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Genetics of familial cardiomyopathies and arrhythmias

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Summary

Molecular cardiology has become an important tool in understanding the aetiology, pathogenesis and development of familial cardiomyopathies and arrhythmias. The knowledge of genotype-phenotype correlations in certain pathologies has changed the concepts of therapy. In monogenic diseases, genetic testing offers a new complementary diagnostic approach. A genetic test can be used to confirm a clinically determined diagnosis, predict prognosis in a clinically affected patient, or provide options for therapy in patients and in clinically unaffected relatives of a patient with the disease producing mutation. In pure forms of familial hypertrophic cardiomyopathy mutations in several genes coding for sarcomeric proteins have been identified, indicating wide locus heterogeneity. Various disease genes are implicated in familial dilated cardiomyopathy in the pure form or in combination with other diseases. In the long QT syndrome and Brugada syndrome, mutations in ion channel genes can cause the disease; one of those genes is also implicated in progressive cardiac conduction defect. In other familial diseases like the arrhythmogenic right ventricular cardiomyopathy, anyone of the numerous chromosomal loci can be involved, but only one gene has been identified so far. The same gene is also involved in catecholaminergic polymorphic ventricular tachycardia. From genotype-phenotype studies, correlations between gene-mutations and the clinical course of the disease have become clear. As only a few families with the same mutations have been studied, data have to be considered as preliminary and any conclusion must be regarded as tentative. This emphasizes the need to study genotype-phenotype correlations in a large number of families.

Key words: molecular cardiology; inherited; cardiomyopathies; arrhythmias; gene mutations; genotype-phenotype-correlations

Introduction

During the last decade, molecular cardiology has provided important new insights into the mechanisms responsible for inherited cardiomyopathies and arrhythmias. As a result of the ability to detect the disease-causing genes and their proteins, it has become obvious that multiple cellular components are involved in the different pathologies. The genetically determined cardiomyopathies and arrhythmias are inherited as an autosomal dominant trait, but for some, an autosomal recessive inheritance has also been identified. In monogenic diseases a mutation in a single gene is sufficient to cause the disease phenotype, whereas double or compound heterozygous mutations, homozygous mutations or gene modifiers can influence the phenotype dramatically. By analysing families with the same pathology it was apprehended that most of the mutations are private mutations, indicating that most of the families have a different mutation.

If a gene-test is considered, genetic counselling of the patient is necessary, and informed consent has to be obtained. It is crucial to determine the phenotype of the family in a sporadic case or in the individual if a disease is caused by mutations in a single gene. The strategy of testing depends on the characteristics of the disease gene, like the gene-size and available samples. If several genes are known to be involved, the choice of the targeted gene should be determined by factors like the established genotype-phenotype-correlations. Some genes can be excluded by linkage analysis, which can be performed in large families. Theoretically all genes involved in a pathology can be screened, but in a routine diagnostic setting it is time-consuming and technically impossible. At

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present, mutations in disease genes can be detected after gene amplification by polymerase chain reaction (PCR), followed by a mutation screening technique (single strand conformation polymorphism [SSCP], denaturating high performance liquid chromatography [DHPLC] or other) and finally by sequencing. These techniques are highly specific if different conditions are analysed and if the PCR primers largely surround the exons and important intronic sites. The sensitivity depends on several factors, particularly, one cannot exclude the implication of another not yet identified gene and/or the fact that the PCR primers may hide a point mutation.

In some familial cardiomyopathies and arrhythmias chromosomal loci and genes are known, while in others, loci have been discovered but the disease genes have not yet been identified. This review will focus on inherited cardiomyopathies and arrhythmias for which at least one responsible disease gene is known and genotype-phenotype-correlations studies are, at least in part, available. It is important to know that the range of inherited monogenic and multigenic cardiovascular diseases is even wider.

