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Genomic Landscapes and Clonality of De Novo AML

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We agree that it is important to understand whether mutations are responsible for the initiation of AML or cooperate with initiating mutations to cause disease progression or relapse.[1,2] Whereas initiating mutations may be more likely to appear in founding clones, cooperating mutations might appear either in founding clones or subclones derived from founding clones. In our study, it was not possible to define the clonal architecture for all samples, both because AML genomes harbor a comparatively small number of mutations and because for 150 of 200 samples, only exome sequencing was performed. Nevertheless, we have used the data in Table S6 (available with the full text of our article at NEJM.org) to identify variants in significantly mutated genes that can be assigned with high confidence to either a founding clone or a subclone.

Mutations in some genes appear almost exclusively in founding clones, which suggests that they are disease initiators. These genes include *RUNX1* (9 of 9 mutations in founding clones), *NPM1* (3 of 3), *U2AF1* (5 of 5), *DNMT3A* (38 of 40), *IDH2* (13 of 14), *IDH1* (15 of 17), and *KIT*(5 of 6). In contrast, mutations in *NRAS* (1 of 12 in founding clones), *TET2* (13 of 18), *KRAS*(4 of 6), *CEBPA* (3 of 5), *WT1* (3 of 6), *PTPN11* (4 of 8), and *FLT3* (6 of 13), are often found in subclones, suggesting that they are often cooperating mutations. Many additional genomes will need to be tested to make these tentative assignments more definitive.

References

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Since publication of their article, the authors report no further potential conflict of interest.