REVIEW

Genetics and sports

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ABSTRACT

There have been great scientific and technical advances in biomedicine in the last few years, particularly after the description of the human genome. These improvements have gradually been applied in diverse fields that have gone beyond the study of the disease to enter the study of health. The latter includes research in the field of physical and sports activity. Genetics therefore provides the scientific knowledge that helps us to optimise the performance of high level sportsmen/women, to reap the benefits of carrying out physical exercise and/or to perform a safe sports practice by evaluating the risk of a hereditary disease associated to sudden death in sportsmen/women.

KEY WORDS: Genetics. Sport. Physical condition. Sudden death. Arrhythmic syndromes.

RESUMEN

La biomedicina ha experimentado grandes avances científicos y técnicos en los últimos años, especialmente después de la descripción del genoma humano. Estas mejoras se han aplicado gradualmente en diversos ámbitos, que han sobrepasado el estudio de la patología para adentrarse en el estudio de la salud. En esta última se incluyen investigaciones en el campo de la actividad física y el deporte. La genética, por tanto, aporta unos conocimientos científicos que pueden ayudarnos a optimizar el rendimiento de un deportista de alto nivel, rentabilizar los efectos de la práctica del ejercicio físico y/o llevar a cabo una práctica deportiva segura, evaluando el riesgo de una enfermedad hereditaria asociada a la muerte súbita en deportistas.

PALABRAS CLAVE: Genética. Deporte. Condición física. Muerte súbita. Síndromes arrítmicos..

Introduction

The importance of adhering to an active healthy lifestyle is well documented. In adults, research has shown the importance of physical activity for the prevention of cardiovascular disease, metabolic syndrome, type 2 diabetes, and obesity as well as promoting longevity[1-4]. In children and adolescents, a recent review indicates that taking part in some physical activity is associated with a series of positive effects on health[5].

To the extent that sporting activities have been made official, whether through participation in regulated activities or with more competitions, a larger group has made the leap from purely recreational to amateur competition, where the athletes themselves look for continuous improvement in their ability to play a sport. So it is not strange to suggest that those who participate in sports are looking to improve their performance through more rigorous training and better nutrition. The progress made in molecular level understanding of physical capacity, including genetic factors, generates more interest in the technology in order to predict anything from the best type of exercise, to the risk of suffering a muscle injury.

Within the context of genetic advancement in sports, the information with reference to sudden death in sports practitioners caused by hereditary genetic diseases stands out. Even though very infrequent, the sudden death of an athlete has an instantaneous impact through the media, creating significant social alarm.

The sciences of physical activity and sports are an area of research that can't escape the changes being experience in molecular biology, and specifically in the field of human genetics and genomics. As such, whether the purpose is to study the impact of a training program targeting performance,

Received: 8 May 2009 / Accepted: 13 May 2009

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to analyse the effects of physical activity, or to evaluate the risk of suffering from a hereditary disease associated with sudden death in sports practitioners, human genome information has become an important element for different research projects.

Genetics

Many important historical events have taken place in order to prepare the human genetic map. From publication of Charles Darwin's *Origin of the Species* (1859), to Gregor Mendel's pea experiments (1865), the launch of the Human Genome Project (1990), the preparation of a detailed map of human genetics (1995) and finishing the human genome sequence (2003), in the last 25 years the study of molecular biology has experienced a significant revolution and currently its influence is highly relevant in the science fields[6].

All living organisms have their own genetic information contained in the DNA molecule (deoxyribonucleic acid). In it are found the units of heredity, genes. We humans have 30,000 genes distributed in 23 pairs of chromosomes located in the nucleus of our cells (22 autosomal pairs and 1 pair of sex chromosomes) and a single mitochondrial chromosome. Each pair of chromosomes (counterparts) has the same genes – of which we have two copies called alleles. Each gene contains the necessary information for protein synthesis; it is an organism's functional unit, given that the organism's smooth operation is based on the perfect synthesis of all necessary proteins.

The DNA molecule is made up of 4 different types of nucleotides repeated millions of times. The majority of DNA do not encode proteins and those fragments that do are called genes. In the encoder portion of the gene, each group of three nucleotides is encoded for a specific amino acid. This is a chained process; the three first nucleotides encode the first amino acid, the three following the second, and so on. The order followed by the nucleotide sequence in the DNA determines this synthesis. The progressive accumulation of all of the gene's amino acids leads to the creation of protein. In the human genome at least 1.5% of these are described as containing sequences that encode proteins[7]. The rest of the material may help proper functioning, but its purpose has not yet been clearly established.

On occasion insertion, deletion, or change in the order of the nucleotides may occur. They are genetic defects called mutations; they can produce the synthesis of a different or defective protein causing disease. Whether an individual develops a disease caused by mutation or not, depends on the importance of the particular protein to the overall functioning of the human body. If the mutation affects the DNA of a germinal or reproductive cell, it will be transmitted to subsequent generations causing hereditary disease.

