Genome-wide association studies mislead on cardiac arrhythmia risk gene

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Although genome-wide association studies have linked DNA variants in the gene SCN10A with increased risk for cardiac arrhythmia, efforts to determine the gene's direct influence on the heart's electrical activity have been unproductive. Now, scientists from the University of Chicago have discovered that these SCN10A variants regulate the function of a different gene, SCN5A, which appears to be the primary gene responsible for cardiac arrhythmia risk. The SCN10A gene itself plays only a minimal role in the heart, according to the study, published in the *Journal of Clinical Investigation* on March 18.

"Significant effort has been invested into understanding the function of SCN10A in cardiac rhythm control, with underwhelming results," said study co-leader Ivan Moskowitz MD, PhD, associate professor of pediatrics, pathology and human genetics at the University of Chicago. "It turns out that the genetic variation within SCN10A that confers arrhythmia risk actually functions on a different gene. This study highlights the fact that DNA variation associated with disease can have regulatory impact on functional targets located a considerable distance away."

Mutations within the SCN10A gene are linked with increased risk of Brugada Syndrome, which causes cardiac arrhythmias and is a leading cause of death amongst youth in some parts of the world. Genome-wide association studies—large scale experiments that look for genetic variants across the human genome with statistical associations to certain traits or diseases—were used to identify these variants, but follow-up studies have been unable to determine their function.

Curious about previous ambiguous results, Moskowitz and his colleagues looked for other genes with links to SCN10A. First, they discovered that the region of SCN10A that conferred arrhythmia risk physically contacted a neighboring gene—SCN5A—which is well-known to have an important role in cardiac arrhythmias and sudden cardiac death. They then showed that these contacts are functional, and that by removing the implicated sequences from SCN10A, expression of SCN5A was profoundly diminished.

When they analyzed large-scale human data, the team found that the SCN10A variant originally identified for Brugada Syndrome risk was associated with lowered levels of SCN5A. But the variant had no detectable effect on the levels of SCN10A.

Taken together, the evidence suggests that any link between SCN10A and cardiac arrhythmia is due to its connection with SCN5A expression. Through the results of this study, Moskowitz believes scientists will now focus on the correct gene, SCN5A, to better understand genetic risk for cardiac arrhythmia and hopes this will lead to more accurate diagnostics and potential therapies in the future.

This study also illustrates how highly-publicized genome-wide association studies can be misleading for researchers. Study co-leader Marcelo Nobrega, PhD, an associate professor of human genetics at the University of Chicago, published a similar finding for a gene associated with obesity, on March 12th in Nature.

"Genome-wide association studies have been very successful in implicating genetic variation associated with a host of human diseases and traits," Moskowitz said. "However cases like this study demonstrate that we must be more careful to evaluate the functional target of genome-wide association study hits, before we jump to conclusions that can have costly implications for how we investigate human health and generate disease diagnostics and therapies."

More information: "A common genetic variant within SCN10A modulates cardiac SCN5A

expression," *Journal of Clinical Investigation*, 2014.