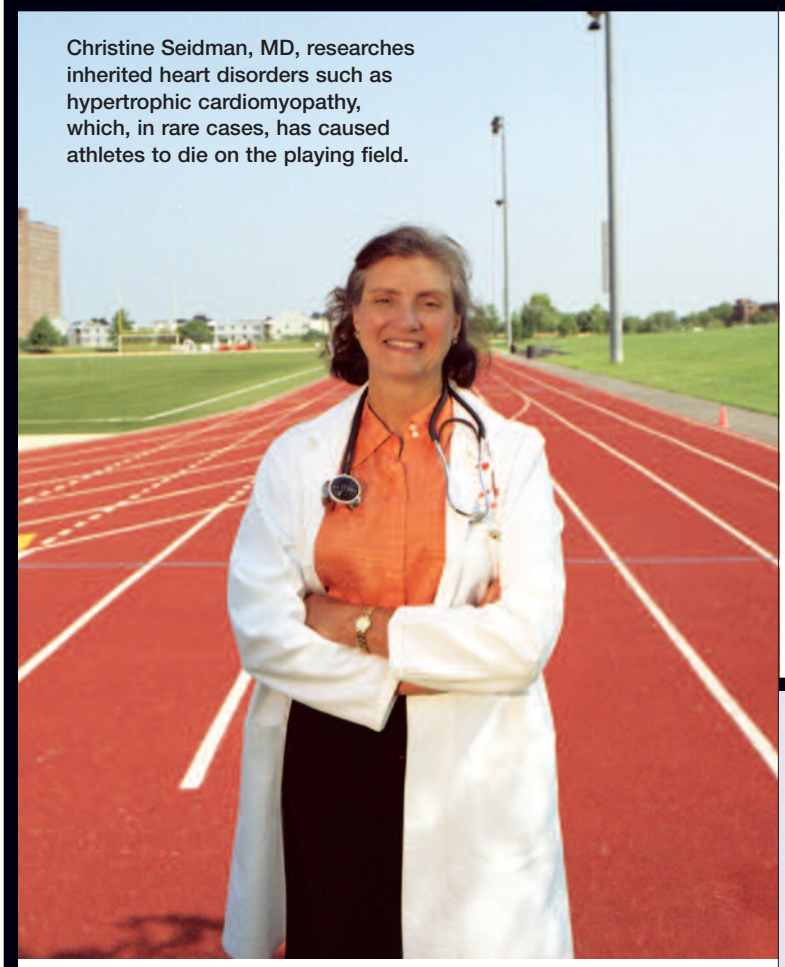
From one generation to the next

Geneticists are zeroing in on treatments for inherited heart disorders, including hypertrophic cardiomyopathy



Christine Seidman, MD, researches inherited heart disorders such as hypertrophic cardiomyopathy, which, in rare cases, has caused athletes to die on the playing field.

LIKE OTHERS IN HER FAMILY, Wendy Trevedi* has a big heart.

Specifically, her heart's left ventricle, which pushes oxygen-rich blood through her body, has thickened. It's a sign of hypertrophic cardiomyopathy, or HCM, a condition that can lead to heart failure and deadly changes in heart rhythm. It's the most common inherited cardiovascular disorder, affecting as many as one in 500 people. Most experience only mild symptoms and live a normal lifespan. In rare cases, the first sign is sudden death, often during or after exercise.

At one time, Trevedi thought she had dodged the syndrome that so cruelly stalked her family. Two of her uncles died of heart failure in high school. A third passed away at age 32 with four children, two of whom inherited the condition. Her grandmother died of it when her mother was 18, and now her mother awaits a heart transplant. In Trevedi's case, at age 25, near-fainting episodes signaled the condition's onset.

"We want to understand why a heart functions magnificently for years and then starts to fail in so many ways," says Christine Seidman, MD, director of Brigham and Women's Cardiovascular Genetics Center. She aims to understand the fundamental changes in people who share the disease in hopes of finding better treatments and preventing heart failure.

Seidman and her husband, Jonathan, both professors at Harvard Medical School, and their colleagues discovered the first human HCM gene in 1990 by meticulously analyzing and correlating variations in DNA and the occurence of disease in members of a Canadian family with HCM. This research mapped the first HCM gene, work that led to the identification of a gene mutation that caused HCM in the family.