Hereditary diseases are classified as:

1. Chromosomal alterations, with the deletion or addition of a part of or an entire chromosome.

2. Polygenic diseases (the most frequent), where the disease is due to the interaction of different genes.

3. Monogenic diseases. Just one gene is primarily responsible for this disease, and its hereditary pattern follows the laws of Mendel which are:

– Autosomal dominant diseases. One of the hereditary alleles is defective and the other is normal. The dominant nature of the disease means that with just one allele affected by a mutation it can cause disease. Descendents have a 50% chance of being carriers of the disease if one of the parents is affected. Each generation is affected and men as well as women can inherit and transmit the disease.
– Autosomal recessive diseases. Both alleles must be defective for the disease to occur. As such, it is a less common form than autosomal dominant disease. If both parents are carriers, their descendents have a 25% chance of suffering from the disease and a 50% chance of being carriers.
– Diseases linked to sex. Women provide one of the X chromosomes. Men, having only one X chromosome, suffer from the disease if they inherit the mutated chromosome.
– Mitochondrial diseases. Always transmitted by females, because the mitochondrial chromosome always pertains to the mother. As such there is no male to male transmission.

In general, all human beings show small variations called polymorphisms in some part of their DNA. Unlike mutations, polymorphisms in general, do not cause diseases but can alter the response of an individual to them, producing variations in predisposition, development, and response to treatment[8,9].

Basic concepts: genetics, genomics, genotype, and phenotype

The evolution experienced by molecular biology has led to, among other things, more common and sometimes indiscriminate use of a particular vocabulary. Due to that situation, we thought it best to conceptualize some of those terms and create a framework for the subject we are dealing with in this article.

First of all we should differentiate genetics from genomics. Genetics is understood to be the biological sciences that attempt to understand how biological heredity is transmitted from one generation to the next and how those processes develop. A goal of genetics is to study heredity patterns and how they are transmitted from parents to children. On the other hand, genomics includes a set of sciences and techniques dedicated to the integrated study of the function, evolution, and origin of the genomes[6,10]. Even though genetics and genomics are conceptually different, they share some basic areas of study such as genes and DNA.

Genotype and phenotype are two more basic concepts that should be kept in mind to help understand issues arising from the research in this area. Genotype refers to all of an individual's genetic material. The visible features of an individual are called phenotype[6,10]. For example, in the case of diseases, if an individual is genetically predisposed to suffer from cardiovascular diseases such as Brugada Syndrome, we are talking about genotype. If this disease manifests on its own and develops, we are talking about phenotype.

A QUESTION OF DESIGN

In *Origin of the Species* Charles Darwin shows that all organisms must work to survive and that only the vigorous, healthy, and happy are capable of multiplying. In fact, we could say that exercise has been programmed in our genes since the Palaeolithic era. The environmental factors that our ancestors had to face, where fitness was an important factor in survival, caused our genes to evolve in relation to the environment in which they lived[11,12].

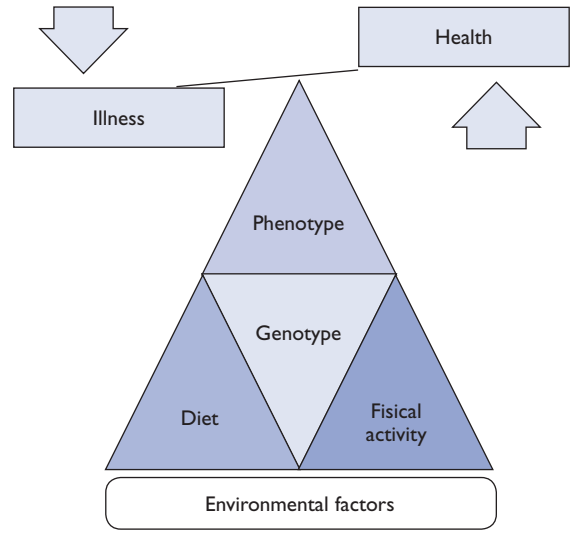
The environmental factors of well-off societies are very different from those of the Palaeolithic era; so we find ourselves with an evolutionary design incompatible with our current environmental conditions. This fact induces many of the diseases our society suffers from today[11].

Between genotype and phenotype, environmental factors (food, physical activity, hygiene habits, etc.) play a very important role. Whether individually or collectively, these factors can interact with the genotype and be precursors to the manifestation of phenotypes (fig. 1).

FITNESS GENOTYPES AND PHENOTYPES

To discuss fitness and genetics, first we need to decide what we mean by fitness and what its characteristics are. The concept of fitness may have different interpretations depending on the

Figure 1 Genotype-phenotype relationship.



area we are dealing with. In keeping with the subject of this article, we would like to identify what health related fitness and the kind of fitness related with sports performance are.

In the health field, fitness can be seen as the degree of energy and vitality a person needs to be able to perform common daily tasks: actively enjoy free time, handle unforeseen emergencies without excessive fatigue, prevent certain diseases deriving from sedentariness, and facilitate maximum development of intellectual capacity, thoroughly enjoying life. From the sports perspective, fitness is a performance component and the maximum optimization of the components of fitness is a goal[13-16].

