TP53 gene variant in people of African descent linked to iron overload, may improve malaria response

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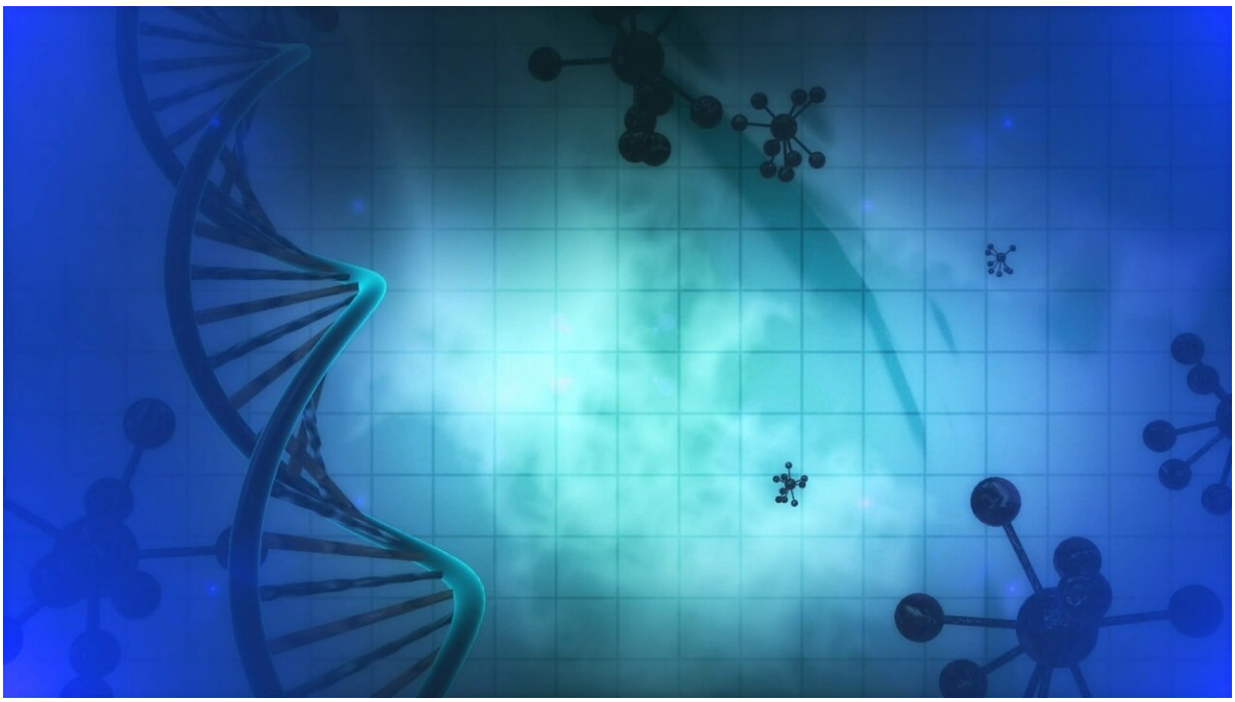

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In a study by The Wistar Institute and collaborators, a rare, African-specific variant of the TP53 gene called P47S causes iron accumulation in macrophages and other cell types and is associated with poorer response to bacterial infections, along with markers of iron overload in

African Americans. Macrophage iron accumulation disrupts their function, resulting in more severe bacterial infections. The study, published online in *Nature Communications*, also showed that P47S macrophages exhibit improved response to the malaria toxin. This effect may confer protection against generalized inflammation associated with signs of acute malaria pathology.

The TP53 gene possesses numerous genetic variants, some of which are common in the population. Wistar scientists have previously shown that the P47S gene variant, which exists in populations of African descent, is associated with increased cancer risk in African Americans due to defects in an iron-mediated modality of cell death called ferroptosis. They have now discovered another notable effect of disrupted iron metabolism in cells that carry the P47S variant.

"We discovered that macrophages from mice carrying the P47S variant accumulate iron and this impairs their ability to mount an inflammatory response against bacterial infections, making them more susceptible to these diseases," said Farokh Dotiwala, M.B.B.S., Ph.D., assistant professor in the Vaccine & Immunotherapy Center and corresponding author of the study. "The flip side of diminished inflammation is that these mice have a more favorable response to malaria toxin hemozoin, that is responsible for most of the lethal symptoms in the acute phase of disease."

Along with Wistar's Maureen E. Murphy, Ph.D., Ira Brind Professor and leader of the Molecular & Cellular Oncogenesis Program at Wistar, and a co-senior author on the study, Dotiwala and his team found the frequency of the P47S variant to be significantly higher in African Americans from the HEIRS study (Hemochromatosis and Iron Overload Screening). Studying a mouse model carrying the human P47S variant of TP53, generated by the Murphy lab, researchers observed increased iron accumulation in macrophages.

Macrophages from P47S mice with higher iron content were less effective at controlling the growth of different bacterial species in vitro, which reflected faster disease progression and worse outcome.

To dissect the mechanisms of increased susceptibility of P47S mice to bacteria, Dotiwala and colleagues used proteomics to reveal changes in protein levels in macrophages. This approach showed modulation of several proteins involved in the immune response, particularly in metabolic pathways that are essential for macrophages to kill bacteria, such as the arginine pathway, and in ferroptosis. These changes reduced the ability of P47S macrophages to kill bacteria and were reversed by targeting three different affected pathways, thus highlighting future therapeutic potential.

Given the prevalence of the P47S gene variant in malaria-endemic regions of sub-Saharan Africa, the team asked whether this variant could confer a survival advantage to malaria infection. P47S mice injected with the malaria toxin hemozoin showed a weaker inflammatory response than mice carrying the common p53 gene variant. This may limit disease severity, which is a consequence of the massive generalized inflammatory response triggered by the toxin and mostly mediated by macrophages.

"While warranting further studies in humans, we believe that mechanistic knowledge obtained from studying the P47S variant provides a stepping stone in the field of personalized medicine to help address disparities arising from such polymorphisms," said Donna George, Ph.D., associate professor of genetics at the Perelman School of Medicine of the University of Pennsylvania and co-senior author on the study.

This study may also help understand the connection between the TP53 gene variant and iron overload disorders as well as the increased

occurrence of certain bacterial infections and cancers found in African Americans.

More information: African-centric TP53 variant increases iron accumulation and bacterial pathogenesis but improves response to malaria toxin, *Nature Communications* (2020). DOI: 10.1038/s41467-019-14151-9

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