS	Japan	Sporadic	p.V435fs	p.R525H	*DNMT3A, KMT2A_PTD*
69,M	sAML	Japan	Sporadic	p.A500fs	p.D490Y	*SRSF2*
85,M	Higher-risk MDS	Japan	Sporadic	-	p.G530D, p.S493Y	-
92,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.E345D	*ASXL1, TP53*
82,M	Lower-risk MDS	Japan	Sporadic	-	p.R471Q, p.E131K	-
73,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*ASXL2, CEBPA, GATA2, GNAS, JARID2, NF1, PDS5B, SH2B3, SRSF2, USP9X*
76,F	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*CUX1, SRSF2, TP53*

76,F	Higher-risk MDS	Japan	Sporadic	p.F183S	p.P321L	*NFE2*
70,M	sAML	Japan	Sporadic	p.A500fs	p.G530D	*CUX1*
69,M	Higher-risk MDS	Japan	Sporadic	p.E256K	p.T227M	*PPM1D*
71,M	Higher-risk MDS	Japan	Sporadic	p.S363del	-	-
79,M	Higher-risk MDS	Japan	Sporadic	p.E7*	-	*ZRSR2*
72,F	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	-
66,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*TP53*
66,M	Higher-risk MDS	Japan	Sporadic	p.E7*	p.P321L	*JAK2, SUZ12*
68,M	Higher-risk MDS	Japan	Sporadic	-	p.R525H, p.R323H	*EZH2*
74,F	sAML	Japan	Sporadic	-	p.L373P, p.R525H	-
72,M	Higher-risk MDS	Japan	Sporadic	p.E7*	p.L390H, p.R525H	*ASXL1, BCORL1, SF3B1, TET2*
67,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*GNAS*
74,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	*ASXL1, PPM1D, TP53*
64,M	Higher-risk MDS	Japan	Sporadic	p.S363del	p.R525H	*ASXL1*
76,F	sAML	Japan	Sporadic	p.A500fs	-	*ASXL1, PPM1D*
77,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*DNMT3A*
77,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*ASXL2, PHF6*
71,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.G530D	*DNMT3A*
57,F	sAML	Japan	Sporadic	p.Y279*	p.R525H	*ASXL1, CUX1*
71,NA	Lower-risk MDS	Japan	Sporadic	p.A500fs	p.H518N	-
63,M	sAML	Japan	Sporadic	p.Y259C	p.H91Y, p.R525H	*DNMT3A*
69,M	Higher-risk MDS	Japan	Sporadic	-	p.R525H, p.L237*	*ASXL1, CREBBP, RUNX1*
74,M	pAML	Japan	Sporadic	p.A500fs	p.R525H	*U2AF1*
61,M	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	*CUX1*
72,M	sAML	Japan	Sporadic	p.T529fs	p.R525H	*CUX1, EZH2, SETBP1, TET2*
89,M	sAML	Japan	Sporadic	-	p.R525H	*JAK2, U2AF1*
84,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	-
44,F	sAML	Japan	Sporadic	p.A500fs	p.R525H	*CUX1, SRSF2, STAG2*
72,M	sAML	Japan	Sporadic	-	p.R525H	*SRSF2*
64,M	Higher-risk MDS	Japan	Sporadic	p.S363del	p.G530D	*DNMT3A, TET2*
46,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
69,M	MDS/MPN	Japan	Sporadic	p.A500fs	-	*ASXL1, EZH2, RUNX1, TET2*
65,M	pAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, CBL, SETBP1, TET2*
66,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	-	*TP53, U2AF1*
68,F	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	*DNMT3A, PHF6, TERT*
81,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
80,M	Lower-risk MDS	Japan	Sporadic	-	p.Y451C, p.L87V, p.G586R	*ASXL1, DNMT3A, TP53, U2AF1, WT1*
75,F	Higher-risk MDS	Japan	Sporadic	p.G577*	p.V333I, p.T236M	*CUX1, ETV6, GNAS, PIGA, TP53, U2AF1*
76,M	Lower-risk MDS	Japan	Sporadic	-	p.R22S	*ASXL1, BCORL1, ETNK1, RUNX1, TP53, U2AF1*
66,M	pAML	Japan	Sporadic	p.Q208R	p.R525H	-
86,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*TET2, TP53*
65,M	Lower-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	*EZH2, TP53*
76,M	sAML	Japan	Sporadic	p.A500fs	p.L390F	*DNMT3A, KMT2A_PTD, RUNX1, SRSF2*
78,M	pAML	Japan	Sporadic	c.645-2A>G	p.R525H	*DNMT3A, U2AF1*
35,M	Higher-risk MDS	Japan	Sporadic	p.P432S	-	-
45,M	Higher-risk MDS	Japan	Sporadic	p.Y259C	p.R525H	*KMT2A* PTD
70,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	-
59,F	sAML	United Kingdom	Sporadic	p.M316fs	p.E345D	*CUX1, TP53*
72,M	Higher-risk MDS	United Kingdom	Sporadic	p.D140fs	p.R525H	*DNMT3A*
75,M	sAML	United Kingdom	Sporadic	p.D140fs	-	-
74,M	sAML	United Kingdom	Sporadic	p.M1I	p.A403-D407delinsH	*CHEK2*
68,M	Higher-risk MDS	United Kingdom	Sporadic	p.D140fs	p.R525H	-
71,M	sAML	United Kingdom	Sporadic	p.D140fs	-	*PHF6, RAD21*
64,M	Higher-risk MDS	United Kingdom	Sporadic	p.Q329*	p.G530S	-
72,M	Higher-risk MDS	United Kingdom	Sporadic	p.D140fs	p.P321L	*ASXL1, EZH2, ZRSR2*
68,M	sAML	United Kingdom	Sporadic	p.R323C	p.R525H	*CUX1, PHF6, SRSF2*
63,F	sAML	United Kingdom	Sporadic	p.M316fs	-	-
69,F	Lower-risk MDS	United Kingdom	Sporadic	-	p.G524R	*SRSF2, TET2*
80,M	Higher-risk MDS	United Kingdom	Sporadic	p.D140fs	p.G589R	*DNMT3A*

