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Clinical Perspective

Genetic testing to predict sudden cardiac death: current perspectives and future goals

Silvia G. Priori [a,b,*]

[a] Director of Cardiology and Molecular Cardiology, Maugeri Foundation, Pavia, Italy
[b] Department of Molecular Medicine, University of Pavia, Pavia, Italy

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ABSTRACT

It is known that monogenic traits may predispose young and otherwise healthy individuals to die suddenly. Diseases such as Long QT Syndrome, Brugada Syndrome and Arrhythmogenic Right Ventricular Cardiomyopathy are well known causes of arrhythmic death in young individuals. For several years the concept of "genetic predisposition" to sudden cardiac death has been limited to these uncommon diseases. In the last few years clinical data have supported the view that risk of dying suddenly may cluster in families, supporting the hypothesis of a genetic component for sudden cardiac death. In this review I will try to provide an overview of current knowledge about genetics of sudden death. I will approach this topic by discussing first where we stand in the use of genetics for risk stratification and therapy selection in monogenic diseases and I will then move to discuss the contribution of genetics to patient profiling in acquired cardiovascular diseases.

Sudden cardiac death (SCD) is a major cause of mortality in Western countries: its incidence is estimated to range between 300,000 and 400,000 cases per year in the USA and a similar number in Europe. The definition of its incidence is complicated by the loose definition of SCD and by the fact that, in most instances, it is unwitnessed. In most textbooks SCD is defined as an "unexpected death occurring within one hour from onset of symptoms in an individual with stable clinical conditions before the onset of the life-threatening arrhythmic event". It is estimated that 80% of SCD occur in individuals with ischemic heart disease: accordingly, the prevalence of SCD increases with age.

The term "juvenile SCD" is used to refer to SCD that occurs in individuals under the age of 40 years: it has been suggested that approximately 15,000 juvenile SCD/year occur in Europe and 10,000 juvenile SCD/year in the USA. Most of the SCD in the young occur as a consequence of inherited diseases, mainly cardiomyopathies or channelopathies. Anatomical abnormalities (anomalous coronary arteries), myocarditis, ruptured aortic aneurysms are among non-genetic conditions associated with juvenile SCD.

Prevention of SCD heavily depends on the availability of risk stratification algorithms that allow to identify the subset of individuals at higher risk of cardiac arrhythmias in the larger pool of patients with common diseases such as heart failure. A similar risk stratification process to identify subjects with higher risk of SCD applies to patients affected by monogenic diseases that predispose to SCD. Unfortunately,

* Molecular Cardiology – IRCCS Salvatore Maugeri Foundation, Via Maugeri, 10-27100 Pavia, Italy. Tel.: +39 0382 592040; fax: +39 0382 592059.
E-mail address: silvia.priori@fsm.it.
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however, the clinical ability to identify risk factors that predispose to life-threatening arrhythmias is limited: risk indicators are at most able to identify broad categories of individuals with higher risk, but they remain far from being able to quantify *individual risk* of dying suddenly.

The term personalized medicine has been recently introduced to refer to the ability to integrate clinical, molecular and environmental markers of risk of becoming sick or dying. Although the term has been most successfully applied to oncology, there is hope that it may be possible to identify specific prognostic biomarkers in other fields of medicine, including cardiology.

In this editorial, I will try to summarize how clinical genetics may help in designing a personalized approach to the prevention of SCD by integrating clinical and molecular data. I will approach this topic by discussing first where we stand in the use of genetics for risk stratification and therapy selection in monogenic diseases and I will then move to discuss the contribution of genetics to patient profiling in acquired cardiovascular diseases.

1. Molecular genetics and prevention of SCD in Inherited Arrhythmogenic Diseases (IADs)

IADs are considered uncommon diseases with an estimated prevalence between 1 in 500 to 1 in 10,000, with an average prevalence of around 1 in 2,000. IADs can be divided in two groups: "cardiomyopathies" that are disorders presenting abnormal structure and function of cardiac muscle and "channelopathies" that have no structural abnormalities of the heart, but predispose to life-threatening arrhythmias. In these genetic diseases the prognosis is influenced by the type of causative mutation. For example, in Long QT Syndrome (LQTS) there are major differences in outcome among the three most common genetic variants of the disease: LQT1 (caused by mutations in the *KCNQ1* gene that encodes for a potassium channel), LQT2 (caused by mutations in the *KCNH2* gene that encodes for another potassium channel) and LQT3 (caused by mutations in the *SCN5A* gene encoding for the cardiac sodium channel). In this setting patients affected with LQT1 have the most favorable prognosis, they respond well to medical treatment with beta-blockers and they do not need an Implantable Cardioverter Defibrillator (ICD).[1] Patients with LQT2 and LQT3 have a more severe prognosis and a reduced response to beta-blockers, thus they may need to be protected by an ICD. Based on these data a risk stratification scheme has been proposed for LQTS patients, which combines clinical parameters such as gender and the duration of QT interval as well as molecular data, such as the "gene" in which the causative mutation is located.[1] Accordingly, LQTS patients with a higher risk of death are patients with mutations in the *KCNH2* gene and in the *SCN5A* gene, who also have a QTc duration that exceeds 500 ms.

More recently the field has advanced thanks to the evidence that the location of the mutation within the coding region of the causative gene can add information to risk stratification schemes and the mutations located in functionally relevant regions of the protein are the most deleterious.[2] Among the IADs Long QT Syndrome is clearly the disease that is closest to having a personalized management and risk profiling schemes that integrate clinical characteristics and the individual genetic background. It is expected that, as our knowledge advances, it will become possible to extend the contribution of genetics to the prediction of outcome in other cardiomyopathies and channelopathies.

