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Lessons of nature from trisomy-8 myeloid neoplasia: the riddle of oncogenic clonal drives

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Disclosures
The authors declare no competing financial interests.

Data sharing statement

All relevant clinical and genetic data have been included in the main text of the article and Supplementary Material. For additional information, please contact the corresponding author: visconv@ccf.org

Contributions
Hussein.A. supervised the study, collected, analyzed, interpreted clinical and molecular data, and wrote the manuscript. A.D., L.G., Y.K., S.U. analyzed and interpreted data. Z.B. collected molecular data and specimens. C.G., C.B-P., Hassan.A. participated, collected, analyzed, and provided important feedback original data. T.H. provided genomic data. J.P.M., and V.V. provided invaluable help to the manuscript preparation, generated, and conceived the study design, designed figures and tables, and edited the manuscript. All authors participated in the critical review of the paper.

Trisomy 8 (+8) is a common chromosomal aberration in myeloid neoplasia (MN) as it affects 5-10% of myelodysplastic neoplasm (MDS) and acute myeloid leukemia (AML). Frequently, +8 occurs along other chromosomal aberrations; nevertheless, isolated (iso) +8 presents in 30-40% of +8 AML and has discrete prognostic roles in MDS or AML which appear to be disease-context dependent.[1] Indeed, it's considered an intermediate risk abnormality in AML (per the 2022 ELN) while it's less detrimental in MDS (per the IPSS-M).[2, 3]

The clinical phenotype of +8 AML was associated with *RUNX1* and *ASXL1* mutations compared to normal karyotype (NK) AML in some studies while with an increase in *TP53* and *IDH1/2* mutations in others.[4-6] The mutational landscape of +8 MDS has been less intensely studied, and it is possible that the varying prognostic impact of +8 in AML and MDS is related to distinct co-mutational patterns.

While detection of structural defects on chromosome 8 (chr.8) has improved, the contributing factors driving the clonal pathogenesis as repercussion of a gain of chr.8 remain elusive.[7] Early studies identified an up-regulation of inflammatory and immune pathways in +8 MDS with later involvement of *WT1* in T-cell directed myelosuppression.[8, 9]

To investigate the contributing genomic and oncogenic factors in +8, we took advantage of our large MDS (n=3588), AML (n=6788), and bone marrow failure disorders (BMF; n=685) cohorts which were assembled from our institution and public series (**Supplemental Table 1**). Clinical, molecular, and demographic data were collected through review of published data along with the electronic medical records of patients at our institutions in accordance with the protocols and written consent approved by Institutional Review Boards (IRB-5024) and the Declaration of Helsinki.

Among BMF patients, we identified 5 cases with aplastic anemia (AA; 4 AA/PNH; 1 AA without PNH, 4/5 females) carrying +8. Median age of AA carrying +8 was 60.9 vs 45.9 years for non +8 patients. Median PNH clone size in AA/PNH was 2.7%. The AA case had +8 in complex karyotype and poor outcome while the AA/PNH cases had iso +8 and were pancytopenic (median Hgb 8.8 g/dL, WBC $2.2x10^9$/L, and PLTs $15x10^9$/L). We identified 641 +8 AML patients, including 294 iso +8 and 347 non-iso +8 AML (**Figure 1A**). Iso +8 AML had higher percentages of secondary AML (sAML, 17.0 *vs* 11.0%, *P*=0.001) arising from antecedent MDS (14.0 *vs* 8.7%, *P*=0.004) *vs* NK AML. Iso +8