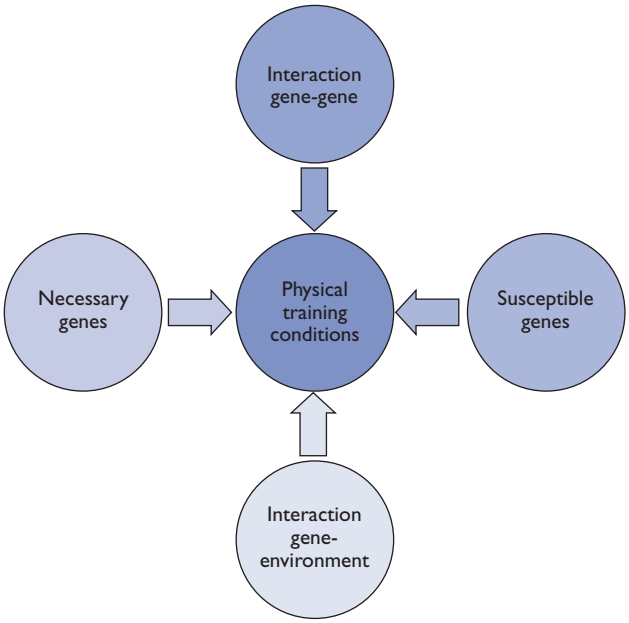
For the purposes of establishing a criterion to help us understand some of the aspects of this article, and without getting into a conceptual debate or nuances, we consider fitness to be made up of physical capacities. We can classify these capacities in motor or basic capacities (strength, aerobic/anaerobic endurance, and speed), coordinating and perceptive-motor capacities (general/specific coordination and balance), the resulting capacities (agility), and the facilitating capacities (flexibility-elasticity, muscle/joint mobility)[14]. Beyond this classification, we would agree that conditional capacities are based mainly in energetic and coordination processes preferably in regulation and conduction of the central nervous system[53].

Whether from the perspective of sports or physical exercise, all of these fitness elements can be measured in one way or another. From $VO_{2max.}$ ($ml \cdot Kg^{-1} \cdot min^{-1}$ o l/min), time (sec.), speed (m/s) and strength (kg.), etc. As an example, a person

can have a genetic substrata (genotype) related to cardiovascular endurance that could manifest itself as values of VO_{2max} (phenotype) that are measurable and modifiable by different environmental conditions such as training loads, food, etc.

Nevertheless, we shouldn't have a Mendelian view of the individual in regards to fitness phenotypes as there are many factors that interact: social, physiological, metabolic, cellular, and molecular. In addition, the effect of genetic material on fitness phenotypes is also determined by susceptible genes that can predispose a phenotype, and by the interaction among different genes, questions that are still being studied. Because of this, fitness phenotypes are called complex phenotypes as they occur with complex disease phenotypes (fig. 2).

Figure 2 Interaction of the different elements in the physical condition.



The human gene map for fitness

After completion of the human genome sequence, research has been done and continues being done to determine the genes implicated in different fitness phenotypes. Preparation of this genetic map relies on the contribution of various research projects done year after year. However, the interpretation of the results of these studies must be understood within the context of the strategy used for the research.

Research strategies

In human studies, research methods are based on genetic epidemiology, and more recently on molecular studies. Broadly, genetic studies can be classified in two large groups. First, there are those based on genetic epidemiology, focusing on family and individual phenotypes. Second, there are those more related to molecular biology that attempt to measure DNA variation based on candidate gene markers.

To analyze the genetic base of complex phenotypes, such as physical capacity, there are three major methods[17-20]. First, there are *heritability* studies that attempt to evaluate genetic and environmental contributions to the phenotypes of members of the same family, twins, or individuals adopted by families. For example, some estimate that the degree of heritability of the VO_{2max} is approximately 50%, as related to muscle fibre type between 40% and 50%, and for muscle strength 70%.

The second major method uses *Genome-wide linkage scans,* consisting of a genetic examination of markers found in the entire human genome in a very large group of individuals enabling subsequent associations between each marker and specific phenotypes. There is an attempt to locate human genome regions that have a high probability of being related to the consumption of oxygen, % of body fat, or the regulation of heart rate.

The third major strategy, and one of the most used, is the study of *candidate-gene association.* It involves looking for a candidate gene believed to influence the regulation of one of the fitness phenotypes. From there, the most common variations of this gene (allele) are studied in a large number of subjects. At this point two types of research may be encountered. The first studies a single variation of the gene (allele) of a specific subject, and in the other they study control cases to try and see if a gene or its variation is more common in elite athletes than in the normal population. These two research options are those that were used to identify a number of fitness associated genes, whether in the general population or in elite athletes.

Genes and fitness

The genes added to the fitness genome are published annually in the *The Human Gene Map for Performance and Health-Related Fitness Phenotypes*. Although the studies relating to fitness phenotypes are varied, we present some examples. In case control studies related to endurance sports we find genes like AMPD1, PPARGC1A and ACE, and with speed tests we have ACTN3. In the case of *association* studies with candidate genes we find phenotypes studied like VO_{2max} associated with

genes like ADRB2, HLAA, CFTR and HIF1A, the post-exercise lactate associated with genes like ACE, or strength associated with DI01 and IGF2[20] (table I).

