Role of Genetic Testing in Patients with Ventricular Arrhythmias in Apparently Normal Hearts

Nynke Hofman, PhD[a], Arthur A.M. Wilde, MD, PhD[b,*]

KEYWORDS

• Ventricular arrhythmias • Sudden cardiac death • Genes • LQTS • CPVT • Brugada syndrome • SQTS • ERS

KEY POINTS

- It is important to perform cardiological investigations in family members who have died suddenly, and also when there is a negative autopsy.
- Ventricular arrhythmias without structural heart disease are responsible for ~35% of patients who have a sudden cardiac death before the age of 40 years.
- It is important to isolate the DNA of persons who have died suddenly to confirm a (later diagnosed) familial arrhythmia.
- When a pathogenic (causal) mutation is identified in the proband, predictive testing of family members can be offered, leading to timely treatment of identified affected (presymptomatic) individuals.

INTRODUCTION

Ventricular arrhythmias are a major cause of death and usually occur in patients with structural heart disease. Ventricular arrhythmias without structural heart disease are a rare but potentially life-threatening symptom in young patients. Molecular autopsies and/or cardiological investigation of family members have revealed that the primary electrical diseases (ie, the channelopathies) underlie up to 35% of these sudden deaths[1–3] in individuals 1 to 40 years old and up to 70% in infants.[4] During the last 20 years an important part of the molecular basis of the ion channelopathies, including long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS), has to a large extend been identified. Increased knowledge of the genetic basis of the disease sometimes leads to gene-specific treatment in known or suspected disease carriers. From the start it has been proposed that intensive collaboration between cardiologists, clinical geneticists or genetic counselors, and molecular geneticists is warranted for the most accurate patient care as well as research purposes.

Molecular genetic testing usually starts with the proband (the first person in a family who presents with symptoms of a suspected inherited disorder). Molecular testing was for many years targeted to the most likely gene involved (most likely based on the patient/family history and clinical parameters; eg, the morphology of the ST-T segments and the result of the exercise test). With the development of next-generation sequencing (NGS) technology the approach of genetic testing for

[a] Department of Clinical Genetics, Academic Medical Center, M0-229, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands; [b] Department of Cardiology, Academic Medical Center, B2-239, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands
* Corresponding author.
E-mail address: a.a.wilde@amc.nl

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cardiac channelopathies has changed substantially. Extended gene panels can be screened in a short period of time at a low cost. When a pathogenic (causal) mutation is identified in the proband, predictive testing of family members can be offered, leading to timely treatment of identified affected (presymptomatic) individuals. For the inherited arrhythmia syndromes it has been shown that during a follow-up of 3 to 4 years prophylactic treatment was installed in up to 70% to 80% of presymptomatically tested patients with LQTS and CPVT.[5] Besides the identification of a pathogenic mutation, in the past few years research has revealed the importance of genetic variants that (potentially) modify the clinical phenotype (ie, genetic modifiers). These variants have direct or indirect effects; for example, by modifying protein expression on the severity of the phenotype. This article reviews the current molecular understanding of the primary electrical diseases of the heart that are associated with sudden cardiac death, and provides a summary of the causal genes (**Table 1**).

THE MECHANISM OF ELECTROPHYSIOLOGY AND ELECTROPHYSIOLOGIC ABNORMALITIES

Ion channels are transmembrane proteins that conduct ions through the cell membrane. They provide the cellular basis for cardiac electrical activity. The channels have specific ion selectivity and are responsible for timely regulation of the passage of charged ions across the cell membrane in myocytes (the process of depolarization and repolarization). Depolarization is caused by an inward current of positively charged ions (ie, sodium and calcium ions) into the cell. Repolarization is caused by potassium and calcium channels (outward current of, respectively, K^+ and Ca^{2+} ions). Impairment in the flow of ions in and out of heart cells leads to a disturbance of the cardiac action potential morphology and provides a substrate for cardiac arrhythmias. This aberrant behavior of ion channels can be caused by pathogenic mutations in the genes that encode for these proteins.

MOLECULAR GENETICS OF LONG QT SYNDROME

LQTS is an inherited arrhythmia syndrome, characterized by an abnormally prolonged QT interval and abnormal T-wave morphology leading to life-threatening arrhythmias and sudden cardiac death. Jervell and Lange-Nielsen[6] first described LQTS in 1957. They reported a family with a prolonged QT interval and congenital deafness, many years later shown to be caused by a homozygous KCNQ1 mutation. The disorder, now known as the very rare Jervell and Lange-Nielsen syndrome, is inherited as an autosomal recessive trait. In 1963 and 1964 respectively Romano and colleagues[7] and Ward[8] described families presenting with QT prolongation, recurrent syncope, and sudden death, without deafness and transmitted as an autosomal dominant trait. Based on a population study, the prevalence of LQTS is now estimated as being as high as 1 in 2000.[9]

The diagnosis is made on the patient's history (episodic dizziness, syncope, palpitations, triggers of [near] syncope and family history), and by abnormal QT-interval prolongation on the electrocardiogram (ECG). The symptoms may be confused with epilepsy.[10] In 2010 Viskin and colleagues[11] described that patients with LQTS have an insufficient QT-interval shortening in response to the mild abrupt tachycardia provoked by standing up from a supine position, which can easily be used as a noninvasive bedside test to reach the diagnosis. Alternatively, the response of the QTc interval during exercise, and in particular during the recovery phase of an exercise test, is abnormal for the most important LQT subtypes.[12]

The values of the QTc (rate corrected using the Bazett formula) differ slightly between men and women and are age specific. The risk of cardiac events is higher in boys until the teenage years, but higher in women during adulthood.[13–16]

The Role of Genetic Testing in Long QT Syndrome

Mutations in at least 15 genes have been reported (see **Table 1**).

Genetic testing reveals a mutation in 60% to 75% of patients with a clear phenotype, and this proportion is even higher in familial cases.[17–20] LQT1, LQT2, and LQT3, named in chronologic order of identification, are by far the most commonly found genotypes, accounting for at least 85% of the genotyped LQTS.[21] In these most common subtypes there is a clear phenotype-genotype correlation: syncope and sudden death are most commonly triggered by exercise and swimming in KCNQ1 mutations (LQT1) and occur mostly at rest with SCN5A mutations (LQT3). Arrhythmias in LQT2, with mutations in KCNH2, are often triggered by acoustic stimuli (alarm clocks, telephones) and stress.[22,23] Female LQT2 carriers should receive extra monitoring in the months after delivery, because this period has been identified as a period of increased risk, possibly because