Circulation: Genomic and Precision Medicine

EDITORIAL

HCN4 Gene Polymorphisms and Tachycardia-Induced Cardiomyopathy

True or Spurious Association?

See Article by Nakano et al

Chia-Ti Tsai, MD, PhD

Tachycardia-induced cardiomyopathy (TIC) is cardiomyopathy as a consequence of prolonged tachyarrhythmia that is reversible after control of the underlying arrhythmia. TIC should be suspected in patients with left ventricular dysfunction in association with tachycardia of >100 beats/min without other identified cause of heart failure.[1,2] Atrial fibrillation (AF) is the most common cause of TIC because of poorly controlled ventricular rates that worsen ventricular function.[3] Several pathophysiological mechanisms have been proposed,[4,5] but the exact disease mechanism of TIC is still unknown. In nowadays, genetic studies for complex trait diseases are popular because of their advantages to define the genetic architecture of complex traits and diseases, provide new insights into normal physiology and disease pathophysiology and serve as predictors for disease susceptibility.[6]

Currently little is known about patient factors that increase vulnerability to TIC. Whether there are reliable genetic markers of TIC is also unknown. It has been reported that angiotensin-converting enzyme gene polymorphisms were associated with increased serum angiotensin-converting enzyme levels and a higher incidence of TIC.[7] The cardiac *HCN4* gene and its encoding protein, the cardiac hyperpolarization-activated cyclic nucleotide-gated I_f channel, are essential for normal heart impulse conduction and a critical mediator of heart rate control.[8–12] Because of its critical role in heart rate control, the possibility has been raised that *HCN4* may be involved in TIC pathogenesis and there is an association between *HCN4* single-nucleotide polymorphisms (SNPs) and TIC.

In this issue of the journal, Nakano et al[13] sought to investigate whether *HCN4* gene SNPs was associated with TIC using an AF population undergoing pulmonary vein isolation as their study population. They enrolled 930 AF patients, compared 17 *HCN4* gene SNPs between AF subjects with TIC (N=73) and without TIC (N=857) and found rs7172796, rs2680344, rs7164883, rs11631816, and rs12905211 were significantly associated with TIC. They concluded that *HCN4* gene might determine the susceptibility to TIC in patients with AF. The results are reasonable because molecular studies of the conduction system have found that HCN4 is expressed not only in the sinus node but also the atrioventricular node.[14,15] Furthermore, cardiac hyperpolarization-activated cyclic nucleotide-gated I_f channel blocker ivabradine has been demonstrated to be effective to control ventricular rates in patients with AF.[16,17] Therefore, *HCN4* SNPs may be potential genetic risk markers for TIC in AF patients, and may be used for the risk stratification of TIC which facilitate early therapeutic intervention (eg, stricter heart rate control or early rhythm control) to prevent heart failure in AF patients with an *HCN4* risk allele.

Key Words: Editorials ■ atrial fibrillation ■ genetic markers ■ heart failure ■ heart rate ■ tachycardia

http://circgenetics.ahajournals.org

Although appealing, further scrutiny is merited before incorporating the results of this study into clinical practice. This is basically a single-gene genetic association study. The most critical part of genetic association study is the definition of disease phenotype (case and control phenotypes) and its case number. An inappropriate definition of case or control phenotype or a small case number may lead to a spurious association. In this study, TIC was defined as those AF patients with an AF attack associated with a ventricular rate >140 beats/min and echocardiographic left ventricular ejection fraction (LVEF) <40% and improvement of LVEF within 6 months. Decreased echocardiographic LVEF is very common in patients with an AF attack and a very high ventricular rate even for a short period of time because at this high ventricular rate the echocardiographic measurement of LVEF is not reliable and tends to reveal a lower value. Therefore, a better definition of TIC is those with persistence of decreased LVEF when the ventricular rate is normal. Furthermore, patients in the TIC group might have a rapid ventricular rate simply because they are not well treated, or had poor compliance to rate-control drugs, but did not belong to the real TIC case group with a genetic susceptibility to TIC. Finally, patients who were genetically susceptible to TIC might be selected as control patients if their ventricular rates were well controlled either by drugs or lifestyle modification. With the confounding of drug treatment, it is difficult to clearly define which patient is having a genetic susceptibility to TIC.

Moreover, an AF population undergoing pulmonary vein ablation served as the study population in this study, which might not reflect or be characteristic of a general AF population. This may generate a selection bias. The patients undergoing pulmonary vein isolation may represent those AF patients who have severer symptoms or more AF attack. The patients may be susceptible to TIC simply because of frequent AF attacks before pulmonary vein isolation, but not genetically susceptible to TIC. This also raises the problem of using a single time point to define TIC in this study. Finally, in nowadays genetic studies with SNPs in a single gene are less attractive because of the awareness that many of the complex trait diseases are not caused or determined by a single gene. The case number of the TIC group was also very low in this study which might significantly bias the results.

