Advising a cardiac disease gene positive yet phenotype negative or borderline abnormal athlete: Is sporting disqualification really necessary?

Pascale Richard,1,2,3 Isabelle Denjoy,2,4 Véronique Fressart,1,3 Mathew G. Wilson,5 François Carré,6 Philippe Charron2,3

ABSTRACT
The sudden cardiac death (SCD) of an athlete is a rare and tragic event, often caused by a number of inherited heart muscle disorders, namely the cardiomyopathies and primary arrhythmia syndromes (also known as cardiac ion channelopathies). Recent advances in the understanding of the molecular genetics of these heritable cardiovascular diseases present new challenges for clinicians who manage athletes with these types of heart muscle conditions. Unfortunately, the clinical heterogeneity of many of these SCD diseases are also matched by the genotypic heterogeneity associated with the pathogenesis of the disease. A particularly challenging situation arises when the sports physician and attending cardiologist are presented with an athlete who demonstrates a familial context of inherited cardiac disease or presents mild cardiac abnormalities suggestive of inherited cardiac disease. Alongside the complete cardiovascular evaluation, genetic testing may be proposed as an additional diagnostic tool in this clinical conundrum. However, debate still remains on how extensive the screening should be, in particular the use and interpretation of genetic testing in that setting. The aim of this review is to examine the role of genetic testing within the diagnostic algorithm of preparticipation screening of athletes. This will be achieved by providing the sports medicine physician with genetic knowledge for the main inherited cardiac diseases known to cause SCD. Furthermore, it will examine current knowledge for the role of genetic testing upon the prediction of SCD, concluding with its impact upon the sport eligibility and the disqualification conundrum.

INTRODUCTION
The appropriate diagnosis of an inherited heart disease has become a major issue in preparticipation screening of athletes, as these diseases represent the main causes of sudden cardiac death (SCD) in athletes under the age of 35 years.1–4 A diagnostic conundrum occurs when the physician is presented with an athlete who demonstrates a familial context of inherited cardiac disease or presents mild cardiac abnormalities suggestive of inherited cardiac disease. Alongside the complete cardiac evaluation, genetic testing may be proposed as an additional diagnostic tool in this challenging situation. Indeed, given the therapeutic strategies now available to prevent sudden death, such as the implantable cardioverter-defibrillator, the necessity for early identification of certain cardiomyopathies or primary arrhythmia syndromes in competitive athletes has become magnified. The aim of this review is to examine the role of genetic testing within the diagnostic algorithm of preparticipation screening of athletes. This will be achieved by providing the sports medicine physician with current cardiac genetic knowledge for the main inherited cardiac conditions known to cause SCD. Furthermore, it will examine current knowledge for the role of genetic testing upon the prediction of SCD, concluding with its impact upon the sport eligibility and the disqualification conundrum.

Molecular basis of inherited cardiac diseases at risk of sudden death in competitive athletes
Adrenergic stress during competitive sport is a commonly accepted trigger for arrhythmia and SCD, in the presence of underlying inherited cardiac disease such as cardiomyopathy (diseases with structurally and functionally abnormal myocardium in the absence of common condition sufficient to cause it),3 primary arrhythmia syndromes (pure electrical diseases mostly due to ion channel dysfunction)5 or vascular disease (such as Marfan syndrome).6 In an examination of 1866 young athletic SCD’s, the most common cause was hypertrophic cardiomyopathy (HCM) (56%), but other inherited diseases were also frequently observed; namely ‘possible’ HCM (17%), arrhythmogenic right ventricular cardiomyopathy (ARVC) (4%), long QT syndrome (LQTS) (4%), aortic rupture (3%) and dilated cardiomyopathy (DCM) (2%).3 A common theme across recent histopathological studies is the under-reporting in the frequency of primary arrhythmia syndromes, as this diagnosis is usually missed by necropsy. For the cardiac geneticists, however, ion channel diseases can be identified via postmortem genetic analyses in up to 10–30% of cases who often demonstrate normal conventional necropsy.8–10

