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Gaining ground on sickle cell disease

Gene variants could help predict disease severity

July 29, 2008

Although sickle cell disease is a single-gene disorder, its symptoms are highly variable. In a study published online July 14 by the *Proceedings of the National Academy of Sciences*, scientists at Children's Hospital Boston and the Dana Farber Cancer Institute (DFCI), in collaboration with the Broad Institute of MIT and Harvard, report five gene variants that could potentially be helpful in predicting sickle cell disease severity, perhaps even leading to better treatment approaches in the future.

The gene variants influence blood levels of fetal hemoglobin (HbF), which are known to affect symptom severity in sickle cell disease--with some patients experiencing frequent, severe pain crises and organ damage, while others are scarcely aware of their disease.

"Our study is a first step towards a better understanding of fetal hemoglobin regulation in patients with sickle cell disease," says Guillaume Lettre, PhD, of the Broad Institute and Children's Hospital Boston, and co-first author on the paper. "But further validation experiments are needed before these findings can become useful in the clinic."

"Eventually, understanding the factors giving rise to heterogeneity in HbF levels might allow us to take severely affected patients and make them more like those with more benign symptoms," adds Vijay Sankaran, co-first author on the paper with Lettre and an MD-PhD student in the laboratory of Stuart Orkin, MD. (Orkin is chair of pediatric oncology at DFCI and a Howard Hughes Medical Institute investigator at Children's.)

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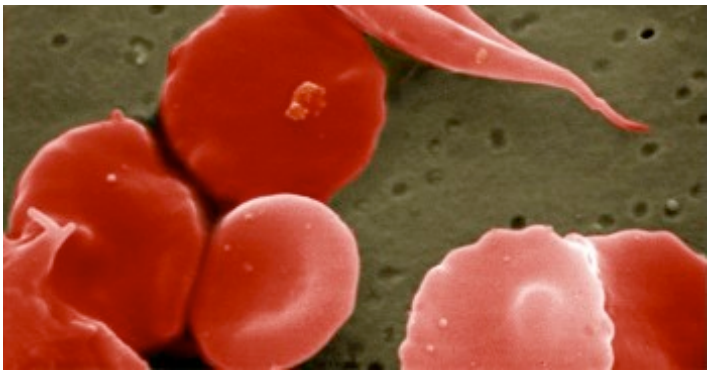
About sickle cell disease

Stuart Orkin, MD

Joel Hirschhorn, MD, PhD



Normal red blood cells contain hemoglobin A as their main substance and, being soft and round, easily squeeze through tiny blood vessels. In sickle cell disease, an abnormal type of hemoglobin (S) is produced instead. Red blood cells become stiff and distorted, blocking blood flow through the vessels and eventually causing tissue damage.

In sickle cell disease, a single genetic mutation results in the production of an abnormal type of hemoglobin, the main component of red blood cells. The abnormal hemoglobin molecules tend to form long chains, causing red blood cells to become stiff and sickle-shaped. The distorted cells have difficulty passing through blood vessels and can block the smaller vessels, resulting in severe pain and eventual organ damage as tissues are robbed of their blood supply. The sickle-shaped red blood cells also have a very short lifespan, causing patients to be chronically anemic.

Previous research had established that retaining high levels of another type of hemoglobin--HbF, found at high levels in the fetus' can ameliorate sickle cell disease symptoms. At birth, HbF comprises between 50 to 95 percent of a child's hemoglobin, gradually declining as the switch is made to adult hemoglobin production--consistent with clinicians' observations that newborns diagnosed with sickle cell disease usually do not become symptomatic until they are about a year old. Population studies in Saudi Arabia and parts of India had identified groups of sickle cell patients with very high levels of HbF and relatively benign forms of the disease, and additional epidemiologic studies led by Orah Platt, MD, chief of laboratory medicine at Children's, showed that HbF is an ameliorating factor. "The more you have, the better off you are," says Sankaran.

Studying 1600 patients with sickle cell disease, the researchers found that previously identified DNA sequence variants in three chromosome locations (small regions on chromosome 2, 6, and 11) were associated with high or low HbF levels. When they added these five variants to a model previously designed by Platt to predict disease severity, which also factors in age, sex, degree of anemia and HbF levels, the model's predictive ability was enhanced.

The findings need to be validated in large, prospective clinical studies, but the researchers are hopeful about the possible future clinical implications of their work. "As we find gene

variants that regulate HbF levels or predict severity, we might eventually want to genotype patients for these variants, to get more predictive information on their disease," Sankaran says.

Finally, once this study is validated, understanding how these variants actually affect HbF levels might someday lead to new drugs that do the same thing. "If we can gain better insight into what these variants are doing, we may eventually have better, more targeted therapies for sickle cell disease," adds Sankaran.

Lettre and Sankaran shared first authorship of the paper. Orkin and Joel Hirschhorn, MD, PhD, of Children's and the Broad Institute, were senior authors.

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Children's Hospital Boston is home to the world's largest research enterprise based at a pediatric medical center, where its discoveries have benefited both children and adults since 1869. More than 500 scientists, including eight members of the National Academy of Sciences, 11 members of the Institute of Medicine and 12 members of the Howard Hughes Medical Institute comprise Children's research community. Founded as a 20-bed hospital for children, Children's Hospital Boston today is a 397-bed comprehensive center for pediatric and adolescent health care grounded in the values of excellence in patient care and sensitivity to the complex needs and diversity of children and families. Children's also is the primary pediatric teaching affiliate of Harvard Medical School. For more information about the hospital and its research visit:
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