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Short communication

The role of genetics in primary ventricular fibrillation, inherited channelopathies and cardiomyopathies

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ABSTRACT

Sudden cardiac death (SCD) has a strong familial component; however, our understanding of its genetic basis varies significantly according to the underlying causes. When coronary artery disease is involved, the predisposing genetic background is complex and despite some interesting findings it remains largely unknown. Quite different is the case of monogenic structural and non-structural heart diseases, in which a number of disease-causing genes have been established and are being used in clinical practice.

As SCD can be the first clinical manifestation of inherited syndromes, in order to ascertain the cause of death, it is extremely important to include molecular autopsy among the standard post-mortem examinations. Indeed, molecular screening of the major disease-causing genes in the deceased person is often the only way to achieve a post-mortem diagnosis in channelopathies, which may prove crucial for the identification and management of at risk family members.

Overall, these data, together with the inclusion in current guidelines of molecular screening for diagnosis and/or risk stratification of specific inherited cardiac diseases, exemplify how research on the genetic basis of SCD may be deeply translational, while the transition of genetic testing from the research to the diagnostic setting is already improving every-day clinical practice.

1. Introduction

Sudden cardiac death (SCD) is the leading cause of death in the Western world [1]. The term SCD actually describes a clinical outcome but does not by itself reveal the distinct pathophysiological mechanisms that may largely dictate or subtly underlie its occurrence. In the general population, and in the vast majority of cases, SCD occurs in the context, and often as the first manifestation, of coronary artery disease. In the young and athletes however, the majority of SCD incidents may be attributed to inherited cardiac diseases, such as cardiomyopathies and channelopathies. Predisposition to SCD has been shown to be genetically-influenced [1]. In the setting of SCD in the young this predisposition is largely defined by monogenic genetic causes, while in the general population SCD may be the final outcome of an overall predisposing genetic background.

2. SCD in the general population: primary ventricular fibrillation

Sudden cardiac death from ventricular fibrillation (VF) during acute myocardial infarction (MI) is also called "primary ventricular fibrillation" and multiple epidemiological studies have supported the presence of a genetic background favouring its occurrence [1]. Two main strategies have been used so far to identify the genetic basis of SCD during MI.

A) *The first strategy aimed at the identification of an association between genetic variants and markers of SCD risk, such as the length of the QT interval.* Indeed, as a prolonged QTc is associated with an increased risk of SCD among patients with coronary artery disease [2,3], genetic variants associated with a prolonged QTc could be genetic markers of SCD. Outstanding genome-wide association studies (GWAS) have been published in the last years and all demonstrated a robust association between *NOS1AP*, which encodes a nitric oxide synthase adaptor protein, and QT interval duration in the general population [4]. Particular *NOS1AP* SNPs have been shown to double the risk of SCD in LQTS patients [5] and also to contribute to an increased SCD risk in white adults from the Atherosclerosis Risk In Community Study and the Cardiovascular Health Study [6]. This association was reconfirmed in the Rotterdam Study [7]. Another SNP that we [8] and others

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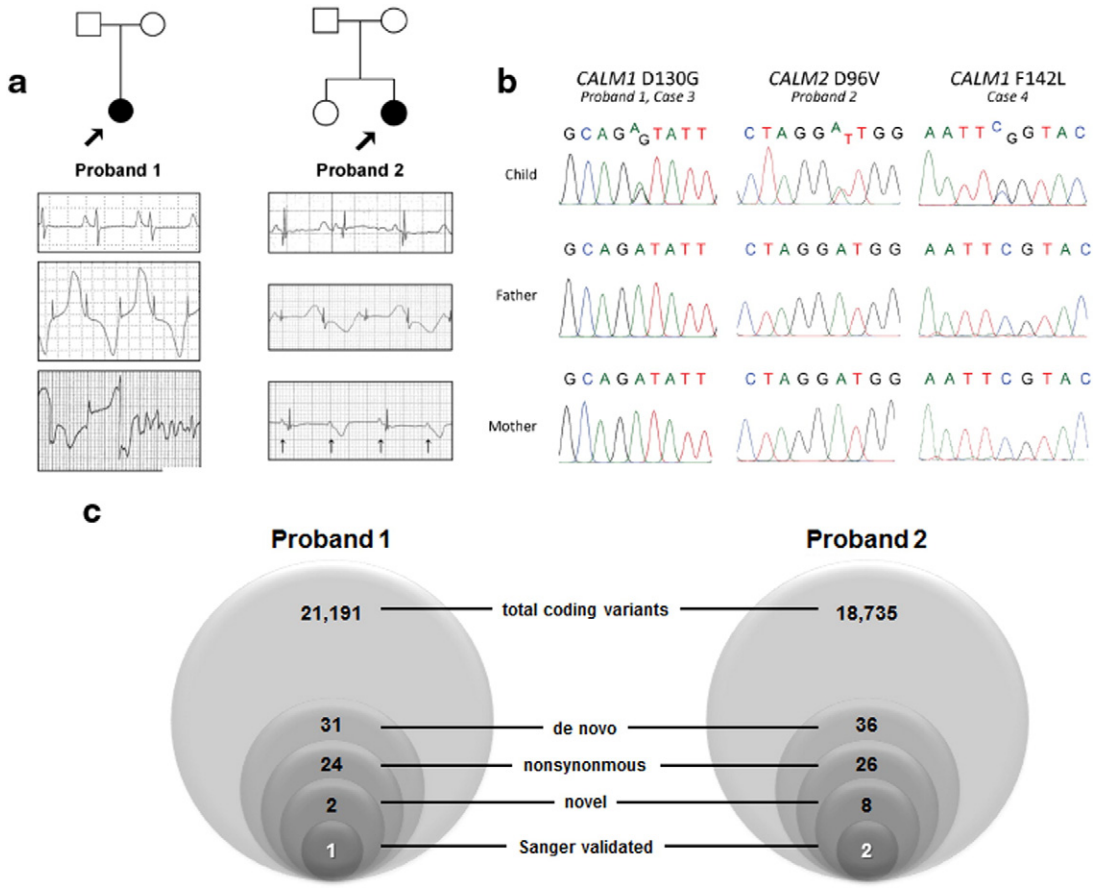

