Title: Clonal evolution preceding cancer revealed using single-cell DNA sequencing and computational modelling

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The acquisition and expansion of cancer driver mutations can predate cancer diagnosis by decades. However our understanding of the evolution that occurs in these early stages of cancer development is incomplete because most studies focus only on sequencing the malignant clone that “wins” the evolutionary race. The representation of driver mutations in the stem cells which do not transform into the malignant clone provides a window into this precancerous evolutionary arms race. We apply single-cell DNA sequencing to the bone marrow of 18 Acute Myeloid Leukaemia (AML) patients and build phylogenetic trees to show how AML evolved from healthy ancestral haematopoietic stem cells (HSCs). The sizes of intermediate clones and shapes of these phylogenetic trees are the outcome of selection forces and mutation during precancerous development, thus encoding information about the past history of somatic evolution. By coupling data with large-scale simulations and mathematical modelling, we show that highly variable observations in clonal compositions across individuals are consistent with a simple k-hit staircase model. Using machine learning methods, we can infer selection levels as well as mutation rates during preleukemic progression based on the observed phylogenies of the preleukemic HSCs present at AML diagnosis. This showcases the potential of making updated AML risk forecast for an individual as their HSC clonal composition change over lifetime based on our quantitative understanding of precancerous somatic evolution.