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## New Inherited Disease Can Cause Early Aortic Rupture

Researchers have identified a new inherited syndrome that can cause the heart's aorta to rupture earlier than other aortic aneurysm syndromes, such as Marfan syndrome. They said the newly identified syndrome is a relatively common disorder, which can be corrected with surgery if it is diagnosed early.

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— **Harry C. Dietz**

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The researchers also found that the new genetic disorder offers important lessons about the complexities of disease-causing malfunctions in a particular gene which produces the receptor for a protein known as transforming growth factor beta (TGF $\beta$ ).

TGF $\beta$  is a chemical messenger that influences the growth and other physiological functions of cells. Receptors are proteins embedded in the membranes of cells, which activate cell responses when a chemical messenger such as TGF $\beta$  plugs into them.

The researchers, led by Howard Hughes Medical Institute investigator Harry C. Dietz, published their discovery of the new syndrome in an advance online publication on January 30, 2005 in the journal *Nature Genetics*. Dietz and his colleagues at Johns Hopkins School of Medicine collaborated on the studies with researchers from Ghent University Hospital in Belgium, McGill University in Canada, Northwestern University School of Medicine, University of Wuerzburg in Germany, and New York University School of Medicine.

According to Dietz, there had been considerable controversy over whether mutations in the TGF receptor could cause Marfan syndrome, a genetic disorder that affects connective tissues and causes dilation of blood vessels and abnormal heart valves. People with the disease can suffer abrupt, lethal aortic rupture. It had been known that an underlying genetic cause of Marfan syndrome is a deficiency of the structural protein fibrillin-1, said Dietz.

However, he said, some individuals had symptoms that resembled Marfan syndrome, but did not satisfy all the diagnostic criteria for the disease. "It was a big question mark in everyone's mind about what this all meant," said Dietz. "We were seeing people in our clinic with inherited forms of aortic aneurysm who did not have Marfan syndrome, but who did have a number of distinguishing features. These included widely spaced eyes, cleft palate, divided uvula, and premature fusion of the skull bones. These people had aneurysms that behaved differently from any other previously described inherited form of aortic aneurysm.

"The aneurysms in such patients were widely distributed throughout the arterial circulation, rather than strictly at the aortic root near the heart," said Dietz. "They were very aggressive in early childhood and often led to death; and they also were demonstrated to tear and rupture at a smaller size that was not associated with risk in any other known aortic aneurysm syndrome."

Analysis of these patients' tissues suggested that they had fundamental disorders in the behavior of their cells, said Dietz. The researchers considered defects in TGF $\beta$  receptor as a possible cause, because studies in mice had shown TGF $\beta$  signaling to be important in the development of blood vessels, and the face and skull.

Analysis of one type of TGF $\beta$  receptor gene in ten families with the disease revealed that six of these families had mutations that might be predicted to reduce signaling. The mutations were found in only one of two copies of the gene in these families.

"That was a curious finding, because we had previously associated too much TGF $\beta$  signaling with features of Marfan syndrome," said Dietz. "But here was a suggestion that too little TGF $\beta$  signaling could lead to manifestations of this new condition that had some overlap with Marfan syndrome.

"We reasoned that it might be possible that a mutation that caused too little signaling could lead to compensatory events that might lead to excessive TGF $\beta$  signaling," said Dietz. When the scientists analyzed the genetic activity in the patients' tissues, they discovered that many genes regulated by TGF $\beta$  were, indeed, chronically overactivated.

“When we analyzed samples of aortic wall cells from these patients, we found overexpression of TGF $\beta$ -responsive genes like collagen genes and the connective tissue growth factor gene,” said Dietz. They also found evidence of activation along the signaling pathway regulated by TGF $\beta$ .

Furthermore, in the other four families with the disorder, the researchers found mutations in a second type of TGF $\beta$  receptor that cooperates with the first type to propagate signaling in the cell.

Dietz emphasized that the findings illustrate the importance of taking into account compensatory mechanisms in understanding the origin of genetic disease. “We have to respect the complexity of biological systems,” he said. “It’s easy to infer that in a tightly controlled artificial system, when you take away half the receptor, you should get less signaling. But this disorder shows that you have to respect the fact that this is not a fully controlled system; that there are attempts at compensation in biological systems. Those compensatory effects are going to be difficult to predict with certainty, but they have important implications for understanding the pathogenesis of disease and developing new treatment strategies.”

Thus, Dietz and his colleagues are planning additional studies of families with the disorder, as well as mouse models, to understand the complexities of such signaling disorders and how to best treat them.

He said that there are drugs on the market that both lower blood pressure and reduce TGF $\beta$  signaling. While such drugs might be a “magic bullet” that both relieves stress on the fragile aorta and corrects altered cell signaling, Dietz pointed out that the molecular effects of such drugs might also be detrimental in some tissues and at select critical points in development.”

Dietz emphasized that early clinical recognition of the new disorder is critical to treatment. “This new syndrome seems to be relatively common, and it can cause aortic rupture earlier than other aortic aneurysm syndromes,” he said. “We’d like clinicians to know that there are important, unambiguous distinguishing features of this new syndrome that are different from Marfan syndrome and other forms of aortic aneurysm.

We have shown that, once diagnosed, surgery is successful if done early in individuals with this new syndrome.” According to Dietz, such diagnosis will require going beyond the use of echocardiograms and listening to heart sounds. Additional steps such as examining for a cleft uvula and wide-set eyes and performing a three-dimensional computerized tomographic scans are necessary to diagnose the syndrome, he said.