Nature Reviews Cancer | Published online 15 Jul 2016; doi:10.1038/nrc.2016.75

GENETICS

Acute myeloid leukaemia: driving the driver

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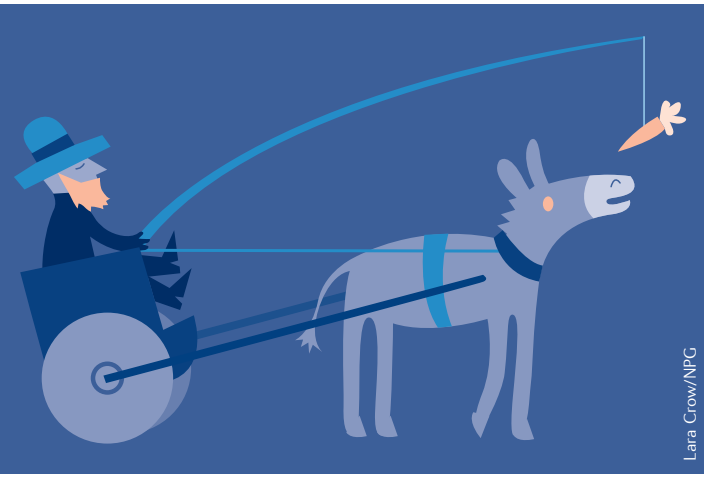

Lara Crow/NPG

Acute myeloid leukaemia (AML) is not only a complex disease presenting with more than one driver mutation but also a dynamic one that evolves over time and in which multiple clones can coexist at any point. Papaemmanuil *et al.* have now further investigated which mutations drive AML and classify the disease in distinct subgroups associated with different diagnostic features and clinical outcomes.

The authors analysed cytogenetic and clinical data from 1,540 patients with AML. They sequenced 111 genes known to be driver genes in cancer and identified 5,234 driver mutations, with at least one driver mutation in 96% of the samples and two or more mutations in 86% of the samples.

Although patterns of co-occurring mutations and mutual exclusivity have been described previously in AML, the high number of samples in this study enabled Papaemmanuil *et al.* to identify many new gene–gene correlations as well as differences in patterns of co-mutation, for example, nucleophosmin (*NPM1*) mutations associated with mutations in $NRAS^{G12/13}$ but not those in $NRAS^{Q61}$, and with mutations in isocitrate dehydrogenase 2 $(IDH2)^{R140}$ but not those in $IDH2^{R172}$.

The authors also established patterns of clonal evolution. They found that mutations in genes encoding epigenetic modifiers, such as DNA methyltransferase 3α (*DNMT3A*), *ASXL1*), *IDH1*, *IDH2* and *TET2*, occurred in the founding clone and were almost never found in isolation, which suggests that they require a co-occurring mutation to initiate AML. By contrast, mutations in genes encoding members of the RAS pathway generally occurred late in leukaemogenesis, and *NPM1* mutations often occurred after mutations in *DNMT3A*, *IDH1* or *NRAS*.

The characterization of many new genes involved in AML, multiple driver mutations per patient and co-mutation patterns led the authors to re-evaluate the current genomic classification of AML, which could not have classified 50% of the patients in the study. The new classification included 11 different subgroups: the largest subgroup included patients with mutations in *NPM1* (27% of the cohort) 73% of whom also harboured mutations in epigenetic modifiers. The second largest subgroup (18% of the cohort) was defined by mutations in genes regulating RNA splicing (*SRSF2*, *SF3B1*, *U2AF1* and *ZRSR2*), chromatin (*ASXL1*, *STAG2*, *BCOR*, *MLLPTD*, *EZH2* and *PHF6*) or transcription (*RUNX1*). Another subgroup included patients (13%) with mutations in *TP53*, chromosome gain or loss, and copy number alterations.

This new classification enabled 80% of patients with identified driver mutations to be unambiguously assigned to a single subgroup, whereas 4% met criteria for two or more categories and 11% remained unclassified, potentially because they harboured mutations in driver genes not sequenced or because some group-defining mutations had been missed.

Finally, the new classification also enabled prognostic stratification, as the effect of individual mutations, such as those in *NPM1*, can be considerably altered by the presence or absence of mutations in *NRAS*, *IDH1*, *IDH2*, *PTPN11*), fms related tyrosine kinase 3 (*FLT3*), and chromatin and spliceosome. Prognostic effects of some driver mutations were influenced by the presence or absence of mutations in other genes. For example, $FLT3^{ITD}$ conferred a particularly poor prognosis when combined with *NPM1* and *DNMT3A* mutations.

Although the authors stress that a genomic classification does not presuppose clinical relevance, it can certainly help in defining the pathophysiology of the disease and possibly the way it can be treated.

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ORIGINAL ARTICLE Papaemmanuil, E. *et al.* Genomic classification and prognosis in acute myeloid leukemia. *N. Engl. J. Med* **374**, 2209–2221 (2016)