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Beyond 17p13.1: recurrent 17p11.2 breakpoints in *TP53*-altered acute myeloid leukemia

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Contributions

Authors DM and SB contributed substantially to the conceptualization, design, conduct, and analysis of this investigation. Data were collected by DM, SS, AS, and SB.

Statistics analysis was performed by SB and DM. RS reviewed all cytogenetic information for accuracy. BG, EJ, JEK, DWC, and DEG all contributed to the analysis and revised the manuscript. All authors contributed substantially to the writing of the manuscript, with DM as the lead author. All authors read and approved the final manuscript.

Data sharing

All anonymized data used in this investigation are available from the corresponding author on request.

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Figure 2 created in <https://BioRender.com>

TP53 alterations are found in 5-10% of *de novo* acute myeloid leukemia (AML) and are associated with genomic instability, karyotype complexity, and poor clinical outcomes.^{1,2} Although *TP53* point mutations are well-characterized in AML, the mechanisms through which *TP53* may become altered by cytogenetic changes to its locus on 17p remain poorly defined. Prior studies have largely described 17p abnormalities as aggregate categories, such as deletions or isochromosomes, without detailed analysis of breakpoint distribution.^{2,3,4} To address this gap, we combined clinical next-generation sequencing (NGS) with comprehensive cytogenetic and fluorescence in situ hybridization (FISH) analysis in a large real-world cohort of *TP53*-altered AML to define the structural architecture of 17p changes and determine whether breakpoint patterns reflect non-random genomic vulnerability. We identified recurrent clustering of mappable 17p breakpoints at the locus 17p11.2, a region approximately 8.5 Mb distant from the *TP53* locus at 17p13.1.

The electronic medical record system of Northwell Health (NY) was queried for new diagnoses of AML between January 1st, 2019 and December 31st, 2024. Cases were selected if they were found at diagnosis to have a *TP53* point mutation identified by NGS and/or a cytogenetic alteration involving 17p identified by clinical FISH and/or karyotyping. Cases without NGS and cytogenetics available from bone marrow samples at diagnosis were excluded.

NGS was performed using either the OnkoSight Myeloid Malignancies NGS panel (GenPath, Elmwood Park, New Jersey, USA) or the FoundationOne Heme panel (Foundation Medicine, Boston, MA, USA). FISH was performed according to standard clinical protocols using fluorescent-labeled probes with scoring of 200 interphase nuclei

per probe. The panel included a probe targeting the *TP53* locus at 17p13.1. Karyotyping was conducted per standard clinical protocol, with 20 metaphase spreads using Giemsa banding.

TP53 variant allele frequencies (VAFs) were compared using the Mann-Whitney U test. Subgroup comparisons utilized Fisher's exact test. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). This investigation was deemed exempt by the Northwell Health Institutional Review Board and was conducted in accordance with the Declaration of Helsinki.

A total of 957 AML cases were identified between 2019 and 2024. Of these, 104 cases harbored at least one *TP53* alteration or 17p cytogenetic abnormality at diagnosis. 13 cases were excluded due to incomplete NGS or cytogenetic data, leaving 91 evaluable cases. The median age of diagnosis was 73 (range: 35 – 92 years). 62.6% (n= 57) were *de novo*, 16.5% (n= 15) had a prior myeloid neoplasm history (secondary AML), and 20.9% (n= 19) had history of prior cytotoxic chemotherapy and/or radiation (treatment-related AML).

85.7% (n=78) of cases harbored at least one *TP53* somatic mutation identified by NGS, while 69.2% (n=63) demonstrated at least one cytogenetic alteration involving 17p (Figure 1). Concurrent *TP53* point mutation and 17p structural alteration was observed in 54.9% (n= 50) of cases. In contrast, 30.8% (n=28) of the cohort had a *TP53* mutation without a detectable 17p cytogenetic change while 14.3% (n=13) of the cases in this cohort had a 17p alteration but lacked a *TP53* point mutation. Seven cases demonstrated 17p abnormalities detected by FISH but not by karyotyping, suggesting the presence of submicroscopic deletions or cryptic structural rearrangements not

captured by conventional cytogenetic methods. Of those with evaluable variant allele frequency (VAF, n= 45), the median *TP53* VAF was 43.7% (range: 9.0% – 97.5%). There was no significant difference in median *TP53* VAFs between cases with and without concurrent 17p cytogenetic changes (43.0% vs 44.5%, respectively; p=0.749).

