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Prognosis in *NPM1* mutant acute myeloid leukemia: age and per-mutation permutations?

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In this issue, Gil and colleagues at PETHEMA seek to account for age and co-mutational interdependencies to resolve the genomic landscape of nucleophosmin-1 mutant (*NPM1*mt) acute myeloid leukaemia (AML)[1]. To do so, they leveraged a real-world registry cohort of 1360 patients with *NPM1*mt AML treated in the era of 7+3, with harmonised cytomolecular data. They provide a large-scale description of characteristics in a cohort with higher median age (64) than existing clinical-trial derived datasets, in particular with 287 patients over 75 years of age. Within the intensively treated subset, the authors characterise the prognostic impact of co-mutational combinations and disentangle the impacts of genes which have been grouped together in previous analyses.

Mutational burden appeared to increase with age with a per-gene age-dependent increase in spliceosome and *TET2* variants. Previously observed interdependencies in *NPM1*mt AML, such as mutual exclusivity patterns (*TET2/IDH1/IDH2 or DNMT3A/SRSF2)* and enrichment of co-occurrence (*IDH2+SRSF2* and *TET2+SRSF2*) all appearing strongest with increasing age. The adverse prognostic effect of myelodysplasia-related gene (MRG) variants appeared driven by increasing mutational burden and enrichment in *SRSF2* variants. Pair and trio combination analysis showed *SRSF2* and *TET2* pairs also conferred worse outcomes. In line with prior analyses, non-ABD *NPM1* variants and *KRAS* (but not *NRAS*) variants emerged as independently adverse, and non-internal-tandem-duplication, non-tyrosine-kinase-domain *FLT3* variants (*FLT3*-other) appeared to be protective.

Age-related differences in AML phenotypes have long been recognised and include an enrichment with advancing age of low blast counts, dysplasia, treatment resistance, and an increasing relative abundance of small genomic variants over larger structural variants such as fusion genes[2]. Disentangling the impact of these changes from the inherent adverse effect of advanced age has long been a challenge, requiring very large datasets to determine whether any independent effects remain. Adding to this challenge is that many previous analyses relied on focused clinical trial cohorts fit for induction[3], necessarily excluding older adults. Population data from large prospectively collated real-world registries such as this allow for analysis of a sufficiently sized older stratum of patients to help resolve gene-specific, age-dependent associations.

MRGs characterise the pathology of secondary AML (sAML), which exhibits a strong age-dependent incidence, constituting the predominant form of AML in the elderly[4]. In 2015, Lindsley and colleagues proposed the molecular definition of sAML on the basis of the relative abundance of mutations in eight genes in 93 clinical sAML patients compared to de novo AML[5]. Subsequently, larger sAML analyses (and disease classification schemas) have tended to pool patients with mutations in these genes together, rather than analysing individual genes themselves, and repeatedly shown adverse aggregate outcomes. In *NPM1*mt cohorts however, more inconsistent impacts have been reported vis-a-vis MRG. To resolve this, a recent meta-analysis of young, induction-eligible *NPM1*mt AML patients did show a discernible effect of MRG on prognosis, albeit to a hazard ratio for OS of 1.3, smaller than the difference between ELN risk strata, with a trend toward being driven predominantly by *ASXL1* variants in that analysis[6].

How do we reconcile the different reports on the impact of MRG in the *NPM1*mt versus sAML contexts, and the previous inconsistent findings in *NPM1*mt cohorts? Within sAML, a recent pooled analysis of nearly five thousand patients possessed sufficient statistical power to demonstrate that *ASXL1*, *RUNX1*, *SF3B1* and *U2AF1* variants drove worse outcomes than *SRSF2* or *STAG2*[7]. The incidence of specific MRG variants differ substantially between *NPM1*mt AML and sAML: *ASXL1, RUNX1 and SF3B1* variants are uncommon in *NPM1*mt AML, where *STAG2* and *SRSF2* predominate. Evidently the proportion of each constituent gene within “MRG” skews prognostic analyses in a given cohort, and perhaps the tendency to lump all 8 (or 9) genes together has confounded prior analyses.

Adding to the caution with grouping apparently biologically related genes together, Gil and colleagues demonstrate here that *KRAS* co-mutations*,* but not *NRAS,* are adverse, despite their ubiquitous lumping as “RAS” genes in prior analyses and prognostic models[8]. This differential *KRAS* vs *NRAS* prognostic signal has been seen elsewhere[9], and further large studies are required to determine the context specific effects of each gene, and indeed different variants within each gene. The protective nature of the *FLT3*-other variant grouping requires further study into the already highly revelatory ongoing work into the domain-specific and variant-type-specific behaviour of *FLT3* variants, but clearly not all *FLT3* variants are alike. Finally, the *NPM1* mutation types themselves appear to have distinct and age-dependent associations, and merit consideration as individual variables when studied at scale.

Caution is advised in over-interpreting the deleterious prognostic effects detected for individual variables such as *SRSF2* variants in clinical practice. Crucially, *NPM1*mt AML is amenable to measurable residual disease (MRD) assessment, a powerful orthogonal tool for prognostic discrimination. Cocciardi et al. suggest that the prognostic effect of MRG are captured in MRD analyses, so employing *SRSF2* or mutation-pair/trio for risk stratification may not be necessary when MRD results are available. Notably, the effect size of post-course 2 MRD positivity outweighs that of the adverse features proposed here[3,10].

We are left with a more granular picture of adverse genomic risk factors within *NPM1*mt AML through a chronological lens, including the familiar *DNMT3A*/*FLT3*-ITD/*NPM1* trio in younger adult AML and an emerging oligoclonally layered disease in older adults. These age-resolved findings demonstrate the power of large-scale harmonised data registries and the risks of categorical lumping in understanding outlook. Looking forward, novel treatment paradigms for *NPM1*mt AML will no doubt reshuffle these prognostic determinants and future investigators would do well to learn from Gil and colleagues’ study, prospectively collecting and carefully annotating data to allow for the avoidance of lumping and therefore more nuanced findings.

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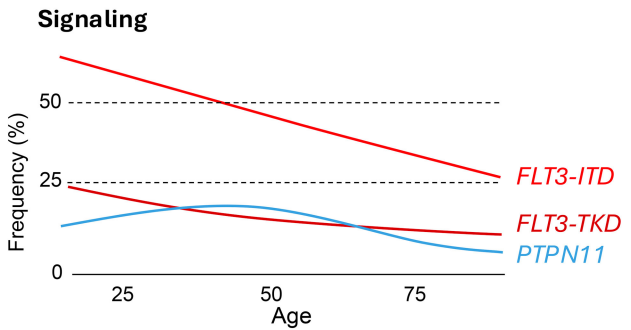
Figure captions

Figure 1 – conclusions and lessons from Gil et al's study[1]

A) Mutation frequency changes with age, and these changes have age specific prognostic significance
B) Previous analyses 'lumping' genes into apparently biologically relevant groups risks missing nuance within these groups

Age-related changes in mutation frequency

Architecture varies with age with prognostic relevance



Refined prognostic impact risk of biologically related genes

'Lumping' genes together risks missing prognostic nuance