



The Johns Hopkins Heart Institute Cardiovascular REPORT

FOCUS ON INHERITED CARDIAC DISEASE

SUMMER 2007

Bringing Genetics to the Bedside

Not all “idiopathic” dilated cardiomyopathy stems from an unknown cause.



Dan Judge

THE CASE: JS is a 36-year-old man who was referred to Johns Hopkins for genetic evaluation in the setting of dilated cardiomyopathy. He was well until five years ago, when he developed symptomatic bradycardia, with a Holter monitor showing several 3-second pauses. After a pacemaker was inserted at another hospital, JS showed marked improvement. His cardiac size and function were normal at that time.

He returned to work and also enjoyed farming and camping. He did not smoke or use alcohol to excess. Routine health screening showed normal blood pressure and heart rate, but elevated LDL cholesterol. He was treated with a statin. Three years ago, he began to notice that he was feeling weaker, but he continued to be very active. One year ago, a serum creatine kinase level was 450 U/L. The statin was stopped, but his symptoms persisted. Repeat creatine kinase testing several weeks later remained high, suggesting a primary disorder of skeletal muscle. Despite this, he remained active, without cardiac symptoms, such as chest pain or shortness of breath.

Evaluation by a neurologist for the high creatine kinase included a muscle biopsy showing nonspecific muscle pathology. An echocardiogram showed left ventricular dilation with normal wall thickness and an ejection fraction of 25 percent. He was referred to cardiologist **Dan Judge** for further evaluation.

THE HOPKINS APPROACH: Judge, the medical director of the new Johns Hopkins Center for Inherited Heart Disease, recognized the constellation of dilated cardiomyopathy, conduction disease and skeletal muscle disease as likely a genetic condition. His first priority was to determine the pattern of inheritance of this condition in the family. On further questioning, JS remembered having a maternal uncle who had been diagnosed with cardiomyopathy and died suddenly at age 24. Judge advised JS that both of his parents, his only sibling, his children and his maternal uncle's only child should have echocardiograms, which were arranged with the referring cardiologist. Then, suspecting that the

diagnosis could be X-linked Becker muscular dystrophy, Judge conferred with **Kathryn Wagner**, a neuromuscular genetics specialist at Hopkins. After evaluating JS, Wagner arranged for specific staining of his skeletal muscle biopsy. The dystrophin staining was normal, indicating that JS did not have Becker muscular dystrophy.

Judge also arranged genetic counseling and subsequent clinical genetic testing for a lamin A/C mutation. The testing, performed after JS and his wife met with a genetic counselor and all of their questions were answered, identified a mutation in one copy of the lamin A/C gene (*LMNA*).

TREATMENT DECISION: Judge and the genetic counselor explained to JS that each of his three children (ages 12 to 16 years) has a 50 percent risk of inheriting the same genetic predisposition to this condition. The children were referred to their pediatricians for both echocardiograms and ECGs. The family was advised

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Consultation: Joseph Marine

Director of Electrophysiology, Johns Hopkins Bayview Medical Center

As a specialist in heart arrhythmias, how do you fit into the Johns Hopkins Hypertrophic Cardiomyopathy Clinic?

Hypertrophic cardiomyopathy (HCM) is primarily a heart muscle disease causing thickening of the walls of the left ventricle. Most patients do well with medical treatment, but some are susceptible to heart rhythm disturbances, such as atrial fibrillation and ventricular tachycardia. We provide consultative support for this group of HCM patients. We provide advice on medical treatment, implant pacemakers and ICDs, and perform catheter ablation of atrial fibrillation.

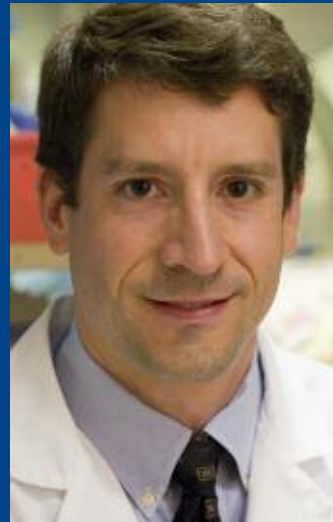
Several years ago, in large trials looking at the effects of pacing the right ventricle in patients with HCM, researchers concluded that this method wasn't particularly effective. Do you agree?

