haematologica
Journal of the Ferrata Storti Foundation

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Received: August 4, 2026.
Accepted: August 7, 2026.

Citation: Isolde Summerer and Wolfgang Kern. Trisomy 8 in myeloid neoplasms: more than a passenger alteration?
Haematologica. 2026 Aug 20. doi: 10.3324/haematol.2026.301767 [Epub ahead of print]

Trisomy 8 in myeloid neoplasms: more than a passenger alteration?

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Authorship Contributions: Both authors designed and wrote the manuscript.

Disclosures: WK declares part ownership of MLL Munich Leukemia Laboratory. IS is employed by the MLL.

In this issue of *Haematologica*, Awada *et al.*[1] present a comprehensive genomic analysis of trisomy 8 (+8) in myeloid neoplasms, integrating data from more than 10,000 patients with acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), and bone marrow failure disorders across institutional and public series. The large sample size provides statistical power for robust conclusions about a cytogenetically defined subgroup that is numerically rare in individual datasets.

Trisomy 8 is one of the most common cytogenetic aberrations in myeloid neoplasms, present in approximately 5–10% of MDS and AML cases. It may occur as the sole karyotypic abnormality (iso +8) but is frequently accompanied by other aberrations or part of a complex karyotype.[2] In the 2022 ELN classification, +8 is assigned to the intermediate-risk group in AML. Similarly, in MDS, +8 falls into the intermediate cytogenetic risk category of the IPSS-R, a classification that is carried forward into the IPSS-M, which additionally incorporates the prognostic contribution of co-occurring somatic mutations.[3,4]

Awada *et al.* analyzed 294 iso +8 AML and 199 iso +8 MDS cases in comparison to cases with normal karyotype (NK) and demonstrated that the genomic context rather than the phenotype is the primary determinant in +8 myeloid neoplasms. As central finding they revealed a characteristic co-mutational fingerprint. Iso +8 AML was significantly enriched for mutations in splicing factors (*SRSF2*, *U2AF1*), chromatin modifiers (*ASXL1*, *EZH2*), the lineage transcription factor *RUNX1*, and the cohesin gene *STAG2*, while inversely associated with mutations in *NPM1*, *FLT3*, *DNMT3A*, and *CEBPA*. In iso +8 MDS, a similar but not identical pattern was observed, with overrepresentation of mutations in *ASXL1*, *EZH2*, *RUNX1* and *STAG2*. This pattern closely mirrors the set of myelodysplasia-related (MR) gene lesions used in current classifications: WHO-HAEM5 defines AML-MR by the presence of specific somatic mutations (*ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*) or cytogenetic abnormalities (including del(5q)/−5, −7/del(7q), del(17p), complex karyotype, and others), while the ICC additionally recognizes *RUNX1* mutations as well as trisomy 8 among its MR-defining criteria.[5,6]

Both iso +8 MDS and AML cases showed worse overall survival than their NK counterparts, and iso +8 remained an independent adverse factor in multivariable models. The rather large confidence interval of the survival curves for iso +8 cases still suggest an uncertainty of this conclusion. A stratification by the mere presence of MR-mutations, or in general high-risk mutations, in a multivariate analysis might contribute to further clarify prognostic factors. The prognostic impact of +8 appears to be largely

modulated by the accompanying MR mutational background rather than by the cytogenetic abnormality itself. Huber *et al*.[7] recently analyzed a cohort of 460 AML patients with non-typical MR-defining chromosomal lesions according to WHO or ICC. In this cohort, 80% of cases showed +8, while the remaining abnormalities (del(20q), del(11q), del(12p), −13/del(13q) and idic(X)) were individually rare. Importantly, 86% of these patients carried WHO-defined MR gene mutations, most frequently *ASXL1* and *SRSF2* and *RUNX1*-mutated cases had additional MR mutations. Only a small subset of patients showed atypical MR cytogenetics without MR mutations. These mutation-negative cases had a markedly superior overall survival compared with WHO-defined AML-MR, an advantage that remained even after exclusion of *TP53*-mutated AML from the analysis. Together, these results indicate that atypical MR-type chromosomal lesions such as +8 do not, by themselves, reproduce the poor prognosis of AML-MR and should not automatically qualify for AML-MR in the absence of MR-defining mutations. They also support the notion – consistent with the findings of Awada *et al.* – that in AML with +8 the adverse risk is largely driven by the MR-type mutational background.

The transcriptomic data presented by Awada *et al.* add important dimensionality to this concept: *PVT1*, a long non-coding RNA on 8q24.21, emerged as a top overexpressed oncogene whose expression correlated significantly with clone size, while *MYC* overexpression, encoded on the same chromosomal locus, did not reach significance in correlation with clonality. The authors postulated a mechanistic link between *PVT1* and miRNA-29 sponging –leading to upregulation of the anti-apoptotic WAVE1 protein – thereby offering a molecularly plausible route by which the extra copy of chromosome 8 could amplify leukemogenic fitness in a mutation-dependent manner.

