Origin of a hereditary east Texas bleeding disorder

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Fifteen years ago, a hematologist came to Dianna Milewicz, M.D., Ph.D., with a puzzle: Multiple generations of an East Texas family suffered from a moderately severe bleeding disorder, but it wasn't hemophilia.

"No surgeon would do elective surgery because they bled too much after surgery," said Milewicz, professor and director of the Division of Medical Genetics at The University of Texas Health Science Center at Houston (UTHealth). "So we collected DNA and plasma from the family and were able to determine that a genetic variant in the Factor V gene was causing production of an abnormal form of the Factor V protein, which we called FV-Short. Factor V is a protein known to be important for the blood to clot."

But her team at the UTHealth Medical School couldn't pinpoint exactly how the variation was causing the clotting problem until they collaborated with Björn Dahlbäck, M.D., Ph.D., from Lund University, Malmö, Sweden.

"Dr. Dahlbäck is a world expert on Factor V and he was very excited about the research," said Milewicz, who holds the President George H.W. Bush Chair in Cardiovascular Research. She is also on the faculty of The University of Texas Graduate School of Biomedical Sciences and director of the John Ritter Research Program in Aortic and Vascular Diseases at UTHealth.

"I was indeed very excited when hearing about the puzzling results because the knowledge at the time on the role of FV in coagulation could not explain the bleeding disorder. It has been a great privilege to work with Dr. Milewicz and her colleagues to decode the unexpected and intriguing mechanisms on how FV-Short caused the bleeding disorder," said Dahlbäck who holds the chair as professor of Blood Coagulation Research at Lund University, Malmö, Sweden.

The results were published in today's online issue of the *Journal of Clinical Investigation*. Milewicz and Dahlbäck are senior co-authors.

Genes make proteins that do everything from giving cells shape and structure to helping carry out biological processes. To make the proteins, genes go through a process called alternative splicing that creates coded portions, called exons. The researchers discovered that a mutation in exon 13 of the coagulation FV gene caused a short form of the protein due to changes in the splicing of the exons. That FV-Short protein was unexpectedly found to form a complex in blood with tissue factor pathway inhibitor (TFPI), a protein that inhibits coagulation of the blood. An overabundance of the combined FV-Short/TFPI in the bloodstream keeps the blood from clotting in the affected family members. Other researchers have been looking at ways to inhibit TFPI, which could lead to a treatment for this family's clotting disorder.

What Milewicz called traditional genetics and "old-fashioned biochemistry" by lead co-author Lisa Vincent, Ph.D., led to the discovery of the FV-short protein in the blood of affected family members.

Dahlbäck's work determined how the FV-Short was causing the problems with clotting the blood. Milewicz said studying this family with a rare blood disorder has provided further insight into how the blood clots.

"We knew there was something wrong with these patients' FV, but proving it required discovering unique properties of FV in coagulation," Vincent said. "After many trials and tribulations, our true success is finally being able to provide an answer to the family about their medical issues."

More information: Coagulation factor VA2440G causes east Texas bleeding disorder via TFPI?, *J Clin Invest.* 2013;123(9):3777–3787. DOI: 10.1172/JCI69091
Factor V, tissue factor pathway inhibitor, and east Texas bleeding disorder, *J Clin Invest.* 2013;123(9):3710–3712. DOI: 10.1172/JCI71220

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