Sudden cardiac death in young athletes: Literature review of molecular basis

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Abstract

Intense athletic training and competition can rarely result in sudden cardiac death (SCD). Despite the introduction of pre-participation cardiovascular screening, especially among young competitive athletes, sport-related SCD remains a debated issue among medical personnel, sports communities and laypersons alike, and generates significant media attention. The most frequent cause of SCD is a hidden inherited cardiomyopathy, the athletes may not even be aware of. Predictive medicine, by searching the presence of pathogenic alterations in cardiac genes, may be an integrative tool, besides the conventional ones used in cardiology (mainly electro and echocardiogram), to reach a definitive diagnosis in athletes showing signs/symptoms, even borderline, of inherited cardiomyopathy/channelopathy, and in athletes presenting family history of SCD and/or of hereditary cardiac disease. In this review, we revised the molecular basis of the major cardiac diseases associated to sudden cardiac death and the clinical molecular biology approach that can be used to perform risk assessment at DNA level of sudden cardiac death, contributing to the early implementation of adequate therapy. Alterations can occur in ion channel genes, in genes encoding desmosomal and junctional proteins, sarcomeric and Z-disc proteins, proteins for the cytoskeleton and the nuclear envelope. The advent of next generation sequencing (NGS) technology has provided the means to search for mutations in all these genes, at the same time. Therefore, this molecular approach should be the preferred methodology for the aforesaid purpose.

Introduction

Regular physical activity is a powerful tool for improving health and helps to prevent many disorders, including cardiovascular risk factors, obesity, depression, anxiety, musculoskeletal problems and stress.1-3 Numerous epidemiological studies have shown an association between moderate aerobic exercise and decreased risk of coronary heart disease,4-6 reduced risk of ventricular fibrillation in patients affected by a first myocardial infarction,7-9 as well as a reduction of overall death and cardiovascular mortality in cardiac patients subjected to adequate training programs.8,10 Furthermore the use of biochemical and haematological tests to evaluate risk factors in athlete is of relevance and interest at the amateur, competitive and elite level.11

However, for a small number of individuals physical exercise can increase the risk of sudden cardiac death (SCD).12,13 In particular, vigorous activity can transiently increase the risk of SCD in asymptomatic young athletes carrying genetic mutations predisposing to arrhythmic diseases.14,15

Sudden cardiac death is the most frequent medical cause of sudden death in athletes. Estimates vary widely based on the analyzed population, sports-associated SCD represents about 6% of the overall SCD burden.16,17 In Europe and North America the incidence of SCD is 2 athletes of 100,000 per year.18 In the Veneto region of Northern Italy, where >110,000 athletes were evaluated over a 21-year follow-up period, the incidence of SCD was 2.6/100,000 person-years in male athletes and 1.1/100,000 person-years in their female counterparts.13 The incidence varied by sex, the risk of SCD being higher in men than in women.15 Some athlete subgroups, specifically African Americans, male basketball and football players, appear to be at higher risk in the United States, whereas male soccer players had a higher incidence of SCD than other athletes in Europe.18,19 This observation suggests that individuals participating in sports of high dynamic and low isometric intensity are at higher risk of death. Few studies report prevalence of sports-related sudden death in the general population. Of note, paper of Marijon et al. showed that only 6% of sports-related sudden death in the general population occur in young competitive athletes, the remaining involving amateur athletes.20

Though SCD is rare, its occurrence in athletes who are often young and presumably healthy has a large emotional and social impact on the surrounding community. Therefore, considerable effort has been made to better understand the causes of SCD in athletes and to discover optimal strategies for prevention.

To this aim, the clinical molecular biology laboratory has acquired an increasingly relevant role for the early identification of molecular alterations that can be causative or co-causative of SCD in athletes.21 It is important to identify the specific DNA defect associated with a clinically manifest heart disease in an athlete, and, above all, to recognize the possible individual predisposition to develop a latent heart disease, before the disease can manifest itself with the fatal event of SCD.

In this review we will discuss genetic causes of sudden cardiac death in athletes, with particular emphasis on challenges in molecular diagnostics of inherited cardiac disease, like channelopathy and cardiomyopathy.

