Nevada geneticist teams to identify mutant gene causing vascular disease

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Colleen A. Morris, M.D., a clinical geneticist at the University of Nevada School of Medicine, and researchers and cardiologists from the University of Utah and Indiana University, have discovered that mutations of the elastin gene in the number seven (7) chromosome can cause narrowing of major arteries, heart failure and death.

"Finding a single gene that affects the large blood vessels of the heart gives us insights into the genetic factors which cause congenital heart disease," says Dr. Morris, an assistant professor in the Department of Pediatrics and director of the clinical genetics program. "This discovery may lead to better understanding of common vascular disorders such as atherosclerosis, a disease that causes stroke, heart attack and blood clotting in hundreds of thousands of Americans."

Elastin is a structural protein that has elastic or rubber-like qualities. The walls of arteries are primarily composed of alternating rings of smooth muscle and elastic fibers. In addition to their function as major conduits for blood, arteries dampen changes that occur in blood pressure with each heart beat and help maintain blood pressure and flow during cardiac relaxation. These resilient vascular functions are mediated by elastic fibers, the main component of which is elastin.

Investigators discovered that mutations in the elastin gene in chromosome 7 cause supravalvular aortic stenosis (SVAS), an inherited disease that induces narrowing of arteries such as the aorta and pulmonary arteries. If untreated, this disorder may lead to heart failure and death. In one family, for example, three individuals died of SVAS; two children (18 months and 3 years) died during surgery and

one 39-year-old died of heart failure after refusing surgery. Although symptoms of SVAS usually begin in

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childhood, the disorder may occur later in life. SVAS occurs approximately once in every 25,000 live births.

The scientists reported their findings in two publications. The first study, which will be published on April 15, 1993 in the *Proceedings of the National Academy of Sciences*, showed that a gene causing SVAS was located on chromosome 7 near the elastin gene. In the April 9, 1993 issue of *Cell*, these investigators demonstrated that an inherited chromosomal translocation found in members of a SVAS family disrupted the elastin gene, strongly suggesting that mutations in elastin cause SVAS.

The scientists examined genetic material from members of several SVAS families, looking for significant patterns in the way genes are passed from one generation to the next. They found that individuals having the vascular disorder also inherited mutant copies of the elastin gene from one parent. The work will substantially improve diagnosis of SVAS, making disease prediction possible at, or even before, birth. The ability to predict the onset of SVAS may enable prevention of the disorder using new medical therapies; currently the only treatment for SVAS is open-chest surgery.

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SUPRAVALVULAR AORTIC STENOSIS

What is supravalvular aortic stenosis? Supravalvular aortic stenosis, or SVAS, is a vascular disease that causes narrowing of arteries like the aorta and pulmonary arteries. If untreated, this disorder can lead to heart failure and death.

How is SVAS inherited? Scientists now know that the disease involves an inherited mutation that damages the elastin gene, which is located on chromosome 7. Each child of a parent with this disorder has a 50% chance of inheriting the damaged gene.

Who gets SVAS? SVAS occurs in approximately 1 in 25,000 live births.

When does SVAS appear? SVAS typically strikes children and young adults, but its effects can become apparent at any age.

What is the outlook? If untreated, SVAS can cause heart failure and death. Current therapy consists of open-chest surgery. Research indicates that diagnosis can now be made at, or even before, birth. Further studies should provide new medical therapies that prevent the vascular obstructions that ultimately cause problems for affected individuals.

Why is this work important? These studies will help predict and prevent this inherited vascular disease and may improve our understanding of common vascular disorders like atherosclerosis.

Genesis of a Vascular Disease. Supravalvular aortic stenosis (SVAS) is an inherited disorder of the vascular system. Normal blood vessels have three major layers. The intima is a thin layer of cells separating the structural portion of the vessel from blood in the lumen. The outermost layer of the vessel, called the adventia, is composed of loose connective tissue and is thought to support the vessel. the main structural components of the artery are located between these two layers, in the media. The media is composed of alternating layers of smooth muscle cells and elastic fibers, shown as black wavy lines in the magnified view at right. Elastic fibers are similar to rubber in that they are easily stretched but always snap back to their original shape, giving the blood vessel its flexibility and resilience.

Researchers believe that SVAS is caused by mutations in the gene encoding elastin, the major component of elastic fibers. These mutations cause abnormal development and weakening of elastic fibers, leading to damage and scarring of the media. As a result, individuals affected by SVAS develop hard, noncompliant arteries that are predisposed to further damage. Researchers believe that over time the constant stress of each heartbeat, in a scarred and noncompliant blood vessel, damages the thin intimal layer, eventually causing obstruction or blockage of the lumen. The resultant obstruction of blood flow can lead to heart failure and death.