Rare genetic event massively predisposes people to a form of leukemia

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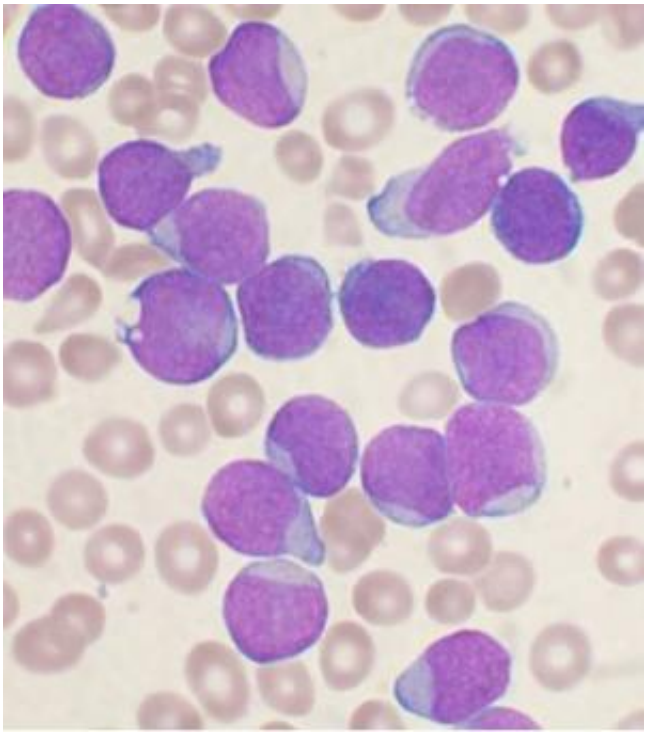

A Wright's stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Researchers have found that people born with a rare abnormality of their chromosomes have a 2,700-fold increased risk of a rare childhood leukaemia. In this abnormality, two specific chromosomes are fused together but become prone to catastrophic shattering.

Acute lymphoblastic leukaemia, or ALL, is the most common childhood cancer. Scientists previously found that a small subset of ALL patients have repeated sections of chromosome 21 in the genomes of their leukaemia cells. This form of ALL – iAMP21 ALL – requires more intensive treatment than many other types of ALL. The scientists used modern DNA analysis methods to reconstruct the sequence of genetic events that lead to iAMP21 ALL.

The team noticed that some patients with iAMP21 ALL were born with an abnormality in which chromosome 15 and chromosome 21 are fused together. The researchers wanted to discover if this type of fusion (known as a Robertsonian translocation) was connected with this rare form of ALL. They found that the joining of the two chromosomes increases a person's risk of developing the rare iAMP21 form of ALL by 2,700 fold.

"Advances in treatment are improving patients' outcomes, but iAMP21 ALL patients require more intensive chemotherapy than other leukaemia patients," says Professor Christine Harrison, co-lead author from Newcastle University. "Although rare, people who carry this specific joining together of chromosomes 15 and 21 are specifically and massively predisposed to iAMP21 ALL."

"We have been able to map the roads the cells follow in their transition from a normal genome to a leukaemia genome."

The team developed new insights for analysing genome data that can reveal the sequence of complicated genetic changes that cause a healthy cell to become cancerous. They can now take a cancer cell at one point in time and deduce the relative timing and patterns of mutational events that occurred in that cell's life history.

The team sequenced nine samples from iAMP21 ALL patients, four

with the rare Robertsonian translocation event and five that occurred in the general population. They found that for the four patients with the Robertsonian translocation, the cancer was initiated by a catastrophic genetic event known as chromothripsis. This event shatters a chromosome - in this case the joined chromosomes 15 and 21 - and then the DNA repair machinery pastes the chromosome back together in a highly flawed and inaccurate order. In the five other patients, the cancer was initiated by two copies of chromosome 21 being fused together, head to head, usually followed by chromothripsis.

"This is a remarkable cancer – for patients with iAMP 21 ALL we see the same part of the genome struck by massive chromosomal rearrangement," says Yilong Li, a first author from the Wellcome Trust Sanger Institute. "The method we've developed can now be used to investigate genetic changes in all cancer types."

The team found a consistent sequence of genetic events across the patients studied. Although the events at first sight seem random and chaotic, the end result is a new chromosome 21 in which the numbers and arrangement of genes are optimised to drive leukaemia.

The team will now use this method to decipher the genetic events that underlie many different cancer types.

"What is striking about our findings is that this type of leukaemia could develop incredibly quickly – potentially in just a few rounds of cell division," says Dr Peter Campbell, co-lead author from the Wellcome Trust Sanger Institute. "We now want to understand why the abnormally fused chromosomes are so susceptible to this catastrophic shattering."

More information: Li Y, Schwab C, Ryan S, et al (2014) 'Constitutional and somatic genomic rearrangements coherently restructure chromosome 21 in acute lymphoblastic leukaemia'.

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