Research findings key for understanding, interpreting genetic testing for long QT syndrome

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Results of a long QT syndrome (LQTS) study published in the current issue of Circulation play an important role in understanding genetic testing's role in diagnosing disease, according to the senior author, Michael Ackerman, M.D., Ph.D. A pediatric cardiologist at Mayo Clinic, Dr. Ackerman directs Mayo's Long QT Syndrome Clinic and is the director of the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory.

LQTS is a disorder of the electrical system of the heart that affects 1 in 2,500 people. In LQTS, approximately 5 percent to 10 percent of the time, its first symptom is sudden death, often related to physical exertion or auditory triggers such as an alarm clock. However, many cases can be diagnosed following warning signs such as sudden fainting spells or a family history that suggest its potential presence and from objective data derived from an ECG, exercise or epinephrine QT stress testing, and genetic testing. The condition was first clinically described in 1957, but the first LQTS genes were not discovered until 1995. In 2004, the first genetic test for LQTS became clinically available in North America.

This multicenter study also involved Arthur Wilde, M.D., Ph.D., Academic Medical Center, Amsterdam, The Netherlands, and scientists from PGxHealth. Dr. Ackerman says genetic testing results of nearly 400 patients with a strong clinical diagnosis of LQTS and nearly 1,400 healthy volunteers showed that there is a "background noise" rate of rare

variants present in about 4 percent of healthy Caucasian volunteers, and that the mutation type and location are critical determinants to distinguish this background noise from true LQTS-causing mutations.

The *Circulation* paper is another critical piece in the maturation of LQTS genetic testing from discovery, translation, implementation, and now post-implementation interpretation, Dr. Ackerman says.

"This study demonstrates what we've long suspected in genetic testing circles - that genetic tests are not merely binary tests but are probabilistic tests whereby some test results are going to provide 'no-doubt-about-it' disease mutations, whereas other test results may report a mutation whose pathogenicity is uncertain," says Dr. Ackerman. "Our research shows that genetic testing is just one piece of the diagnostic puzzle that a physician needs to look at."

The results show that genetic testing does not always give a "yes or no" answer for LQTS or other diseases, and it means that physicians need to meticulously interpret genetic test results with the same scrutiny and tenacity as any other diagnostic test such as the electrocardiogram (ECG), Dr. Ackerman says.

Surprisingly, although there are nearly 1,500 genetic tests that physicians can order for patients, this genetic "signal-to-noise" ratio has been exposed for only a small handful of them, including breast cancer genetic testing and now long QT syndrome testing. For personalized, individualized medicine to succeed, the medical community must begin to grasp the probabilistic nature of genetic testing, he says.

Source: Mayo Clinic (news : web)