Possibly the gene variants, as well as being associated with sports performance, are found in people that exercise to benefit their health. In general, these variants studied in elite athletes are very common in the population. Those genes related to energy metabolism, cardiorespiratory response to maximum exercise, etc., are important factors for the general population as well as the athlete. Although the study of the genetic characteristics of high level athletes contributes valuable information regarding the benefits of physical exercise for the general population, we must note that not all variants we find in first rate athletes should be seen as a health reference in the fitness world. This is the case with those genetic variants that a long distance runner might have that enable him to conserve energy during long periods of intense physical activity, given that this would not be valuable in little active or sedentary individuals.

Table I Most important gens associated with sports.

Objective	Gen
Endurance	*PPARD*
	Nuclear respiratory factors (NRF2)
	PGC-1alpha
	HIF-1alpha
	EPAS-1and HIF-2alpha
	Haemoglobin
	Skeletal muscle glycogen synthase (GYS1)
	ADRB2
	CHRM2
	VEGF
Muscular	*CK-MM*
	ACTN3
	MLCK
	ACE
	AMPD1
	IGF-1
Tendon	*ABO blood group*
	COL1A 1 and *COLSA 1*
	TNC
Psychology	*Serotonin transporter gene (SHTT)*
	BDNF
	UCP2

Adapted from Lippi, 2009[9].

Genetics and sudden death in athletes

Sudden cardiac death is defined as death from cardiac causes occurring in the first hour after the first symptoms. Sudden death is found in 1/1000 in the general population, but increases significantly if there is a more serious cardiac pathology. Sudden death in athletes is not frequent[21,22] even though the real incidence may be larger than thought due to the fact that certain conditions like ion channelopathies, which predispose to lethal arrhythmias, are not associated with structural heart disease, and therefore the cause of death remaining unclear. Approximately 80% of non-traumatic sudden death in young athletes is caused by hereditary cardiovascular anomalies; as such, they have a repercussion on families[23-25]. The majority (>80%) of sudden cardiac deaths (SCD) in young athletes occur during or immediately after excercise[26]. This suggests that exercise may be a cardiac arrhythmia trigger in those individuals with certain cardiac disorders.

Most SCD in athletes occurs in young men (12-40 years old). Often SCD is the first symptom of the disease. SCD is usually directly related to exercise and at autopsy, it could be completely normal (suspicion of arrhythmogenic disease) or abnormal with the detection of structural cardiac alterations[24,26-28]. Among structural diseases, the most written about are hypertrophic cardiomyopathy (HCM), causing 40% to 50% of the cases, and arrhythmogenic right ventricular dysplasia (ARVD), the most frequent cause of SCD in athletes in certain areas of Italy.

There are multiple genetically determined cardiac pathologies, with or without accompanying structural cardiopathy, that may predispose to the appearance of arrhythmias and sudden death[29-31]. These diseases are the product of alterations in the genetic encoding of four large families of proteins:

- Sarcomeric proteins, which generate strength in the cardiac myocyte and are responsible for hypertrophic cardiomyopathy[32].
- Cytoskeletal proteins, which transmit the strength to the adjacent cells that cause dilated cardiomyopathy[33].

- Proteins that encode ion channels, responsible for maintaining the intra and extracellular ion balance, as well as responsible for familiar arrhythmias[34].
- Desmosomal proteins enable structure maintenance and intercellular communication.

But there is a significant overlap between genes and diseases[35]; for example troponin T can cause dilated cardiomyopathy as well as hypertrophic cardiomyopathy[36,37]; the sodium channel SCN5A is one of the genes responsible for the Brugada Syndrome, long QT syndrome type 3 (LQTS3), and also familial conduction alterations[38,39].

Diseases

Brugada Syndrome

Brugada Syndrome (BrS) has a characteristic ST segment elevation that is easily identifiable in the cases with a "classic pattern". Unfortunately, non-specific or incomplete changes of the ST segment, or right bundle branch block are common in the general population. If there is a suspicion that the disease is present, then in these less classic cases it is advisable to perform an ajmaline test, in which the intravenous administration of the sodium inhibitor can unmask the diagnostic electrocardiographic pattern.

It is thought that the physiopathological mechanism responsible for ST elevation and susceptibility to ventricular arrhythmias is an imbalance between input and output of ion currents during phase 0 and 1 of the action potential. Until now, only two genes were associated to the disease (SCN5A, sodium channel encoding, and GPD1L, glycerol-3-phosphate deshydrogenase-1). Curiously there is no information with respect to sudden death in athletes caused by Brugada Syndrome, but given that the ecg pattern can become worse during febrile episodes, clinical practices have begun advising those affected by the disease not to participate in sports due to the increase in body temperature, a fairly controversial decision (Table 2).

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial disease that causes exercise and/or stress induced SCD. CPVT is a disorder of intracardiac calcium aggravated by sympathetic stimulation. Mutations of the ryanodine receptor (Ryr2), calsequestrin 2 CASQ2), and ankyrin-2 (ANK2)) produce calcium overload that has been linked with the disease. (Table 2).

