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


Provided by Memorial Sloan Kettering Cancer Center
