REVIEW

Hypertrophic Cardiomyopathy: Recent Evidence on Genotype-Phenotype Correlation

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ABSTRACT

Hypertrophic cardiomyopathy (HCM), in contrast to common prejudications, has been recognized as the most common genetically determined cardiac disease. It is inherited with an autosomal dominant pattern and many different mutations in numerous genes responsible for the production of sarcomere proteins and other regulatory molecules contributing to the systolic function of cardiac myocyte have been identified. The natural course of the disease is benign in the majority of cases and most patients achieve near-normal life expectancy. Unfavorable prognosis is established mainly on the basis of clinical, morphological and family history data. The genotype contributes undoubtedly to the clinical picture. However, the existing data do not allow for a consistent genotype-phenotype correlation and hence genetic information is not incorporated in modern risk assessment clinical tools. In this brief review we summarize the recent data on the genetic characterization of HCM (***Rhythmos 2015;11(1):8-11***).

Key Words: hypertrophic cardiomyopathy; genetics; genotype; phenotype; sudden cardiac death

Abbreviations: HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death

INTRODUCTION

Once considered a rare and exotic disease, today hypertrophic cardiomyopathy (HCM) has been recognized as the most common genetic cardiac disease, with a prevalence in the general population exceeding 1/500.[1] In the past decade significant advances have been made regarding its genetic screening, imaging modalities and management, which have favorably modified the prognosis of the disease, and near-normal life expectancy can be achieved in many patients with HCM.[2] Not surprisingly however, certain subtypes of the disease carry a malignant potential and a predisposition for severe complications and even premature sudden cardiac death (SCD). Genetic testing has hopefully been considered as a prognostic factor, in terms of its correlation with certain disease subtypes featuring particular structural or electrophysiological characteristics related to a less benign prognosis. Unfortunately a strong relation has not yet been established and there are still gaps in our understanding of the molecular pathophysiology. Recent evidence [3-33] on this matter is briefly reviewed here.

EPIDEMIOLOGY

Hypertrophic cardiomyopathy is a disease reported worldwide with similar genotypic, phenotypic, and imaging characteristics among different races and nations. It affects both genders equally, and in contrast to the common perception it is a rather frequent condition, affecting 1/500 individuals in the general population. This implies that usually the disease is clinically silent and long-term survival is a common outcome. The clinically evident cases may represent more aggressive subforms causing limiting symptoms or events which lead to targeted investigation and eventually diagnosis. The incidence of SCD in children and adolescents with HCM reaches 1-2% and is slightly lower (0.5-1%) in older individuals. [4,5]

BASIC PATHOPHYSIOLOGY

Normal myocardial contraction and relaxation plays a cardinal role in the ability of the heart to produce the appropriate output to meet the needs of the periphery. In HCM, variable mutations of the sarcomere, Z-discs or calcium – handling proteins may result in distorted use of adenosine triphosphate (ATP) and energy deficiency, impaired excitation-contraction coupling and increased collagen synthesis and deposition, leading eventually to myocardial hypertrophy, disarray and fibrosis. These morphological changes cause impaired cardiac relaxation initially, full-blown heart failure progressively and predispose to atrial and ventricular arrhythmias. [6-8]

GENETICS

Hypertrophic cardiomyopathy is a monogenic disease inherited with an autosomal dominant pattern. It presents variable expressivity and penetrance which increases with advancing age. [9-11] However, nearly half of the cases are sporadic, with de novo mutations arising in the affected persons that do not exist in their parents. Today over 1500 mutations have been identified as causative and numerous genes are implicated, encoding for proteins of the sarcomere (thick and thin filaments), Z-discs and Ca^{+2} – handling proteins. Most of them are unique to specific families and approximately 50% of the genetically characterized patients are found to share mutations in the thick or thin filament protein genes.[12,13] Specifically, 40% of HCM cases are caused by mostly missense mutations in MYH7 and MYBPC3, which are the two most common implicated genes and encode for proteins constituting the thick filaments. Mutant thin filament proteins are associated with 5-15% of HCM and mutations are detected in actin, troponins I, T or C and tropomyosin. Protein elements of the Z-discs, which interfere between sarcomeres and consist of the platform actin filaments that are anchored to, have also been recognized as potential sites of mutations, responsible for rare cases of HCM

phenotype. Telethonin, vinculin, ankyrin and other molecules are relevant. A small percentage of patients may also carry mutations in genes encoding Ca^{+2} –regulating proteins, namely phospholamban, calsequestrin 2, calreticulin 3 and junctophilin 2. The dysfunctional proteins lead to altered calcium regulation and systolic or diastolic failure. The genes considered causative are summarized in Table 1. Clinically, the disease has by definition a standard morphological characteristic, the hypertrophy of the left ventricle. However, often the same mutation produces different clinical syndromes. [14] This suggests that modifying factors also contribute to the final phenotype. These factors may be environmental influences or the result of the expression of other, still unknown genes. Due to the phenotypic variability, a consistent correlation between genotype and clinical presentation cannot be established. However, some associations are more evident than others. Mutations in MYBPC3 present in older age, carry less risk for SCD and have a less malignant course. MYH7 mutations have unfavorable prognosis and are characterized by significant hypertrophy. [15] Mutations in TNNT2 are rarely accompanied by hypertrophy before adulthood, while this is the case in older individuals. [16] Multiple mutations lead to early presentation of the disease, severe cardiac hypertrophy and increased risk for SCD compared to patients with a single mutation. [17] This observation suggests a somewhat additive effect of multiple pathologic genes when present simultaneously. Furthermore, gene polymorphisms in the renin-angiotensin-aldosterone system components, androgen receptors and calmodulin III may add to the final HCM phenotype. [18-20]