It is true that most patients with HCM and severe outflow tract obstruction that is not well controlled with medication are more likely to benefit from septal reduction surgery—myectomy—or alcohol septal ablation. But we have found that for some patients, pacing is a viable third op-

tion for improving pressure inside the heart, especially when you hope to avoid or want to defer a more invasive approach.

How do you determine who might be a candidate?

We certainly wouldn't recommend pacing for everyone. It should be reserved for a very select group. For example, Ted Abraham, who directs Hopkins' HCM clinic, recently referred a patient in his mid-50s who had severe symptoms of outflow tract obstruction including shortness of breath and leg swelling. We implanted a dual-chamber cardioverter defibrillator and referred him for septal ablation. In the meantime, we applied dual-chamber pacing, and the patient improved so much in one month that he ended up not needing the ablation procedure after all.



What about patients with HCM and atrial fibrillation?

Hypertrophic cardiomyopathy may cause the myocytes to be disarranged in the atria, and the thickened left ventricular muscle causes elevated pressure in the left atrium. As a result, about 25 percent of HCM patients develop atrial fibrillation (AF) and tend to be more symptomatic with it than patients without HCM. It is important for most of these patients to take an anticoagulant (warfarin) to prevent stroke. Anti-

arrhythmic drugs can also be used to maintain normal rhythm, and catheter ablation is an option for selected symptomatic patients who do not respond to medical treatment. Patients who have atrial fibrillation and outflow tract obstruction going for septal reduction surgery may also receive surgical treatment of their AF at the same time.

Bringing Genetics to the Bedside

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to consider the options of continued periodic screening with these studies or proceeding with presymptomatic genetic testing for their father's lamin A/C mutation in the children.

Meanwhile, because mutations in this gene are associated with increased risk of sudden death, Judge referred JS to **Joseph Marine**, director of cardiac electrophysiology at Johns Hopkins Bayview Medical Center. After Marine's Holter examination showed several episodes of nonsustained

ventricular tachycardia, he decided to change the patient's pacemaker to an implantable cardioverter-defibrillator.

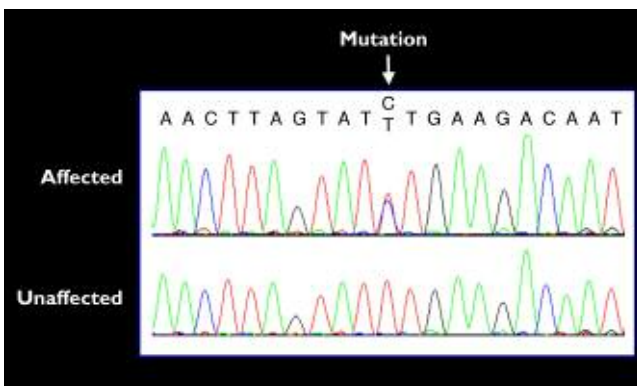
DISCUSSION: Once considered solely in the realm of research, genetic testing has developed rapidly over the last few years to the point where clinical genetic testing is now available for many conditions, such as inherited forms of cardiomyopathy and arrhythmia. Among individuals with "idiopathic" dilated cardiomyopathy, studies have shown that 25 percent to 35 percent have a first-degree relative with the same condition. Recognizing a pattern of inheritance within the family can allow people with early forms of cardiomyopathy to be diagnosed and treated before the onset of symptomatic heart failure.

Hypertrophic cardiomyopathy is more often recognized to occur in family members, and individuals at risk often face significant concern regarding the possibility of developing this condition. If a responsible mu-

tation is identified in a clearly affected family member, others within the family can be tested for this mutation.

Judge is quick to point out that genetic testing is not for everyone. Risks include employment discrimination, difficulties obtaining life insurance, discovery of non-paternity, and problems with relationships within a family. Because of the risks and complexity of such testing, the approach in Hopkins Cardiology is to require genetic counseling and consent prior to any clinical genetic testing.