Cardiac diseases in young athletes

Cardiac diseases associated with SCD differ in young vs older athletes, the SCD cause being elusive even after autopsy in young subjects. Guidelines of the European Society of Cardiology (ESC) encouraged molecular autopsy22 in addition to the standard autopsy, as it may allow the post-

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Inherited cardiomyopathies are characterized by both allelic heterogeneity, which occurs when mutations within the same gene can produce different phenotypes, and genetic heterogeneity, occurring when mutations within different genes produce the same phenotype.

For example, SCN5A gene mutations are associated with distinct cardiopathies, such as long QT syndrome, Brugada syndrome, and also to HCM or DCM. Instead, DCM may be caused by mutations in sarcomeric, cytoskeletal, gap junction and even ion channel genes. Variable penetrance and incomplete expression are common in all cardiomyopathies, even among related subjects sharing the same pathogenic allele, and may reflect the action of modifier genes, epigenetic changes, environmental factors, or other factors such as age, gender, ethnicity or physical activity. To establish the diagnosis of inherited cardiomyopathy, the elucidation of family history and comprehensive assessment of pedigree is the foremost necessity, but it may not be sufficient. Electrocardiography, echocardiography and cardiac magnetic resonance imaging may not reveal subclinical anomalies present in asymptomatic subjects harbouring mutations. Thus, genetic test in the proband and cascade family screening is a valuable tool to exactly diagnose an inherited cardiomyopathy and to identify family members at disease-risk in preclinical stage. Furthermore, bioinformatics approach and functional studies can help to predict the pathogenicity of new variants found during genetic screening.

In this regard, ESC and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend molecular testing to improve the diagnosis and management of patients and at-risk family members. By these considerations, in 2013 the new cardiomyopathy classification system MOGE(S) has become necessary. MOGE(S) can assist in the diagnosis and management of each cardiomyopathy patient, classified following five attributes: Morpho-functional characteristic (M); Organ involvement (O); Genetic or familial inheritance pattern (G); Etiological description (E) of genetic defect or nongenetic underlying cause; and functional Status (S), using the ACC/AHA stage (A to D) and the New York Heart Association (I to IV) functional classes. The “S” notation is especially useful when mutation carriers are healthy, or if they demonstrate imaging-verified early abnormalities suggestive of cardiomyopathy.
Generally, gain of function mutations of sodium channel or loss of function mutations of potassium channels prolong cardiac action potential, producing a prolonged repolarization in cardiac cells and prolonged QT interval on the ECG. These three genes, together, explain up to 75% of LQTS clinical diagnosed patients, while the remaining genes contribute up to an additional 5-10% of LQTS cases.2,7,27,28 Of note, subjects carrying mutations in KCNQ1 gene are at high risk to develop VT/VF during physical activity.

About 20-25% of Brugada patients carry loss of function mutations in the SCN5A gene. In addition, CACNA1C, SCN10A, CACNB2, ABCC9 genes, among about 30 other associated genes, are each responsible for just over 5% of positive genotype patients, while the remaining genes are very rare2,7,27,28 (Appendix Table 1). Overall, known susceptibility BrS genes explain about 40% of cases, indicating that about 60% of BrS patients remain genetically unresolved. Furthermore, genome-wide association studies (GWAS) have demonstrated that common genetic variants increase susceptibility to Brugada syndrome, suggesting a polygenic way of inheritance, also.40

Physical activity, increasing parasympathetic tone and body temperatures, may precipitate fatal arrhythmias in BrS asymptomatic subjects.

CPVT is a rare channelopathy with both autosomal-dominant and, less commonly, autosomal-recessive inheritance,31,82 showing polymorphic ventricular tachyarrhythmia, which can lead to syncope or SCD under physical stress or emotional conditions. Clinical symptoms and higher risk of cardiac events occur in youth particularly in males.83,84 CPVT is, generally, caused by gain of function mutations in RYR2 gene, coding the ionic channel for the release of calcium from the sarcoplasmic reticulum, which plays a crucial role in regulating intracellular calcium concentrations. RYR2 gene is mutated in about 60% of CPTV patients, while only a small percentage of subjects carry mutations in other genes (Appendix Table 1).95-98