Inherited cardiac disease: genes and inheritance
The main genes involved in inherited cardiac disorders are indicated in figure 1. The mode of inheritance for most of these diseases is autosomal dominant, but in particular phenotypes such as syndromic diseases or paediatric patients with cardiomyopathies, recessive, X-linked or mitochondrial modes of inheritance may also be observed (figure 1A, bottom). The familial aggregation is not always recognised, making it difficult to conclude about a familial/genetic disease. Sporadic
cases should be considered as part of genetic disease (usually with autosomal dominant inheritance), especially for HCM and ARVC, either because of a de novo mutation (mutation not transmitted from a parent) or because of incomplete penetrance in the parent (mutation without cardiac expression).11–13

HCM is characterised by the presence of increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease, etc) sufficient to cause the observed abnormality with a disease prevalence of 1/500.14 The usual mode of inheritance is autosomic dominant, characterised by genetic heterogeneity, with more than 900 different mutations described in more than 13 genes (Sarcomere Protein Gene Mutation Database http://cardiogenomics.med.harvard.edu). These genes encode the proteins that form various components of the contractile apparatus of the sarcomere. The global efficiency of mutation screening in index cases is of 30 to 65%. A study of nearly 200 independent HCM patients reported that 42% of genotype-positive patients had mutations in myosin-binding protein C (MYBPC3), 40% in \( \beta \)-myosin heavy chain (MYH7), 6% in troponin T (TNNT2), 6% in troponin I (TNNI3) and 4% in regulatory myosin light chain (MYL2) (figure 1A).16

<table>
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<tr>
<th>Phenotypes</th>
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<th>Gene symbol</th>
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Figure 1A  Main phenotypes and genes responsible for cardiovascular inherited diseases with their respective frequency. (A) Cardiomyopathies and (B) rhythm disturbances. This figure is only reproduced in colour in the online version.
ARVC has an estimated prevalence of 1/2000–1/5000 in the general population and is histologically characterised by the replacement of myocytes within the right ventricular myocardium by adipose and fibrous tissue.19 20 The disease is transmitted as an autosomal-dominant trait, with five of the responsible genes encoding the major components of the cardiac desmosome (figure 1A). According to the different number of published studies, the global efficiency of mutation detection is 30–70% in index cases. Data from our laboratory of 135 independent French patients indicate that plakophilin-2 (PKP2) is the predominant gene mutation (31% of patients), followed by desmoglein-2 (DSG2, 10%), desmoplakin (DSP, 4.5%), desmocollin-2 (DSC2, 1.5%) and junction plakoglobin (JUP, 0%).21

DCM is defined by left ventricular (LV) dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease, sufficient to cause the impairment and prevalence is estimated to be 1/2500.5 22 DCM is a sporadic disease in approximately 65% of cases and a familial disease in 35%. Familial forms are characterised by a great genetic heterogeneity (>30 causal genes reported), as well as a huge diversity of related proteins and underlying pathways such as nuclear envelope, cardiac sarcomere, ion channels, transcription factors and dystrophin-associated cytoskeletal complex.12 23 24

Figure 1B continued.
New directions

However, the yield of genetic testing for DCM is relatively low, with a global rate of mutation detection of around 20–30% in index cases, and most mutations related to lamin A/C (LMNA, ~5–10%), β-myosin heavy chain (MYH7, ~3–7%), cardiac troponin T (TNNT2, ~4%), myosin-binding protein C (MYBPC3, <1%), sodium channel (SCN5A) and α-myosin heavy chain (MYH6) (figure 1A).25–28