Familial cardiomyopathies

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by a left and/or right ventricular hypertrophy that is usually asymmetric and involves the interventricular septum. Morphological changes include hypertrophy and disarray of myocytes and fibrosis. Arrhythmias and sudden cardiac death (SCD) are common [1], and HCM often results in heart failure. The familial type of primary hypertrophic cardiomyopathy (FHC) includes a group of HCM lacking a defined aetiology and is characterized by a high rate of morbidity and mortality. FHC is an autosomal dominant disease with incomplete penetrance. Its prevalence is 1/500 in young adults [2]. Eleven genes have been identified in the aetiology of the pure form of FHC (table 1). They all encode proteins of the cardiac sarcomere. Recently, mutations in the *PRKAG2* gene, coding for the γ2-subunit of the AMP-activated protein-kinase, were found to be responsible for familial Wolff-Parkinson-White-Syndrome (WPW) with cardiac hypertrophy [3] or for WPW with conduction defect and absence of cardiac hypertrophy [4]. Around 150 mutations have been identified [5], and most of them are found in genes *MYH7*, *MYBPC3* and *TNNT2*. By systematic screening of nine of the eleven genes, recent data have shown that 88% of genotyped families present a mutation in the *MYBPC3* and *MYH7* genes ([6], AHA 2001).

Mutations leading to FHC are missense or frameshift mutations. The molecular mechanisms have not been completely elucidated. Missense mutations result in stable mutant proteins that act by a dominant negative effect on the structure or function of the sarcomere (poison peptide hypothesis). In contrast, frameshift mutations result in unstable truncated proteins, and therefore act as "null-allele" leading to haploinsufficiency of the "wilde-type" protein (haploinsufficiency hypothesis) [7].

The FHC phenotype is first influenced by factors varying the penetrance, like age and gender [8]. Second, the phenotype depends on the

Table 1

Familial hypertrophic cardiomyopathy genes, proteins and mutations.

Gene	locus	protein	mutations	frequency
MYH7	14q11.2–q12	β-myosin heavy chain (β-MyHC)	70	>35–50%
MYH6	14q11.2–q12	α-myosin heavy chain (α-MyHC)	1	?
MYL3	3p21.2–p21.2	ventricular essential myosin light chain (MLC-1s/v)	2	<1%
MYL2	12q23–q24.3	ventricular regulatory myosin light chain (MLC-2s/v)	8	<1%
ACTC	15q14	α-cardiac actin (α-cAct)	5	?
TNNT2	1q32	cardiac troponin T (cTnT)	14	15–20%
TNNI3	19p13.4	cardiac troponin I (cTnI)	8	<1%
TNNC1	3p21.3	cardiac troponin C (cTnC)	1	?
TPM1	15q22.1	α-tropomyosin (α-TM)	5	<5%
MYBPC3	11p11.2	Cardiac myosin-binding protein C (cMyBP-C)	30	>15–20%
TTN	2q24.3	Titin	1	?
PRKAG2	7q36	AMP-activated protein kinase (AMPK)	2	?

Eleven FHC genes code for sarcomeric proteins: genes *MYH7*, *MYH6*, *MYL2* and *MYL3* code for the thick filament proteins, genes *TNNC1*, *TNNI3*, *TNNT2*, *TPM1* and *ACTC* for the thin filament proteins, and gene *MYBPC3* codes for the myosin-binding protein C. The titin-protein, coded by *TTN*, is the third filament of the sarcomere. Gene *PRKAG2* codes for the γ2-subunit of the AMP-activated protein kinase.
The last column indicates the frequency of the mutations found in the different genes.

responsible mutation. In the *MYH7* gene several mutations are associated with a high risk of SCD: Arg403Gln, Arg719Trp, Arg453Cys and Arg723Gly. In contrast, hearts with the mutations Gly256Glu, Val606Met and Leu908Val have a good prognosis as regards arrhythmic events [9, 10]. Mutations in the *MYBPC3* gene are associated with mild hypertrophy in young patients, late onset of symptoms and good prognosis before the age of forty [11, 12]. The penetrance and clinical presentation of mutations in *TNNT2* vary widely: some mutations lead to subclinical hypertrophy associated with high SCD-risk [13, 14], and others are completely penetrant but without a high risk for arrhythmic events [15]. Third, the phenotype depends on the complexity of the genotype. About 8% of the families have a complex genotype with homozygous, double or compound heterozygous mutations [6]. A homozygous Arg869Gly mutation is associated with early onset of severe left ventricular hypertrophy, systolic dysfunction and atrial fibrillation [16]. Double heterozygous mutations in the *MYH7* and *MYBPC3* genes lead to significant hypertrophy, but are not strictly associated with a high SCD-risk [17]. Finally, about 25% of genotypically affected patients do not develop a FHC phenotype. This could be explained by environmental and/or genetic factors. Modifier polymorphisms have been identified in the genes coding for the angiotensin converting enzyme [18, 19], endothelin [20] and the angiotensin II type 1 receptor [21].