SQTs is a very rare cardiac channelopathy, characterized by peculiarly short QT intervals and increased susceptibility to develop atrial and ventricular tachyarrhythmia, which may arise later on physical activity.99,100 The main symptom is the cardiac arrest (up to 40%).101 Mutations (generally of the gain of function type) in KCNQ1, KCNH2, KCN2, CACNA1C, CACNB2, CACNA2D1, SCN5A and SLC4A3 genes are involved in disease (Table 1), although the diagnostic sensitivity of genetic test for SQTs is low (15-25%).99,101-103

Globally, the diagnostic sensitivity of genetic test for channelopathies is variable, ranging from 70-85% in LQTS to 15-25% in SQTs; therefore, genetic screening in genes known to cause cardiac channelopathies might result unsuccessful in around 15-30% of patients with LQTS, 40% of patients with CPVT, and 60-85% of patients with BrS or SQTs.

In the last decade it has become evident that hereditary channelopathies can also be caused by mutations in genes encoding cardiac ion channels regulatory proteins, such as transcription factors and proteins involved in the expression, intracellular transport and subsequent subcellular localizations of ion channels.94 For example, pathogenic variants in Calsequestrin (CASQ2), encoding the calsequestrin 2 protein, and calmodulin genes (CALM1, CALM2 and CALM3) are involved in the intracellular calcium homeostasis and are associated with LQTS and/or CPVT.95-98 Of note, CASQ2 mutations trigger SCD with a frequency higher than RYR2 mutations.99

Mutations in genes encoding other ion-channel associated proteins, such as caveolin (CAV3), ankryns (ANK3, ANK2), synctrophin (SNTA1), and yotiao (AKAP-9) are now implicated in the genesis of the channelopathies, although they affect only a very small proportion of arrhythmic patients.94,100-107

### Arrhythmogenic ventricular cardiomyopathy

Arrhythmogenic ventricular cardiomyopathy is an inherited heart muscle disease, showing typically ECG abnormalities and ventricular arrhythmias.108

ACM is characterized by a progressive loss of myocytes and fibro-fatty replacement; biventricular involvement is often observed in later stages.

ACM is reported to cause 0.08-3.6% of SCDs/year;109 however patients with known genotype are characterized by mortality <1%, as reported in recent literature.110

Mutations in desmosomal genes are found in about 50-60% of ACM patients, defining desmosomes as major factors in ACM pathogenesis.111-113 Desmosomes are intercellular junctions that provide strong adhesion between cells and link, intracellularly, to the intermediate cytoskeleton filament. They are found in tissue that experience intense mechanical stress, such as cardiac muscle tissue and epidermis. The linkage between the intermediate filaments and the desmosomal adhesion molecules is mediated by desmoplakin and the armadillo proteins plakoglobin and plakophilin. Thus, desmosomes contain desmoplakin, plakoglobin and at least one isoform each of plakophilin and the desmosomal cadherins desmocollin and desmoglein. A number of other accessory proteins are associated with desmosomes. Desmosomal genes related to ACM (Appendix Table 1) include PKP2, DSG2, DSC2, JUP and DSP, encoding plakophilin-2, desmoglein, desmocollin, plakoglobin, desmoplakin, respectively. PKP2 is the most frequently mutated gene in ACM patients, associated with about 30-40% of cases.114,115 Plakophilins exhibit dual localization, in the desmosomes as well as in the nucleus, where they can trigger fibroadipocytic replacement of cardiac myocytes by suppression of Wnt/beta-catenin pathway.116

Of note, mutations in desmosomal genes are found in about 5% of DCM cases, suggesting that there are little differences, in some cases, between ACM and DCM.108,117

Mutations in αT-catenin (CTNNNA3) and N-cadherin (CDH2) are also associated with ACM.118,119 Both proteins are present in the area composita at the cardiac intercalated disc. Alpha-T-catenin binds plakophilins contributing to the formation of the area composita, which strengthens cell-cell adhesion in contractile cardiomyocytes. This involvement shows that the pathogenesis of ACM extends beyond desmosomes. Area composite is a mixed-type junctional structure composed of both desmosomal and adherents junctional proteins. Physiologically, important interactions exist between the cardiac desmosome and gap and adherents junctions, with the resulting integrity of the intercalated disc and its important role in both mechanical and cellular electrical stability dependent on adequate functioning of all three subunits.