Long QT Syndrome

Long QT Syndrome is characterized by prolongation of the QT interval in a resting ECG (> 470 ms for men and > 480 ms for women as a diagnostic, and 440-470 as a limit). The syndrome was initially related to loss of function in the potassium channels and increased function in the sodium channel. In all cases, the consequence is a prolonged action potential that facilitates depolarization, a substratum of ventricular arrhythmias (table II).

Clinically, up to 30% of LQTS cases have a QT interval at the limits of normal that require additional studies (phenotype, genetic, or both) in order to reach a diagnosis. Given the variety of mechanisms that drive the LQTS, identification of the causal mutations is crucial for orienting therapy. Nevertheless, the results of genetic analysis are negative in a third of patients, accentuating the need to improve phenotypic detection.

Short QT Syndrome

Short QT Syndrome (SQTS) is characterized by the presence of shortening of the QT in ECGs (<340 ms suspect and <320 clear diagnostic) and clinically by the presence of syncopal episodes, paroxysmal atrial fibrillation, and/or lethal arrhythmias. Even though the cases of some affected families have been published, there is little information about the disease. SQTS has been linked to mutations in genes that encode potassium channels. Three genes have been identified up to now; this fact demonstrates that the disease is genetically heterogeneous. Even though clinical studies and physiopathology have suggested quinidine as the appropriate treatment for STQS-1, the high incidence of SCD justifies implant of a defibrillator in the majority of cases (table II).

Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a familial cardiac muscle disease[40] characterized by structural changes (progressive right ventricular replacement of the myocardium by fibroadipose tissue), and clinically characterized by ventricular arrhythmias, with a high risk of cardiac arrest[41,42].

Even though the disease[43] has been studied for 25 years, certain forms of ARVD are not easy to diagnose. Early diagnosis of the disease is difficult because there is no clear pattern of how

Table II Ionic diseases of genetic origin

Channel	Disease	Heretability	Locus	Gen
Sodium	Long QT 3	Autosomal dominant	3p21-23	*SCN5A*
	long QT 10	Autosomal dominant	11q23	*SCN4B*
	Brugada Syndrome (SBr)	Autosomal dominant	3p21	*SCN5A*
		Autosomal dominant	3p24	*GPD1-L*
	Lev-Lenègre Syndrome	Autosomal dominant	19q13.2	?
		Autosomal dominant	3p21	*SCN5A*
	Atrial fibrilation (AF)	Autosomal dominant	3p21	*SCN5A*
Sodium relation	Long QT 9	Autosomal dominant	3p25	*Cav3*
Potassium	Long QT 1	Autosomal dominant	11p15.5	*KCNQ1*
	Long QT 2	Autosomal dominant	7q35	*KCNH2*
	Long QT 5	Autosomal dominant	21p22.1-22-2	*Mink(KCNE1)*
	Long QT 6	Autosomal dominant	21p22.1-22-2	*MiRP1(KCNE2)*
	Long QT 7	Autosomal dominant	17p23.1-24.2	*KCNJ2*
	Long QT 1	Autosomal recessive	11p15	*KCNQ1*
	Long QT 5	Autosomal recessive	21q22	*Mink*
	Short QT 1	Autosomal dominant	7q35	*HERG(KCNH2)*
	Short QT 2	Autosomal dominant	11p17	*KCNQ1*
	Short QT 3	Autosomal dominant	17q23	*KCNJ2*
	Atrial fibrilation	Autosomal dominant	10q22	?
		Autosomal dominant	11p15.5	*KCNQ1*
		Autosomal dominant	11q23	*KCNA5*
		Autosomal dominant	12p13	*KCNE3*
		Autosomal dominant	21q22	*KCNE2*
		Autosomal dominant	17q23	*KCNJ2*
Calcium	SBr and short QT 4	Autosomal dominant	12p13.3	*CACNA1C*
	SBr and short QT 5	Autosomal dominant	10p12.33	*CACNB2b*
	Timothy Syndrome (QTL8)	Autosomal dominant	12p13.3	*CACNA1C*
	Polymorphic ventricular tachycardia (TVP)	Autosomal dominant	1q42	*RYR2*
		Autosomal recessive	1p13	*CASQ2*
Calcium relation	Long QT 4	Autosomal dominant	4q25-27	*ANKB (ANK2)*

the tissue is affected. MRI is a useful tool for diagnosis, but interpretation is difficult in some cases. Also, in some patients malignant ventricular arrhythmia may be the first sign of ARVD. Genetic tests help in clinical diagnosis because we can now diagnose nearly 60% of cases thanks to genetic studies targeting the analysis of desmosomal protein mutations (Table 3).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium characterized by left ventricular asymmetric hypertrophy, with findings of disarray of the myocytes and fibrosis[44,45]. It is the most frequent cardiovascular genetic

Table III Genes involved in arrythmogenic right ventricular dysplasia (ARVD)