Among the primary arrhythmia syndromes, LQTS is characterised by prolonged QT interval on ECG, syncope and sudden cardiac death due to ventricular tachyarrhythmias.29–30 The prevalence is estimated to be 1 in 2500 in the general population,31 32 but two studies reported a high prevalence of LQTS founder mutations in the Finnish (0.4%) and Norwegian (1%) populations.33 34 LQTS is usually of genetic origin, with autosomal-dominant inheritance and an efficiency of mutation identification of 40–60% in index cases.29 35 Three common forms of LQTS represent the majority of cases; LQT1, a slow outward delayed rectifier potassium current abnormality encoded by mutations of KCNQ1 gene; LQT2, a rapid component outward delayed rectifier potassium current abnormality encoded by mutation of KCNH2 gene; and LQT3, a gain-of-function sodium channel abnormality encoded by mutation of SCN5A gene. Mutations in KCNQ1 represent 50% of genotyped LQTS, KCNH2 40% and SCN5A accounts for less than 5% of LQTS patients.36 However, it should be noted that some rare mutations have been identified in the auxiliary subunits of ion channels (figure 1B).3 37–39

There are several other inherited cardiac diseases that can cause sudden death that the genetic cardiologist may face within the athletic community. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder (prevalence 1/10 000) characterised by adrenergic-induced bidirectional and polymorphic ventricular tachycardia.30 32 Responsible genes for CPVT encode the cardiac ryanodine receptor (RYR2) and the cardiac calsequestrin 2 (CASQ2; figure 1B). Despite rarely a cause of SCD in athletes, yet worthy of mention in this review are the conditions of Brugada syndrome or short QT syndrome. The global rate of mutation identification in index cases is 65% in CPVT and 20–30% in Brugada syndrome.40

Penetrance of mutations and natural history of the diseases

Penetrance is defined by the proportion of mutation carriers with an obvious clinical expression, such as an abnormal ECG and/or echocardiogram. However, when considering the lifetime cumulative risk of expressing the phenotype, penetrance may be complete (100% risk of developing the disease with age) or incomplete (<100% risk of developing the phenotype). Mutations responsible for inherited cardiac diseases exhibit a variable penetrance, typically increasing with age. The onset of the cardiac expression (phenotype) is therefore usually delayed with a strictly normal cardiac examination for many years, and may explain why some athletes may perform extraordinary physical achievements for many years without any detection of inherited cardiac disease. The general natural history of these diseases is normally characterised by three important progressions; (1) a silent stage without personal symptoms, normal cardiac examinations and a normal ECG/echocardiogram (NB: the mutation is already detectable at this stage), (2) a second stage without symptoms but with detectable cardiac expression of the disease on ECG or echocardiogram (frequently delayed after 20 years of age for the majority of cardiomyopathies) and (3) a third stage with symptoms, obvious cardiac expression of the disease or sometimes the occurrence of unexpected SCD.

When considering the lifetime risk of developing the disease, penetrance may be nearly ‘complete’ after 50–60 years of age, in most cases in HCM or DCM (penetrance: ~95%).11 41 whereas for other mutations or diseases such as ARVC, LQT and Brugada syndromes, incomplete penetrance is commonly observed.5 42 Furthermore, the age for the phenotypic expression onset is also different according to the disease type, with frequent cardiac expression in young children and even neonates for LQTS but infrequent expression before 10 years of age for HCM or ARVC. Penetrance is also influenced by gender, as the expression of disease is more frequent with earlier onset in males for HCM, DCM, ARVC and Brugada syndrome, whereas LQTS cardiac expression is more frequent in females.6 11 43

Variable expressivity and genotype–phenotype correlations

Patients with an inherited cardiac disease usually present a variable severity in phenotypic expression, called expressivity, with dramatic differences in the age at onset, degree of symptoms, severity of ECG/echocardiography features, risk of complications and response to medical treatment. This variability is observed in patients sharing the same genetic mutation, both at interfamilial and intrafamilial levels, suggesting that epigenetic factors as well as environmental factors may act on the severity of the phenotype.12

However, the variability in the disease severity is accentuated between families by a great genetic heterogeneity with multiple genes, multiples mutations within the genes, various pathogenic mechanisms of mutations that could be involved in a given patient. The precise underlying gene and mutation may contribute to the variable expressivity of the phenotype,6 44 45 what is known as phenotype–genotype correlations and may have important consequences for genetic counselling and medical management of the athlete. Such correlations have been observed although they still require to be confirmed by the study of large populations and a prospective follow-up.

