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Inherited Heart Disorder May Affect More People

Most news stories about familial hypertrophic cardiomyopathy invariably describe young athletes who die suddenly, felled by a heart condition that no one had suspected.

Now a research team led by Hughes investigators Christine Seidman and Jonathan Seidman at Brigham and Women's Hospital and Harvard Medical School has discovered a form of the disorder that doesn't manifest until middle age. This finding suggests that familial hypertrophic cardiomyopathy (FHC) encompasses a wider syndrome of defects and is likely to affect more people than once thought.

"We may be able to better diagnose older patients whom we did not realize may be suffering from FHC, as well as screen families at risk for the disorder," said Christine Seidman, an author of the study, which was published in the April 30 issue of the *New England Journal of Medicine*.

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While there is currently no treatment for FHC, knowing that a middle-aged person has a mutation means that doctors can watch closely for symptoms that the disease may be progressing. Monitoring patients also increases the chances that secondary clinical problems related to FHC are correctly diagnosed and treated, Seidman said.

The genetic disorder underlying FHC causes structural defects in heart tissue that make it less elastic and unable to withstand high heart rates. Dysfunction arises when mutations affect proteins of the cardiac sarcomere, the source of heart muscle contraction.

Scientists knew that some protein defects were linked directly to sudden death in young people. Seidman and others were puzzled by a subset of patients who appeared to have FHC, yet did not have mutations in the known "FHC genes." She helped organize an international team of researchers from Japan, the United Kingdom, Canada, Iceland, and other medical schools in the United States to study this subset of patients. The results of the 10-year study led to the *NEJM* article.

"We all had studied families with FHC that we couldn't make sense of. There were mutations in some proteins, but not in others," she said. "We tried to do linkage analysis, but the data implied that our diagnoses of FHC were incorrect."

The answer came only after Hideshi Nimura of Kagoshima University in Japan sequenced the entire gene for cardiac myosin-binding protein C, a structural protein in the sarcomere. Sequencing the gene allowed the researchers to see that individuals within those families had mutations but did not manifest the signs of FHC.

The researchers characterized 12 separate mutations in myosin-binding protein C that caused FHC in 16 families. Outward symptoms of FHC often do not develop in these families until age 40 or older. Variations in the severity of the disease can exist within a single family, Seidman said, so it is important that screening for symptoms of the disease start early and continue through middle age and beyond.

The study also helps to explain other diseases that have puzzled physicians, such as variation in the severity of common, and often deadly, left ventricular hypertrophy in the elderly. "It raises the possibility that a proportion of what is ostensibly acquired left ventricular hypertrophy has been genetically determined at a single locus, and points to the need for family studies of left ventricular hypertrophy in elderly hypertensive patients," says Thomas Traill, a cardiologist at The Johns Hopkins University School of Medicine.

Furthermore, studies of patients who survive to middle age and beyond despite fundamental genetic mutations that cause FHC may reveal insight into how the disorder in general can be treated, Seidman said.