manifested more dysplastic than hyperproliferative phenotype (WBC, median: 8.6 *vs* 14.4 x10^9/L, *P*=0.02; Platelets, median: 47.5 *vs* 63.0 x10^9/L, *P*=0.01). After median follow up of 45.3 months, and consistent with other reports, iso +8 AML had worse median overall survival (mOS) *vs* NK AML (23.0 *vs* 32.1 months, *P*=0.0055; **Figure 1B**).[1] Yet, a significant difference in mOS was exclusively seen in primary +8 *vs* NK AML (pAML, 21.5 *vs* 34.5 months, *P*=0.0002) while not in sAML (14.7 *vs* 24.3 months, *P*=0.32; **Figures S1A-B**). Similarly, iso +8 MDS had a significantly worse mOS (18.0 *vs* 61.0 months, *P*<0.0001) compared to NK MDS (**Figure 1C**). In total, mOS for both iso +8 MDS and AML was poor and similar (**Figure S1C**). Cox proportional analyses of factors influencing OS further confirmed iso +8 as an independent predictor of poor survival in both MDS and AML (**Supplemental Table 1**). Patients with iso +8 AML receiving intensive chemotherapy regimens were noted to have shorter survival (**Figure S1D**). We further collected results of deep targeted sequencing panels (Truseq, Nextera) and diagnostic NGS to investigate the differences in molecular profiles in young versus old (<50; 50-60; >60) iso + 8 AML compared to NK AML. *ETV6*, *EZH2*, *IDH1*, *RUNX1*, *SRSF2*, *STAG2* and *U2AF1* mutations were significantly associated with age >60 iso +8 AML while *DNMT3A* and *FLT3* were more common in age >60 NK AML. *ASXL1* was associated with iso +8 AML and *NPM1* with NK AML in all age groups (**Supplemental Table 1**).

Our experience using machine learning in MN suggested that distinct features might reconcile +8 with specific genomic-functional clusters.[10, 11] Indeed, our analysis of MDS and sAML grouped +8 in one specific molecular cluster (MC-1) characterized by 90% of +8 in association with *ASXL1*, *TET2* and *RUNX1* (**Figure S2A-B**), while +8 was mostly restricted to genomic cluster 3 (GC-3) in AML (**Figure S2C-D**). Therefore, we studied the molecular associations of +8 AML and identified signatures that were more enriched in iso +8 AML *vs* NK AML (**Figure 1D**): lineage transcriptional factors (*RUNX1*, 33.1 *vs* 17.0%, *P*<0.0001), chromatin modifiers (*ASXL1,* 37.1 *vs* 12.6%, *P*<0.0001; *EZH2,* 10 *vs* 3%, *P*< 0.0001), splicing factors (*SRSF2,* 29.9 *vs* 13.8%, *P*<0.0001; *U2AF1*, 12.6 *vs* 3.2%, *P*<0.0001), *IDH2* (25.5 *vs* 19%, *P*=0.04) and *STAG2* (13.4 *vs* 7.3%, *P*=0.02). The latter was previously reported by our group.[12] In contrast, *FLT3* (32.5 *vs* 42.1%, *P*=0.01), *DNMT3A* (24.6 *vs* 35.0%, *P*= 0.002), *NPM1* (14.2 *vs* 44.6%, *P*< 0.0001) and *CEBPA* (6.9 *vs* 12.3%, *P*=0.02) were more frequent in NK AML

(**Figure 1D**). We then focused on iso +8 MDS *vs* NK MDS and found *ASXL1* (48.3 *vs* 18.8%; *P*< 0.0001), *EZH2* (19.0 *vs* 3.6%; *P*<0.0001), *RUNX1* (31.0 *vs* 12.2%; *P*=0.0002), and *STAG2* (25.6 *vs* 5.9%; *P*< 0.0001) were more frequent in iso +8 MDS (**Figure 1E**). Iso +8 pAML had more *NPM1* mutations than iso +8 sAML (17.2 *vs* 2.9%; *P*=0.03), while the latter had more *FLT3* (23.7 *vs* 3.4%; *P*=0.031), *IDH1* (23.5 *vs* 5.1%; *P*=0.01), *IDH2* (25.4 vs 6.9; *P*=0.0016) mutations compared to iso +8 MDS which was enriched with *SF3B1*, *STAG2*, and *TET2* (**Figure 1F**). Multivariate comparison of AML and MDS showed that +8 AML was associated with *FLT3* (OR 6.3, 95%CI 1.3-50.2 *P*=0.038), *IDH1* (OR 6.3, 95%CI 1.8-30.3, *P*=0.0078), *IDH2* (OR 7.7, 95%CI 2.2-33.3, *P*=0.003), *NRAS* (OR 4.8, 95%CI 1.4-20.1, *P*=0.02), *PTPN11* (OR 13.4, 95%CI 1.4-337.8, *P*=0.048), and *TP53* (OR 12.4, 95%CI 2.8-109.9, *P*=0.005), while +8 MDS had higher odds of *ASXL1* (OR 0.39, 95%CI 0.2-0.9, *P*=0.021) and *SF3B1* (OR 0.3, 95%CI 0.08-0.1, *P*=0.0009) (**Supplemental Table 1**).