Based on their data, Awada *et al.* propose that iso +8 myeloid neoplasms represent a distinct entity. At the same time, +8 is characterized by broad clinical and genetic heterogeneity: it is encountered across the entire spectrum of myeloid disease and premalignant states – from clonal cytopenia of undetermined significance (CCUS) through MDS or chronic myelomonocytic leukemia (CMML) to overt AML – and is often present in small (sub)clones rather than as a primary aberration. A similar pattern has been observed in *RUNX1*-mutated AML: *RUNX1* mutations overlap with such a broad range of defining molecular features which led to discontinue 'AML with *RUNX1* mutation' as a distinct disease category in WHO-HAEM5.[5]

Despite the substantial insights provided by Awada *et al*., several questions remain. The present study does not address CMML, a disease in which the prognostic significance of +8 is particularly controversial: while the CPSS[8] and CPSS-mol[9] classify +8 as a high-risk cytogenetic abnormality in CMML, the BLASTmol[10] assigns +8 as non-unfavorable with low cytogenetic risk. Also, published series are limited by small CMML patient numbers with isolated +8. Additional comprehensive cross-entity studies comprising large cohorts of CCUS, MDS, CMML and AML patients might thus help to further elucidate the role of +8 in myeloid neoplasms. Including the reconstruction of clonal hierarchies in which +8 arises, and incorporating direct mutation-stratified comparison of survival can contribute to determining conclusively whether +8 independently shapes the genetic background and thus prognosis or rather its co-mutational partners.

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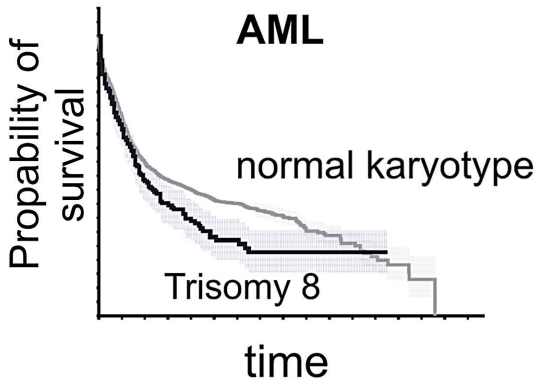
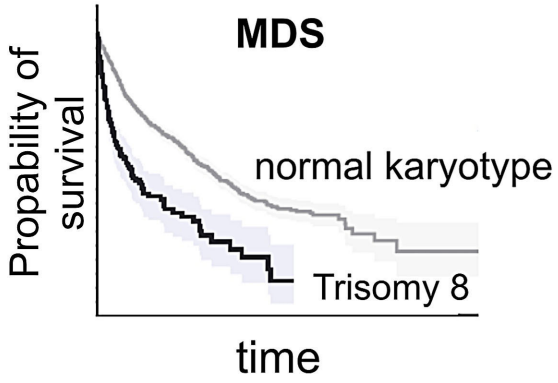
Figure legend:

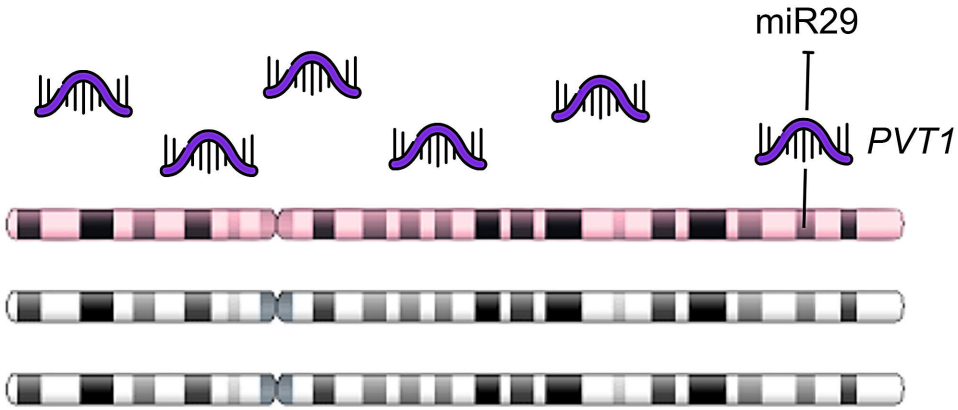
Figure 1. Characteristic findings from Awada *et al.* a Overall survival effect, b Specific gene expression signature, c Distinct mutation profile. AML: acute myeloid leukemia; MDS: myelodysplastic neoplasm; NK: normal karyotype.

a Overall survival effect





b Specific Gene expression signature



c Distinct mutation profile