Journal of Arrhythmia 32 (2016) 418–425

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Review

Genetics of Brugada syndrome

Jyh-Ming Jimmy Juang, M.D., MS2, Ph.D.[a,*], Minoru Horie [b]

[a] Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[b] Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan

ARTICLE INFO

Article history:
Received 18 February 2016
Received in revised form
3 May 2016
Accepted 6 July 2016
Available online 12 September 2016

Keywords:
Genetics
Brugada syndrome

ABSTRACT

In 1992, the Brugada syndrome (BrS) was recognized as a disease responsible for sudden cardiac death, characterized by a right bundle-branch block with ST segment elevation in the leads V1 and V2. This syndrome is highly associated with sudden cardiac death, especially in young males. BrS is currently diagnosed in patients with ST-segment elevation showing type 1 morphology $\geq$ 2 mm in $\geq$1 leads among the right precordial leads V1 or V2 positioned in the 2nd, 3rd, or 4th intercostal space, and occurring either spontaneously or after a provocative drug test by the intravenous administration of Class I antiarrhythmic drugs. With accumulated findings, the BrS inheritance model is believed to be an autosomal dominant inheritable model with incomplete penetrance, although most patients with BrS were sporadic cases. *SCN5A*, which was identified as the first BrS-associated gene in 1998, has emerged as the most common gene associated with BrS, and more than 10 BrS-associated genes have been identified thereafter. Mutation-specific genetic testing is recommended for the family members and appropriate relatives following the identification of BrS-causative mutations in an index patient. In addition, comprehensive or BrS1 (*SCN5A*) targeted genetic testing could be useful for patients in whom a cardiologist has established a clinical index of suspicion for BrS based on the patient's clinical history, family history, and the expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

Over the past 20 years, extensive research in this field has allowed better understanding of the pathophysiology, genetic background, and management of BrS even though controversies still exist. In this review article, a background of genetics, the genetic background of BrS, the genotype and phenotype relationship, the role of genetic screening in clinical practice, and the interpretation of the identified genetic variants have been addressed based on this understanding.

Contents

* Corresponding author at: Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, and National Taiwan University College of Medicine, Taipei, Taiwan. Tel.: +886 2 23123456; fax: +886 2 23951841.
E-mail address: jjmjuang@ntu.edu.tw (J.-M. Juang).

http://dx.doi.org/10.1016/j.joa.2016.07.012

1. Background of basic genetics

The human genome contains approximately 3 billion nucleotide base pairs contained in 23 chromosome pairs. Each chromosome contains hundreds to thousands of genes and the estimated 30,000 genes in the human genome express approximately 100,000 proteins [1]. The Human Genome Project (HGP) was proposed in the 1980s and was completed in 2003. The 1000 Genomes Project was conducted between 2008 and 2015, generating the largest public catalogue of human variations and genotype data. The completion of these projects provides a source book for biology, medicine, and genetic research.

Sanger sequencing was used for the genetic screening of BrS and was considered the gold standard for DNA sequencing in the subsequent two and a half decades [2]. In the past few years, new technologies (large-insert clone arrays, oligonucleotide arrays, target-gene sequencing, whole-exome sequencing (WES), and whole-genome sequencing (WGS)) have been developed, thus allowing the detection of medium- to large-sized genomic regions at a single nucleotide resolution. These technological genomic advancements are able to provide high-throughput screening and can detect genetic variations in patients with high accuracy and reduced cost. Although scientists and policy advisers deal intensively with the interpretation and handling of the onslaught and ambiguity of genome-wide data, we are rapidly moving toward a new era of genetic research for BrS, which is full of opportunities as well as a mountain of challenges.

2. Terminology

2.1. Polymorphism vs. mutation

The genome of any person is more than 99% similar to that of an unrelated individual. This tiny variability allows individuals to be distinguished by means of genetic testing. When a nucleotide change occurs in more than 1% of the general population, it is called a “polymorphism.” In contrast, a mutation occurs in less than 0.5% of the population and is defined as a permanent change in the nucleotide sequence that results in altered amino acids. The terms “mutation” and “polymorphism” have been used widely but often lead to confusion because of incorrect assumptions regarding their respective pathogenic and benign effects. In 2015, the American College of Medical Genetics and Genomics (ACMG) recommended that both terms be replaced by the term “variant” with the following modifiers: (i) pathogenic, (ii) likely pathogenic, (iii) uncertain significance, (iv) likely benign, or (v) benign [3].

2.2. Penetrance and expressivity

In medical genetics, penetrance is the proportion of individuals with the mutation who exhibit clinical symptoms. For example, in a family with 10 members, if 4 out of 10 are carriers of a pathogenic variant in the *SCN5A* gene but only 2 of the 4 carriers have type 1 BrS ECG, the penetrance in this family is 50%. The penetrance of BrS is lower than that of the congenital long QT syndrome. In a study conducted in 2000, Priori et al. estimated that the overall disease penetrance across 4 small BrS families harboring mutations in the *SCN5A* gene was 16% based on their ECG analysis (range 12.5–50%) [4]. In contrast, the mean penetrance across multiple long QT syndrome subtypes in a population-based study was shown to be ~40% (range 25–100%) [5,6] (Fig. 1).

Expressivity is used to describe the variations in a phenotype among individuals carrying the same pathogenic variants. Different degrees of expression in different individuals may be due to variation in the allelic constitution of the remaining genome or due to environmental factors. For example, individuals in the same BrS family who carry the same *SCN5A* pathogenic variant could show different electrocardiographic patterns ranging from Brugada type I ECG to conduction disturbance, or even long QT.

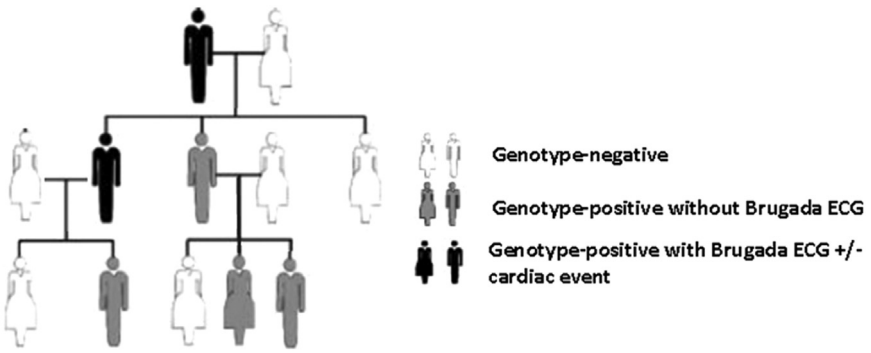

Fig. 1. An example of a representative multi-generation pedigree displaying incomplete penetrance (33%) and variable expressivity as some individuals display Brugada ECG without any cardiac events.