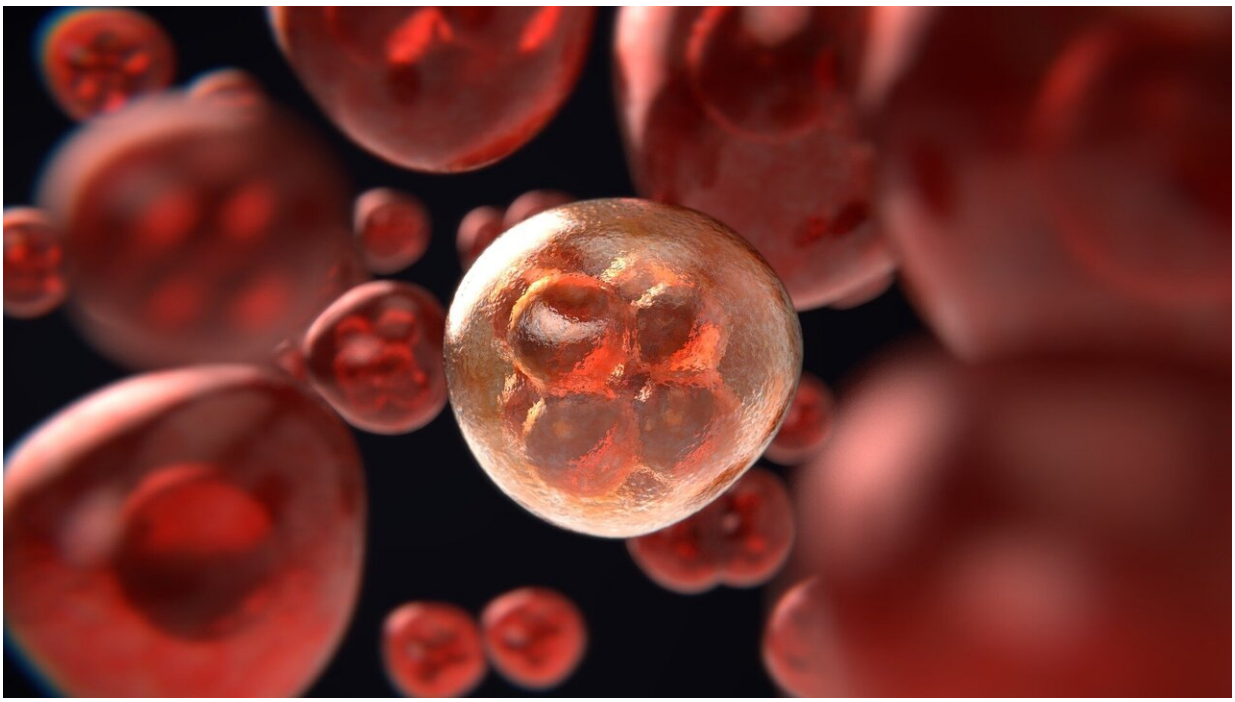
MedicalXpress

Large international study pinpoints impact of TP53 gene mutations on blood cancer severity

August 3 2020



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Considered the "guardian of the genome," *TP53* is the most commonly mutated gene in cancer. *TP53*'s normal function is to detect DNA damage and prevent cells from passing this damage on to daughter cells. When *TP53* is mutated, the protein made from this gene, called p53, can

no longer perform this protective function, and the result can be cancer. Across many cancer types, mutations in *TP53*are associated with worse outcomes, like disease recurrence and shorter survival.

As with all our genes, *TP53* exists in duplicate in our cells. One copy we get from our mothers, the other we get from our fathers. Up until now, it has not been clear whether a mutation was needed in one or both copies of *TP53* to affect cancer outcomes. A new study led by researchers at Memorial Sloan Kettering definitively answers this question for a blood cancer called myelodysplastic syndrome (MDS), a precursor to acute myeloid leukemia.

"Our study is the first to assess the impact of having one versus two dysfunctional copies of *TP53* on cancer outcomes," says molecular geneticist Elli Papaemmanuil, a member of MSK's Epidemiology and Biostatistics Department and the lead scientist on the study, published August 3 in the journal *Nature Medicine*. "From our results, it's clear that you need to lose function of both copies to see evidence of genome instability and a high-risk clinical phenotype in MDS."

The consequences for cancer diagnosis and treatment are immediate and profound, she says.

A large, definitive study

The study analyzed genetic and clinical data from 4,444 patients with MDS who were being treated at hospitals all over the world. Researchers from 25 centers in 12 countries were involved in the study, which was conducted under the aegis of the International Working Group for the Prognosis of MDS whose goal is to develop new international guidelines for the treatment of this disease. The findings were independently validated using data from the Japanese MDS working group led by Seishi Ogawa's team in Kyoto University.

"Currently, the existing MDS guidelines do not consider genomic data such as *TP53* and other acquired mutations when assessing a person's prognosis or determining appropriate treatment for this disease," says Peter Greenberg, Director of Stanford University's MDS Center, Chair of the National Comprehensive Cancer Network Practice Guidelines Panel for MDS, and a co-author on the study. "That needs to change."

Using new computational methods, the investigators found that about one-third of MDS patients had only one mutated copy of *TP53*. These patients had similar outcomes as patients who did not have a *TP53* mutation—a good response to treatment, low rates of disease progression, and better survival rates. On the other hand, the two-thirds of patients who had two mutated copies of *TP53* had much worse outcomes, including treatment-resistant disease, rapid disease progression, and low overall survival. In fact, the researchers found that *TP53* mutation status—zero, one, or two mutated copies of the gene—was the most important variable when predicting outcomes.

"Our findings are of immediate clinical relevance to MDS patients," Dr. Papaemmanuil says. "Going forward, all MDS patients should have their *TP53* status assessed at diagnosis."

As for why it takes two "hits" to *TP53* to see an effect on cancer outcomes, the study's first author Elsa Bernard, a postdoctoral scientist in the Papaemmanuil lab, speculates that one normal copy is enough to provide adequate protection against DNA damage. This would explain why having only one mutated copy was not associated with genome instability or any worse survival rates than having two normal copies.

Given the frequency of *TP53* mutations in cancer, these results make a case for examining the impact of one versus two mutations on other cancers as well. They also reveal the need for clinical trials designed specifically with these molecular differences in mind.

"With the increasing adoption of molecular profiling at the time of cancer diagnosis, we need large, evidence-based studies to inform how to translate these molecular findings into optimal treatment strategies," Dr. Papaemmanuil says.

More information: Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-1008-z , www.nature.com/articles/s41591-020-1008-z

Provided by Memorial Sloan Kettering Cancer Center