Disease	Locus	Gen
ARVD 1	14q23-24	*TGFβ3*
ARVD 2	1q42-q43	*RyR2*
ARVD 3	14q12-q22	*?*
ARVD 4	2q32.1-q32.3	*?*
ARVD 5	3q21.3-3p23	*LAMR-1*
ARVD 6	10p12-p14	*?*
ARVD 7	2q35	*Desmin*
ARVD 7	10q22.3	*ZASP*
ARVD 8	6p24	*Desmoplaquin (DSP)*
ARVD 9	12p11	*Placofilin-2 (PKP2)*
ARVD 10	18q12.1-q12.2	*Desmoglein-2 (DSG2)*
ARVD 11	18q12.2	*Desmocollin-2 (DSC2)*
Naxos	17q21	*Placoglobin (JUP)*

Table IV Genes involved in hypertrophic cardiomyopathy

Locus	Gen
14q12	*MYH6*
14q12	*MYH7*
11p11.2	*MYBPC3*
12q24.3	*MYL2*
3p21	*MYL3*
1q32	*TNNT2*
19q13.4	*TNNI3*
15q22.1	*TPM1*
15q14	*ACTC*
2q24.3	*TTN*
3p	*TNNC1*
11p15.1	*CRP3*
17q12	*TCAP*

alteration, with an incidence of 1 in 500 in the general population, especially effecting young people[46-48]. Clinical manifestations appear initially as diastolic dysfunction and as systolic in more advanced cases, meaning the patient can be asymptomatic or suffer cardiac failure or sudden death. The rate of death is greater in young patients (frequently athletes) than in adults and the first signs of the disease can be specifically sudden death. The disease is considered familial in 90% of cases, generally with an autosomal dominant hereditary pattern, the exception being cases with mitochondrial DNA mutations (mtDNA), which are inherited from the mother. More than 400 mutations[49-50] (table IV) have been identified.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by ventricular dilation that alters systolic function, mainly in the left ventricle. Patients present signs of cardiac failure, palpitations, or sudden death. The prevalence is 1 in 2,500 people. There are multiple factors that that can trigger dilated cardiomyopathy, making it a highly heterogeneous entity. Nevertheless, systematic studies of the families of patients with dilated cardiomyopathy indicate that at least 35% of the cases are hereditary[51]. The arrhythmias shown by patients with familial dilated cardiomyopathy are usually the same as in the acquired forms with atrioventricular and intra-ventricular conduction, ventricular arrhythmias, and atrial fibrillation. These patients normally develop progressive deterioration of the ventricular function and die of cardiac failure or arrhythmias.

In 1994 the first DCM locus with atrioventricular block in chromosome 1 was found[52]. The scenario of this disease is extremely complex given that the usefulness of genetic clinical analysis is limited. Twenty mutations have been found in genes that encode cytoskeleton, cell nucleus, and sarcomere proteins. Some of the most significant mutations (30%) are found in the lamin A/C gene (LMNA)[53] that encodes a protein found in almost all types of cells and whose function is to provide nucleus integrity with mechanical support[54]. Other genes such as MYH7 and TNNT2, previously identified as causes of hypertrophic cardiomyopathy, can also cause dilated cardiomyopathy. In addition, SCN5A, a gene that was thought to only cause electrical disease[55] (Chart 5) was identified in a family with SCD mutation.

Genetic disease sports recommendations

In 1994 the 26th Bethesda conference for formulating guidelines for participation in competitive athletic sports with

Table V Genes involved in dilated cardiomyopathy

Locus	Gen
14q12	*MYH7*
15q14	*ACTC*
1q32	*TNNT2*
15q22.1	*TPM1*
2q24.3	*TTN*
11p15.1	*CRP3*
17q12	*TCAP*
Xp21	*Distrofin*
2q35	*Desmin*
10q22.1-10q23	*Metavinculin*
4q12	*β-sarcoglican*
5q33	*δ-sarcoglican*
Xq28	*Tafacin*
1q21	*Lamin A/C*
6q22.1	*Fosfolamban*

an identified cardiovascular alteration[56] was organized. Experts in cardiovascular sports medicine and sports cardiology drew up recommendations by consensus, providing a base for the medical assessment of patients. The guidelines depend on the nature and seriousness of the cardiovascular anomalies and the classification of the sport in question.

In nearly a third of SCDs, the autopsy reveals no structural or morphologic anomaly. It is possible that in these cases the origin of death could be purely electric and in the cases of familial disease, a channelopathy. Known entities such as polymorphic ventricular tachycardia, idiopathic ventricular fibrillation, short and long QT syndromes, and Brugada Syndrome are entities included under this epigraph of channelopathies.

Sudden death in young athletes always has an important repercussion in the media. Owing to the superhuman efforts that they make, there are some clear criteria regarding participation in competitive sports[56-60].

Athletes with a clear diagnosis of HCM, ARVD or DCM, should not participate in most competitive sports, with the possible exception of less intense sports (for example, bowling, golf, or curling). This is independent of the presence of symptoms and the magnitude of the hypertrophy of the left ventricle (HLV), or the obstruction of the exit tract in the case of HCM.