Mutations associated with a high SCD risk are important when considering therapeutical options, like the implantation of a cardioverter/defibrillator. Further studies in large and numerous families and animal models will help to identify the underlying mechanisms of the pathogenesis of FHC.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilation with impaired contraction, often with involvement of the right ventricle. It represents a leading cause for cardiac transplantation due to heart failure. The prevalence is nearly 40/100,000 [22]. The 5-year mortality rate varies between 15 and 50%, SCD accounts for 30% of deaths in DCM. At least 25% of the DCM are familial [23]. Familial DCM is clinically and genetically heterogeneous. Autosomal dominant DCM, pure or in association with other pathologies, is the most common segregated form, whereas autosomal recessive and X-linked inheritances are rare. Table 2 gives an overview of the DCM inheritance patterns, genes and their

Table 2

Familial dilated cardiomoypathy phenotypes, genes and proteins.

Inheritance	phenotype	locus	gene	protein
Autosomal dominant	pure DCM	9q12–q13	?	
	pure DCM	1q32	?	
	pure DCM	2q24.3–q31	*TTN*	titin
	pure DCM	6q12–q16	?	
	pure DCM	2q35	*DES*	desmin
	pure DCM	5q33	*SGCD*	δ-sarcoglycan
	pure DCM	15q11– qter	*ACTC*	actin
	pure DCM, early onset	14q11.2	*MYH7*	β-myosin heavy chain
	pure DCM, early onset	1q32	*TNNT2*	cardiac troponin T
Autosomal dominant +	DCM + CD	1q21	*LMNA*	lamin A/C
	DCM + CD	2q14–q22	?	
	DCM + CD + SND	3p22–p25	?	
	DCM + MVP	10q21–q23	?	
	DCM + hearing loss	6q23–q24	*EYA4*	eyes absent 4
	DCM + CD + LGMD	6q22–q23	?	
	DCM + CD + MD (AD-EDMD)	1q21	*LMNA*	lamin A/C
	DCM + CD + LGMD (LGMD1B)	1q21	*LMNA*	lamin A/C
Autosomal recessive	LGMD +/– cardiomyopathy	17q21	*SGCA*	α-sarcoglycan
	LGMD + severe cardiomyopathy	4q12	*SGCB*	β-sarcoglycan
	LGMD + cardiomyopathy (Brazil)	5q33	*SGCD*	δ-sarcoglycan
X-linked	Pure DCM	Xp21.3	*DYS*	dystrophin
	DCM lethal in infancy	Xq28	*TAZ*	tafazzin
	DCM + myopathy (Barth-Syndrome)	Xq28	*TAZ*	tafazzin
	DCM + CD + MD (XL-EDMD)	Xq28	*EMD*	emerin

Abbreviations: DCM, dilated cardiomyopathy; CD, conduction defect; SND, sinus node dysfunction; MVP, mitral valve prolapse; LGMD, limb girdle muscular dystrophy; MD, muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; AD, autosomal dominant; XL, X-linked.

proteins, and the resulting phenotypes (adapted from [24]). Thirteen genes have been identified, coding for proteins of the cytoskeleton and interacting elements, sarcolemma and sarcomere. Pure DCM is inherited as an autosomal dominant trait and six disease genes have been identified: *TTN*, *DES*, *SGCD*, *ACTC*, *MYH7* and *TNNT2*. Autosomal dominant DCM can be associated with other cardiac and/or muscle pathologies or hearing loss; several loci, but only two genes, *LMNA* and *EYA4*, have been identified. Autosomal recessive DCM, a rare disease due to mutations in the genes coding for sarcoglycans, is always associated with limb girdle muscular dystrophy. In the X-linked DCM, a broad range of clinical pictures is possible due to mutations in genes *DYS*, *TAZ* and *EMD*.

Due to the wide clinical and genetic heterogeneity and the lack of genotype-phenotype correlation studies in representative populations, the impact of a genetic test in DCM is still limited. Studies of the molecular defects of DCM and the disease genes in large populations will provide important insights into the mechanisms of heart failure and may lead to the modification of treatment options.