Finally, we used RNASeq on a subcohort of patients to define overexpressed oncogenes in +8 MN (**Figure 2**).[13] Detailed information on patients, genetic studies, and IPSS-M for the MDS cohort is provided in **Supplemental Table 1**. We mapped the expression changes of chr.8 genes in 560 patients of which 52 had +8. Rank correlation assessed the extent of similarity across the genes. We found four clusters (C10, C12, C14, C15) with C10 and C15 being represented by 40% of +8 patients with variable clonal size. There was no significant difference in lower- *vs* higher-risk MDS (**Figure S2E-G**). In C10, both +8 and non +8 patients had similar demographic, clinical, and molecular characteristics, with *ASXL1*, *SRSF2*, *RUNX1*, and *TET2* being common (**Supplemental Table 1**). Similarly, iso +8 and non +8 cases comprising C15 had a similar clinical-molecular phenotype with *ASXL1* and *SF3B1* mutations (**Supplemental Table 1**). We found 414 overexpressed genes at 0.3 logFC cutoff. Linear regression tests were used to study correlations between clonality and specific gene expression. Among top overexpressed genes, we identified several genes with reported oncogenic potential such as the toll-like receptor LY96, the anti-apoptotic protein BAG4, the human oncogene WHSC1L1/NSD3, the tyrosine protein kinase LYN, the proto-oncogene MYC and the long noncoding RNA *PVT1* (**Figure 2** and **3A**). The latter is a gene characterized by amplification in several tumors and its overexpression is associated with increased *MYC* activity irrespective of changes in

expression.[14] *PVT1* epigenetically silences miRNAs in AML and acts as a molecular sponge for miRNA-29 to increase *WAVE1* (a negative regulator of apoptosis) and facilitate AML progression.[15] Although in our cohort RNASeq did not allow for the study of miRNAs, it still provided a more precise quantification of the global mRNA expression patterns. It is possible that the effects of the gene dosage observed in +8 cases might be reflected in the presence of genetic predisposition. To address this point, we analysed data of WGS and WES which were available for a total of 1103 patients with 219 patients carrying +8. A panel was designed for 163 genes known to be targets of germline hits and associated with predisposition to cancer and BMF. Detected variants were filtered using the following criteria: (i) excluding variant allele frequency (VAF) < 0.3; (ii) excluding CADD < 15; (iii) excluding variants annotated as benign in ClinVar; (iv) excluding variants confirmed as somatic variants in COSMIC; and (v) excluding variants present only in tumor DNA sample. Of 219 patients with +8, 15 cases (3 cases with iso +8; 12 cases with non-iso +8) carried pathogenic/likely pathogenic variants with known genetic predisposition (**Supplemental Table 1**). Gene variants enriched in telomerase machinery, DNA repair, and Fanconi anemia gene category (**Figure 3B**). Comparison of frequency of each variant in our cohort with the one in general population (gnomAD) found increased frequency in our cohort of +8 with some variants not estimated in general population (**Supplemental Table 1**).

Our data suggests iso +8 MN represents a distinct entity defined by dysplastic phenotype due to genotypic enrichment in *RUNX1* while inversely associated with *FLT3* and *NPM1*. Iso +8 AML frequently develops from antecedent MDS, which is supported by similar co-mutational patterns enriched in epigenetic modifiers in both iso +8 MDS and AML *vs* NK, with further acquisition of *FLT3*, *IDH1*, and *NRAS* contributing to iso +8 MDS progression to sAML. Recent studies also suggest that acquiring an extra chr.8 leads to *RUNX1* overexpression via chromatin remodelling. This overexpression of *RUNX1* seemed to coincide with LOF mutations which in turn pose a selective self-renewal advantage in +8.

The key culprit oncogenes implicated in +8 MN may be located on the extra chr.8 itself. Indeed, we found specific and relevant transcriptomic changes (*PVT1*) pertinent to +8 MN and whose role in driving leukemogenesis is well-established.

