CANCER GENETICS

How to predict the future

> prediction models to distinguish individuals who have a high risk of developing AML from those with ARCH

The onset of acute myeloid leukaemia (AML) is preceded by the serial acquisition of somatic mutations in single haematopoietic stem and progenitor cells (HSPCs), which then clonally expand. However, AML-associated mutations can also accumulate in HSPCs of healthy individuals during normal ageing, an event known as clonal haematopoiesis of indeterminate potential (CHIP) or age-related clonal haematopoiesis (ARCH). Previous studies using whole-exome sequencing of peripheral blood cells from large prospective cohorts revealed that ARCH is associated with an increased risk of haematopoietic malignancies; yet these studies were not powered to detect risk associated specifically with progression to AML or with individual genes. To this end, two new studies published in *Nature* and *Nature Medicine* have generated prediction models to distinguish individuals who have a high risk of developing AML from those with ARCH, years before diagnosis of the disease.

Both groups took advantage of a nested case–control study design to obtain cohorts of individuals with AML from larger population studies as opposed to using an unselected population. Targeted deep sequencing of previously collected peripheral blood samples was then performed to analyse genes known to be involved in AML.

Abelson et al. sequenced samples from 124 individuals with AML collected on average ~7 years before diagnosis (pre-AML cases) and 676 age-matched and gender-matched controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohort of > 500,000 individuals. This revealed that ARCH with a putative driver mutation was more frequent in pre-AML cases (73.4%) compared with controls (36.7%). Furthermore, a higher median number of mutations and variant allele frequency (VAF), indicative of larger clone size, per individual were associated with progression to AML. Mutations in individual genes, including *TP53*, *IDH2* and the spliceosome genes *SRSF2* and *U2AF1*, also contributed to risk of progression.

Desai et al. used the prospective Women's Health Initiative study of more than 160,000 women to select 212 women with AML and, similarly, 212 age-matched controls. Analysis of this cohort revealed that mutations in specific genes, such as *DNMT3A*, *TET2*, *TP53*, *IDH2*, *JAK2* and genes encoding splicing factors, were more common to individuals who eventually developed AML than controls. Importantly, having a mutation in one of the high-risk genes at a median of 9.6 years before diagnosis was associated with higher odds of developing AML compared with unaffected individuals, independent of age. In addition, progression to AML was more likely in those cases with greater clonal complexity (>1 mutated gene) and mutations present at >10% VAF. Interestingly, the penetrance of the mutations was not equal amongst the high-risk genes as all individuals with mutations in *TP53*, *IDH1* or *IDH2* developed AML.

Besides these genetic models, Abelson et al. also investigated the predictive power of clinical parameters. This line of investigation revealed a significant correlation between greater red blood cell distribution width (RDW) and increased risk of subsequent AML. Along with other risk factors identified from blood counts, RDW was used in a machine-learning approach to generate a clinical data-driven prediction model that was capable of predicting AML 6–12 months before diagnosis, with high specificity (98.2%), albeit low sensitivity (25.7%).

Although the models developed in these two studies show it is feasible to detect a pre-malignant state in healthy individuals, years before the diagnosis of AML, the next challenge will be to improve their sensitivities and specificities as well as design preventative interventions for those individuals at higher risk.

Credit: Michael Austen/Alamy

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ORIGINAL ARTICLES Abelson, S. et al. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature* **559**, 400–404 (2018) | Desai, P. et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat. Med.* **24**, 1015–1023 (2018)