2. Is susceptibility to SCD influenced by genetic factors in the general population?

In the last few years, several clinical studies demonstrated that having a family history of SCD is associated with a significant increase in the individual risk of dying suddenly. The Paris prospective study[3] was one of the first observational studies suggesting that family history of SCD on either the paternal or the maternal side of the family is associated with a relative risk of 1.89 of dying suddenly and that the presence of family history of SCD on both sides of families is associated with an hazard ratio of 9.4 of dying suddenly. These data were later confirmed by Friedlander et al[4] who showed that a parental history of early-onset sudden death (age <65) is associated with an increased risk of SCD (odds ratio $= 2.69$), after adjustment for parental history of myocardial infarction and other risk factors. These data encouraged investigators to design studies to search for common genetic variants called single nucleotide polymorphisms (SNPs) that could predispose to the risk of sudden death.

3. How to search for genetic markers that predispose to SCD?

The first method used to search for the genetic basis of SCD is called "candidate gene approach". This approach tests the hypothesis that SNPs located in genes that are known to cause SCD in patients with IADs or in genes that are known to modify electrical parameters that predispose to SCD, e.g. the QT interval, could predispose to SCD in the general population. This method proved to be quite useful and allowed for the identification of several common DNA variants linked to increased risk of SCD.

One of the first SNP identified as an indicator of susceptibility to develop SCD was the S1102Y[5] polymorphism in the gene encoding for the cardiac sodium channel *SCN5A*. This DNA variant is present in 13% of the African-ancestry population and it was shown to significantly increase the risk of SCD in the Afro-American population ($P = 0.000028$). Similarly, Albert et al[6] identified SNPs in the *SCN5A* gene associated with risk of SCD in Caucasian women, while in the same study no SNPs associated with SCD risk in men were found. In another study, Dr Albert and colleagues analyzed a population of 516 SCD cases and 1522 matched controls of European ancestry and investigated 147 SNPs for association with SCD. Two SNPs located in intron 11 of the *KCNQ1* gene and in intron 1 of the *SCN5A* gene were significantly associated with sudden/arrhythmic death.[7] These data demonstrated that common variants in genes that cause LQTS may also increase risk of SCD in the general population.

As previously mentioned, the other set of candidate SNPs investigated to test whether they predispose to SCD are located on genes that modulate duration of cardiac repolarization, such as SNPs located at the *NOS1AP* locus (Nitric oxide synthase 1 adaptor protein). Kao et al genotyped a series of SNPs in the *NOS1AP* locus in 498 SCD cases and 19,295 controls.[8] The SNP most strongly associated with QT interval, called rs16847548, was also associated with increased risk for SCD in the general population. Interestingly, SNPs in NOS1AP have also been associated with QT prolongation and cardiac events in LQTS.[9]

4. Genome Wide Association Study (GWAS): a powerful approach to search for SNPs linked to SCD

The second type of studies used to investigate the genetic substrate of SCD is called Genome Wide Association Studies (GWAS). At variance with the candidate gene approach that focuses on a selected number of SNPs located on genes that modulate electrophysiological parameters, GWAS intends to test large panels of unselected SNPs in normal individuals and in group of patients with specific diseases, to identify which SNPs may predispose to their occurrence. To summarize the results of GWAS studies that investigated the genetic predisposition to SCD, I report the interesting results by Arking et al[10] who performed a meta-analysis of GWAS studies on predisposition of SCD including 3119 SCD cases and 11,146 controls.[10] This study identified a strong signal for SCD susceptibility at locus 2q24.2. In this study the strongest association maps to an intron in *BAZ2B* gene, however, the signal also extends to the *WDSUB1* and *TANC1* genes. All three genes are expressed in human heart and may act during cardiogenesis and modulate the development of the autonomic nervous system.

5. How do all these data come together and what to expect for the future?

This brief overview has highlighted that in the past ten years major advances have been made in the attempt to define the genetic imprinting that predisposes to SCD. The rapid development of our understanding of the genetics underlying Mendelian arrhythmogenic syndromes has clearly paved the way to the application of molecular genetics to investigate the heritable component of sudden death in the general population.

The evidence that common DNA variants located in genes that cause Long QT Syndrome and Brugada Syndrome, namely *KCNQ1* and *SCN5A*, predispose to SCD the general population is quite intriguing and certainly deserves more investigation. The knowledge that the duration of intervals of the electrocardiogram is largely determined by genetic factors is now an established finding that has reinforced the importance of the duration of QT interval in the general population and its association with SCD. The observation that polymorphisms in the gene *NOS1AP*, that is the strongest modifier of QT interval duration, are critically associated with augmented risk of SCD in the general population represents a major finding that, if confirmed in prospective studies, may change our approach to risk stratification for SCD. Finally, GWAS studies have suggested that few genes that encode proteins with unknown function but highly expressed in the heart, may also harbor critical DNA variants that influence the probability of dying suddenly.

The bulk of knowledge produced in this field has established "genetics of SCD" as a novel and rapidly progressing topic of research that is likely to redefine risk stratification algorithms for cardiovascular diseases. As we look to the future we have to remember that all the DNA variants identified so far do not act in isolation, but rather they are deeply influenced by a mutual interaction and by the modulation induced by the environment. Studies that incorporate the cumulative effect of different SNPs, as well as the influence of the "exposome" defined as the lifelong environmental influence that acts on the genetic substrate, have not yet been performed and they represent the new challenge for the future advancement of the field.

Conflicts of interest

The author has none to declare.

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