84,M	Lower-risk MDS	United Kingdom	Sporadic	p.R369G	p.E2*	-
70,F	sAML	United Kingdom	Sporadic	-	p.R525H	*EZH2, TET2*
73,M	sAML	United Kingdom	Sporadic	p.M1I	-	*BCOR*
72,M	Lower-risk MDS	United Kingdom	Sporadic	p.G173R	p.G530D	-
80,M	Lower-risk MDS	United Kingdom	Sporadic	p.A492fs	-	-
76,M	Higher-risk MDS	United Kingdom	Sporadic	p.D140fs	p.R525H	*ASXL1, PHF6, RUNX1*
63,M	Lower-risk MDS	United Kingdom	Sporadic	p.P321L	-	-
90,F	MDS/MPN	United Kingdom	Sporadic	p.D140fs	-	*CUX1, SRSF2, TET2*
78,F	sAML	United Kingdom	Sporadic	p.D140fs	p.V408F	*SETBP1, SRSF2*
76,F	pAML	United Kingdom	Sporadic	p.G173R	p.P321L	*DNMT3A, KRAS, NPM1*
55,M	pAML	United Kingdom	Sporadic	p.D140fs	-	-
71,F	Higher-risk MDS	United Kingdom	Sporadic	p.L428P	p.C264R	-
68,F	Higher-risk MDS	United Kingdom	Sporadic	p.M1I	p.G530S	*ASXL1, CBL, EZH2, SETBP1*
76,M	Higher-risk MDS	United Kingdom	Sporadic	p.K102fs	p.R471Q	*CUX1*
83,F	sAML	United Kingdom	Sporadic	p.M1I	p.R525H	-
75,F	MPN	United Kingdom	Sporadic	p.V412I	-	*IDH2, PPM1D*
44,M	Lower-risk MDS	United Kingdom	Sporadic	c.138+1G>C	p.P321L	-
74,M	Lower-risk MDS	United Kingdom	Sporadic	c.435-1G2A>1A2C	p.P321L	*ETV6*
81,F	sAML	United Kingdom	Sporadic	p.Q210K	p.R525H	-
63,F	sAML	United Kingdom	Sporadic	p.L373P	p.R525H	*SRSF2*
81,F	sAML	United Kingdom	Sporadic	p.I240del	p.R525H	*TET2*
60,M	sAML	United Kingdom	Sporadic	p.K102fs	p.R525H	-
79,M	sAML	United Kingdom	Sporadic	p.M316fs	p.R525H	*ASXL1, RUNX1*
52,M	pAML	United Kingdom	Sporadic	c.435-1G2A>1A2C	p.G530S	*CUX1*
73,M	sAML	Japan	Sporadic	p.T529fs	p.R525H	*TP53*
69,M	sAML	Japan	Sporadic	p.Y259C	p.K494E	*TP53*
78,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*WT1*
52,F	Higher-risk MDS	Japan	Sporadic	-	p.A376V	*CEBPA, TP53*
63,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*TP53*
53,F	sAML	Japan	Sporadic	-	p.R525H	*SETBP1*
79,M	Lower-risk MDS	Japan	Sporadic	p.R323C	p.P379L	-
73,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.V517E	-
76,M	Higher-risk MDS	Japan	Sporadic	p.E7*	-	-
71,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*SMC3*
77,M	Lower-risk MDS	Japan	Sporadic	p.S363del	p.G530S	-
66,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
75,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*DNMT3A, TP53*
20,M	pAML	Japan	Sporadic	p.A500fs	-	-
54,F	sAML	Japan	Sporadic	p.A500fs	p.R525H	-
73,M	sAML	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, CBL, DNMT3A*
60,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	-	*ASXL1, SETBP1, U2AF1*
70,M	Higher-risk MDS	Japan	Sporadic	c.571+2T>G	p.R525H	*DNMT3A*
48,F	pAML	Japan	Familial	p.A500fs	-	-
76,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	-
67,M	sAML	Japan	Sporadic	p.L548P	p.P379Q	*CUX1*
70,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*ASXL1, SETBP1*
51,M	Higher-risk MDS	Japan	Sporadic	p.E440del	-	-
66,F	Higher-risk MDS	Japan	Sporadic	p.R323H	p.R525H	-
49,M	Lower-risk MDS	Japan	Sporadic	p.A500fs	p.A346T	*ASXL1, EZH2*
84,M	Higher-risk MDS	Japan	Sporadic	p.A500fs	p.R525H	*CUX1*
83,M	Lower-risk MDS	Japan	Sporadic	p.V504I	-	*SF3B1*
65,M	AML	Japan	Sporadic	p.A500fs	-	-
70,M	pAML	Germany	Familial	p.D140fs	p.R525H	-
44,F	sAML	Germany	Familial	p.D140fs	-	-
45,M	pAML	Germany	Familial	p.D140fs	p.R525H	-
64,M	Lower-risk MDS	United States	Familial	p.I396T	p.R525H	-
66,M	Lower-risk MDS	United States	Familial	p.I396T	p.R525H	-
67,M	Higher-risk MDS	United States	Familial	p.D140fs	p.R525H	*TP53*
73,M	sAML	United States	Familial	p.D140fs	-	-
56,M	pAML	United States	Familial	p.D140fs	-	-
72,M	Higher-risk MDS	United States	Sporadic	p.D140fs	p.R525H	*RUNX1*