In HCM patients, genotype–phenotype correlations have shown that mutations in troponin T (TNNT2) usually cause mild hypertrophy that can escape clinical detection, but are associated with a high risk of premature SCD15 46 47 whereas mutations in myosin-binding protein C (MYBPC3) have been associated with delayed onset of HCM and significantly lower risk of SCD.48 49 In DCM patients, high mortality related to both heart failure and premature SCD have been described in patients with LMNA mutations.50 In ARVC patients, a high risk of left ventricle dysfunction was associated with desmoplakin (DSP) or desmoglein-2 (DSG2) mutations.21 51 In LQTS patients, cardiac events are often determined by the underlying genotype. In LQT1 phenotype, involving mutations in KCNQ1, cardiac events are mostly triggered by adrenergic stimulation, typically exercise. In LQT2 phenotype, involving mutations of KCNH2, cardiac events are triggered by emotion and in LQT3 patients with mutations in SCN5A cardiac events are triggered by sleep/rest. Efficacy of β-blocker treatment is also variable in LQTS patients according to the underlying gene: very efficient to reduce syncope and SCD in LQT1, whereas less efficient in patients with SCN5A mutations.5 52–54

Not only the gene but also the precise mutation within a given gene might be important. For example, in LQT1 patients, the higher risk of SCD concerns patients with mutations in the transmembrane domains of the protein encoding for the pore of the channel55 56 and in DCM patients, a higher risk of SCD was associated with the LMNA mutations that led to truncated proteins (mutations disrupting the reading frame during translation).50
Recent molecular findings also shed light on the intrafamilial variability of these diseases, especially in HCM and ARVC. Even in the context of familial forms and a dominant inheritance, a subset of the patients (3–10%) may carry more than one heterozygous mutation, so-called multiple mutations (either in the same gene or in another gene). Interestingly, these patients exhibit a more severe phenotype and a more frequent risk of SCD. Additional factors may also modulate the phenotype and contribute to the intrafamilial variability, such as common genetic polymorphisms or acquired/environmen-
tal factors (such as myocarditis), but they are still poorly under-
stood and further research is required in this specialised area.

GENETIC TESTING IN PRACTICE

Genetic testing was developed in some authorised medical labora-
tories for the purpose of routine use in order to improve both genetic counselling and the medical management of patients and relatives with inherited cardiac pathologies, and these basic principles are applicable to all populations including high-level athletes.

The molecular testing begins with a blood sampling of an index patient with an obvious form of a disease (with a certain or possible genetic origin), for which genes of interest are tested for mutation by sequencing (determination of the primary sequence of genes). For most cardiac diseases, the analysis concerns several genes and all the coding sequences of each of these genes. The process can therefore be quite long-winded and results for the index patient may often take several months. In HCM and ARVC, genes are tested according to their frequency in a short time. NGS can be used for the simultaneous analysis of numerous target disease or candidate genes for a given disease. Inherited cardiomyopathies and rhythm disturbances, 50–70 disease genes could be analysed simultaneously.

GENETIC TESTING AND THE INTERPRETATION OF RESULTS IN ATHLETES

In the case of an athlete with a suspected cardiomyopathy or ion channelopathy, there are two different situations for the recommendation of mutation analysis to be performed (figure 2).
The first situation is when there is a family history of cardiac hereditary disease and the mutation is identified in the athlete’s family. Genetic testing can be proposed to the athlete (asymptomatic with a normal or borderline cardiac examination) in order to search for the presence or absence of the specific mutation previously identified in their family. The process leads to a rapid and appropriate answer whereby (1) the presence of the mutation in the athlete is identified, leading to complete cardiac examination, and the discussion on specific preventive therapy or lifestyle modifications, together with effective management and regular medical follow-up or (2) the identified mutation in the family is absent within the athlete. Thus, the athlete can be discharged without the need for further cardiac examination; only the basic risk of the disease prevalence in the general population remains. The second situation is when there is no family history of cardiac hereditary disease, but the athlete may present borderline cardiac abnormalities on ECG or echocardiography and/or symptoms, however not sufficient per se to confirm a diagnosis of a cardiomyopathy or primary cardiac arrhythmia. In such cases, where there is adequate evidence to consider the hypothesis of an inherited disease, genetic testing can be proposed directly to the athlete.

