MedicalXpress

Scientists ID ten genes associated with a risk factor for sudden cardiac death

March 22 2009

(PhysOrg.com) -- One minute, he's a strapping 40-year-old with an enviable cholesterol level, working out on his treadmill. The next, he's dead.

That an abnormality in his heart's electrical system had managed to stay on the Q.T. — until it proved lethal — is characteristic of sudden cardiac death, which annually claims more than a quarter million Americans. A dearth of discernable symptoms and lack of detectable molecules circulating in the blood makes the prediction of sudden cardiac death largely dependent on genetic risk factors.

Having identified 10 common variants of genes that modify the timing of the contraction of the heart, known as the QT interval, scientists in the Johns Hopkins University School of Medicine, in collaboration with an international contingent of researchers, now provide new insight about the underpinnings of the QT interval which, when prolonged or shortened, predisposes to sudden cardiac death.

QT interval, which is determined from a standard electrocardiogram (ECG), reflects the time it takes for the heart (ventricles) to contract and then reset for the next heartbeat.

Publishing March 22 in *Nature Genetics*, the international team including researchers from the Technical University in Munich, Johns Hopkins and others, used DNA samples previously collected for epidemiological studies to analyze the genomes of 15,842 individuals whose QT intervals

had been measured by electrocardiogram. With DNA microarray chips, each able to assess hundreds of thousands of markers in each sample, followed by bioinformatic techniques to increase the number of markers, the researchers screened approximately 2.5 million markers to detect subtle alterations in the sequences of these genomes that modify the QT interval.

By focusing on 2.5 million sites in a genome of 3 billion sites, the scientists surveyed one-one-thousandth of nearly 16,000 genomes. This relatively small but "still extremely powerful" screen correlates genomic architecture with QT intervals, according to Aravinda Chakravarti, Ph.D., a professor in the McKusick-Nathans Institute of Genetic Medicine.

These common variants at 10 locations across the genome represent perhaps dozens of yet-to-be-identified genes that affect this trait, Chakravarti adds. Of the 10, one that had been previously identified — Nos1ap — was confirmed. Several others were suspected culprits, the effects of which hadn't been demonstrated in preliminary screens.

"However, almost half were surprising new genes that no one would have guessed as being involved in cardiac biology," says Dan Arking, Ph.D., an assistant professor in the McKusick-Nathans Institute of Genetic Medicine. "So it really does open up a new world of investigation because these are genes that would have never come up if we had only focused on a list of known candidate genes."

A separate study, led by Christopher Newton-Cheh, M.D., M.P.H., of the Massachusetts General Hospital Center for Human Genetic Research and Cardiovascular Research Center , found similar results from more than 13,000 individuals. "We were very reassured to see such strong replication in two independent studies," says Newton-Cheh.

While any single genetic variation in any one individual does not necessarily imply a significant alteration to QT interval, much less increased risk of sudden cardiac death, there is meaning that resides in the collective.

The power of this genetic analysis is a result of screening many thousands of samples, says Chakravarti: "We're not very good at predicting what happens to any one, single sample. It's sort of like, I could examine in great detail how important my vote was in the last election, but it's trivial compared to the collective vote. An individual's genome is important as part of the study's whole, but individually, it's of little consequence."

Likewise, if scientists analyze the effect on QT interval by any one of the genetic variants, the alteration amounts to just a couple milliseconds, which is not a huge amount, says Arking: "But if you put all 10 genetic variants together, that bumps up the QT interval by about 20 milliseconds, which is significant."

This latest study builds on research published in 2006, when a screen of 100,000 sites in individuals of European ancestry first showed that the Nos1ap gene is associated with the QT interval; and subsequent research showing that sequence changes in Nos1ap are also a risk factor for sudden cardiac death. A third paper, published in January 2009 in *PLoS one*, widened the original screen to include multiethnic populations; that study confirmed that Nos1ap genetic variants alter QT interval in all populations and, in fact, have a stronger effect in women than men.

"The reason people die from this cardiovascular disorder is because we know nothing about the antecedents," Chakravarti says. "It's like a truck barreling down a slope: there's no way to stop it. The only way out is to understand the science of this in a deep, meaningful way. If we know, we can begin to intervene."

More information: The paper, "Common variants at ten loci modulate the QT interval duration in the QTSCD Study" appears in *Nature Genetics* March 22. www.nature.com/ng/index.html

Source: Johns Hopkins Medical Institutions