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Scientists hope 'molecular autopsy' explains puzzling death

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When Richie Quake, a 19-year-old engineering student, was found dead in his bed in Yardley, Pa.,, his family was devastated. But when a conventional autopsy of the apparently healthy young man offered no answers, his parents were gripped by another medical concern: Could a silent but deadly condition be hiding in other members of the family?

Today, scientists at the Stanford School of Medicine are on a quest to find out, searching samples of Richie's tissue for genetic clues that might explain why the young man's heart suddenly stopped.

The "molecular autopsy" is believed the first time that whole-genome sequencing has been used to seek a cause of death, although the Stanford team has used more focused genetic scans to investigate 17 other sudden unexplained deaths.

Dr. Euan Ashley and his medical research team are scanning Richie's DNA for errors that might cause irregular beating of the heart, invisible during traditional dissection.

"We're applying new technologies to an age-old practice, trying to work out why someone died, after they died," said Ashley, who directs Stanford's Center for Inherited Cardiovascular Disease. Nearly half of healthy young people have normal findings at autopsy, so their deaths remain a mystery.

"Because so many of these conditions can be familial, it becomes more

important for surviving relatives," he said. "This has the opportunity to save lives."

The team's data is still under analysis, and their conclusions won't be published until later this year. But they say they are zeroing in on a set of suspect gene mutations linked to one particular type of rare and poorly understood cause of sudden cardiac death, caused by faulty electrical signaling in a beating heart.

If confirmed, the genomes of surviving family members could be searched for similar flaws, and their health monitored closely.

Richie Quake seemed to be in perfect health. It was a morning three years ago when the black belt in karate lingered in bed because he felt a little chilly. Later that day, the Drexel University student was scheduled to work at a nearby theme park, dressed in a Big Bird costume.

"I kissed him good night the night before when he gave me a shirt for my birthday," his father, Richard, told Stanford Medicine magazine. "My wife talked to him that morning. . . . She said 'OK, I love you,' and she kissed him goodbye."

After an autopsy, the coroner blamed a fluttering heart, or arrhythmia. But that's a symptom, not a cause.

"He was a very bright teenager, very active, a good kid," recalls Stanford bioengineering professor Stephen Quake, a cousin of Richie's father. "It's been a very difficult experience for everyone, especially his immediate family, when there is no explanation, no closure.

"We wondered: Is there something we missed? For his sisters, and my kids, I wondered: What can we do for them to make sure we're taking the best care of them?"

Anguished by the unexplained death, Richie's father insisted the coroner collect both blood and tissue samples. "I told him, 'I need you to save everything you possibly can for future testing,'" Richard Quake, a sales manager for an Internet auto auction site, told Stanford Medicine. "At the time, I really had no idea why I said that."

Encouraged by cousin Stephen, who last year had his own genome sequenced for under $50,000 and published in the journal Lancet, Richard Quake sent tissue samples to Stanford.

Such cardiac death is generally linked to a problem in the pumping heart. The heart operates on electrical impulses that rhythmically stimulate the vessels, so blood can be pumped to the body. These electrical impulses are controlled by pores called "ion channels." Death can occur when the proteins for these ion channels do not function properly.

Stanford is not the only research facility searching, post-mortem, for killer genes. In Canada, a molecular autopsy of a 21-year-old college student found a genetic mutation that causes a heart problem called Long QT Syndrome. When tested, her mother was found to have the same mutation.

At the Mayo Clinic in Minnesota, Dr. Michael Ackerman has performed molecular autopsies of 49 young people who died suddenly. In seven cases, he found suspect mutations in a gene called RyR2, which regulates the influx of calcium into heart cells.

Such defects are dubbed "the perfect assassin" by Ackerman, because they leave no trace.

After Richie's death, his father sent his tissue to other university labs to see if they could find known mutations. But tests came back negative.

So the Stanford team has expanded the search, using powerful computers to scan all 6 billion nucleotide letters in Richie's genome, focusing on regions that regulate proteins in the heart muscle. Since there's no formal list, it's a big undertaking. To make matters worse, such defects are rare; a mutation could even be unique to a single family.

So far they have identified 200 genetic variants in the young man's genome, many never before associated with disease. Which one was lethal? That's what the Stanford scientists hope to learn.

"It's a situation where we're as blind as we can be - the sudden death of a healthy 19-year-old," Ashley said. "We have no other helpful side information."