mds foundation
the myelodysplastic syndromes foundation, inc.

PRESS RELEASE

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LARGE INTERNATIONAL STUDY PINPOINTS IMPACT OF TP53 MUTATIONS ON BLOOD CANCER SEVERITY

Having two mutated copies of the TP53 gene — as opposed to a single mutated copy — is associated with worse outcomes in myelodysplastic syndrome and acute myeloid leukemia.

YARDVILLE, NJ, AUG. 25, 2020 — A large international study led by researchers at Memorial Sloan Kettering finds that having two mutated copies of the *TP53* gene, as opposed to a single mutated copy, is associated with worse outcomes in myelodysplastic syndrome and acute myeloid leukemia. The findings have immediate clinical relevance for risk assessment and treatment of people with myelodysplastic syndrome.

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, which can result in cancer. Across many cancer types, mutations in *TP53* are associated with much worse outcomes, like disease recurrence and shorter survival.

As with all genes, there are two copies of *TP53* in our cells. One copy we get from our mothers, the other we get from our fathers. Until now, it was unclear whether a mutation in one copy of *TP53* was enough to cause worse outcomes, or if mutations in both copies were

necessary. 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 Dr. Elli Papaemmanuil, a member of the Epidemiology and Biostatistics Department at MSK and the lead scientist on the study, whose results were 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, MULTICENTER 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 in collaboration with investigators in the International Working Group for Prognosis in MDS (IWG-PM) whose goal is to develop new international guidelines for the treatment of this disease. Findings were independently validated using data from the Japanese MDS working group led by Dr. Seishi Ogawa's group at Kyoto University.

"Currently, the existing guidelines do not consider genomic data, like *TP53* and other acquired mutations, when assessing a person's prognosis or determining appropriate treatment for this disease," says Dr. Peter Greenberg, Director of Stanford University's MDS Center, Chair of the National Comprehensive Cancer Network Practice Guidelines Panel for MDS, and a participant in the study. "Studies are ongoing reflecting this need for change."

Tracey Iraca, MDS Foundation Executive Director stated, "This study is important in updating the IPSS-R to include molecule information in light of the more personalized treatments now being explored for MDS patients."

Using new computational methods and the database and collaborative input of the IWG-PM, 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 — that is, good response to treatment, low rates of disease progression, and better survival. Two-thirds of patients, on the other hand, had two mutated copies of *TP53*. These patients

had much worse outcomes — including treatment-resistant disease, rapid disease progression, and low overall survival. In fact, the researchers found that *TP53* mutation status — either 0/1 or 2 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, Dr. Elsa Bernard, a postdoctoral scientist in the Papaemmanuil lab and the study's first author, speculates that having 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 over having two normal copies.

Given the frequency of *TP53* mutations in cancer, these results argue for examining the impact of one versus two mutations in 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.

PARTICIPATING MDS FOUNDATION CENTERS OF EXCELLENCE:

Karolinska Institute (Sweden), University of Pavia (Italy), La Fe University Hospital (Spain), Radboudumc Medical Center Nijmegen (The Netherlands), Amsterdam UMC (The Netherlands), Cochin Hospital (France), Chang Gung Memorial Hospital (Taiwan), Medical University of Vienna (Austria), Hannover Medical School (Germany), University Hospital Dresden (Germany), Federal University of Ceara (Brazil), University of Oxford (United Kingdom), Institute of Hematology and Blood Transfusion (Czech Republic), University Medicine Göttingen (Germany), Saint-Louis Hospital (France), Saint James's University Hospital (United Kingdom), Chulalongkorn University (Thailand), Nagasaki University (Japan), Kyoto University (Japan), Chugoku Central Hospital (Japan), Tokyo Medical University (Japan), Massachusetts General Hospital, Vanderbilt-Ingram Cancer Center, University of Rochester Medical Center, Dana-Farber Cancer Institute, UC San Diego Moores Cancer Center, Stanford University Cancer Institute, Memorial Sloan Kettering Cancer Center (United States).

ADDITIONAL PARTICIPATING CENTERS:

Düsseldorf MDS Registry (Germany), Gruppo Romano Laziale MDS (Italy), University of Bologna (Italy), Institut Josep Carreras (Spain), Aou Careggi Hospital (Italy), Democritus University of Thrace (Greece), Hospital Israelita Albert Einstein (Brazil), Rete Ematologica Lombarda (Italy), Japanese Data Center for Hematopoietic Cell Transplantation (Japan), Tsukuba University (Japan), Gifu Municipal Hospital (Japan), Kobe City Medical Center General Hospital (Japan), Gifu University (Japan), NTT Medical Center Tokyo (Japan), Osaka Red Cross Hospital (Japan), Kurashiki Central Hospital (Japan), Sasebo City General Hospital (Japan)

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The MDS Foundation, Inc. is an international non-profit advocacy organization whose mission is to support and educate patients and healthcare providers with innovative research into the fields of MDS, Acute Myeloid Leukemia (AML) and related myeloid neoplasms in order to accelerate progress leading to the diagnosis, control and cure of these diseases.

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