Researchers describe spontaneous cure of rare immune disease

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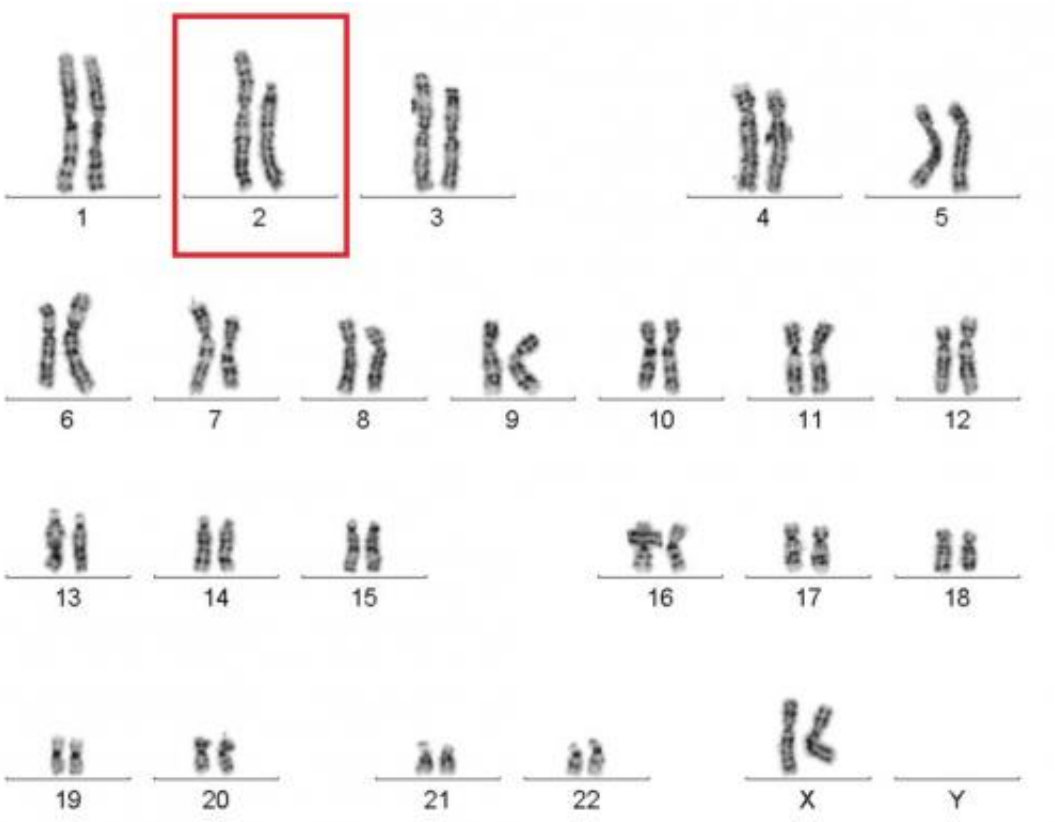

This is an image of all 46 chromosomes of the cured WHIM syndrome patient shows that one copy of chromosome 2 (red box) is significantly shorter than the other, a loss of genetic material caused by chromothripsis. As a result of this random event, the patient experienced a fortuitous deletion of a mutant copy of the gene responsible for WHIM syndrome--*CXCR4*--in the immune cells most affected by the mutation. Credit: NIAID

A genetic phenomenon called chromothripsis, or "chromosome shattering," may have spontaneously cured the first person to be documented with WHIM syndrome, according to researchers at the National Institutes of Health (NIH). The patient was the subject of a 1964 study that first described the disorder, a syndrome of recurrent infections, warts and cancer caused by the inability of immune cells, particularly infection-fighting neutrophils, to leave the bone marrow and enter the bloodstream. In 2003, researchers identified the genetic mutations responsible for the disease, which occur in the *CXCR4* gene.

As an adult, the patient contacted NIH's National Institute of Allergy and Infectious Diseases (NIAID) to evaluate herself and two of her children, who eventually were diagnosed with WHIM syndrome. The patient reported that her symptoms resolved in her 30s, indicating that she had maintained disease remission for nearly 20 years.

In their study, NIAID researchers identify chromothripsis, the abrupt fragmentation of a chromosome, as the reason for the cure. Such severe changes often cause cells to die, unless they confer a survival advantage, which occurs during the development of some cancers. The researchers show that chromothripsis caused a random and fortuitous deletion of the mutant *CXCR4* gene in the patient. Presumably, a stem cell lacking mutant *CXCR4* survived and eventually repopulated all of the patient's neutrophils, which now appear to function normally. The study is the first to link chromothripsis to a positive outcome.

There currently are no approved treatments for WHIM syndrome, but NIAID scientists are evaluating the drug plerixafor in clinical trials with promising results. Researchers also are exploring how to apply the study findings to improve bone marrow transplantation, which relies on the ability of donor stem cells to repopulate in a recipient.

More information: McDermott DH et al. Chromothriptic cure of

WHIM syndrome. *Cell* DOI: 10.1016/j.cell.2015.01.014 (2015).