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Genes or Environment? Researchers Probe Sudden Death

A mouse model of familial hypertrophic cardiomyopathy (FHC) is providing scientists with valuable information about whether genes or environment trigger sudden death.

FHC is a devastating disease that kills people in the prime of life with very little warning. Over a period of years, the heart wall of those with FHC thickens to an abnormal degree, and death can result from vigorous exertion or prolonged stress on the heart. Some with FHC die even though there is no apparent triggering event.

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— Jonathan G. Seidman

During the past decade scientists have made remarkable progress in uncovering the genes associated with the disease. They know, for instance, that FHC can be caused by many different mutations in contractile proteins that make up the heart wall. Such genetic information has made possible a blood test to detect the presence of faulty genes in people who have a family history of sudden death. And researchers have had success in studying those mutations to predict the severity of the disease. But they are still a long way from knowing who will die suddenly or whether factors like high blood pressure or extreme stress will trigger sudden death.

A group of geneticists and cardiologists at HHMI at Harvard Medical School and Brigham and Women's Hospital in Boston have now developed a mouse model of FHC that should greatly enhance genetic studies of the disease. In the past, animal models of hypertrophy (thickened heart wall) have been available, but none is a mirror of FHC in humans, said project leader Jonathan Seidman, a Hughes investigator at Harvard Medical School.

Seidman and his wife, Christine E. Seidman, a Hughes investigator at Brigham and Women's Hospital, reported in *Science* that they have bred mice with single point mutation in the gene for myosin, a muscle protein found in the heart. Using embryonic stem cell technology, the researchers changed a single nucleotide in the myosin gene from arginine to glutamine, and then bred mice that matured with the mutation in their genes. "We selected this particular mutation," said Jonathan Seidman, "because we knew from our work with FHC families that individuals with this mutation have a relatively short life expectancy."

Mice with mutations in both copies of the myosin gene died within seven days of birth. Those mice with one altered myosin gene lived one to two years before dying, a life expectancy that reflects human FHC.

One of the most important features of the mouse model of FHC is that it will now allow the Seidmans to study to what extent genetics or environment influences FHC. For example, the scientists can now subject mice to strenuous exercise and see how that exertion affects the size of the heart muscle wall. Likewise, they might wish to breed FHC mice with alterations in genes that control blood pressure and see if those genes have an impact on survival. "We are now in a much better position than before to examine background factors that might also control the severity of this disease," said Jonathan Seidman. "Such information could one day be extremely useful when making recommendations to patients about how they should live their lives."