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Review

Recent advances in genetic testing and counseling for inherited arrhythmias

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ABSTRACT

Inherited arrhythmias, such as cardiomyopathies and cardiac ion channelopathies, along with coronary heart disease (CHD) are three most common disorders that predispose adults to sudden cardiac death. In the last three decades, causal genes in inherited arrhythmias have been successfully identified. At the same time, it has become evident that the genetic architectures are more complex than previously known. Recent advancements in DNA sequencing technology (next generation sequencing) have enabled us to study such complex genetic traits.

This article discusses indications for genetic testing of patients with inherited arrhythmias. Further, it describes the benefits and challenges that we face in the era of next generation sequencing. Finally, it briefly discusses genetic counseling, in which a multidisciplinary approach is required due to the increased complexity of the genetic information related to inherited arrhythmias.

Contents

Abbreviations: ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; BrS, Brugada syndrome; CHD, coronary heart disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; GWAS, genome wide association study; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter defibrillator; NGS, next generation sequencing; LQTS, long QT syndrome; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; WES, whole exome sequencing

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1. Introduction

Sudden cardiac death (SCD) is a tragic event and the aftermath is devastating to the surviving family and community. SCD occurs in nearly 400,000 cases every year in the US [1]. In adult populations, cardiomyopathies and cardiac ion channelopathies, along with coronary heart disease (CHD), are the most common conditions that predispose patients to SCD. According to recent epidemiological studies of SCD in Western countries, CHD, cardiomyopathies, and ion channelopathies are diagnosed in ~75%, 10–15%, and 1–2% of the SCD cases, respectively [2]. In Japan, approximately 50,000 new cases of SCD are diagnosed every year [3]. CHD is less common in Japan than in Western countries: CHD, cardiomyopathies, and ion channelopathies account for 50–60%, 30–35% and 10% of the SCD cases, respectively [2]. In children or adults younger than 35 years of age, cardiomyopathies and ion channelopathies account for significant proportions of SCD [4]. Because of the low survival rate in aborted SCD cases ($\leq$10%) [2], identification of patients at risk of arrhythmia is very important for the prevention of SCD.

Inherited arrhythmia-susceptibility genes have been successfully identified in the last three decades. This has broadened both our understanding of the mechanisms and the clinical management of inherited arrhythmias. At the same time, it has become evident that the genetic architectures of inherited arrhythmias are actually more complex than previously known, involving more genetic components than a single gene locus. A recent advance in sequencing technology (next generation sequencing [NGS]) has facilitated the search for such genetic components spread over the genome.

This article provides a concise overview of genetic testing for inherited arrhythmias used in current clinical practice. It also provides a short introduction to NGS technology. Further, it briefly discusses genetic counseling, in which a multidisciplinary approach is required due to the increased complexity of genetic information regarding inherited arrhythmias. Because this article aims to provide basic knowledge regarding inherited arrhythmias for readers who are unfamiliar with this field, more detailed clinical and genetic characteristics of inherited arrhythmias are not within the scope of this article and can be found elsewhere [5–11].

2. Genetic testing for inherited arrhythmias

2.1. Classic genetic testing: candidate gene approach

Disease-causing genes for inherited arrhythmias have been successfully identified in the last three decades, resulting in a large impact on patient care. This success has largely been through the use of classical linkage mapping. Linkage mapping is performed in affected family members, followed by candidate gene sequencing within an identified disease susceptibility locus. Such analysis was performed with the assumption that inherited arrhythmias are Mendelian (monogenic) disorders and that a single mutation contributes substantially to the risk. In Table 1, the most commonly identified genes in inherited arrhythmias are shown.

Presently, genetic testing for causal genes in a proband is used to confirm diagnosis. Genetic testing can also be used to perform cascade screening (mutation-specific testing) in family members of genotype-positive probands to exclude a diagnosis (in the case of a negative test) or to allow targeted testing (in the case of a positive test) [11]. Diagnostic, therapeutic, and prognostic values of genetic testing are most relevant in long QT syndrome (LQTS) wherein genotype–phenotype correlation (i.e. the association between a certain mutation [genotype] and clinical characteristics [phenotypes]) is robust. In catecholaminergic polymorphic ventricular tachycardia (CPVT), genetic testing plays an important role in diagnosis. The clinical utility of genetic testing is limited in the remaining inherited arrhythmias [11], because of as yet unknown genotype–phenotype correlation or because of the low yield of genetic testing (Fig. 1).

Genotype–phenotype correlation is complicated when some phenotypes, such as electrocardiographic abnormalities and arrhythmias, do not manifest in all individuals carrying the same gene mutation (incomplete penetrance), and when the type and severity of the phenotypes vary between genotype-positive individuals (variable expressivity) [12]. For example, in families with Brugada syndrome (BrS) that carry the familial *SCN5A* mutation, not all affected family members (mutation carriers) show diagnostic type 1 BrS ECG or other symptoms [13]. Such puzzling phenomena are the focus of ongoing genetic research. Meanwhile, consensus reports provide recommendations to guide clinicians in the appropriate use of genetic testing for inherited arrhythmias [11]. It is important to keep in mind that in any inherited arrhythmia, clinical examinations are critical for accurate diagnosis before genetic testing is implemented.

2.2. New sequencing technology: next generation sequencing (NGS)

As suggested by the incomplete penetrance and variable expressivity seen in mutant genotypes, the genetic architecture of inherited arrhythmias is more complex than initially thought. It is hypothesized that in addition to a mutation in a single disease-susceptibility gene, as seen in pathogenic variants found in $<$1% of the general population, other genetic (and environmental) factors are involved in the ultimate manifestation of inherited arrhythmias [10]. In recent years, it became possible, using NGS technology, to screen for such common or rare variants (frequency in the general population $>$1–5% and $<$1%, respectively) [14]. These variants have a smaller impact on disease risk than mutations, but have an aggregated influence on disease manifestation.

Table 1
Major genes associated with inherited arrhythmias.

Disease	**Genes** (yield, %)
Long QT syndrome	*KCNQ1* (30–35), *KCNH2* (25–30), *SCN5A* (5–10) [25]
Catecholaminergic Polymorphic Ventricular Tachycardia	*RYR2* (60–65),*CASQ2* ($<$5) [47,49]
Brugada Syndrome	*SCN5A* (20) [60]
Hypertrophic cardiomyopathy	*MYBPC3* (30–40), *MYH7* (20–30), *TNNT2* (10), *TNNI3* (7) [66]
Dilated cardiomyopathy	*TTN* (~25) [80]
Arrhythmogenic right ventricular dysplasia/ cardiomyopathy	*PKP2* (46), *PLN* (5) [62]

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