Fig. 1. A) Representative electrocardiographic recordings from two probands with early onset, life-threatening cardiac arrhythmias. Upper trace represents baseline ECG for both probands. Middle trace illustrates T-wave alternans. Lower trace for proband 1 illustrates onset of ventricular fibrillation following a period of T-wave alternans. Lower trace for proband 2 illustrates 2:1 AV block (arrows mark p-waves coincident with atrial depolarization). B) DNA sequence traces indicating heterozygous calmodulin gene mutations identified in the four LQTS cases (the first mutation is in common between two cases). C) Sequential filters were applied to the pool of variants discovered by exome sequencing in the two probands. Total coding variants include all synonymous, non-synonymous and canonical splice site single nucleotide variants as well as small insertions or deletions within captured exons. *De novo* variants are those found in the proband but not in either parent. Novel variants were considered those absent in the general population (dbSNP, 1000 Genomes).

[9]have identified as a genetic modifier of arrhythmic risk in LQTS that was subsequently associated with life-threatening arrhythmias following acute MI [10] is the *KCNH2*-p.K897T polymorphism. This common genetic variant, in the setting of reduced outward current levels caused by post-MI ion channel remodelling, reduces just as much the I_{Kr} current [8] so as to create a potential substrate for the development of torsades de pointes [10].

B) *A more direct but also more difficult strategy to follow, is aimed at testing directly an association between genetic variants and SCD risk*. The most difficult part of this approach is the collection of an adequate number of patients with primary VF. One study,

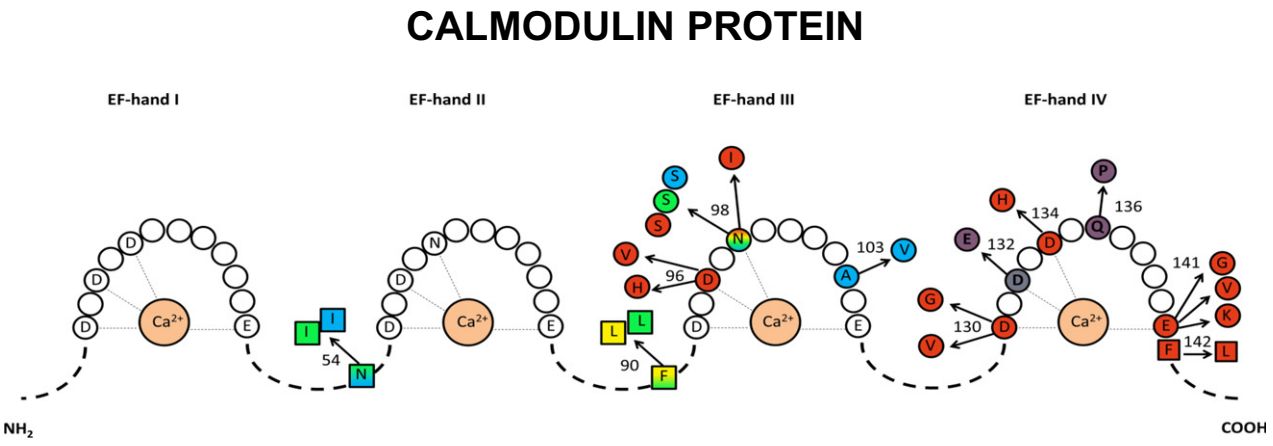

Fig. 2. Schematic model of the calmodulin protein showing the Ca^{2+}-binding loops (EF-hands I–IV). Amino acids directly involved in the binding of Ca^{2+} ions are identified within the dotted line. Color-substituted amino acids represent mutations so far identified, either in Ca^{2+}-binding loops (circle), or in linker/N-terminal/C-terminal regions (square). Each solid color stands for a defined phenotype: red for LQTS, light blue for CPVT, green for sudden unexplained death, yellow for IVF. Shaded colours represent an LQTS/CPVT overlap phenotype.