If a mutation is identified, then the diagnostic information is crucial for the athlete and their family, leading to appropriate cardiac examination and long-term management. The interpretation of the genetic variant is, however, a very important step that requires several criteria to be studied including (1) the absence from an ethnically matched control population of at least 400 chromosomes and from web access polymorphisms data bases; (2) the nature of the mutation, where non-sense mutations as insertions, deletions and stop codons are usually pathogenic verses substitution of amino acids that may be questionable and (3) in silico modelisation of the consequences (location of the mutated residue in a conserved amino acid sequence, predicted secondary structure regions from published reports and the databank such as UniProtKB/Swiss-Prot). If no mutation is identified in this second situation, no conclusive diagnosis can be drawn since a mutation is not always identified in patients with obvious familial disease. Finally, if only a genetic variant of unknown significance is identified in this second situation, then no conclusion can be drawn. The interpretation of the result in this second scenario is therefore very important and it should be borne in mind that only a positive result (identification of a pathogenic mutation) is meaningful.

RISK OF CARDIAC DEATH AT THE EARLY STAGE OF INHERITED CARDIAC DISEASES

The risk of cardiac complications in patients with an obvious form of inherited cardiac disease is well known, as well as the deleterious role of intensive or competitive sport practice through the occurrence of ventricular arrhythmia. For athletes, specific therapeutic management often includes high-intensity sporting restriction, as underlined by international consensus recommendations. In contrast, however, the risk of a cardiac event at an earlier stage, in athletes carrying a causal mutation but without obvious cardiac expression of the disease, is poorly understood.

Hypertrophic cardiomyopathy

A limited number of sudden deaths have been described in asymptomatic patients without overt hypertrophy but carrying sarcomeric gene mutation. McKenna et al described two families with five premature sudden deaths (from 17 to 44 years) in patients without macroscopic hypertrophy, but with widespread myocardial disarray on histological examination, and ECG repolarisation abnormalities in alive relatives in a family. Several years later, the p.Arg94Leu mutation in the troponin T (TNNT2) gene was identified in this family in two relatives with abnormal ECG and in one of the deceased patients (postmortem analysis). Another report described two patients resuscitated from a cardiac arrest caused by ventricular fibrillation in which a clinical diagnosis of HCM could not be made at the time of the event but after several years due to the evolution of the phenotype, and because of the diagnosis of HCM in a family member. A mutation in the β-myosin heavy chain (MYH7) gene was eventually identified in each patient (p.Leu517Arg and p.Arg858Leu, respectively). Comprehensive risk stratification for SCD in sarcomeric mutation carriers without clinical HCM expression is poorly understood at the present time. The most recent and largest study was performed in 559 mutation carriers without clinical HCM. One risk factor for SCD was observed in 50% of the mutation carriers (including 4% with non-sustained VT and 14% with abnormal blood pressure response during exercise) and ≥2 risk factors were observed in only approximately 5% of mutation carriers. However, a short follow-up (5.5 years) study of sarcomeric mutation carriers without clinical HCM expression revealed only two SCD (0.15% per person-year) and suggests that for this population with 82% of patients with an MYBPC3 mutation, a good prognosis can be observed. On the contrary, in a study of 75 TNNT2 mutation carriers including 54 without clinical HCM at baseline, the rate of major cardiac events was 0.93% person-year suggesting the role of the mutated gene in the risk stratification. Although it is unclear at present as to whether risk factors for SCD are also of prognostic importance for HCM mutation carriers without manifested disease; thus, the findings suggest careful follow-up of the mutation carrier.