62,M	Higher-risk MDS	United States	Sporadic	p.D140fs	-	-
85,M	sAML	United States	Sporadic	p.D140fs	p.R525H	-
58,M	Higher-risk MDS	United States	Sporadic	p.D140fs	-	-
69,M	MDS/MPN	United States	Sporadic	p.D140fs	-	*KRAS, SETBP1*
88,M	Higher-risk MDS	United States	Sporadic	p.D140fs	-	-
71,M	pAML	United States	Sporadic	p.D140fs	-	-
68,M	sAML	United States	Sporadic	p.D140fs	-	*NRAS*
64,M	Lower-risk MDS	United States	Sporadic	-	p.R525H	-
68,M	Higher-risk MDS	United States	Sporadic	-	p.R525H	-
63,M	pAML	United States	Sporadic	-	p.R525H	-
66,M	Lower-risk MDS	United States	Sporadic	-	p.R525H	*RUNX1, TP53*
46,M	Higher-risk MDS	United States	Sporadic	-	p.R525H	-
70,F	Lower-risk MDS	United States	Sporadic	-	p.E247K	-
68,M	pAML	United States	Sporadic	-	c.1230+1C>T	-
53,F	AML	United States	Familial	p.P78fs	p.R525H	*JAK2*
80,M	sAML	United States	Familial	p.P78fs	-	-
NA,M	AML	United States	Familial	p.Q90*	-	-
60,M	AML	United States	Familial	p.K108fs	-	-
72,F	sAML	United States	Familial	p.D140fs	-	-
67,M	Higher-risk MDS	United States	Familial	c.435-1G2A>1A2C	-	-
65,M	sAML	United States	Familial	p.G218D	-	-
36,F	Higher-risk MDS	United States	Familial	p.G218D	-	*TET2*
67,M	Higher-risk MDS	United States	Familial	p.E265K	-	-
54,F	MDS	United States	Familial	p.L283fs	-	-
62,M	Lower-risk MDS	United States	Familial	p.C338Y	-	*TP53*
65,F	AML	United States	Familial	p.L373P	-	-
80,M	sAML	United States	Familial	p.K381*	-	-
75,M	MDS	United States	Familial	p.Q429*	-	-
71,M	AML	United States	Familial	p.A492fs	-	-
64,F	Higher-risk MDS	United States	Familial	p.A500fs	-	-
72,M	Higher-risk MDS	United States	Familial	p.Q410fs	-	*EGFR*
67,F	AML	United States	Familial	p.M1I	-	-
72,M	MDS	United States	Familial	p.M1I	-	-
73,M	AML	United States	Familial	p.M1I	-	-
65,M	AML	United States	Familial	p.M1I	-	-
52,M	AML	United States	Familial	p.M1I	-	-
65,M	AML	United States	Familial	p.M1I	-	-
73,M	sAML	United States	Familial	p.Q41*	-	*ASXL1*
69,F	sAML	United States	Familial	p.D140fs	-	*JAK2*
73,M	sAML	United States	Familial	p.D140fs	-	*SMC3, TP53*
66,M	Higher-risk MDS	United States	Familial	p.P258L	-	*ASXL1*
50,M	MDS	United States	Familial	p.R339L	-	-
51,M	MDS	United States	Familial	p.R339L	-	-
87,F	MDS	United States	Familial	p.R339L	-	-
63,M	MDS	United States	Familial	p.R369G	-	-
62,F	AML	United States	Familial	p.R369G	-	-
67,M	MDS	United States	Familial	p.L574fs	-	-
80,F	AML	United States	Sporadic	p.E512fs	p.R525H	*CBL, DNMT3A, SF3B1*

