



Clinical implication of next-generation sequencing for sudden arrhythmia death syndrome

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Unexpected sudden cardiac death in the young (SCDY) is tragic occurrence and causes terrible grief for the parents, families, school members, and friends of the stricken individuals. In study of a Caucasian population, it was found that 75% of SCDY cases were not caused by coronary artery disease, which is main cause of sudden cardiac death in adults. Most of these incidents, rather, are caused by inheritable sudden arrhythmic death syndrome (SADS) or genetic cardiomyopathy (GCM), and the prevalence of these diseases ranges from 1/1,000 to 1/10,000.

SADS includes long QT syndrome (LQTS), short QT syndrome, Brugada syndrome (BrS), catecholamine polymorphic ventricular tachycardia, and many kinds of cardiomyopathies. LQTS, for example, is an inborn and inheritable heart disease of a structurally normal heart but entails an increasing risk of life-threatening arrhythmia, such as torsade de pointes (TDP, a form of irregular heartbeat that originates from the ventricles). The condition is so named because of the appearance of a prolonged QT interval on the electrocardiogram. The prevalence of long QT syndrome is close to 1:2000 with the mean age of onset around 10 ± 20 years old. The patients with LQTS can present with palpitations, syncope, and sudden death due to ventricular tachycardia/fibrillation (1). In 1957, Jervell and Lange-Nielsen described the first cases of autosomal-recessive LQTS with concomitant bilateral sensorineural deafness, providing the first description of an inherited arrhythmia syndrome associated with sudden cardiac death in structurally normal hearts (2). In 1963 and 1964, Drs. Romano and Ward described the autosomal-

dominant version of LQTS with an isolated cardiac phenotype (3,4). No LQTS-causal gene was discovered until 1995 when Mark Keating's research team used linkage analysis with single-strand conformation polymorphism and DNA sequence analyses to identify the KCNH2-encoded Kv11.1 potassium channel and the SCN5A-encoded Nav1.5 sodium channel in families with LQTS (5,6). Two and a half decades later, 14 more minor LQTS-susceptibility genes have been discovered. All 17 genes account for nearly 70–80% of disorders (7) which indicates that LQTS is typically inherited as an autosomal-dominant trait, is rarely inherited recessively, is and characterized by a severe cardiac phenotype and sensorineural hearing loss (8,9). Due to the limitations in genetic technology, it took nearly four decades before the first LQTS gene was discovered. BrS was reported in 1992 (10), and the first gene, *SCN5A*, was identified in 1998 (11). The history of genetic discovery in BrS is shorter than that of LQTS because of the improvement of genetic molecular technology.

In the past decades, Sanger sequencing was used for genetic screening of single-gene diseases and was considered the gold standard for DNA sequencing (12). However, it is laborious and time-consuming. The more recently developed high-throughput next-generation sequencing (NGS) is able to screen hundreds to thousands of genes in a week, a capacity which greatly outstrips that of Sanger sequencing. In addition, NGS can detect single-nucleotide variants in medium- to large-sized regions with high accuracy and reduced cost (13–17). Thus, novel genes can be discovered at a greater speed possible than

with Sanger sequencing (13,18-22). The main challenge in the rapidly growing field of NGS technologies is to cope with the analysis of a vast sequencing database through advanced bioinformatics tools (23,24). An important advantage of sequencing data is its quality, robustness, and low noise. It should be noted that a successful NGS project requires expertise both in the wet lab and in the realm of bioinformatics in order to produce high quality data and data interpretation.

According to 2011 American/European Heart Rhythm guidelines, genetic testing has become part of standard care in clinical practice (class I recommendation) for SADS and GCM. This is because the inheritable mode of these diseases is mainly autosomal dominant, which means the genetic mutation of parents with SADS has a 50% chance of being transmitted to parents' children. For example, from a clinical testing standpoint, any patient with a strong clinical index of suspicion for a LQTS diagnosis or an asymptomatic patient with an unequivocal prolonged QTc (>480 ms during prepuberty, >500 ms during adulthood) in the absence of other clinical conditions should be offered clinical LQTS genetic testing (25,26). As a further illustration, the 2013 HRS/EHRA/APHRS expert consensus recommended that 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 electrocardiography and/or provocative drug challenge testing) phenotype (27). Since disease penetrance of BrS is incomplete and age-related, genetic testing may be used for diagnostic purposes and for the screening of at risk family members. In summary, for patients, genetic testing can help doctors make a diagnosis, adjust medications, and predict prognosis. For family members, genetic testing can provide early identification of those family members at risk, and possibly allow early treatment, preventing unnecessary anxiety. Although genetic testing is helpful for SADS patient care, testing genes for which sufficiently strong scientific evidence for disease causation is lacking entails a risk of misinterpreting the genetic information and potentially under/over diagnosing SADS in the patient and family members. Furthermore, ancestral differences may also impact the interpretation of the pathogenicity classification of a variant (28). Consequently, patients may be subjected to unnecessary anxiety and physical consequences. Thus, genes with disputed or limited evidence for causation of these diseases are currently not recommended for diagnostic

purposes through routine testing (29-31).

In conclusion, as we enter the era of genomics, the application of high-throughput NGS technology may discover an array of novel genetic variants or genes in inherited diseases, which could revolutionize the understanding of these disease mechanisms. However, the infrastructure of whole genome or whole exome sequencing for clinical practice is not yet mature enough to support a practical understanding in both physicians and patients, who must still struggle with interpreting vast tracts of genetic data.

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Footnote

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