Arrhythmic right ventricular cardiomyopathy

ARVC is characterised by a high occurrence of SCD, even as a first clinical manifestation as suggested by the relatively frequent identification of ARVC at necropsy after unexpected SCD. Bauce et al described the case of a 13-year-old DSP mutation carrier, considered as clinically unaffected during familial screening, who died suddenly 2 years later (ECG performed 8 months before death for sports eligibility demonstrated only incomplete right bundle branch block). In a large study of 12 500 trained athletes in Italy, were found with abnormal negative T waves on ECG and in one of the deceased patients (postmortem analysis) another report described two patients resuscitated from a cardiac arrest caused by ventricular fibrillation in which a clinical diagnosis of HCM could not be made at the time of the event but after several years due to the evolution of the phenotype, and because of the diagnosis of HCM in a family member. A mutation in the β-myosin heavy chain (MYH7) gene was eventually identified in each patient (p.Leu517Arg and p.Arg858Leu, respectively). Comprehensive risk stratification for SCD in sarcomeric mutation carriers without clinical HCM expression is poorly understood at the present time. The most recent and largest study was performed in 559 mutation carriers without clinical HCM. One risk factor for SCD was observed in 50% of the mutation carriers (including 4% with non-sustained VT and 14% with abnormal blood pressure response during exercise) and ≥2 risk factors were observed in only approximately 5% of mutation carriers. However, a short follow-up (5.5 years) study of sarcomeric mutation carriers without clinical HCM expression revealed only two SCD (0.15% per person-year) and suggests that for this population with 82% of patients with an MYBPC3 mutation, a good prognosis can be observed. On the contrary, in a study of 75 TNNT2 mutation carriers including 54 without clinical HCM at baseline, the rate of major cardiac events was 0.93% person-year suggesting the role of the mutated gene in the risk stratification. Although it is unclear at present as to whether risk factors for SCD are also of prognostic importance for HCM mutation carriers without manifested disease; thus, the findings suggest careful follow-up of the mutation carrier.

Premature SCD has been described in early stage of DCM, specifically related to LMNA mutations that are associated with early conduction defects and/or ventricular arrhythmia. In a study of 19 LMNA mutation carriers with normal LV ejection fractions but with significant conduction defects requiring pace maker, a defibrillator was also systematically implanted and a high rate of appropriate implantable cardioverter defibrillator (ICD) therapy was observed (42% at 34±21 months), indicating a high prevalence of ventricular arrhythmia and thus, risk of sudden death before the onset of cardiac failure. Moreover, the recent case
study report of the SCD of a 35-year-old woman with a LMNA mutation (c.908-909delCT), who demonstrated normal LV function and without significant conduction disease,\textsuperscript{31} suggests the possibility that early and severe ventricular arrhythmia may be the only phenotypic expression of the disease.

**Long QT syndrome**

A recent study observed that the cumulative probability of aborted cardiac arrest or SCD in LQTS mutation carriers with normal-range QTc intervals (<440 ms) was significantly lower than in those with prolonged QTc intervals (4% vs 15%, p<0.001); but was however significantly higher than in those unaffected family members without mutation (4% vs 0.4%, p<0.001).\textsuperscript{55} Importantly, the authors identified subgroups of genotype-positive yet phenotype-negative relatives who were at significant risk of SCD (ie, LQT1 and LQT3 with transmembrane-missense mutations). This specific subgroup of mutation carriers with normal QTc interval might therefore benefit from early β-blockers intervention, in addition to sport restriction and avoidance of QT-prolonging medications.