It is recommended not to practice competitive sports in the case of genetic arrhythmia diseases, especially due to the implications that the adrenergic surge could trigger arrhythmia. Recommendations in the case of Brugada Syndrome are less clear, but due to the association of the disease with fever, it is considered necessary to advice against participating in sports due to the increase in body temperature during sport.

Evaluation of athletes with characteristics of possible cardiac disease

Cardiovascular evaluation in young athletes targets the identification of conditions that could be a risk of sudden death for the athlete. Ideally, all athletes should, at a minimum, be evaluated in order to diagnose possible cardiovascular alterations before any athletic participation. But people who participate regularly in sports should have a basic clinical evaluation (physical examination and clinical history) and a resting electrocardiogram.

After basic clinical examinations of the athletes, it is important to give priority to deeper studies of those athletes that present a greater risk of having hereditary cardiac anomalies. These are of course symptomatic athletes, and those that have a family history of familial disease associated with sudden death.

Among the studies to be carried out, currently a genetic study can be considered. Genetic studies are effective in cases of known hereditary disease, but not so much if the cause of sudden death or the symptoms are still not known. In the latter case, the quantity of genes that must be analyzed is so great that it is not economically feasible. In the next months it will be possible to analyze these cases rapidly, thanks to the technological development of diagnostic chips targeting arrhythmic diseases.. This chip enables analysis of more than 20 genes in a reduced amount of time, improving service and especially cost.

Conclusions

Throughout history, society has found a special place for the few who are faster, stronger, and physically gifted. There are several studies that indicate that genes may play an important role in the fitness of elite athletes, although it is early to try to identify if a single gene or group of genes can

Table VI Differences between 26.ª Bethesda and ESC

	Clinical criteria and permited sports	
	ACC	**ESC**
Carriers without genetic phenotype (HCM, DCM, ARVD)	All sports	Only recreational sports
LQTS	> 0,47 men	> 0,44 men
	> 0,48 women	> 0,46 women
	Low intensity competition sports	Recreational
Non-sustained ventricular tachycardia	Without CV disease, all competitive sports. With CV disease, low intensity competition sports	Without CV disease, all sports. With CV disease, only recreational sports

ACC: American College of Cardiology; HCM: hipertrophic cardiomyopathy; DCM: dilated cardiomyopathy; ARVD: arrythmogenic right ventricular dysplasia; ESC: European Society of Cardiology; LQTS: long QT syndrome.
Adapted from Pelliccia, 2008.

determine the sports potential of an individual. Genetics can also determine the risk of sudden death in an athlete. When SCD happens to an athlete, it is tragic news with significant social impact.

As such, it is clear that in the coming decades a field of research is opening where we must include, and adapt to, genomic technology and bioinformatics with a goal of understanding the influence of genetics on the fitness of individuals and their risk for disease.

References

1. Durstine JL, Thompson PD. Exercise in the treatment of lipid disorders. Cardiol Clin. 2001;19:471-88.
2. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc. 2001;33 Suppl 6:S484-92; discussion S493-84.
3. Kohl HW, 3rd. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sports Exerc. 2001;33 Suppl 6:S472-83; discussion S493-474.
4. Rennie KL, Johnson L, Jebb SA. Behavioural determinants of obesity. Best Pract Res Clin Endocrinol Metab. 2005;19:343-58.
5. Strong WB, Malina RM, Blimkie CJ, et al. Evidence based physical activity for school-age youth. J Pediatr. 2005;146:732-7.
6. Passarge E. Genética. Texto y atlas. Madrid: Panamericana; 2005.
7. Birney E, Stamatoyannopoulos JA, Dutta A, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007;447:799-816.
8. Brugada R. Bases genéticas de las arritmias. Rev Esp Cardiol. 1998;51:274-85.
9. Brugada R, Roberts R. The molecular genetics of arrhythmias and sudden death. Clin Cardiol. 1998;21:553-60.
10. Novo FJ. Genética humana. Conceptos, mecanismos y aplicaciones de la genética en el campo de la biomedicina. Madrid: Pearson Educación; 2007.
11. Campillo JE. El mono obeso. Madrid: Crítica; 2004.
12. Booth F, Chakravarthy M, Gordon S, et al. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J Appl Physiol. 2002;93:3-30.
13. Rodríguez F, Sancha de Prada JA, Valls C. Exercici i Salut. Barcelona: Pòrtic; 1997.
14. Generalitat de Catalunya. Guia de Prescripció de l'Exercici Físic per a la Salut. Barcelona: Direcció General de Salut Pública i Secretaria General de l'Esport; 2007.
15. Weineck J. Entrenamiento total. Barcelona: Paidotribo; 2005.
16. American College of Sports Medicine ACSM's Guidelines for exercise testing and prescription. Maryland: Lippincott Williams & Wilkins; 2006.
17. Bouchard C, Malina R, Pérusse L. Genetics of fitness and physical performance. Champaing: Human Kinetics; 1997.

