



# Trends in Molecular Sciences

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## Genome-Wide Hunt Reveals Links to Abnormal Rhythms Behind Sudden Death, Heart Damage

*A study among almost 50,000 people worldwide has identified DNA sequence variations linked with the heart's electrical rhythm in several surprising regions among 22 locations across the human genome. The variants were found by an international consortium, including Johns Hopkins researchers, and reported Nov. 14 in the Nature Genetics advance online publication.*

Among the notable discoveries were variations in two side-by-side genes that regulate electrically charged particles to produce signals that start contraction of the heart and register as pulsing waves seen on heart monitors. One of the genes, named SCN5A, was known to be involved in controlling how signals start from specialized muscle cells and travel across the heart to cause its rhythmic contractions. Its neighbor, SCN10A, previously was an unsuspected player in cardiac electrical activity.

The study's genome-wide hunt focused on the QRS interval, a measure of electrical depolarization in the main lower pumping chambers of the heart (ventricles), easily detectable with a simple EKG machine. A prolonged QRS interval suggests a diseased ventricular conduction system and has been associated with increased risk for sudden cardiac death, among other heart disorders.

Fifteen genome-wide association or so-called GWAS studies among healthy American and European populations who had EKGs were combined for large-scale meta-analysis. Each GWAS reported what effects were observed at which locations in a scan of 2.5 million Single Nucleotide Polymorphisms (SNPs) throughout the genome. Pronounced snips, SNPs are sites where a single letter in the DNA code is variable. Study subjects whose EKGs showed prolonged QRS intervals had SNPs in common with each other.

"The size of the study really gave us the power to identify many genes not previously suspected to play a role in heart conduction," says Dan Arking, Ph.D., Assistant Professor in the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine.

To further investigate one of the 22 regions deemed significant, team members used mouse hearts to find where in the heart the ion channel protein products of the SCN10A gene form, locating an abundance of them in the fibers that conduct electrical signals. Next, the researchers treated mice with a drug that blocked the function of the ion channels produced by the SCN10A gene, and used EKGs to show that the QRS duration was extended in these animals.

"These genes potentially could be very useful for identifying individuals for whom adverse drug reactions may cause life threatening cardiac events," Arking says.

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Of more than a hundred scientists who contributed to this work, Arking is a corresponding author along with Stefan Kaab of Ludwig-Maximilians-University in Munich, Germany. The lead author is Nona Sotoodehnia, University of Washington.

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J O'Donnell, Claudia Beu Volpato, Mark J Caulfield, John M Connell, Lenore Launer, Xiaowen Lu, Lude Franke, Rudolf S N Fehrmann, Gerard te Meerman, Harry J M Groen, Rinse K Weersma, Leonard H van den Berg, Cisca Wijmenga, Roel A Ophoff, Gerjan Navis, Igor Rudan, Harold Snieder, James F Wilson, Peter P Pramstaller, David S Siscovick, Thomas J Wang, Vilundur Gudnason, Cornelia M van Duijn, Stephan B Felix, Glenn I Fishman, Yalda Jamshidi, Bruno H Ch Stricker, Nilesh J Samani, Stefan Kääh, Dan E Arking. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction.

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