Apart from the acute risk of sudden death at the early stage of an inherited cardiac disease possibly due to the interaction between an arrhythmogenic substrate, adrenergic stress and/or a premature ventricular beat, the potential role of regular intensive physical activity on the development of myocardial dysfunction (diastolic or systolic) has been questioned in the context of cardiomyopathies. Although still speculative, in humans\textsuperscript{62} and animal models, some have suggested a potential deleterious effect. For example, in a mutated ARVC mouse model, endurance training accelerated the development of right ventricular dysfunction (and arrhythmia inducibility) in heterozygous plakoglobin-deficient mice, suggesting that endurance training could accelerate disease occurrence or progression.\textsuperscript{83}

**MANAGEMENT OF ATHLETES WITH A MUTATION BUT A NORMAL OR BORDERLINE CARDIAC EXAMINATION**

To evaluate the risk of SCD associated with competitive sports in the presence of a cardiomyopathy or primary arrhythmia syndrome is a dilemma for the attending cardiologist. This has led to several international recommendations for the preparticipation screening in competitive sports (focused on the identification of a cardiac disease not recognised until now),\textsuperscript{84,85} as well as recommendations for participations of patients (with a recognised cardiac disease) for competitive sports or leisure time physical activities.\textsuperscript{67,68,86–89} The practical management of athletes however remains a challenging issue, as little longitudinal data exist supporting the beneficial role of sporting disqualification upon death rates of athletes identified with an inherited cardiac disease, outside of the Italian experience. Because of this death of data, sporting disqualification should also be viewed as the last intervention available in the cardiologist’s armoury. It can be anticipated that with future improvement in the understanding of such diseases and their potential risk of adverse cardiac events associated with intense sport, the objective should and will be to reduce the number of unnecessary disqualifications and to modulate rather than stop the sports activity of the athlete in question.

It is important to realise that the decision for sporting disqualification is based upon the stage of the disease when it is identified within the athlete. This is due to the fact that the natural history of inherited cardiac diseases is often characterised by a dynamic process and a continuum from (1) an asymptomatic mutation carrying athlete in the absence of cardiac expression or who demonstrates mild-to-borderline abnormalities, (2) an asymptomatic athlete with obvious cardiac expression with or without specific SCD risk factors such as non-sustained ventricular tachycardia in HCM or extremely prolonged QTc interval in LQTS patient and finally (3) an athlete with obvious cardiac expression who presents the occurrence of symptoms and/or cardiac complications. Although the risk of SCD is not always strictly related to the stage of cardiac expression, there is a general consensus on the disqualification of competitive sport in athletes with obvious cardiac expression.\textsuperscript{68,69} These recommendations are supported by the reduced number of sudden deaths in Italy since the development of systematic preparticipation screening in athletes.\textsuperscript{69}

The management of asymptomatic athletes who carry a mutation but without any cardiac expression or with only borderline abnormalities, is a particularly challenging issue without consensus.\textsuperscript{68} The risk of sudden death at this early stage is probably low but not negligible, although available data are limited. In the context of such ‘genotype-positive–phenotype-negative’ athletes, there are significant differences between European and North American policy. Study Groups of the European Society of Cardiology recommend\textsuperscript{86} the disqualification of all mutation carriers (especially within HCM or Marfan athletes), whereas the North Americans (Task Force 4) authorise full competitive sport (except for swimming in individuals with LQT1 mutation).\textsuperscript{86,87}

In our institutions, the management of genotype-positive–phenotype-negative individuals and the subsequent discussion regarding sporting restriction or clearance is based on a case-by-case approach taking into account several factors: (1) the type of gene and mutation identified in the athlete, as some mutations have been acknowledged as being at either a high or low risk for an adverse cardiac events; (2) the familial history and number of premature cardiac deaths as several sudden deaths before 50 years of age in a family represent a known risk factor for HCM and can be considered important in the discussion of sporting restriction with the athlete. Unfortunately, for most primary arrhythmia syndromes, these scientific evidence is lacking; (3) the type of sporting activity undertaken, as highly dynamic sports have been linked with SCD particularly soccer and basketball for HCM and swimming for LQT and finally (4) the presence in the athlete of personal SCD risk factors after prognostic stratification such as non-sustained ventricular tachycardia in HCM mutation carriers.

The following two cases examples from our institutions illustrate the clinical value of genetic testing in the diagnosis of the condition, thus helping in the discussion of sporting restriction or medical clearance for the athlete. One case was brought in as an athlete with symptoms, whereas the second case is ‘predictive’ in the context of a recognised inherited disease in the athlete’s family.