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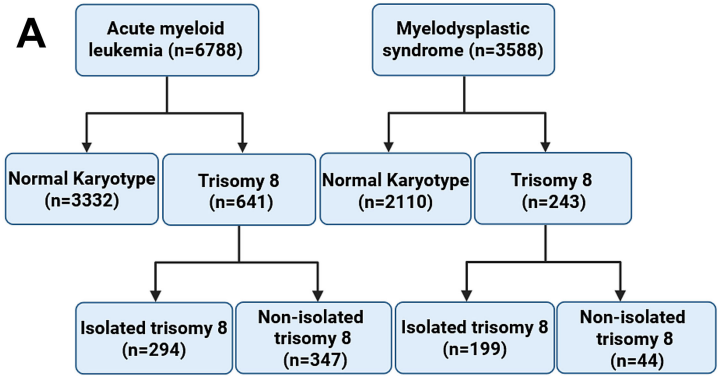
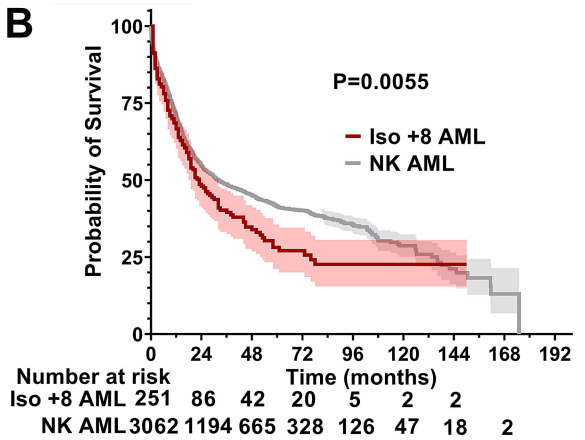
Figure legends

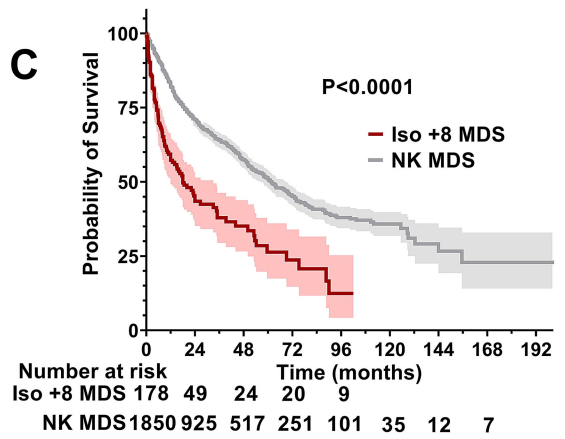
Figure 1. Molecular and clinical features of trisomy 8 myeloid neoplasia. (**A**) Flow diagram of the patients with trisomy 8 (+8) and normal karyotype (NK) acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) included in our study. (**B**) Kaplan-Meier survival curves demonstrating worse survival of isolated +8 AML versus NK AML. (**C**) Kaplan-Meier survival curves demonstrating worse survival of isolated +8 MDS versus NK MDS. (**D**) Comparison of the mutational patterns in iso +8 AML *vs* NK AML. (**E**) Comparison of the mutational patterns in iso +8 MDS *vs* NK MDS. (**F**) Bar chart of comparison of mutational patterns in iso +8 MDS vs iso +8 AML.

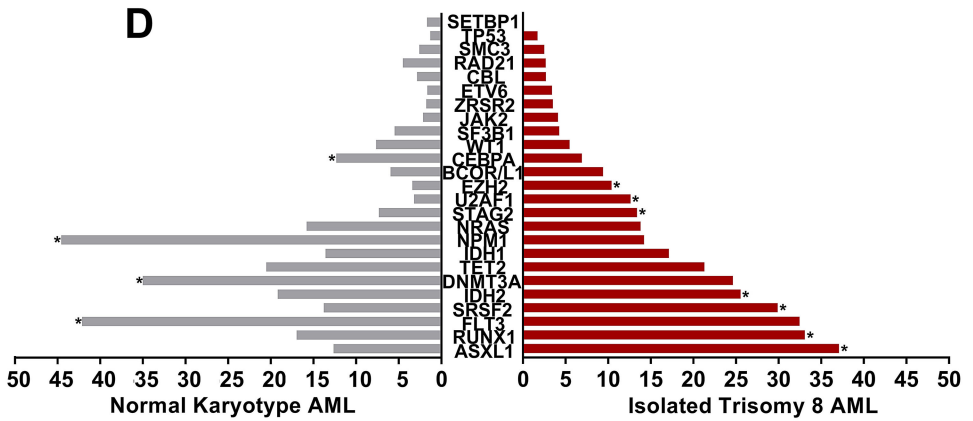
Figure 2. Transcriptomic features of trisomy 8 myeloid neoplasia. Heatmap visualization of the comparison of gene expression of the most differentially expressed genes located on +8 driving in +8 MN vs non +8 myeloid neoplasia. Numbers on the top indicate clusters.