MN:myeloid neoplasms, P/LP: pathogenic/likely pathogenic

Supplemental Table 4. Odds ratios of *DDX41* variants in the Japanese population.

Allele	Counts in healthy donors (n=20,238)	Counts in MNs (n=4,461)	Odds ratio (95% CI)	*P* value	Counts in MDS (n=1,902)	Odds ratio (95% CI)	*P* value	Counts in AML (n=1,688)	Odds ratio (95% CI)	*P* value
p.S493S	260	64	1.12 (0.84 − 1.48)	0.424	27	1.11 (0.72 − 1.66)	0.596	21	0.97 (0.61 − 1.52)	1.000
p.E3K	8	2	1.13 (0.17 − 5.63)	0.699	2	2.66 (0.41 − 13.2)	0.210	0	0.00 (0.00 − 6.89)	1.000
p.A555A	19	5	1.19 (0.43 − 3.23)	0.789	3	1.68 (0.42 − 5.46)	0.430	1	0.63 (0.03 − 3.88)	1.000
p.K187R	15	6	1.82 (0.69 − 4.65)	0.250	2	1.42 (0.23 − 5.74)	0.653	3	2.40 (0.59 − 8.50)	0.157
p.P35R	29	12	1.88 (0.91 − 3.73)	6.81×10^{-2}	4	1.47 (0.47 − 4.25)	0.525	6	2.49 (1.01 − 5.86)	4.88×10^{-2}
p.E256K	4	4	4.54 (1.08 − 19.0)	4.02×10^{-2}	3	7.99 (1.57 − 36.7)	1.70×10^{-2}	1	3.00 (0.12 − 23.0)	0.330
p.A500fs	36	78	9.98 (6.68 − 14.9)	$<1.00\times10^{-3}$	45	13.59 (8.65 − 21.3)	$<1.00\times10^{-3}$	32	10.84 (6.59 − 17.5)	$<1.00\times10^{-3}$
p.E7*	3	7	10.6 (2.79 − 47.5)	$<1.00\times10^{-3}$	7	24.91 (6.56 − 112)	$<1.00\times10^{-3}$	0	0.00 (0.00 − 20.6)	1.000
p.Y259C	5	13	11.8 (4.05 − 34.5)	$<1.00\times10^{-3}$	9	19.24 (6.31 − 59.3)	$<1.00\times10^{-3}$	3	7.20 (1.50 − 29.5)	1.90×10^{-2}
p.S363del	3	15	22.8 (6.43 − 92.3)	$<1.00\times10^{-3}$	11	39.18 (10.7 − 164)	$<1.00\times10^{-3}$	4	16.02 (3.49 − 81.3)	1.00×10^{-3}
Significant alleles#	51	117	10.7 (7.63 − 15.0)	$<1.00\times10^{-3}$	75	16.24 (11.3 − 23.5)	$<1.00\times10^{-3}$	45	7.56 (5.13 − 11.2)	$<1.00\times10^{-3}$

