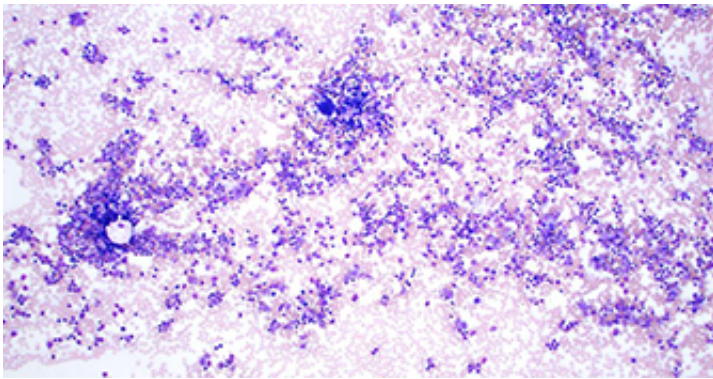


# Scientists trace genomic evolution of high-risk leukemia

March 19 2015, by Carrie Strehlau

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Highly sensitive genomic analysis of acute lymphoblastic leukemia cells reveals for the first time how the malignant cells evolve to cause relapse.

By genomic sequencing of leukemia cells from relapsed patients at different stages, scientists have discovered key details of how acute lymphoblastic leukemia (ALL) cells mutate to survive chemotherapy. These mutations enable the cells to proliferate, causing relapse and often death.

The findings are important because ALL is a leading cause of cancer deaths in children, with 15 percent of ALL patients relapsing with poor survival. The researchers said their findings will lead to new tests to monitor children in remission and to detect signs of relapse.

The research was published in the March 19 issue of the journal *Nature*

*Communications.* Leading the research team were corresponding authors Charles Mullighan, M.D., MBBS(Hons), a member of the St. Jude Children's Research Hospital Department of Pathology; Jinghui Zhang, Ph.D., a member of the St. Jude Department of Computational Biology; and Stephen Hunger, M.D., director of the Center for Childhood Cancer Research at The Children's Hospital of Philadelphia.

In their study, the researchers analyzed the genomes of cells from 20 children who had ALL that returned following treatment. Importantly, the researchers analyzed cell samples taken at three stages—diagnosis, remission and relapse.

Thus, the scientists could analyze in detail the genomes of the cells at the different stages, determining the [mutations](#) that drove the relapse of leukemia. Cancers such as leukemia are not a homogeneous disease. Rather they are a witch's brew of different dividing cancer cells, called "clones," with distinctive sets of mutations. While chemotherapy might kill almost all the clones, some might have escaped therapy, leaving them to multiply to cause relapse.

"In our study we wanted to find out the underlying mechanism leading to [cancer relapse](#)," Zhang said. "When the cancer recurs, is it a completely different cancer, or is it an extension, or change, arising from pre-existing cancer?"

New genomic analytical technologies enabled the scientists to detect with great sensitivity the mutations in both the "rising" and "falling" clones at the different stages. Previous studies have attempted to work backward by genomically analyzing the relapsed clone to try to trace back its origin. However, such analysis would miss the low levels of the cells that, at diagnosis, would ultimately cause relapse.

The researchers' genomic analysis of the cancer clonal cells pinpointed

the mutations that drove the leukemia. They also characterized how diverse those mutations were at both diagnosis and relapse—finding that the [cancer cells](#) were mutating just as wildly and diversely throughout the cancer process.

"This finding was interesting, because most people think that the clone that has the most mutations is more likely to survive therapy and evolve, but that doesn't seem to be the case," Zhang said.

A key finding was that in most cases relapse of the cancer was driven by a minor clone, or "subclone," present at an extremely low level, that survived therapy. This finding has implications for genomic analysis of ALL after a patient's treatment, to determine the likelihood of relapse.

"When we are analyzing for the level of minimum residual disease in monitoring remission in patients, we should not only pay attention to the mutations in the predominant clone," said Zhang. "We should also be tracking what kinds of mutations exist in the minor subclones."

In their analysis, the researchers identified seven specific genes that were highly likely to be mutated in relapsed disease. Researchers at St. Jude and elsewhere are currently exploring the biological functions of the [relapse](#)-related genes, and the results may aid in developing ways to identify drugs to target their function.

More broadly, the methodology of highly sensitive [genomic analysis](#) of [cancer cells](#) that Zhang and her colleagues developed can be applied to explore the evolution of other cancers.

Provided by St. Jude Children's Research Hospital

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