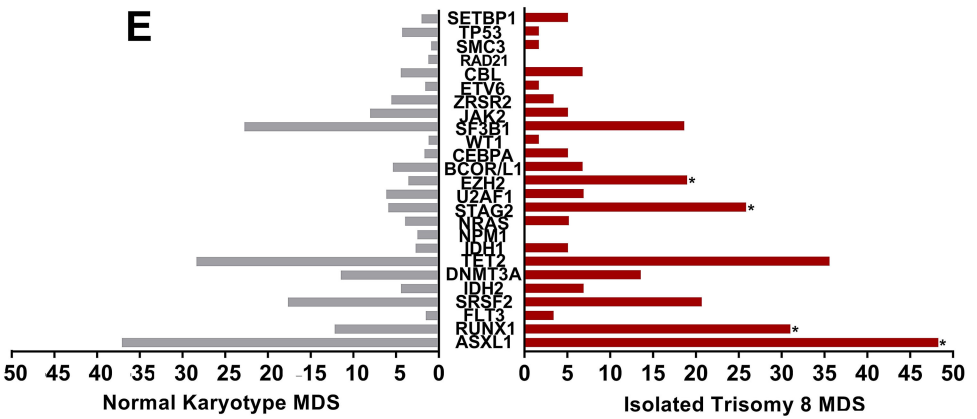
Figure 3. **Genetic predisposition of trisomy 8 myeloid neoplasia.** (**A**) Scheme of chromosome 8 with log correlation of expression with clonality of the identified oncogenes, *PVT1* and *MYC*. (**B**) Bar graph depicting the number of cases with +8 (15/219 sequenced by whole genome and exome sequencing) carrying germline pathogenic/like pathogenic variants in cancer and bone marrow failure predisposition genes. All genes found mutated are represented. Genes were also grouped according to category showing an enrichment in telomerase machinery, DNA repair, and Fanconi anemia.

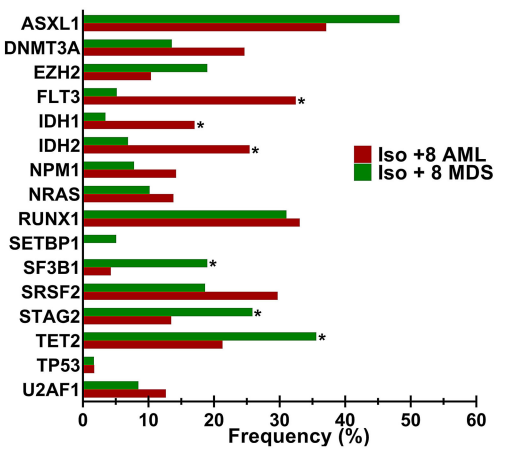

A
Acute myeloid leukemia (n=6788)
Myelodysplastic syndrome (n=3588)
Normal Karyotype (n=3332)
Trisomy 8 (n=641)
Normal Karyotype (n=2110)
Trisomy 8 (n=243)
Isolated trisomy 8 (n=294)
Non-isolated trisomy 8 (n=347)
Isolated trisomy 8 (n=199)
Non-isolated trisomy 8 (n=44)


B
Probability of Survival
P=0.0055
Iso +8 AML
NK AML
Number at risk
Time (months)
Iso +8 AML 251 86 42 20 5 2 2
NK AML 3062 1194 665 328 126 47 18 2


C
Probability of Survival
P<0.0001
Iso +8 MDS
NK MDS
Number at risk
Time (months)
Iso +8 MDS 178 49 24 20 9
NK MDS 1850 925 517 251 101 35 12 7


