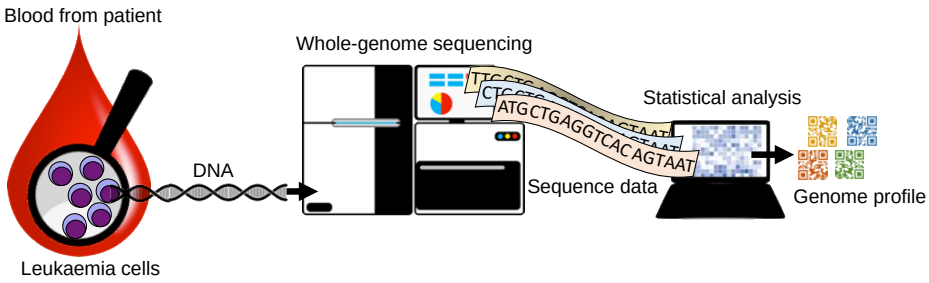
Profiling the entire genome of blood cancer

Study results suggest new classification can be used to predict clinical disease course of patients with leukemia.



This study profiled the entire genome[1] of patients with chronic lymphocytic leukaemia (CLL), an adult form of blood cancer. The research was led by Professor Anna Schuh from the University of Oxford and conducted by Dr Pauline Robbe (RIKEN IMS, Japan) and Dr Kate Ridout (University of Oxford). This work was a great collaborative effort, involving Professor Iñaki Martin-Subero (Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain), Professor Richard Houlston (The Institute of Cancer Research, London), and Dr Dimitrios Vavoulis (University of Oxford), among many outstanding researchers and laboratories across the UK and beyond. This study was part of Genomics England's 100,000 Genomes Project.

The researchers applied a laboratory technology known as whole genome sequencing to classify 485 patients with CLL. With such technology, the authors have systematically characterized all the relevant changes in DNA across the entire leukaemia genome and discovered five new CLL subgroups representing different DNA profiles. Importantly, these subgroups are linked to the clinical disease course, which could improve patient care by informing clinicians on the best treatment course for each patient's DNA profile.

This is the first study to apply this cutting-edge science to such a large number of high-quality samples obtained from uniform, well-defined patient cohorts. The novelty especially lies in linking such high-quality genomic data to high-quality clinical data. In addition, this is the largest international genomic analysis of this type of blood cancer, which demonstrates the value of whole genome sequencing for cancer classification. This research could lead to more personalized patient care.

The full study was published in Nature Genetics on November 4th, and can be accessed here. The official press release can be found here.

Background

Despite recent progress in the treatment of CLL, this blood cancer remains largely incurable. This is to a large extent because there remains so much to learn about the biology of CLL. Studies have shown that every patient's CLL is different and the way patients respond to a particular treatment also varies.

It is known that cancer is fundamentally a disease caused by changes in DNA, called mutations, that are acquired over the lifetime of an individual. One of the underlying reasons for the diversity in patient's cancer profile is the fact that each patient's leukaemia cells carry different genetic changes. These changes have not yet been fully characterized.

The laboratory tools currently used to predict whether or not a patient is likely to respond to a given therapy do not accurately predict the patient's clinical outcome as it only focuses on single abnormalities in the cancer DNA. This is why the team of researchers asked the simple question: 'can we increase the precision of current testing by looking at all the acquired DNA changes in cancer simultaneously?'

Research methods and results

This study analyzed the entire genome sequences from 485 patients with CLL who were enrolled in clinical trials and consented for their samples to be used in the 100,000 Genomes Project run by Genomics England in the United Kingdom.