APICAL HYPERTROPHIC CARDIOMYOPATHY

An atypical presentation of HCM worldwide, the apical type, is relatively common in Japan (15% of cases). [21] Hypertrophy is localized to the apical region of the left ventricle and subsequently it produces no obstructive phenomena. It usually exerts characteristic ECG abnormalities, namely large negative T waves in many leads, mostly anterolateral ones, and, as expected, enormous QRS complexes in precordial leads, mainly V4. Hypertrophy in the apex cannot be electrically counteracted by forces generated in opposite myocardial territories because of the presence of the fibrous cardiac skeleton in the basal parts. On the contrary, vectorial forces generated by hypertrophied lateral, septal, anterior, inferior or midventricular territories can be at least partly counteracted by those of the opposite wall and thus ECG waves are not as impressive in amplitude. [22] In terms of genetic identity, apical HCM is frequently sporadic, although a familial pattern has been reported, with an autosomal dominant inheritance. In most kindreds, the identified mutations are not invariably correlated with apical hypertrophy but with conventional patterns of the disease as well. Mutations reported include troponin I Lys183 deletion, Arg21Cys substitution, troponin T missense mutations Phe110Ile13 and Arg102Leu, β-myosin heavy chain Arg243His, Glu497Asp and Asp906Gly. However, other mutations, such as cardiac actin Glu101Lys and light chain Met149Val missense mutations, have been more consistent in their association with apical HCM. [23]

Table 1. Known Genes Causing Hypertrophic Cardiomyopathy (HCM)

Gene	Protein	Frequency
Thick filament proteins		
MYH7	β-myosin heavy chain	15-25%
MYBPC3	myosin binding protein C	15-25%
MYL2	regulatory myosin light chain	rare
MYL3	essential myosin light chain	rare
MYH6	α-myosin heavy chain	rare
Thin filament proteins		
TNNT2	troponin T	5%
TNNI3	troponin I	5%
TNNC1	troponin C	rare
TPM1	α-tropomyosin	Rare
ACTC1	α-cardiac actin 1	rare
Z-disc proteins		
CSRP3	muscle LIM protein	rare
TCAP	telethonin	rare
VCL	vinculin	rare
LDB3	LIM domain binding 3	rare
ACTN2	α-actinin 2	rare
MYOZ2	myozenin 2	rare
ANKRD1	cardiac ankyrin repeat protein	rare
NEXN	nexilin	rare
Ca+2- handling proteins		
PLN	Phospholamban	rare
CASQ2	calsequestrin 2	rare
CALR3	calreticulin 3	rare
JPH2	junctophilin 2	rare
Other		
TTN	Titin	rare
CAV3	caveolin 3	rare

MIDVENTRICULAR HYPERTROPHIC CARDIOMYOPATHY

Midventricular obstruction in HCM is a rare variant especially in non-Asian populations and occurs in only 1% of HCM patients. [24] In some cases, apical aneurysm may also be evident probably due to the high apical pressure arising from the midventricular obstruction, and this feature indicates more severe disease. Apical aneurysms

develop in 2% of HCM patients and among them, 2/3 have midventricular obstruction and the rest have apical hypertrophy pattern. [25,26] With regard to the genetic testing, midventricular hypertrophy has been associated with mutations of the essential or regulatory light chains of myosin. Regulatory myosin Ala13Thr and Glu22Lys and myosin essential light chain Met149Val are long recognized as causative, although they can also produce other phenotypic variants. These types of mutation are assumed to cause stretch activation response disrupt leading to midventricular obstruction. [27,28]

SUDDEN CARDIAC DEATH

Although not particularly common among HCM patients (1-2% annual incidence), SCD is a dramatic complication and every effort should be made to avoid it. Recently, risk estimation models have been updated and offer an important guidance for clinicians. Age, family history of SCD, non-sustained ventricular tachycardia, syncope, maximum left ventricular wall thickness >30 mm, left atrial diameter, abnormal exercise blood pressure response and left ventricular outflow tract obstruction are the major factors clinically appreciated to contribute to SCD probability. The new risk model endorsed in the recent European guidelines does not take into account blood pressure response during stress testing. [29] Genetic testing has not been incorporated in risk prediction models. In general, patients with sarcomere protein mutations present at younger age and report a higher prevalence of family history of HCM and SCD than those without a mutation. Several studies have reported poor prognosis associated with certain mutations. Unfortunately, their conclusive strength is limited by the small numbers of affected individuals and the scarcity of individual mutations. [30-33] Thus, no robust suggestions can be made regarding the prognostic power of certain genotypes.

CONCLUSION

Without ignoring the risk that such a diagnosis poses upon an individual's life, HCM is now regarded as a more frequent disease and with an overall more favorable natural history than a clinician would reckon. Significant advances have been made in the last decade concerning the genetic analysis of affected individuals and their families. Over 1500 mutations have been identified in >20 genes encoding for structural or functional proteins of the sarcomere. However, most of these mutations usually do not produce a specific phenotype, and many are found uniquely in certain families. Hence, although ambitious and deterministic from a philosophical point of view, the effort to fully characterize a patient by genotype has proven elusive, which is why contemporary risk assessment algorithms do not include genetic information. More research is needed in this field in order to elucidate the complex regulatory mechanisms which govern the translation of a certain genetic identity into the final clinical phenotype.

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