**Case 1**

A 38-year-old male swimmer (training ~6 h/week) was admitted to our cardiology intensive care unit following multiple episodes of faintness that occurred during swimming. Electrocardiogram at admission demonstrated bradycardia (35/65 min) with high-degree atrio-ventricular block. Family history questioning revealed a paternal aunt that died suddenly at age 65 years of age. Echocardiography revealed HCM with a basal diastolic septal thickness of 18 mm, a LV diastolic diameter of 42 mm, and a normal LV ejection fraction (60%). Consequently, a pacemaker was implanted the following day. Genetic testing was performed and the analysis was negative for some genes including the LMNA gene. PRKAG2 sequencing revealed a
heterozygous missense disease causing mutation (p.Ser548Pro), responsible for both conduction defect and the HCM expres-
sion. This result allows for effective family management and screening, thus helping to avoid potential SCD in relatives.

Case 2
A 14-year-old asymptomatic male soccer player (body surface area 1.59 m², training 11 h/week) presented to our department for preparticipation cardiac screening for entry into a profes-
sional soccer school, due to family history. The boy’s father developed DCM, ICD was implanted and a heterozygous muta-
tion in the LMNA gene was identified. The boy’s grandfather had a pace maker at 55 years, but died 5 years later. ECG of the
boy was unremarkable. Echocardiography exhibited moderate enlarged LV end diastolic diameter (LVEDD 55 mm or 33 mm/
m²) with normal ejection fraction (60%) and wall thickness (7 mm). Exercise test, holter ECG and creatine kinase dosage
were normal. In our and others’ experience, isolated enlarged LVEDD has been identified in several cohorts of DCM families,
as an early predictive marker of relatives at risk of developing subsequent obvious DCM. After 5 months of detraining, LVEDD
was not modified, thus predictive genetic testing was proposed that was accepted following extensive family genetic counsel-
lng. Genetic analysis revealed the presence of the LMNA mutation in the boy. Owing to the player’s early cardiac expression and family history, we proposed that competitive sport was
not compatible due to the risk of future occurrence of early ventricular arrhythmia and atrio-ventricular block, in addition to
the risk of DCM. Both the boy and the parents agreed on this course of action, with the boy modifying his career choice.

CONCLUSION
Genetic testing is increasingly performed in the clinical arena, leading to the early identification of athletes at risk of develop-
ing a potential life-threatening cardiac disease. The manage-
ment of asymptomatic athletes who carry a mutation but
without any cardiac expression, or with only borderline abnor-
malities, is a particularly challenging issue without inter-
national consensus. The risk of sudden death at this early stage is
probably low but not negligible. Accordingly, a conservative management is most favourable with education regarding per-
sonal symptoms and annual cardiac follow up; with sporting disqualifi-
cation viewed as a last resort option. We propose that the
management of the genotype-positive–phenotype-negative
athlete and the subsequent discussion of sporting clearance or
restriction is based upon a case-by-case approach taking into
account: (1) the type of gene and mutation identified in the
athlete, (2) the familial history and number of premature
cardiac deaths, (3) the type of sporting activity undertaken and
(4) the presence of potential SCD risk factors after prognostic
stratification.

Future prospective studies of large cohorts of genotyped rela-
tives are required to improve the knowledge on the risk of SCD,
helping to provide optimal management strategies for these
athletes. The recent technological advances that enable high-
throughput sequencing of multiple genes simultaneously will
also revolutionise the diagnostic approach of genomic medicine
but in turn will pose many new challenges for the clinician.
However, it is anticipated that with the improvements of our
understanding of inherited cardiac diseases and their potential
risk for adverse cardiac events associated with intensive sport,
the sports cardiology community will be able to reduce the
number of unnecessary disqualifications and to modulate rather
than stop the sporting activity of the athlete in question.

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New directions


Advising a cardiac disease gene positive yet phenotype negative or borderline abnormal athlete: Is sporting disqualification really necessary?

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doi: 10.1136/bjsports-2012-091318

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