OUTCOME: JS has responded well to standard medications, both an ACE-inhibitor and a beta-blocker, with improvement in his ejection fraction to 35 percent. He has had two episodes of sustained ventricular tachycardia that were successfully treated with pacing. Each of his children has now undergone targeted clinical genetic testing, and none has inherited the mutation that caused his cardiomyopathy with conduction disease. They're now relieved of the burden of lifelong screening exams and tests to look for the disease. ■



DNA sequence analysis shows a heterozygous mutation, indicated by the arrow and both blue (C) and red (T) peaks in the top sample, compared to the bottom sample.

Marfan Syndrome's Grand Theme

Often obscured among the accolades that have accrued to **Victor McKusick** since he launched the nation's first medical genetics division at Johns Hopkins 50 years ago is the fact that he began his career specializing in heart disease. "Some people thought I was committing professional suicide switching from cardiology to focus on rare and supposedly unimportant disorders," says the 1997 Lasker Award winner, "but my interest in medical genetics grew out of treating patients with Marfan syndrome."

Of all that has come from his pre-science—Google medical genetics and you'll get more than 73 million hits—what excites him most is the discovery of a breakthrough treatment for the very disorder that started it all.

In 1956, when McKusick coined the phrase *heritable disorders of connective tissue* to describe Marfan and four related syndromes, he postulated that Marfan's distortions of the skeleton, eye, lungs and aorta were due to a mutation in a single, fibrous element. The "aha" moment seemed to come in 1991 when his colleague **Hal Dietz** showed that mutations in the gene that encodes fibrillin-1—a protein needed for formation of elastic fibers in connective tissue—cause Marfan.

But celebration turned quickly to near despair when Dietz realized that the finding opened no practical avenues for treatment. If Marfan patients were born with a structural predisposition to tissue failure, then they were "like a house with a rotten frame that could only be fixed by tearing it down and starting over," says the pediatric cardiologist. "Things looked so bleak that if I had been only a researcher and not a clinician, I would have turned my attention to something else."

Still, Dietz couldn't shelve the conundrum of how a structural deficiency alone could explain Marfan's



Victor McKusick and the McKusick Professor of Medicine and Genetics, Hal Dietz.

bone overgrowth and thickened mitral valves. Heading back to the lab, he and colleagues created a mouse model of Marfan and ended up finding what McKusick himself admits he would never have predicted: that fibrillin-1 also regulates a key developmental signaling molecule called transforming growth factor beta, and it is an excess of TGF-beta activity that triggers the skeletal, pulmonary and cardiac features of Marfan.

Dietz now saw a therapeutic target and, enlisting the help of cardiologist **Dan Judge**, began scouting for a drug that would block TGF-beta. Their search turned up the hypertension medication losartan. Today, thanks to their rigorous studies showing that Marfan mice treated with losartan are indistinguishable from normal mice, the National Institutes of Health has launched a trial to determine whether losartan has the same robust effect in people.

"We always thought that the Human Genome Project would revolutionize medicine," Dietz says. "Now we have an excellent example of how finding the genes responsible for a disease can lead to rational therapy."

"It's not at all what you expect," says McKusick. "But you do get there." ■

The Losartan Trial

This spring, a much-anticipated clinical study began enrolling people with Marfan syndrome to determine whether a well-known angiotensin receptor blocker can stop—and perhaps even reverse—aortic root enlargement. Funded through the National Heart, Lung and Blood Institute and conducted by the Pediatric Heart Network, the losartan trial is taking place at 16 U.S. sites, plus two in Canada and one in Belgium. At Johns Hopkins, principal investigator Hal Dietz hopes to enroll up to 100 patients. And to that end, he says, "We will partner with referring physicians and centers everywhere." For details, go to www.marfan.org.

Getting to Loey-Dietz in Time

Four years ago, one of the scores of children whose flimsy aortas **Duke Cameron** has reinforced became the first person in the world known to be undergoing valve-sparing aortic root replacement for the newly recognized Loey-Dietz syndrome. And to the gratification of the heart surgeon who today leads the team with the world's longest experience repairing aortic aneurysms in patients with Marfan syndrome, the operation proved equally successful.