Complex karyotype (≥ 3 abnormalities) was highly prevalent in this cohort. Among cases with *TP53* mutation, 92.3% (n=72/78) exhibited complex karyotype compared with 69.2% (n=9/13) in cases without a detectable *TP53* mutation (p=0.033). Similarly, complex karyotype was observed in 93.7% (n=59/63) of cases with 17p alterations versus 78.6% (n=22/28) without 17p involvement (p=0.063). Complex karyotype was present in 100% (n=50/50) of cases with concurrent *TP53* mutation and 17p alteration.

Across the cohort, 60 discrete cytogenetic aberrations involving 17p were identified by conventional karyotyping (Table 1). Monosomy 17 was the most frequently encountered abnormality, representing 53.3% of events. Additional changes included additions (21.7%), subchromosomal deletions (11.7%), translocations (8.3%), isochromosomes (3.3%), and pseudodicentric chromosomes (1.7%) involving 17p. A small subset of cases (n=5) demonstrated two distinct *TP53* point mutations with a 17p deletion on karyotype but no loss of the *TP53* locus by FISH, which may represent cryptic structural rearrangements below the resolution of standard karyotyping. This highlights the limitations in inferring allelic status from standard karyotyping. All mappable breakpoints localized proximal to *TP53* (i.e., between 17p13.1 and the centromere); no breakpoints were identified distal to the *TP53* locus. Among cytogenetic changes with subchromosomal breakpoints amenable to cytogenetic-band-level localization, 68.2% (n=15/22) mapped to the 17p11.2 region. Most cases with

changes involving 17p11.2 (n=14/15) had complex karyotypes and the majority (n=11) co-occurred with at least one *TP53* point mutation.

The recurrent clustering of mappable 17p breakpoints at 17p11.2 identifies a previously underrecognized structural pattern in *TP53*-altered AML. This convergence at a cytogenetically distinct region closer to the centromere suggests that structural 17p abnormalities in AML may reflect locus-specific genomic vulnerability rather than solely random chromosome breakage occurring in the setting of complex karyotype. Importantly, this pattern was observed across structurally heterogeneous abnormalities, including additions, translocations, subchromosomal deletions, and pseudocentric chromosomes.

The convergence of breakpoints at 17p11.2 is biologically consistent with the known structural vulnerability of this region and supports a recurrent structural model for biallelic *TP53* inactivation. The 17p11.2 locus contains well-defined segmental duplications known as Smith-Magenis syndrome repeats (SMS-REPs), which were originally delineated in congenital microdeletion and microduplication disorders of the same name.⁵ These low-copy repeats (LCRs) can promote recurrent deletions and duplications through misaligned recombination and replication-based errors, establishing 17p11.2 as a site of inherent genomic fragility (Figure 2A).⁵ Similar breakpoint clustering within SMS-REP regions has been independently observed across multiple malignancies. Breakpoint clustering within SMS-REP regions has been independently demonstrated with isochromosome i(17q) in CML blast crisis,^{6,7} primary myelofibrosis,⁸ and SNP array-based breakpoint mapping of 17p deletions in chronic lymphocytic leukemia.⁹ Breakpoint clustering within this region has also been described

in pediatric solid tumors.^{10,11,12} The reproducibility of this pattern across disease contexts provides independent support for intrinsic structural susceptibility of 17p11.2. Our findings extend these observations to the broader spectrum of 17p abnormalities occurring in AML.