Familial arrhythmias

Congenital long QT syndrome

Congenital long QT syndrome LQTS) is characterized by abnormal ventricular repolarization with QTc prolongation >440 ms, and high risk of Torsades de pointes and malignant ventricular tachyarrhythmias. LQTS is an autosomal-dominant or -recessive disease in which the sites of dysfunction are the ion channels, which consist of proteins allowing much greater ion flow during the cardiac action potential. The disease prevalence is about 1/5,000. The autosomal-dominant Romano-Ward syndrome is the most common form [25, 26]. A second type, the Jervell-Lange-Nielsen syndrome, which is associated with congenital deafness, is transmitted as an autosomal-recessive trait and has a poor prognosis [27]. Six chromosomal loci and five disease genes have been identified (table 3). Almost 70% of the mutations are missense mutations, and 87% of the mutations are found in genes *KCNQ1* and *KCNH2* [28]. This frequency may change in the future because those two genes were first identified and therefore extensively screened. *KCNQ1 (KvLQT1)* codes for the α-subunit of the slowly activating delayed rectifier potassium ion channel $I_{Ks\alpha}$ and *KCNE1* for the β-subunit; *KCNH2 (HERG)* codes for the α-subunit of the rapidly activating delayed rectifier potassium ion channel $I_{Kr\alpha}$ and *KCNE2* for the β-subunit. *SCN5A* is the gene coding for a cardiac sodium ion channel I_{Na}. The gene of *LQT4* has not been identified yet. Functional consequences of mutations in LQTS genes are a loss of the channel function in the genes encoding the I_{Ks} and I_{Kr} cardiac potassium channels [29], and additional sodium channel activity or gain of function in *SCN5A* mutations [30]. Due to studies performed on the mutations of the three major genes, the QT-interval, and T-wave pattern of the surface ECG, gene-ECG correlations have been established: generally, mutations in *KCNQ1* lead to a broad T-wave, and mutations in *KCNH2* to a low T-wave amplitude with double peak in some cases. Mutations in *SCN5A* are characterized by a very delayed onset of the T-wave [31].

The identification of gene mutations in the LQTS can modify the specific treatment. Beta-blockers are efficient in *LQT1* and *LQT2*, whereas mexiletine, a sodium channel blocker, is a treatment option in *LQT3* [32, 33]. Pacing is important in *LQT3* to avoid tachyarrhythmic events induced by bradycardia. In contrast *LQT2* patients do not benefit from pacing [34]. Triggers associated with the induction of Torsades de pointes and ventricular arrhythmias have been described: physical exercise especially swimming in *LQT1*, auditory stimuli during sleep or rest in *LQT2*, and sleep or rest in *LQT3* [35]. In the presence of certain disease genes, modifications in life-style to avoid triggers are possible. About 10% of mutation carriers present with a normal ECG [36]. In these

Table 3

LQTS genes, proteins and frequency of mutations.

LQT	gene	locus	protein	frequency of mutations
LQT1	*KCNQ1 (KvLQT1)*	11p15.5	Cardiac potassium ion channel $I_{Ks\alpha}$	42%
LQT2	*KCNH2 (HERG)*	7q35–q36	Cardiac potassium ion channel $I_{Kr\alpha}$	45%
LQT3	*SCN5A*	3p21	Cardiac sodium ion channel I_{Na}	8%
LQT4	?	4q25–q27		
LQT5	*KCNE1*	21q22.1–22.2	Cardiac potassium ion channel $I_{Ks\beta}$ subunit *KCNQ1*	3%
LQT6	*KCNE2*	21q22.1	Cardiac potassium ion channel $I_{Kr\beta}$ subunit *KCNH2*	2%

patients the value of a beta-blocker treatment is unclear.

Most of the patients with drug induced LQTS do not have ion channel defects, but they seem to carry a predisposition for malignant arrhythmias [37]. The value of genetic diagnosis is unclear; those patients should avoid any LQTS-provoking drugs.

Gene *SCN5A*: Brugada syndrome and progressive cardiac conduction defect

Brugada syndrome belongs, as the LQTS, to the group of idiopathic ventricular fibrillation, characterized by a primary electrical disease without underlying structural heart pathology. The Brugada syndrome is defined by a right bundle branch block, a right precordial ST-segment elevation and SCD, mainly during sleep [38]. No data are available on the prevalence of the Brugada syndrome, but a study showed that there is a high prevalence (0.1%) of the typical ECG pattern in an apparently healthy population [39]. *SCN5A* is the only gene so far known to be involved in the disease [40]. *SCN5A* mutations are found in about 20% of the patients with clinical Brugada syndrome [41]. Recently, a second locus was found on chromosome 3, indicating locus heterogeneity in this disease [42].