Rare mutations in TMEM43, transmembrane protein 43, located in nucleus inner membrane, are associated with severe ACM phenotypes,120 high penetrance and high SCD risk.111,121,122 This gene contains a response element for PPARy (an adipogenic transcription factor), which may explain the fibrofatty replacement of the myocardium, a characteristic pathological finding in ACM.123

### Hypertrophic cardiomyopathy

Hypertrophic Cardiomyopathy is a myocardial disease, characterized by thickening of the interventricular septum and left ventricular wall, in the absence of clinically

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important abnormal loading conditions or primary valve disease. The most specific histological features include myocyte hypertrophy and disarray, as well as interstitial fibrosis.

HCM is the most common cause of sudden death, particularly in adolescents and young adults, and the most common cause of SCD in athletes, in the United States.\(^{125,124}\) Non-sustained ventricular tachycardia, syncope, family history of sudden cardiac death, and severe cardiac hypertrophy are the major risk factors for sudden cardiac death.\(^{125}\) Furthermore, the presence of underlying but undiagnosed HCM in athletes is among the main causes of SCD, with the majority (60%) of cases occurring during exercise.\(^{27}\)

Hypertrophic Cardiomyopathy is a genetic disease, generally transmitted as an autosomal dominant trait and characterized by marked genetic heterogeneity.\(^{11,126}\) Mutations in about 100 different genes have been described associated to HCM; however, mutations in eight sarcomeric genes are responsible for approximately 60-70% of cases of HCM.\(^{61,126}\) Typically, the most commonly genes involved in HCM are MYBPC3 (myosin-binding protein C3), MYP (myosin heavy chain 1), TNNI2 (cardiac troponin I), TNNI3 (cardiac troponin I), ACTC1 (actin alpha cardiac muscle 1), TPM1 (tropomyosin 1), MYL2 (myosin light chain 2), MYL3 (myosin light chain 3); other six sarcomeric genes are involved in less than 10% of cases\(^{11,127,128}\) (Appendix Table 1). Most sarcomere mutations result in a single amino acid substitution, with the exception of mutations in the MYBPC3 gene, which are most frequently frameshift mutations, and create a premature-termination codon. Allelic balance between mutant and wild-type sarcomere proteins is variable and mutation-specific, reflecting differential stability or efficiency of sarcomere incorporation of mutated protein compared to the wild-type.

About 5% of HCM patients carry multiple sarcomeric mutations: these patients present with more severe disease at an earlier age.\(^{129-131}\) As a result, more extensive genetic evaluation may be warranted in probands presenting with early or severe disease. More rarely (less than 1% of cases) HCM patients present mutations in genes encoding Z-disc or calcium-handling proteins. The sarcomeric Z-disc defines the lateral borders of the sarcomere and is important not only for mechanical stability and force transmission but also for signalling, mechanosensation, mechanotransduction, apoptosis and cell survival. It is composed of numerous proteins, such as titin, myopalladin, nebulacinn, obscurin, actinin, telethonin. However, mutations in Z-disc genes give rise to heterogeneous diseases encompassing various cardiomyopathies such as DCM, HCM, ACM.\(^{132,133}\)

Although the utilization of next-generation sequencing methods has increased the spectrum of the putative HCM related genes, recent studies have suggested that mutations in non sarcomeric genes are very rare cause of HCM.\(^{134,135}\)

### Dilated cardiomyopathy

Dilated cardiomyopathy, characterized by left ventricular enlargement and systolic dysfunction, is a heterogeneous heart disease leading to progressive systolic heart failure and sudden cardiac death. When DCM occurs, in the absence of an identifiable cause, the disease is referred to as idiopathic DCM (IDCM). Familial DCM (FDCM) demonstrates marked genetic heterogeneity and age-dependent penetrance, with disease developing in childhood, adolescence and middle age, but rarely in the elderly. More than 40 genes have been identified in association with non-syndromic FDCM, the majority demonstrating autosomal dominant inheritance.\(^{136}\) They encode cytoskeletal, sarcomeric, nuclear proteins and act through different pathogenetic mechanisms, such as disruption of sarcomere-cytoskeletal interactions or myocyte architecture; amyloid deposition; abnormalities of desmosomal, calcium handling, ion channel function; alterations of mitochondrial energy dynamics or nuclear membrane-cytoskeletal integrity.