These observations are also consistent with a model in which *TP53* dysfunction and locus-specific genomic vulnerability may cooperate. In this model, loss of *TP53*-mediated genomic surveillance may permit survival of cells with abnormal repair intermediates. In this permissive state, intrinsically fragile genomic regions such as the LCR-containing 17p11.2 may be particularly susceptible to defective double-strand break repair.^{3,13} Such events could provide one mechanism through which structural alteration of the remaining 17p allele arises in *TP53*-mutated AML (Figure 2B). However, the cross-sectional nature and cytogenetic resolution of the present study do not establish temporal sequence.

A smaller subgroup (14.3%, n=13) had 17p alterations without a detectable *TP53* point mutation. Similar observations have been reported in hematologic and solid malignancies, including i(17q), where cytogenetic changes involving the 17p11.2 region occurred in the absence of *TP53* coding mutations.^{6,14} Studies of del(17p) in other malignancies suggest that its biological effects may extend beyond *TP53* loss and include contributions from co-deleted genes within the 17p region.^{9,15} This raises the possibility that 17p11.2 abnormalities may have biological consequences independent of *TP53* coding loss, alone.

This study is limited by its reliance on clinically available cytogenetic testing, which lacks the resolution of molecular-level mapping when assigning breakpoints.

Copy-neutral loss of heterozygosity could not be detected with these means and small or cryptic structural abnormalities may also have escaped detection. Higher resolution techniques such as optical genome mapping will therefore be important to confirm whether breakpoints truly converge within defined LCR elements at 17p11.2 and to determine the precise relationship of individual rearrangements to the *TP53* allele.

In summary, this study provides, to our knowledge, the first comprehensive survey of chromosome 17p changes in *TP53*-altered AML and identifies 17p11.2 as a recurrent and non-random breakpoint hotspot across diverse 17p aberrations in *TP53*-altered AML. The clustering of mappable breakpoints at a region centromeric to and cytogenetically distinct from the *TP53* locus at 17p13.1, suggests that 17p abnormalities may be shaped by locus-specific genomic architecture rather than random chromosome breakage, alone. This broader structural architecture is not fully characterized by mutation-centric approaches or locus-restricted FISH assays, providing a potential explanation for why recurrent involvement of 17p11.2 in AML has not been recognized until now. This highlights the limitations of inferring *TP53* allelic architecture from mutation analysis and locus-specific assays, alone. The identification of a subset of cases with diverse 17p changes lacking *TP53* mutations, together with evidence from other myeloid neoplasms, also raises the possibility that recurrent 17p11.2 alterations may affect biologically relevant genes beyond *TP53*. Future investigations incorporating higher-resolution structural mapping capable of resolving individual LCR elements, longitudinal sampling, and functional characterization of candidate 17p11.2 tumor suppressors will be essential to validate this model and define its implications for *TP53* allelic classification, risk stratification, and therapeutic development.

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Figures and tables

Structural change type	Karyotype findings (ISCN)	N
Del(17)	Del(17)	32
Additions	Add(17)	6
	Add(17)(p11.2)	6
	Add(17)(p13)	1
Isochromosome	i(17)(q10)	2
Deletions	Del(17)(p11.2)	6
	Del(17)(p13)	1
Pseudodicentric	Psu dic(17;16)(p13;p11.2)	1
Translocations	t(5;17)(q12; p11.2)	1
	t(7;17)(p13; p11.2)	1
	t(11;17)(q14;p11.1)	1
	t(11;17)(q23;p13)	1
	t(17;18)(p11.2 ;q11.2)	1