D
SETBP1
TP53
SMC3
RAD21
CBL
ETV6
ZRSR2
JAK2
SF3B1
WT1
CEBPA
BCOR/L1
EZH2
U2AF1
STAG2
NRAS
NPM1
IDH1
TET2
DNMT3A
IDH2
SRSF2
FLT3
RUNX1
ASXL1
Normal Karyotype AML
Isolated Trisomy 8 AML


E
Normal Karyotype MDS
Isolated Trisomy 8 MDS


F
ASXL1
DNMT3A
EZH2
FLT3
IDH1
IDH2
NPM1
NRAS
RUNX1
SETBP1
SF3B1
SRSF2
STAG2
TET2
TP53
U2AF1
Iso +8 AML
Iso + 8 MDS
Frequency (%)


20
9
16
19
13
5
15
1
12
10
3
2
8
14
4
7
6
11
Group
NonTri8
Tri8
Centered Expression
10
5
0
−5
−10
Clone
1
0.5
0
ZDHHC2
DCAF13
TAF2
TNKS
PSD3
INTS10
LAPTM4B
PVT1
FBXO25
NDUFB9
POLR3D
ZNF7
ERLIN2
FNTA
RPL7
COX6C
FZD6
CSPP1
ZFP41
OXR1
ANKRD46
PCM1
ELP3
PLAG1
HMBOX1
DECR1
CNOT7
NCOA2
TSNARE1
PPP2CB
PTDSS1
SMIM19
SPIDR
VPS13B
RMDN1
DEPTOR