This study generated large and complex genome sequence data which was analyzed by an international group of researchers based primarily at the University of Oxford in the UK, as well as in Japan and Spain among other countries. Statistical algorithms were used to decipher the sequence data. By comparing the whole genome sequencing data of cancerous and healthy samples of these patients, the team were able to map DNA changes and mutational signatures associated only with the CLL cells and absent from their healthy tissues, which established a unique "CLL genomic profile" for each patient **(figure 1).**

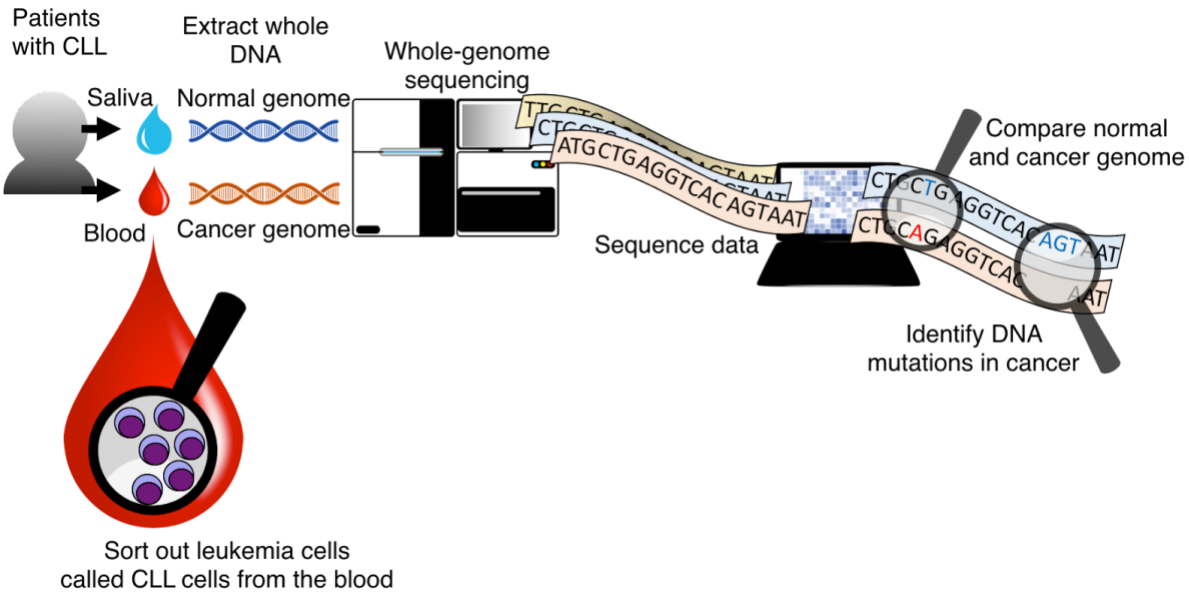


Figure 1. Patients with CLL had their samples profiled by whole-genome sequencing to identify DNA mutations and establish a unique "CLL genomic profile" for each patient.

The team identified 186 distinct and recurrent genomic changes. Some of these genomic changes were already known from previous studies. Many other genomic changes were discovered for the first time, thanks to the use of such state-of-the-art whole genome sequencing technologies, new statistical algorithms and the large cohort of patients.

Although each patient presents a unique CLL genomic profile, the researchers considered all 186 measures together to establish similarities between all patients. They discovered the 485 patients could be divided in five groups with similar cancer genomic profiles **(figure 2)**.

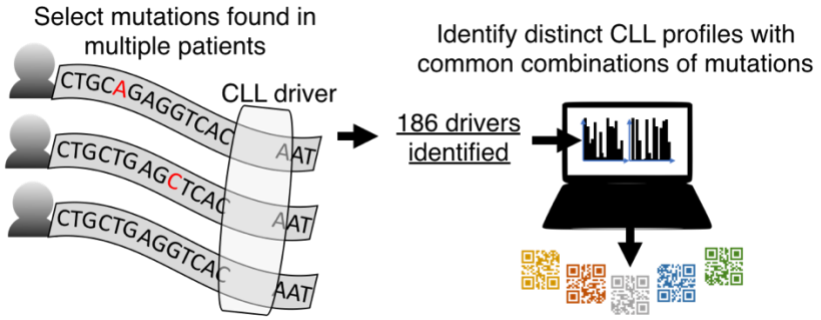


Figure 2. DNA changes detected in multiple patients with CLL were selected for further analysis. They were narrowed down to 186 changes which were then used to identify major CLL genomic profiles