Mutations in *SCN5A* may also cause the *LQT3* and the progressive cardiac conduction defect found in the Lenegre-Lev-disease [43]. Progressive cardiac conduction defect is characterized by continuous alteration of cardiac conduction through the His-Purkinje system, associated with right or left bundle branch block and QRS-complex widening, finally leading to complete atrioventricular block.

The mechanisms by which mutations in *SCN5A* lead to different diseases are unclear, yet. Basically, *SCN5A* mutations implicated in *LQT3* cause a gain of function of the channel, whereas the ones implicated in the Brugada syndrome cause a loss of channel function [44].

Gene *RyR2*: catecholaminergic polymorphic ventricular tachycardia and arrhythmogenic right ventricular cardiomyopathy

Catecholaminergic polymorphic ventricular tachycardia (C-PMVT) is a disease of the group of idiopathic ventricular fibrillation. Affected patients experience polymorphic ventricular extrasystoles and tachycardia during exercise or stress, which can degenerate in malignant ventricular arrhythmias and cardiac death. Gene *RyR2*, which codes for the human cardiac ryanodin 2-receptor protein, is implicated in C-PMVT [45]. This protein induces the release of Ca^{2+} from the sarcoplasmic reticulum into the cytosol. A second gene, *CASQ2*, has been identified in the context of C-PMVT [46]. The encoded calsequestrin protein is an internal constituent of the sarcoplasmic reticulum.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by a fibro-fatty replacement of the right ventricular myocardium with possible involvement of the left ventricle. Monomorphic ventricular tachyarrhythmias with left bundle branch block pattern are typical. The prevalence of ARVC is probably higher than 6/10,000; it is the major cause of SCD in young athletes. Mutations in the *RyR2* gene have been identified in ARVC2. In addition, five chromosomal loci are known [47, 48]. Naxos disease is the autosomal recessive form associated with skin and hair abnormalities. Mutations in the gene coding for plakoglobin, a cell adhesion protein, have been found in this disease [49, 50].

The impact of the gene-test in C-PMVT and ARVC is unclear. Only a few families have been studied so far. Larger population studies are needed to determine genotype-phenotype-correlations, in order to help identify individuals at risk.

Perspectives of genetic studies

For optimal patient care and definition of disease groups, genotype-phenotype correlation studies in numerous large families are needed. The identification of mutations in the major gene is important, but other relevant factors like gene modifiers are also important because they influence the phenotype and clinical course. For certain inherited diseases like FHC, mutations with a high SCD risk have been identified. In the LQTS, identification of mutations profoundly modifies the medical treatment and lifestyle. For other diseases, genotype-phenotype-correlations are not yet available.

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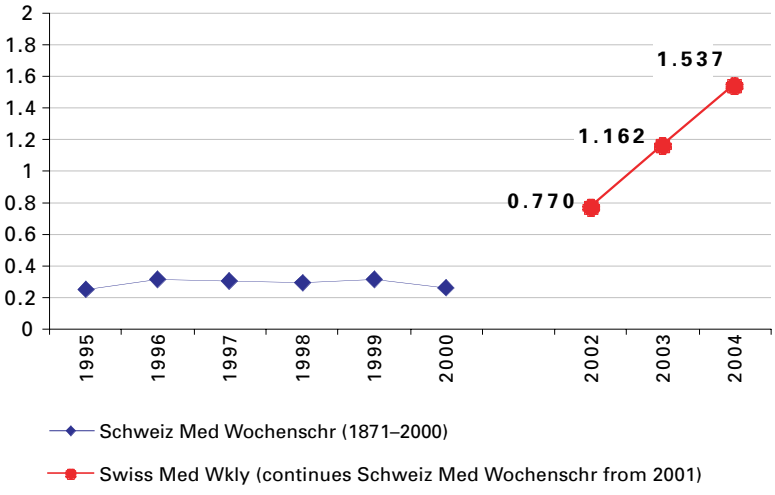

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