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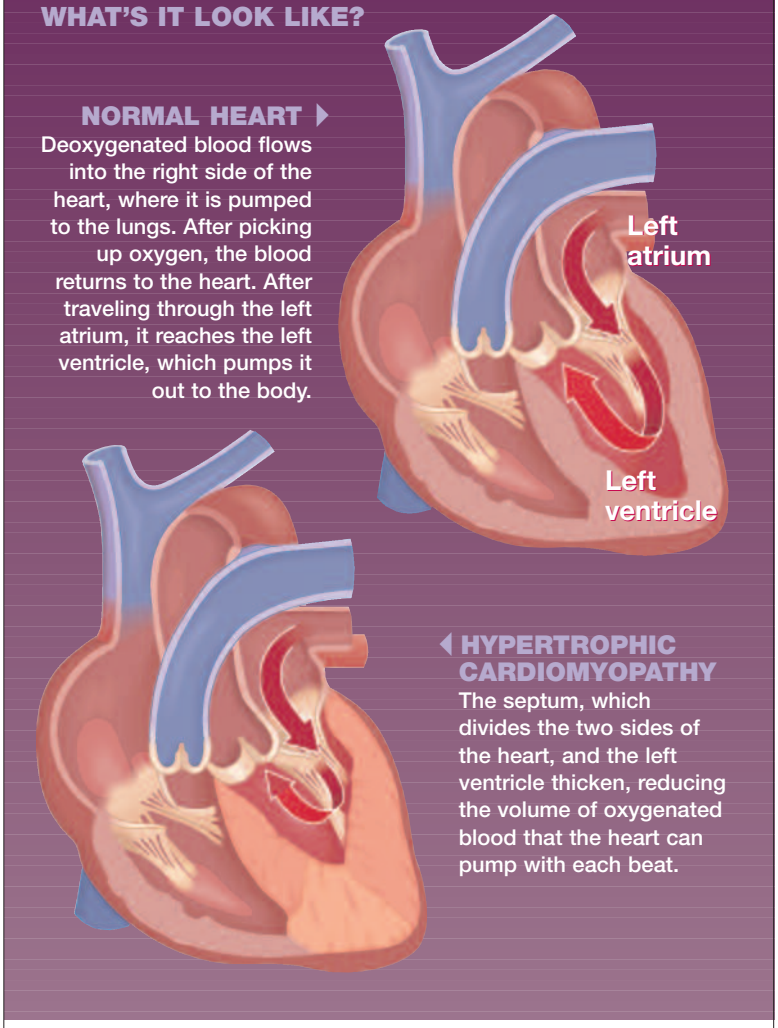
Study of other HCM families, including a genome-wide search of Trevedi's family, revealed mutations in several other genes, all of which are linked to sarcomeres, molecular structures that allow the heart to contract and relax.

"It told us right away that heart disease can look the same clinically from one person to another but have different genetic etiologies," says Seidman. To date, she and others have identified about 400 mutations in 12 genes.

To better understand the disease, Seidman introduced the human HCM mutations into specially bred mice. Subsequent studies are beginning to show how mutations affect heart function. Normally, the electrical impulse that triggers each heartbeat also sends calcium signals racing through heart cells with instructions to shorten and lengthen muscle fibers at a rate of 70 to 100 times a minute, but the mutations somehow interfere with this process.

*Not the patient's real name.

WHAT'S IT LOOK LIKE?



Illustrations by Ed Wiederer

Into the clinic

Researchers are now taking their insights into the clinic. Last year, BWH licensed tests to identify mutations in the eight most common HCM genes to the nonprofit Laboratory for Molecular Medicine run by Harvard Medical School and Partners Healthcare. This is the only U.S. facility that offers licensed, gene-based diagnosis of HCM.

"Genetic testing can minimize the ambiguity of whether a family member is at risk for developing HCM," says Carolyn Ho, MD, the Cardiovascular Genetics Center's medical director.

Although doctors cannot cure or prevent the disease, they can monitor people and prescribe medications or suggest procedures to reduce the risk of an abnormal heart rhythm. For example, Trevedi has an implanted cardiac defibrillator to correct any dangerous swings in her heart rhythm. Ho estimates that people who inherit the mutation have a 90 percent lifelong chance of developing the condition, so Trevedi's two children, who each carry the mutation, have annual echocardiograms.

New treatments are on the horizon, too. Three years ago, the Seidmans reported that young mice with HCM given an anti-hypertensive drug known as a calcium channel blocker developed less thickening of the heart than untreated litter mates. Now, the Seidmans, Ho, and their colleagues plan to test the drug in asymptomatic people with HCM. "We're first in line," Trevedi says of her family.

But how will researchers measure the effect of treatment? The underlying molecular changes of the condition prevent the heart from completely relaxing between contractions, Ho and other researchers have found. Knowing this, they can use a new cardiac ultrasound technique, called Doppler tissue imaging, to detect the effect of the drug on subtle changes in relaxation function long before the heart wall thickens.

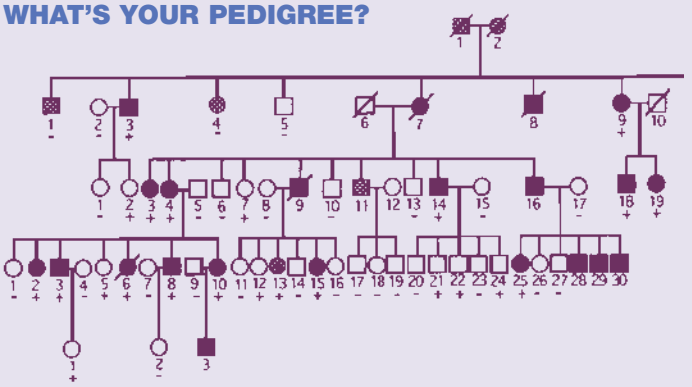
Meanwhile, Seidman's team continues to investigate how different mutations cause the disease so they can develop more powerful, targeted interventions. And they want to learn the secret of why some mice with the mutations, like people, do not develop life-threatening complications.

Research has also exposed a look-alike disease with a different diagnosis and prognosis. Among the 10,000 members of families with HCM in their research database, Seidman's lab discovered a small group with abnormalities in how they use glucose for energy rather than a mutation in the heart's contractile proteins as with typical HCM. "When you think about it, why should those patients be treated the same way?" Seidman says.

Other research aims to identify the underlying cause of familial dilated cardiomyopathy, in which enlarged heart chambers sometimes fail to contract vigorously enough, and other inherited cardiovascular disorders.

"Medical science is such a slow process," says Trevedi. "But each leap in the right direction gives us hope for the future and for generations to come." ■

WHAT'S YOUR PEDIGREE?



This pedigree represents a family with HCM. Circles indicate females; squares, males. Darkened symbols represent affected family members; open symbols, unaffected members; cross-hatching, status unknown. Plus and minus symbols indicate a particular mutation's presence or absence based on DNA testing. Deceased individuals are marked with a slash.