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Team explores STXBP5 gene and its role in blood clotting

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Two independent groups of researchers led by Sidney (Wally) Whiteheart, PhD, of the University of Kentucky, and Charles Lowenstein, MD, of the University of Rochester, have published important studies exploring the role that a gene called STXBP5 plays in the development of cardiovascular disease.

According to Whiteheart, previous genome-wide association studies (GWAS) identified a gene called STXBP5 as a factor that regulates a protein called Von Willebrand factor (VWF).

VWF is an important contributor to normal blood clotting. When the endothelial cells that line a blood vessel are injured, VWF is released into the bloodstream, where it "collects" blood platelets and groups them into bunches as part of the clotting process. VWF abnormalities have been linked to the development of blood clots and other vascular diseases that can cause heart attack and stroke.

"We basically went a step further and looked into how STXBP5 influences blood clotting as a w hole," Whiteheart said. "And what we found has the potential for profound impact down the road in identifying genetic risk factors for cardiovascular disease."

Dr. Lowenstein's group focused on the role of STXBP5 in the endothelial cells that line blood vessel walls and release VWF when damaged.

"This group showed that mice lacking the STXBP5 gene had increased VWF levels in their bloodstream, which would imply that a defective STXBP5 gene is a risk factor for the development of blood clots that cause heart attack and stroke," Whiteheart said. "However, Dr. Lowenstein's group was surprised to see that these STXBP5-knockout mice had increased bleeding, not increased clotting."

Whiteheart's group was able to explain the contradiction with its own research. Their results demonstrated that blood platelets, lacking STXBP5, failed to function correctly, causing the increased bleeding in the STXBP5 deficient mice. The group further showed that SXTBP5 was required for the process whereby platelets assist in normal clot formation, suggesting that STXBP5 plays distinctly different roles in secretion from endothelial cells than from platelets.

"Cardiovascular disease is the leading cause of death in developed countries and is particularly problematic in Kentucky," says Susan Smyth, MD, PhD, director of the Gill Heart Institute at the University of Kentucky. "Researchers at UK are internationally recognized for their work to understand thrombosis and inflammation in cardiovascular disease. Wally's findings on STXBP5 and its effect on VWF add considerably to that body of knowledge and may eventually have important ramifications for how we prevent blood clotting and bleeding."

More information: Whiteheart and Lowenstein's work will be published in the October 2014 edition of the *Journal of Clinical Investigation*.

Provided by University of Kentucky