**TNN** gene, encoding the titin protein, is the most frequently mutated gene in DCM patients (up to 25% of cases, Appendix Table 1).\(^{137,138}\) Titin is an elastic protein, which passively stretched during the diastole and then returns to its initial state. However, it is also a biomolecular scaffold and mediates multiple protein interactions and intracellular signalling cascades, which may exert regulatory functions on muscular activity. The TTN mutations are generally nonsense, splice variants or deletion/insertions mutations, producing a truncated protein. Also mutations in genes encoding for sarcomeric thin and thick filaments (MYBPC3, MYH7, TNN2, TNN3, ACTC1, TPM1, MYL2, MYL3),\(^{137,139}\) and other proteins interacting with titin (myomesin 1 (MYOM1), cardiac ankyrin repeat protein 1 (ANKRD1) and telethonin (TCAP)) have been found in up to 5%-10% of DCM patients\(^{137,138,140-144}\) indicating that a complex network of proteins organized around the central scaffold titin may be defective in DCM.\(^{140}\) About 10% of DCM patients,\(^{146,147}\) show mutations in LMNA gene.\(^{148}\) Lamin A and C are intermediate filament nuclear envelope proteins, encoded by the LMNA gene, implicated in DNA replication, cell-cycle regulation, chromatin organization, differentiation maintenance, nuclear stability, pore positioning, gene expression and signal transduction. Through alternative splicing, a single transcript generates four products, collectively known as lamin A/C. Lamin A/C is associated with the LInker of Nucleoskeleton and Cytoskeleton (LINC) bridge complex, which links the nucleus to the actin cytoskeleton. The major components of the LINC complex are: lamin A/C (LMNA), emerin (EMD), nesprins-1 (SYNE-1) and nesprins-2 (SYNE-2) and SUN-domain containing proteins (SUN1/2).\(^{146}\) Mutations in all these genes are involved in DCM as well as in rare cases of ACM.\(^{148-151}\)

Other cytoskeletal proteins involved in DCM are desmin (DES), dystrophin (DMD), alpha-dystroglycan (DAG1), dystrobrevin (DNTA), sarcomycin (SGCD), syntrophin (SNTA1), phospholamban (PLN), caveolin (CAV3).

Desminopathy is one of the most common intermediate filament human disorders associated with mutations in desmin and alphaB-crystallin proteins. Desmin links desmosomes with the Z disk, helping to connect myofibrils together. This allows the formation of a continuous cytoskeletal network that maintains a spatial relationship between the contractile apparatus and other structural elements of the cell, providing maintenance of cellular integrity, force transmission and mechanochemical signaling. Desminopathy-associated diseases may be associated with DCM, ACM\(^{150,152}\) and restrictive cardiomyopathy.\(^{153}\)

Among the rare DCM genes, SCN5A, FLNC and PLN genes, deserve particular attention. FLNC codes the Filamin C protein, an actin cross-linking molecule, which contributes to the sarcomeric architecture; PLN gene encodes phospholamban protein, a key regulator of the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase pump (SERCA2a), which, in turn, is responsible for the calcium homeostasis.\(^{154,156}\)

DCM patients carrying mutations in SCN5A, FLNC or PLN genes, as well as in LMNA, had a prominent arrhythmogenic phenotype and a higher risk for life-threatening ventricular arrhythmias and SCD. Therefore, early identification of patients carrying mutations in these genes is particular imperative.\(^{139}\)

The great genetic heterogeneity associated to DCM demonstrates a central relevance for cytoskeletal integrity and biomechanical coupling of elastic and contractile...
High-throughput sequencing technology: Next Generation Sequencing (NGS)

The correct molecular diagnostic framework of inherited cardiomyopathies is often very complex, because of high clinical and genetic heterogeneity (Figure 1).160

The sequencing with the traditional techniques such as Sanger sequencing of a lot number of genes requires long execution times and involves a lower diagnostic and analytical sensitivity. These limitations have been overcome by the development of highly productive nucleic acid sequencing techniques (“Next Generation Sequencing”, NGS).161 These methods allow the analysis of a large number of nucleotides, from a single exon or gene, up to the analysis of gene panels, or of the whole exome or genome,127,162 accurately and at extremely competitive costs compared to traditional methods.