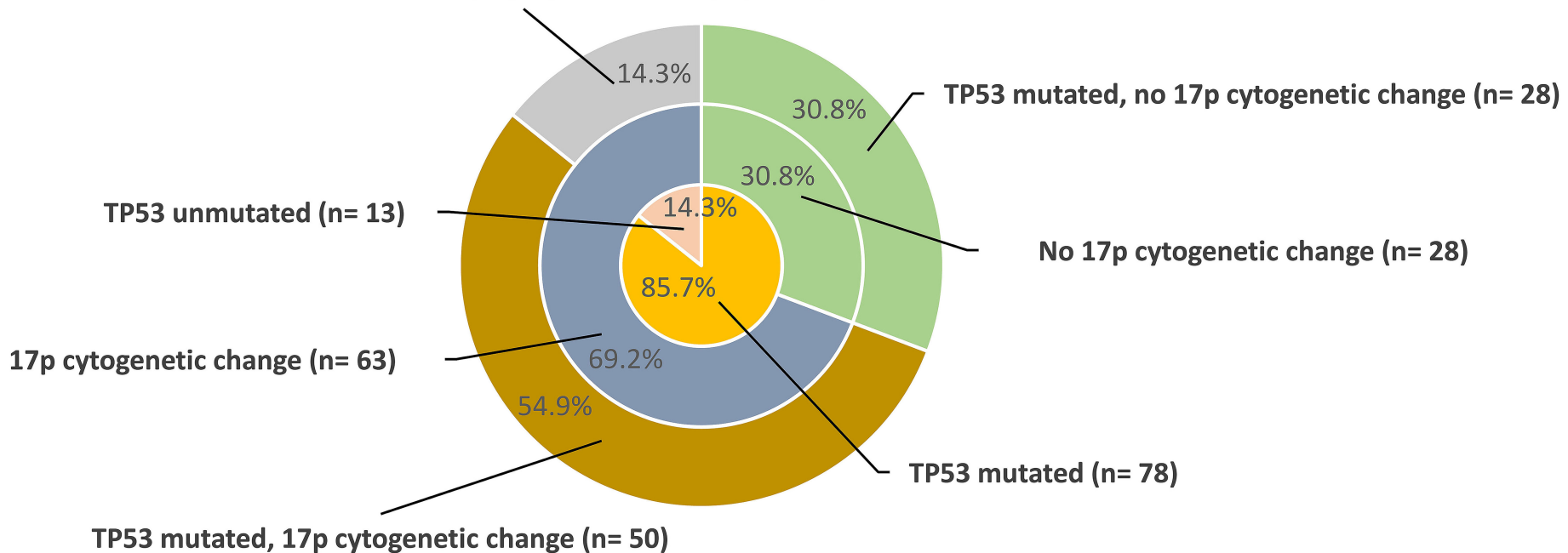
Table 1: Identified chromosome 17 cytogenetic changes. ISCN: International