p.E256K, p.A500fs, p.E7*, p.Y259C, and p.S363del

Supplemental Table 5. Regional distributions of *DDX41* germline variants in the gnomAD database. (ver.2.1.1).

Allele	Annotation	European (n = ~57,000)	Finnish (n = ~11,000)	Ashkenazi Jewish (n = ~5,000)	Latino American (n = ~17,000)	African American (n = ~8,000)	South Asian (n = ~15,000)	East Asian (n = ~9,000)
p.Asp140Glyfs	Nonsense	**22**	0	0	0	**1**	0	0
p.Met1I	Start codon	**19**	**2**	**1**	**1**	0	0	0
p.Arg159*	Nonsense	**4**	0	0	**1**	0	0	0
p.Gln41*	Nonsense	**4**	0	0	0	0	0	0
p.Phe535Serfs	Frameshift	**3**	0	0	0	0	0	0
p.Met316Aspfs	Frameshift	**3**	0	0	0	0	0	0
c.936-1G>T	Splice acceptor site	**2**	0	0	0	0	0	0
p.Gln90*	Nonsense	**2**	0	0	0	0	0	0
p.Arg311*	Nonsense	**1**	0	0	**1**	0	0	0
p.Glu268Aspfs	Frameshift	**1**	0	0	**1**	0	0	0
p.Arg369*	Nonsense	**1**	0	0	0	**2**	0	0
p.Lys102Argfs	Frameshift	**1**	0	0	0	0	**1**	**1**
c.1732+1G>C	Splice donor site	**1**	0	0	0	0	0	0
p.Thr529Argfs	Frameshift	**1**	0	0	0	0	0	0
p.Val517Glufs	Frameshift	**1**	0	0	0	0	0	0
p.Ala492Glyfs	Frameshift	**1**	0	0	0	0	0	0
p.Gly481Alafs	Frameshift	**1**	0	0	0	0	0	0
p.Gly465Alafs	Frameshift	**1**	0	0	0	0	0	0
p.Lys381*	Nonsense	**1**	0	0	0	0	0	0
p.Gln329*	Nonsense	**1**	0	0	0	0	0	0
c.936-1G>A	Splice acceptor site	**1**	0	0	0	0	0	0
c.435-1G>A	Splice acceptor site	**1**	0	0	0	0	0	0
c.435-2A>C	Splice acceptor site	**1**	0	0	0	0	0	0
p.Arg124Glufs	Frameshift	**1**	0	0	0	0	0	0
c.298+2T>A	Splice donor site	**1**	0	0	0	0	0	0
c.138+1G>A	Splice donor site	**1**	0	0	0	0	0	0
p.Gln44*	Nonsense	**1**	0	0	0	0	0	0
p.Pro19Argfs	Frameshift	**1**	0	0	0	0	0	0
p.Tyr167*	Nonsense	0	0	0	**1**	0	0	0
p.Gly23Argfs	Frameshift	0	0	0	**1**	0	0	0
p.Gln48*	Nonsense	0	0	0	0	**3**	0	0
p.Lys597*	Nonsense	0	0	0	0	**1**	0	0
p.Ala403Leufs	Frameshift	0	0	0	0	**1**	0	0
p.Asn397Lysfs	Frameshift	0	0	0	0	**1**	0	0
p.Val412Glyfs	Frameshift	0	0	0	0	0	**5**	0
c.1622-2dupA	Splice acceptor site	0	0	0	0	0	**3**	0
p.Met301Hisfs	Frameshift	0	0	0	0	0	**1**	0
p.Ile520Alafs	Frameshift	0	0	0	0	0	0	**2**
p.Ala500Cysfs	Frameshift	0	0	0	0	0	0	**2**
p.Leu615Trpfs	Frameshift	0	0	0	0	0	0	**1**
p.Tyr507*	Nonsense	0	0	0	0	0	0	**1**
p.Lys392Argfs	Frameshift	0	0	0	0	0	0	**1**
p.Ser217Ilefs	Frameshift	0	0	0	0	0	0	**1**
c.644+1delG	Splice donor site	0	0	0	0	0	0	**1**
p.Ser21Thrfs	Frameshift	0	0	0	0	0	0	**1**
p.Glu3Argfs	Frameshift	0	0	0	0	0	0	**1**