18. Neiderhiser J. Understanding the roles to genome and envirome: methods in genetic epidemiology. Br J Psychiatry. 2001;178 Suppl 40:12-7.
19. Wyszynski D. La epidemiología genética: disciplina científica en expansión. Rev Panam Salud Publica. 1998;3:26-34.
20. Bray M, Hagberg J, Pérusse L, et al. The human gene map for performance and healt-related fitness phenotypes: The 2006-2007 Update. Med Sci Sports Exerc. 2009;41:34-72.
21. Lippi G, Longo UG, Maffulli N. Genetics and sports. Br Med Bull. 2009.
22. Epstein SE, Maron BJ. Sudden death and the competitive athlete: perspectives on preparticipation screening studies. J Am Coll Cardiol. 1986;7:220-30.
23. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. J Am Coll Cardiol. 1986;7:204-14.
24. Corrado D, Thiene G, Nava A, et al. Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. Am J Med. 1990;89:588-96.
25. Opie LH. Sudden death and sport. Lancet. 1975;7901:263-6.
26. Maron BJ, Shirani J, Poliac LC, et al. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA. 1996;276:199-204.
27. Tsung SH, Huang TY, Chang HH. Sudden death in young athletes. Arch Pathol Lab Med. 1982;106:168-70.
28. McCaffrey FM, Braden DS, Strong WB. Sudden cardiac death in young athletes. A review. Am J Dis Child. 1991;145:177-83.
29. Brugada R, Brugada J, Brugada P. Genética y arritmias. Rev Esp Cardiol. 2002;55:432-7.
30. Farwell D, Gollob MH. Electrical heart disease: Genetic and molecular basis of cardiac arrhythmias in normal structural hearts. Can J Cardiol. 2007;23 Suppl A:16A-22A.
31. Farwell D, Gollob MH. Risk stratification for sudden death in heart failure. Minerva Cardioangiol. 2007;55:379-84.
32. Marian AJ, Roberts R. Molecular genetics of hypertrophic cardiomyopathy. Annu Rev Med. 1995;46:213-22.
33. Olson TM, Michels VV, Thibodeau SN, et al. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. Science. 1998;280(5364):750-2.
34. Roden DM, George AL Jr. The cardiac ion channels: relevance to management of arrhythmias. Annu Rev Med. 1996;47:135-48.
35. Cirino AL, Ho CY. Genetic testing in cardiac disease: from bench to bedside. Nat Clin Pract Cardiovasc Med. 2006;3:462-3.
36. Li D, Czernuszewicz GZ, Gonzalez O, et al. Novel cardiac troponin T mutation as a cause of familial dilated cardiomyopathy. Circulation. 2001;104:2188-93.
37. Li G, Martin AF, Solaro JR. Localization of regions of troponin I important in deactivation of cardiac myofilaments by acidic pH. J Mol Cell Cardiol. 2001;33:1309-20.
38. Brugada R, Roberts R. Brugada syndrome: why are there multiple answers to a simple question? Circulation. 2001;104:3017-9.
39. Firoozi S, Sharma S, McKenna WJ. Risk of competitive sport in young athletes with heart disease. Heart. 2003;89:710-4.
40. Nava A, Thiene G, Canciani B, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. J Am Coll Cardiol. 1988;12:1222-8.
41. Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet J Rare Dis. 2007; 2:45.
42. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988;318:129-33.
43. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65:384-98.
44. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287:1308-20.
45. Hughes SE. The pathology of hypertrophic cardiomyopathy. Histopathology. 2004;44:412-27.
46. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003;107:2227-32.
47. Van Driest SL, Ellsworth EG, Ommen SR, et al. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. Circulation. 2003; 108:445-51.
48. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1-8.
49. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. J Cardiovasc Electrophysiol. 2008;19:104-10.
50. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. Cell. 2001;104:557-67.
51. Towbin JA, Bowles NE. The failing heart. Nature. 2002; 415(6868):227-33.
52. Kass S, MacRae C, Graber HL, et al. A gene defect that causes conduction system disease and dilated cardiomyopathy maps to chromosome 1p1-1q1. Nat Genet. 1994;7:546-51.
53. Sinagra G, Di Lenarda A, Brodsky GL, et al. Current perspective new insights into the molecular basis of familial dilated cardiomyopathy. Ital Heart J. 2001;2:280-6.
54. Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol. 2005;45:969-81.
55. McNair WP, Ku L, Taylor MR, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation. 2004;110:2163-7.
56. Maron BJ, Isner JM, McKenna WJ. 26th Bethesda conference: recommendations for determining eligibility for competition in

athletes with cardiovascular abnormalities. Task Force 3: hypertrophic cardiomyopathy, myocarditis and other myopericardial diseases and mitral valve prolapse. J Am Coll Cardiol. 1994;24:880-885.

57. Fagard R, Aubert A, Lysens R, et al. Noninvasive assessment of seasonal variations in cardiac structure and function in cyclists. Circulation. 1983;67:896-901.
58. Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. N Engl J Med. 1985;313:24-32.
59. Maron BJ. Structural features of the athlete heart as defined by echocardiography. J Am Coll Cardiol. 1986;7:190-203.
60. Spirito P, Pelliccia A, Proschan MA, et al. Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports. Am J Cardiol. 1994;74:802-6.