Genotype may identify complication likelihood in sickle cell patients

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Researchers have found a genotype that could help identify sickle cell disease (SCD) patients at greatest risk of common, yet severe, complications of SCD. The findings will be presented today at the American Physiological Society's Physiological and Pathophysiological Consequences of Sickle Cell Disease conference in Washington, D.C.

The chronic breakdown of red blood cells (hemolysis) is a hallmark of SCD that increases during times of illness. Hemolysis leads to the release of hemoglobin—and a protein that binds with it called haptoglobin—that increase a patient's chances of developing acute chest syndrome (ACS). "ACS is defined broadly as increased respiratory effort, fever and a new radiodensity on chest X-ray. ACS is a significant cause of hospitalizations and death in children and adults with SCD," said the study's lead author, Shaina Willen, MD, of Vanderbilt University Medical Center in Tennessee. ACS is a common complication among SCD patients, affecting roughly 50 percent at least once in their lifetime.

HP1-1, HP1-2 and HP2-2 are the three genetic markers (genotypes) associated with haptoglobin. These genotypes predict how effective an individual's haptoglobin is at binding to and clearing away excess hemoglobin. The haptoglobin in people with the HP2-2 genotype is not as effective in hemoglobin-binding, and HP2-2 has been linked to increased cellular (oxidative) damage. The research team hypothesized that patients with the HP2-2 genotype would be more susceptible to SCD-related complications including ACS, pain, stroke, retinal problems in the eyes, kidney disease and high blood pressure in the arteries of the

lungs than patients with HP1-1 and HP1-2 genotypes.

The researchers tested 58 adults with SCD and found that 90 percent of those with the HP2-2 genotype had two or more SCD-related complications compared with 46.7 and 56.3 percent of those with the HP1-1 and HP1-2 genotypes, respectively. "Our study has identified an increased risk for the development of sickle cell disease-related complications among adult participants with the HP2-2 genotype," Willen explained. "We have also found that children with the HP2-2 genotype are at increased risk for the development of pain episodes which is the most common cause of hospitalization in children and adults with SCD.

"This finding may identify both adults and children at risk for developing disease-related complications. The impact of the HP2-2 genotype on the ability of haptoglobin to scavenge products of hemolysis may provide therapeutic targets to investigate related to the oxidative effect of cell-free hemoglobin and the pathophysiology of complications in SCD."

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