In summary, Nakano et al[13] have found the *HCN4* gene SNPs may be new genetic markers for TIC in AF patients. Such an approach aligns with the concept of getting insights into disease mechanism stemming from genetic studies. However, the results should be further validated by larger populations or populations of other ethnicities with scrutiny on case selection before its use in clinical practice.

ARTICLE INFORMATION

Correspondence

Chia-Ti Tsai, MD, PhD, Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei 100, Taiwan. E-mail cttsai1999@gmail.com

Affiliation

Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei.

Disclosures

None.

REFERENCES

1. Gupta S, et al. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol*. 2014;172:40–46. doi: 10.1016/j.ijcard.2013.12.180.
2. Felker GM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077–1084. doi: 10.1056/NEJM200004133421502.
3. Fujino T, et al. Characteristics of congestive heart failure accompanied by atrial fibrillation with special reference to tachycardia-induced cardiomyopathy. *Circ J*. 2007;71:936–940.
4. Sallam K, et al. Finding the rhythm of sudden cardiac death: new opportunities using induced pluripotent stem cell-derived cardiomyocytes. *Circ Res*. 2015;116:1989–2004. doi: 10.1161/CIRCRESAHA.116.304494.
5. Umana E, et al. Tachycardia-induced cardiomyopathy. *Am J Med*. 2003;114:51–55.
6. Jeong YH, et al. Diagnostic approach and treatment strategy in tachycardia-induced cardiomyopathy. *Clin Cardiol*. 2008;31:172–178. doi: 10.1002/clc.20161.
7. Deshmukh PM, et al. Association of angiotensin converting enzyme gene polymorphism with tachycardia cardiomyopathy. *Int J Mol Med*. 2004;13:455–458.
8. Milanesi R, et al. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. *N Engl J Med*. 2006;354:151–157. doi: 10.1056/NEJMoa052475.
9. Baruscotti M, et al. Deep bradycardia and heart block caused by inducible cardiac-specific knockout of the pacemaker channel gene Hcn4. *Proc Natl Acad Sci USA*. 2011;108:1705–1710. doi: 10.1073/pnas.1010122108.
10. Nakashima N, Ishii TM, Bessho Y, Kageyama R, Ohmori H. Hyperpolarisation-activated cyclic nucleotide-gated channels regulate the spontaneous firing rate of olfactory receptor neurons and affect glomerular formation in mice. *J Physiol*. 2013;591:1749–1769. doi: 10.1113/jphysiol.2012.247361.
11. Verrier RL, et al. If inhibition in the atrioventricular node by ivabradine causes rate-dependent slowing of conduction and reduces ventricular rate during atrial fibrillation. *Heart Rhythm*. 2014;11:2288–2296. doi: 10.1016/j.hrthm.2014.08.007.
12. Baruscotti M, et al. A gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial inappropriate sinus tachycardia. *Eur Heart J*. 2017;38:280–288. doi: 10.1093/eurheartj/ehv582.
13. Nakano Y, et al. HCN4 gene polymorphisms are associated with occurrence of tachycardia induced cardiomyopathy in patients with atrial fibrillation. *Circ Genom Precis Med*. 2018;11:e001980. doi: 10.1161/CIRCGEN.117.001980.
14. DiFrancesco D. Funny channel gene mutations associated with arrhythmias. *J Physiol*. 2013;591:4117–4124. doi: 10.1113/jphysiol.2013.253765.
15. Verkerk AO, et al. Pacemaker activity of the human sinoatrial node: an update on the effects of mutations in HCN4 on the hyperpolarization-activated current. *Int J Mol Sci*. 2015;16:3071–3094. doi: 10.3390/ijms16023071.
16. Iliuta L, et al. Ivabradine versus beta-blockers in patients with conduction abnormalities or left ventricular dysfunction undergoing cardiac surgery. *Cardiol Ther*. 2014;3:13–26. doi: 10.1007/s40119-013-0024-1.
17. Wongcharoen W, et al. Ivabradine reduced ventricular rate in patients with non-paroxysmal atrial fibrillation. *Int J Cardiol*. 2016;224:252–255. doi: 10.1016/j.ijcard.2016.09.044.

HCN4 Gene Polymorphisms and Tachycardia-Induced Cardiomyopathy: True or Spurious Association?

Chia-Ti Tsai

Circ Genom Precis Med. 2018;11:
doi: 10.1161/CIRCGEN.118.002223
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1942-325X. Online ISSN: 1942-3268