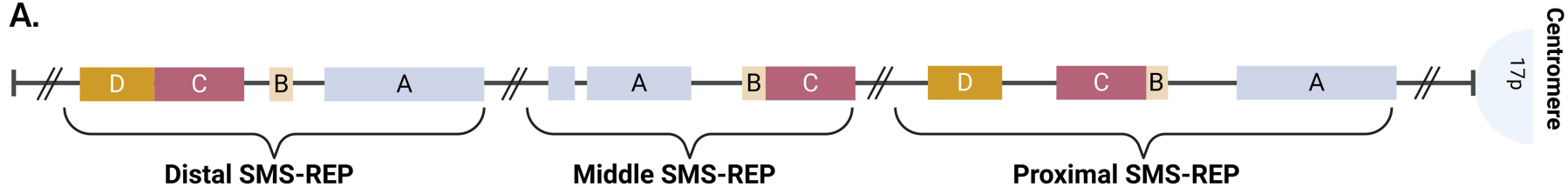
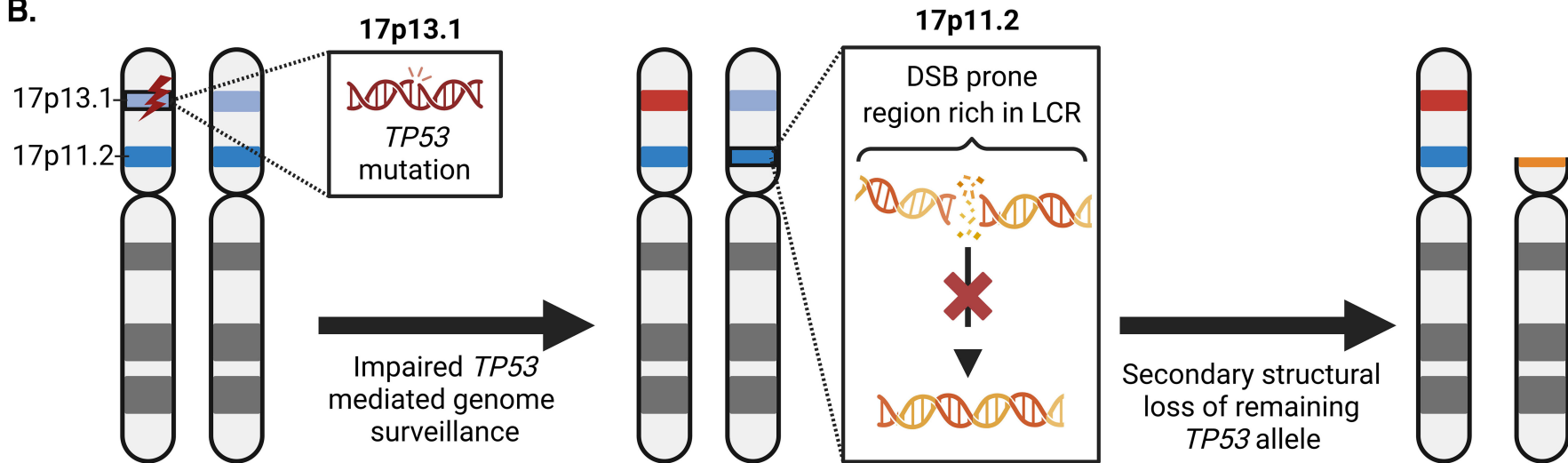
System for Human Cytogenomic Nomenclature, Del: deletion, Add: addition, i: isochromosome, psu dic: pseudodicentric chromosome, t: translocation, der: derivative chromosome. Cytogenetic changes involving 17p11.2 are in bold.

Figure 1: Nested pie chart illustrating *TP53* mutation status and 17p cytogenetic alterations for this *TP53*-altered cohort. Concentric circles describe *TP53* mutation status (inner), 17p rearrangement status (middle), and combined *TP53* mutation and 17p rearrangement status (outer) for this cohort.

Figure 2: Diagrammatic representation of the human SMS-REP region and its contribution to structural changes. (A) Structure of the low-copy repeat gene cluster (SMS-REPs) on chromosome 17p. Regions A, B, C, and D are homologous segments found in the proximal, middle, and distal SMS-REPs (except for D, which is not found in the middle SMS-REP). They are 98% homologous, except for D which is 95% homologous between proximal and distal SMS-REPs. The middle SMS-REP is in the opposite orientation to the proximal and distal SMS-REPs. Aberrant meiotic recombination events can occur between proximal and distal SMS-REPs, resulting in microdeletions and microduplications. (B) Genome architecture–driven model of stepwise *TP53* allelic loss in AML. An initial *TP53* point mutation impairs genomic surveillance and repair fidelity. Double-strand break (DSB) repair occurring within the low-copy repeat (LCR)–rich 17p11.2 region predisposes recurrent structural rearrangements of chromosome 17p. These events frequently delete or disrupt the remaining *TP53* allele, resulting in biallelic inactivation. Abbreviations: SMS-REP, Smith-Magenis syndrome low-copy repeat region.

TP53 unmutated, 17p cytogenetic change (n= 13)



A.**B.**

Supplemental Table 1: Table of all cytogenetics and NGS results for the total cohort. 17p11.2 cytogenetic changes are in bold. FISH: fluorescence in-situ hybridization. NGS: next generation sequencing. This Supplemental Table is available as an Excel file.