INTS9
TMEM67
INTS8
UBE2W
COPS5
RPL23AP53
SNX16
SLC39A14
ANGPT1
CCDC25
TMEM64
SNHG6
C8orf33
GGH
PCMTD1
PEX2
ARHGEF10
SNTB1
AGPAT5
NUDCD1
IKBKB
EIF3E
EBAG9
BMP1
DPY19L4
UBR5
MRPL13
WWP1
ZNF251
CA13
UTP23
MYC
MROH1
PRKDC
STK3
EMC2
ZNF704
CPSF1
ASPH
DDHD2
PKIA
KIF13B
MRPL15
RPL8
LRP12
NDRG1
UBE2V2
NEIL2
VPS28
EIF4EBP1
TPD52
HGSNAT
ZNF623
TOP1MT
TIGD5
VDAC3
ZNF572
FUT10
ATP6V1C1
TCEA1
NSMAF
WRN
FAM86B3P
SAMD12
C8orf82
CHCHD7
FZD3
TSPYL5
KBTBD11
ZNF16
CLN8
ZNF395
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EPHX2
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TRPS1
ZNF252P
SCRIB
NIPAL2
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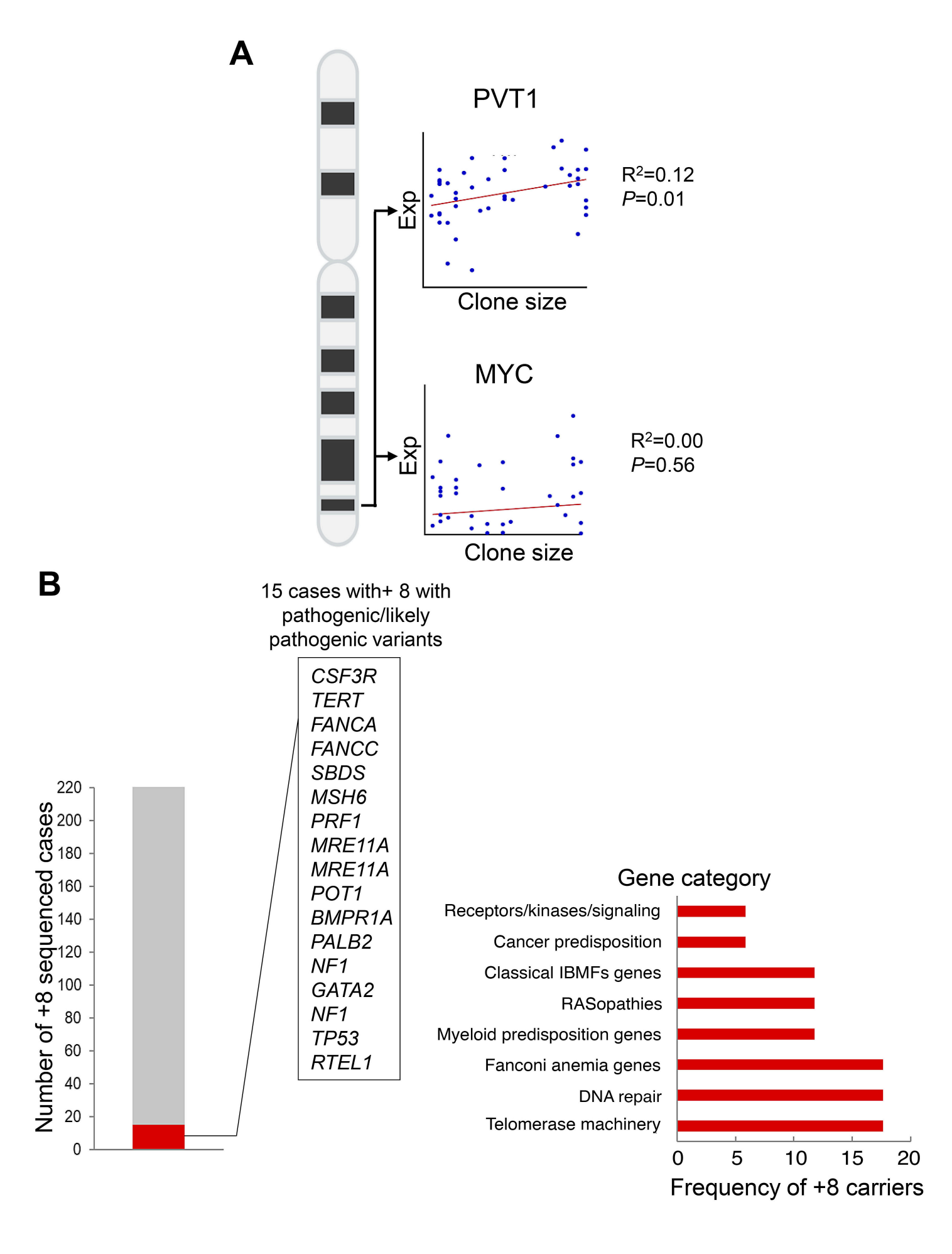

