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Enzyme deficiency protects hepatitis C patients from treatment-related anemia

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Many people who undergo treatment for hepatitis C develop hemolytic anemia, a disorder that destroys red blood cells. In some cases, it is so severe they have to reduce their medication or stop therapy altogether. But now, scientists in Duke University's Institute for Genome Sciences & Policy (IGSP) have discovered two genetic alterations linked to a benign enzyme condition that keep some patients anemia-free.

They say the discovery, appearing online in the journal *Nature*, opens the door to treatment for patients who have never been considered candidates for therapy before and may also hold the key to new drugs that could prevent anemia from developing in the first place.

The protective mechanism is a deficiency in a gene called ITPA. "We found that patients who carried specific functional variants are strongly protected against developing anemia," says David Goldstein, Ph.D., director of the Center for Human Genome Variation in the IGSP and a senior author of the study.

Previous studies had identified the genetic variants as the cause of a deficiency in the production of an enzyme, inosine triphosphatase. But it was only through a genome-wide association study that the Duke team was able to show that these same variants were protective against anemia induced by ribavirin, one of two necessary drugs in hepatitis C treatment.

About 180 million people world-wide are infected with the hepatitis C

virus, and about 30 to 40 percent of them could develop some degree of treatment-related anemia, according to John McHutchison, M.D. associate director for research at the Duke Clinical Research Institute and also a senior author. "It's a big problem. Hemolytic anemia reduces the level of hemoglobin in the blood and robs it of its ability to carry oxygen. Anything that could help us predict who is going to become anemic and who is not could help us better manage therapy and give all patients the best chance of a good outcome."

Goldstein and McHutchison, who had earlier worked together in identifying genetic variants that helped explain race-based differences in response to hepatitis C treatments, believed there was probably a gene-based solution to the anemia puzzle as well.

Working with first authors Jacques Fellay, M.D.; Alex Thompson, M.D., PhD.; and Dongliang Ge, Ph.D., investigators turned to a rich database already at hand: the records of 1286 individuals who had earlier taken part in the IDEAL study, a large, randomized, Duke-led clinical trial that compared leading therapies for hepatitis C.

Researchers separated the patients into three ethnic groups, (988 European Americans, 198 African Americans, and 100 Hispanic Americans) and analyzed their decline in hemoglobin levels during the first month of treatment.

The researchers conducted a genome-wide association study and found several polymorphisms - single-letter DNA alterations - also known as "SNPs or "snips" -associated with reduced hemoglobin levels. But finding an association is just a start: of more biological importance is the identification of the causal variants, the polymorphisms that directly influence hemoglobin levels. Investigators discovered that the two variants known to cause ITPA deficiency appeared almost exclusively on chromosomes that also carried the protective version of the most

associated SNP. Further statistical analysis proved that the two variants were indeed the source of protection from anemia.

McHutchison says the discovery is clinically important. "The beauty of this finding is that it may mean we could consider offering treatment to patients who have additional problems, like coronary artery disease or kidney disease. Right now, we are generally uncomfortable treating these patients because anemia could make their underlying condition worse. If a test could tell us which patients are not going to become anemic, we could consider treating them."

"Most of us trace the birth of pharmacogenetics to a 1957 paper by Arno Moltulsky who argued that important drug responses may often depend on genetic differences among people that are invisible until an individual takes a certain drug," says Goldstein. "These ITPA variants reflect this classic formulation of pharmacogenetics, and suggest to us that there are many other important variants that can and should be found through the careful genetic analyses of patients' drug responses."

Provided by Duke University Medical Center

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