Importantly, these five subgroups were discovered to be associated with different clinical outcomes. Patients with similar genomic profiles were more likely to show prolonged responses to treatment, whereas other groups of patients were not **(figure 3).**

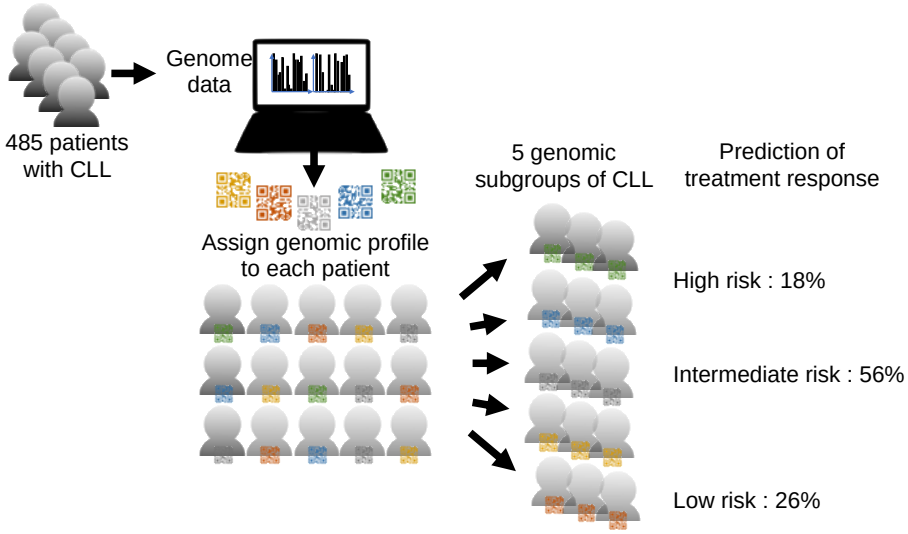


Figure 3. The study included the genome data from 485 patients and defined five new distinct disease profiles. Patients with the same genomic profile presented similar responses to the treatment.

This work shows that using the entire genome is superior in classifying patients into groups compared to conventional approaches that focus only on small, targeted regions of the DNA. With this method, it is now possible to better predict how well patients will respond to a treatment based on their genomic profile.

Expectations for the future

Firstly, the team's analysis identified new genetic drivers of CLL. Future research on these drivers may uncover new mechanisms of CLL initiation and progression, with potential for the development of novel therapeutics.

Secondly, this study paves the way for the routine use of whole genome analyses in the clinic, and to allow risk stratification in all other cancer types. As several novel therapies are being routinely used for patients with CLL, in particular novel targeted therapies, these new genomic subgroups could be used to better guide the selection of therapies for improved patient outcomes. Indeed, this new CLL patient classifier would allow all future patients to be offered the best treatment according to their CLL subgroup, avoiding unnecessary treatments with potentially toxic side-effects. It will also help select the most appropriate patients for clinical trials of new, targeted therapies. This work has the potential to make a significant and positive impact on patients with CLL as well as other cancers in the future.

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Reference

Robbe, P., Ridout, K.E., Vavoulis, D.V. et al. Whole-genome sequencing of chronic lymphocytic leukemia identifies subgroups with distinct biological and clinical features. Nat Genet 54, 1675–1689 (2022).

Supplementary information

[1] Genomic sequencing is the analysis of a person's entire genome, the 3.2 billion letters of their DNA that contain the instructions for making and maintaining their body. It is used by doctors and scientists to identify genetic changes causing specific diseases and conditions. The findings can be used in the development of personalized treatments and care plans, based on an individual's unique genome.