

**ClinGen (Clinical Genome Resource) Expert Panel Evaluates Validity of Genes
Reported to be Associated with Brugada Syndrome: One Gene Reaffirmed;
20 Gene Associations Disputed**

BETHESDA, MD – June 29, 2018 | Clinical laboratories often rely on medical articles and public information on gene disease associations in determining the genes to include on genetic testing panels for specific conditions or the specific results to return to patients. In the case of Brugada Syndrome (BrS), a serious genetic condition that causes a disruption of the heart's normal rhythm and predisposes a patient to sudden arrhythmic death, many clinical laboratories have based their test design and diagnostic reporting on the literature implicating 21 genes with the condition.

Now, an expert panel convened by the NHGRI-funded Clinical Genome Resource (ClinGen) has published the results of their extensive curation of these genes in *Circulation*, the peer-reviewed journal of The American Heart Association (<http://circ.ahajournals.org/content/early/2018/06/27/CIRCULATIONAHA.118.035070>). The group, chaired by Dr. Michael H. Gollob of the Peter Munk Cardiac Centre at Toronto General Hospital, found that only one (*SCN5A*) of the 21 genes typically included on a BrS genetic test (gene panel) has a definitive disease association.

“This work highlights the importance and value of ClinGen’s efforts to standardize and improve the knowledge used by laboratories to guide clinical testing decisions and the interpretation of test results,” said Jonathan Berg, MD, PhD, FACMG Principal Investigator of the NIH grant that supports the ClinGen Cardiovascular Clinical Domain Working Group under which the Brugada Gene Curation Expert Panel completed their work. “Diagnostic conclusions in patients and family members or the decision to implant cardioverter defibrillators in otherwise healthy individuals on the basis of findings from the genes with disputed associations could lead to undue harm,” said senior author, Dr. Gollob.

ClinGen defined and published standards by which gene-disease associations are evaluated as a part of its broader efforts to curate and document the clinical significance of genomic variation ([Strande et al., 2017](#)). This report is the first on the application of these standards to claimed BrS-associated genes and sets the stage for future work evaluating the clinical significance of the variants within clinically relevant genes.

“This work highlights the importance of a systematic approach to gene curation as we move from clinical genetic testing in clinically affected individuals to more broadly offering it to asymptomatic individuals” said Christa Lese Martin, PhD, FACMG, a ClinGen Principal Investigator and Co-Chair of the Gene Curation Working Group.

-more-

There are currently 30 Expert Panels performing gene and variant evaluation. “We expect that ClinGen efforts will continue to reveal other genes with limited or disputed disease associations that are currently included in clinical testing as ClinGen’s evaluation efforts ramp up in the coming months and years” said Heidi Rehm, PhD, FACMG, a ClinGen Principal Investigator. The ClinGen project will continue its work to standardize the processes of evaluating genes implicated in disease, ultimately leading to improved clinical test development, more accurate result interpretation, and higher quality patient care.

About the Clinical Genome Resource

ClinGen is a National Institutes of Health (NIH)-funded resource. Primary funding is through the National Human Genome Research Institute (NHGRI) with additional funding provided by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Cancer Institute (U41 HG006834, U01HG007436 and U4HG009649, U01 HG007437 and U41HG009650, HHSN261200800001E). ClinVar is supported by the Intramural Research Program of the NIH, National Library of Medicine. It is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Four lead organizations are partnered with other organizations to lead the ClinGen effort. The University of North Carolina team is led by Jonathan Berg, MD, PhD, FACMG and is partnered with the Geisinger Health Plan led by Marc Williams, MD, FACMG, the American College of Medical Genetics and Genomics group led by Michael S. Watson, MS, PhD, FACMG, and Kaiser Permanente Center for Health Research led by Katrina Goddard, PhD. A second team involves a partnership between Stanford University School of Medicine led by Carlos Bustamante, PhD and Baylor College of Medicine led by Sharon Plon, MD, PhD, FACMG. The third team is led by Heidi Rehm, PhD, FACMG of the Broad Institute of the Massachusetts Institute of Technology (MIT), and Harvard and Massachusetts General Hospital in Boston, MA and David Ledbetter, PhD, FACMG, and Christa Lese Martin, PhD, FACMG, both of Geisinger Health System, Danville, PA. The ClinVar team is led by Melissa Landrum, PhD, National Library of Medicine, NIH.

About the American College of Medical Genetics and Genomics (ACMG)

Founded in 1991, ACMG is the only nationally recognized medical society dedicated to improving health through the clinical practice of medical genetics and genomics. The American College of Medical Genetics and Genomics (www.acmg.net) provides education, resources and a voice for nearly 2,200 biochemical, clinical, cytogenetic, medical and molecular geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. The College's mission is to develop and sustain genetic initiatives in clinical and laboratory practice, education and advocacy. Three guiding pillars underpin ACMG's work: 1) Clinical and Laboratory Practice: Establish the paradigm of genomic medicine by issuing statements and evidence based or expert clinical and laboratory practice guidelines and through descriptions of best practices for the delivery of genomic medicine. 2) Education: Provide education and tools for medical geneticists, other health professionals and the public and grow the genetics workforce. 3) Advocacy: Work with policymakers and payers to support the responsible application of genomics in medical practice. *Genetics in Medicine*, published monthly, is the official ACMG peer-reviewed journal. ACMG's website (www.acmg.net) offers a variety of resources including Policy Statements, Practice Guidelines, Educational Resources, and a Find a Geneticist tool. The educational and public health

-more-

programs of the American College of Medical Genetics and Genomics are dependent upon charitable gifts from corporations, foundations, and individuals through the ACMG Foundation for Genetic and Genomic Medicine (www.acmgfoundation.org.)

About the Peter Munk Cardiac Centre

The Peter Munk Cardiac Centre is the premier cardiac centre in Canada. Since it opened in 1997, the Centre has saved and improved the lives of cardiac and vascular patients from around the world. Each year, more than 163,000 patients receive innovative and compassionate care from multidisciplinary teams in the Peter Munk Cardiac Centre, and the Centre trains more cardiologists, cardiovascular surgeons and vascular surgeons than any other hospital in Canada. The Centre is based at the Toronto General Hospital and the Toronto Western Hospital and houses the largest clinic in the country devoted to genetic-based arrhythmia and cardiomyopathy diseases. - members of University Health Network. www.petermunkcardiaccentre.ca

-end-