Table S5. Odds ratios of male *vs*. female healthy donors with *DDX41* variants.

Allele	Counts of carriers in male healthy donors	Counts of carriers in female healthy donors	Counts of non-carriers in male healthy donors	Counts of non-carriers in female healthy donors	Odds ratio (95% CI)	*P* value
p.S493S	59	57	5679	5057	0.92 (0.64 – 1.34)	0.709
p.E3K	4	2	5734	5112	1.78 (0.33 – 13.3)	0.691
p.A555A	9	5	5729	5109	1.61 (0.53 – 4.95)	0.434
p.K187R	6	4	5732	5110	1.34 (0.37 – 5.05)	0.758
p.P35R	4	6	5734	5108	0.59 (0.16 – 2.17)	0.531
p.E256K	2	0	5736	5114	Infinitive (0.26 – Infinitive)	0.502
p.A500fs	7	10	5731	5104	0.62 (0.22 – 1.66)	0.345
p.E7*	1	1	5737	5113	0.89 (0.02 – 34.3)	1.000
p.Y259C	0	2	5738	5112	0.0 (0.00 – 3.09)	0.222
p.S363del	1	0	5737	5114	2.7 (0.11 – 65.7)	1.000
all pathogenic#	28	25	5710	5089	1.00 (0.58 – 1.75)	1.000

Pathogenic variants were defined according to the ACMG standards and guidelines.

Supplemental Table 7. Impact of clinical and genetic factors on leukemic progression.

Whole MDS

Univariable

Variables	**Hazard ratio**	**95% confidence intervals**	***P* value**
IPSSR	1.68	1.51–1.87	$<1.0\times10^{-15}$
Lower-risk *vs.* Higher-risk	3.94	3.04–5.11	$<1.0\times10^{-15}$
DDX41 truncating mutation	2.53	1.76–3.62	4.7×10^{-7}

Multivariable*

Variables	**Hazard ratio**	**95% confidence intervals**	***P* value**
IPSSR	1.35	1.18–1.54	7.8×10^{-6}
Lower-risk *vs.* Higher-risk	2.51	1.74–3.60	6.9×10^{-7}
DDX41 truncating mutation	1.7	1.13–2.55	1.1×10^{-2}

***DDX41*-mutated MDS**

Univariable

Variables	**Hazard ratio**	**95% confidence intervals**	***P* value**
IPSSR	1.34	1.00–1.79	4.9×10^{-2}
Lower-risk *v.s.* Higher-risk	5.11	1.61–16.2	5.6×10^{-3}
DDX41 truncating mutation	4.25	2.01–8.97	1.5×10^{-4}

Multivariable*

Variables	**Hazard ratio**	**95% confidence intervals**	***P* value**
DDX41 truncating mutation	5.05	2.18–11.7	1.5×10^{-4}

*Stepwise variable selection by *P* values