Well before cardiologist **Hal Dietz** and his Hopkins colleagues published in 2005 their groundbreaking description of a condition similar to but clinically and genetically distinct from Marfan, they saw that Loey-Dietz syndrome is far more aggressive. Not only is dissection and rupture of the ascending aorta more likely at a younger age and at a significantly smaller root diameter than in Marfan patients, but aneurysms may occur throughout the arterial tree.

The good news, reports Cameron—whose growing number of Loey-Dietz operations includes children as young as 9 months—is that despite becoming surgical candidates when their aortic root diameter measures as little as 3 to 4 centimeters, these patients, like their Marfan counterparts, can be operated on with minimal morbidity.

Loey-Dietz aneurysms appear most often in the ascending aorta, but they also can threaten the transverse, descending thoracic and abdominal aorta, and the thoracic arterial, head or neck, and abdominal arterial branches. As a result, patients require regular monitoring via head-to-pelvis computed tomography angiography so that these distal aneurysms can be repaired as soon as they're diagnosed. "There's a misconception that the tissues are excessively fragile," says vascular surgeon **Jim Black**. "In fact, they hold sutures very well, and we replace with a graft as much of the affected arterial tissue as is technically and anatomically possible to avoid late degeneration at the suture lines."

Given the unpredictable and aggressive nature of Loey-Dietz aneurysms, Hopkins' current approach is to perform surgery very early in the course of disease. "We also hope that newly developed mouse models of the syndrome will point the way to effective medical therapies," says Cameron. "I would like nothing better than to have my surgical intervention for this disease made obsolete." ■



Duke Cameron

Homing In on ARVD

In their quarter-century campaign to accurately diagnose one of the most mysterious causes of sudden cardiac death, scientists are closing in on their quarry with the aid of improved genetic screening. "In many cases," says cardiologist **Hugh Calkins**, "we can now pin it down."

One of every 5,000 people has arrhythmogenic right ventricular dysplasia. But the presence of ARVD too often becomes clear only after an autopsy reveals such telltale signs as a severely dilated right ventricle whose walls are thinned and replaced with fibro-fatty tissue. While getting an accurate early diagnosis can avert deaths in affected people, the condition's genetic links also give it a ripple effect: A third of an afflicted person's children will likely get it.

That link further magnifies the value of accurate early diagnosis. Confirmed cases can trigger prudent family-wide screening, but cases that are merely suspected can bring unnecessary worry and, worse, unnecessary treatment that often includes an implanted device.

The concern is no minor detail. Calkins describes one recent study that scrutinized cases of reported ARVD in which patients were treated. After an elaborate battery of tests using the full gamut of established criteria, most of the suspected diagnoses proved incorrect.

The process of diagnosing ARVD has always been taxing, says Calkins, who heads up a team of 10 specialists here and serves on a task force charged with revising the condition's diagnostic criteria. The current criteria include various combinations of six different factors, ranging from major dilation of the right ventricle (reducing ejection fraction) to EKG readings that show arrhythmias characterized by inverted T waves in the right precordial leads.

While a family history of ARVD is obviously a strong indicator, research conducted at Johns Hopkins has recently brought mutations in one gene—plakophilin-2—to the fore. *PKP2* errors are associated with up to 45 percent of ARVD patients, says senior study author **Dan Judge**. What's more, pa-



Arrhythmia expert Hugh Calkins

tients with a *PKP2* mutation are also more likely to develop ARVD at an early age, which hints at the condition's especially tragic distinction—its disproportionate toll on young athletes. Today, Hopkins is the only U.S. medical center offering clinical genetic *PKP2* testing for ARVD.

If ARVD is caught in advance, arrhythmias can be temporarily relieved with ablation therapy. But, Calkins says, the more optimal long-term solution currently resides with the implantation of a defibrillator.

Calkins hopes the revised criteria for ARVD will be published in early 2008. ■

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Cardiovascular REPORT

The Johns Hopkins Heart Institute *Cardiovascular Report* is one of many ways the Institute seeks to enhance its partnership with its thousands of referring physicians.

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