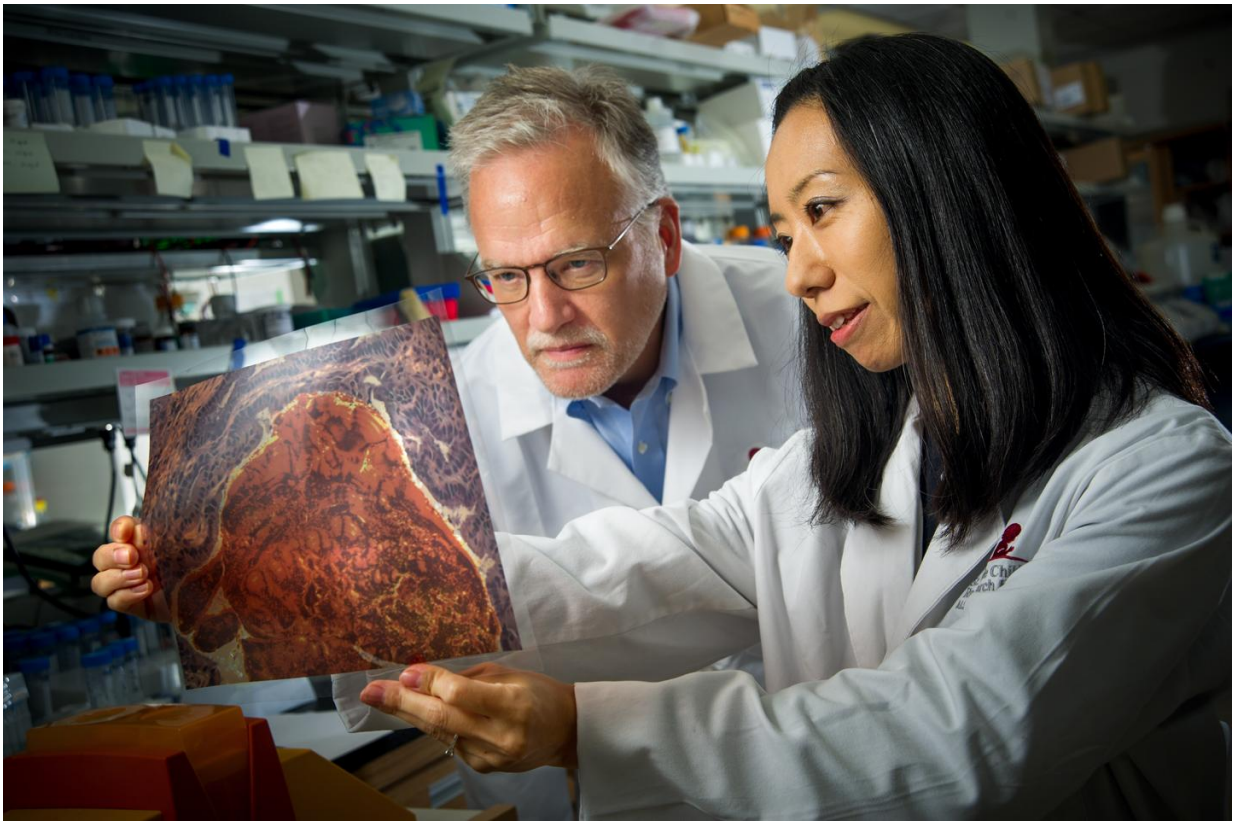
Rare genetic variations may solve mystery of porphyria severity in some patients

August 10 2016



Corresponding author John Schuetz, Ph.D., a member of the St. Jude Department of Pharmaceutical Sciences and Yu Fukuda, Ph.D., a staff scientist in Schuetz' laboratory. Credit: St. Jude Children's Research Hospital / Seth Dixon

An international research team has linked rare variations in a cell

membrane protein to the wide variation in symptom severity that is a hallmark of porphyria, a rare disorder that often affects the skin, liver and nervous system. St. Jude Children's Research Hospital helped to lead the research, which appears today in the journal *Nature Communications* and suggests possible new treatment strategies.

Porphyrias are a family of diseases usually caused by inherited mutations in one of the eight enzymes involved in assembling heme. Heme is a molecule that plays a critical role in oxygen transport, drug metabolism and other vital physiological processes.

In this study, researchers discovered rare variations in the ABCB6 gene, also called Lan. The variations were associated with the toxic build-up in cells of chemicals produced during heme assembly. Investigators reported that the variants were more common in patients with severe porphyria than in those with less severe symptoms.

"One of the mysteries of this disease has been why some individuals with the same genetic defect have mild symptoms while others have severe symptoms and require hospitalization in the intensive care unit," said corresponding author John Schuetz, Ph.D., a member of the St. Jude Department of Pharmaceutical Sciences. "Using gene sequencing, biochemical analysis and a new mouse model of the disease, we have identified variations in ABCB6 as an unexpected genetic modifier of porphyria severity."

The discovery followed DNA sequencing of the protein-coding regions, or exomes, of seven porphyria patients with a history of life-threatening symptoms and hospitalization in the intensive care unit. They were among the 36 porphyria patients treated at the Royal Prince Alfred Hospital in Sydney, Australia, included in the study.

Researchers found that five of the seven patients carried rare versions of

ABCB6 and made little or no functional ABCB6 protein. Sixty-two percent of patients with the rare ABCB6 variants were admitted to the intensive care unit compared to about 7 percent of other patients.

ABCB6 is carried on the surface of red blood cells, where 85 percent of heme is produced. The protein is one of several proteins that export porphyrins and related molecules from liver, blood and other cells. This is the first report linking any porphyrin transport proteins to porphyria.

Researchers have begun screening drugs shown to trigger porphyria in at-risk individuals to see if the symptoms are caused by the medications interfering with porphyrin transport. The results may provide an explanation for drug-induced cases of the disease, particularly in individuals with the rare Langereis (Lan) negative blood type whose red blood cells do not have ABCB6 protein.

"The findings raise hopes for future therapies to reduce excess porphyrins by restoring the supply of ABCB6 protein to more normal levels," Schuetz said.

Working in mouse blood cells in the laboratory, investigators showed that the ABCB6 variants were incapable of porphyrin transport. "Evidence suggests the rare variants reduce expression of the functional or wild-type ABCB6 protein, possibly by disrupting normal protein folding and thus protein stability," said Yu Fukuda, Ph.D., a staff scientist in Schuetz' laboratory, which has a long-standing interest in ABCB6. Fukuda and Pak Leng Cheong, M.D., of Royal Prince Alfred Hospital, are co-first authors.

Working in a mouse model of human porphyria, researchers showed that porphyrin concentrations were significantly greater in cells, urine and feces of mice that lacked Abcb6 compared to other mice. Liver damage also increased.

Exact rates of porphyria are unknown and vary worldwide, according to the National Institute of Diabetes and Digestive and Kidney Diseases. Porphyria is among the possible explanations that have been offered for symptoms reportedly suffered by King George III, the British monarch during the American Revolutionary War.

More information: *Nature Communications* DOI: 10.1038/NCOMMS12353

Provided by St. Jude Children's Research Hospital