The analysis of gene panels by NGS sequencing represents the ideal analytical approach to identify DNA mutations associated with genetically heterogeneous pathologies, such as cardiomyopathies and channelopathies. This approach not only allows to analyze a large number of genes simultaneously in several patients, but, through the identification of further variants associated with the disease phenotype, allows to obtain information also on possible additional genetic factors that can act as phenotype modifiers or predict the patient’s prognosis. Recent evidence supports the importance of a sensible molecular analysis also in athletes showing a reasonable index of suspicion for an inherited cardiomyopathy or channelopathy, in order to early identify or prevent serious complications, up to the risk of sudden death.54,163,164 The use of genetic test by NGS methodologies could be taken as a useful implementation in the path of cardiological prevention for athletes, when the pre-participation screening shows a family history of SCD, cardiomyopathy/channelopathy or, symptoms and/or instrumental signs, even borderline, of cardiac dysfunction. The integrated diagnostic path may result in an exhaustive precise characterization of the underlying cardiac inherited disease.

Conclusions

Subjects practicing routine sports, both at a competitive and amateur level, have a lifestyle characterized by a vigorous and continuous physical effort. However, sudden cardiac death, often due to hidden cardiovascular disease, can suddenly affect even high-value athletes. SCD related to the practice of sports accounts for about 6% of the total SCDs, both in competitive and amateur young athletes.23 In fact, athletes, also asymptomatic, may be at risk of SCD while they’re training or competing, due to cardiovascular defects they may not even be aware of. To date, pre-participation cardiovascular screening of athletes is a life-saving and cost-effective strategy in athletes in whom SCD can be caused by heart muscle diseases and is recommended by both the AHA and ESC. The AHA recommends screening competitive athletes by means of family/personal history and physical examination.165 In Italy, a mandatory state-sponsored screening program exists for all competitive athletes, including symptoms evaluation, family history, physical examination and 12-lead ECG. This protocol was acknowledged by the ESC to propose for a common European conduct.166

A recent study by the Institute of Sports Medicine of Italian National Olympic Committee (CONI), conducted on more than 2,300 athletes who had taken part in the Olympic Games from 2004 (Athens) to 2014 (Sochi), confirms the opportunity to subject athletes to pre-participation cardiovascular screening and other examinations when necessary.167 About 0.2% of these athletes were found to have inherited cardiomyopathies, and globally about 4% showed cardiovascular abnormalities (coronary heart disease, high blood pressure, heart rhythm disorders) all equally asymptomatic.

The main aim of this review is to provide genetic support to prevent sudden cardiac death in young athletes, a highly visible tragedy that generates significant media attention and discussion among medical personnel, sports communities and laypersons alike. We think that genetic cardiomyopathy testing in athletes may be an integrative tool to reach a definitive diagnosis when the pre-participation screening shows personal symptoms (i.e. syncope, arrhythmias) or instrumental signs of heart dysfunction, even borderline, suggesting the presence of an inherited cardiomyopathy/channelopathy.168 Moreover, the genetic test may also be indicated in athletes with a family history of SCD or when a his/her family member is affected by cardiomyopathy/channelopathy and carries a disease-causing mutation. In this setting, the identification of athletes carrying a pathogenic mutation allows to detect individuals at risk in the pre-clinical or asymptomatic phase.

Figure 1. Schematic representation of cardiomyopathies and genes involved in Sudden Cardiac Death, can reflect our work and be used as a cover image. Diagram shows the overlap between the genes associated with Channelopathies, Dilated Cardiomyopathy (DCM), Hypertrophic Cardiomyopathy (HCM), Arrhythmogenic Cardiomyopathy (ACM).
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