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ClinGen Panel evaluates validity of genes reported to be associated with Brugada Syndrome

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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. 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, Ph.D., 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, Ph.D., FACMG, a ClinGen Principal Investigator and Co-Chair of the Gene Curation Working Group.

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, Ph.D., 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.

Provided by American College of Medical Genetics and Genomics

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