A
PVT1
Exp
Clone size
R²=0.12
P=0.01
MYC
Exp
Clone size
R²=0.00
P=0.56
B
15 cases with+ 8 with pathogenic/likely pathogenic variants
CSF3R
TERT
FANCA
FANCC
SBDS
MSH6
PRF1
MRE11A
MRE11A
POT1
BMPR1A
PALB2
NF1
GATA2
NF1
TP53
RTEL1
Number of +8 sequenced cases
0
20
40
60
80
100
120
140
160
180
200
220
Gene category
Receptors/kinases/signaling
Cancer predisposition
Classical IBMFs genes
RASopathies
Myeloid predisposition genes
Fanconi anemia genes
DNA repair
Telomerase machinery
0
5
10
15
20
Frequency of +8 carriers

Supplementary Material

Lessons of nature from trisomy-8 myeloid neoplasia: the riddle of oncogenic clonal drives

Legends to Supplementary Figures

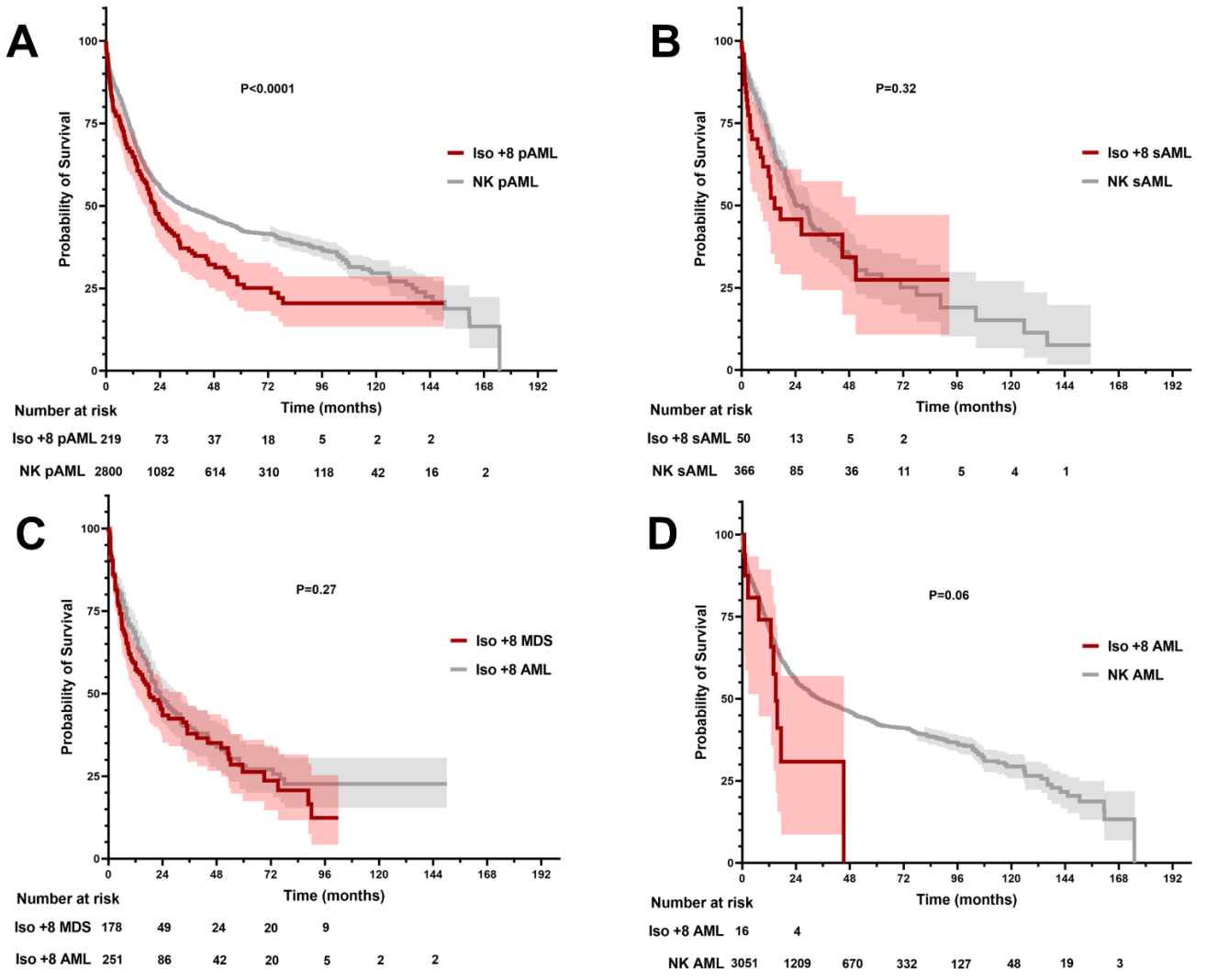
Figure S1. Survival outcomes of patients with trisomy 8. Kaplan-Meier survival curves of overall survival of isolated +8 pAML versus NK pAML **(Panel A)**, isolated +8 sAML versus NK sAML **(Panel B)**, isolated +8 MDS versus isolated +8 AML **(Panel C)**, and isolated +8 AML versus NK AML in patients who have received intensive chemotherapy regimens **(Panel D)**.

Figure S2. Clustering analysis of patients with trisomy 8. (Panel A) Machine learning-based clustering of +8 MDS and sAML. **(Panel B)** Machine learning demonstration of the genomic associations of + 8 MDS and sAML. **(Panel C)** Machine learning-based clustering of +8 pAML and sAML. **(Panel D)** Machine learning demonstration of the genomic associations of + 8 pAML and sAML. **(Panels E, F, G)** Bar charts of the trisomy 8 composition (E), MDS risk types (F), and clone size (G) of the studied clusters.

Legend to Supplementary Table provided as Excel file

Summary of the cohort of acute myeloid leukemia and myelodysplastic neoplasm cases included in our study. The table includes demographics, description, IPSS-M subgroups, factors influencing overall survival of our cohort and publicly available datasets, features of clusters of patients and detailed information of germline pathogenic/likely pathogenic variants found in our cohort of +8.

Supplementary Figure 1



Supplementary Figure 2