Canadian Journal of Cardiology 31 (2015) 1377–1385

Systematic Review/Meta-analysis

A Systematic Review of Phenotypic Features Associated With Cardiac Troponin I Mutations in Hereditary Cardiomyopathies

Jens Mogensen, MD, PhD, Thomas Hey, MD, and Sascha Lambrecht, MS

Department of Cardiology, Odense University Hospital, Odense, Denmark

ABSTRACT

Background: Genetic investigations have established that mutations in proteins of the contractile unit of the myocardium, known as the sarcomere, may be associated with hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and dilated cardiomyopathy (DCM). It has become clinical practice to offer genetic testing in affected individuals to identify causative mutations, which provides the basis for presymptomatic testing of relatives who are at risk of disease development. This ensures adequate clinical follow-up of mutation carriers, whereas noncarriers can be discharged. However, before genetic testing can be used for individual risk assessment and prediction of prognosis, it is important to investigate if there is a relation between the clinical disease expression (phenotype) of the condition and mutations in specific disease genes (genotype).

Methods: We reviewed the literature in relation to phenotypic features reported to be associated with mutations in cardiac troponin I (cTnI; *TNNI3*), which is a recognized sarcomeric disease gene in all 3 cardiomyopathies.

RÉSUMÉ

Introduction : Les enquêtes génétiques ont établi que des mutations des protéines de l'élément contractile du myocarde, connu sous le nom de sarcomère, peuvent être associés à une cardiomyopathie hypertrophique (CMH), une cardiomyopathie restrictive (CMR), et une cardiomyopathie dilatée (CMD). Il est devenu courant en pratique clinique de proposer des tests génétiques chez les individus atteints afin d'identifier des mutations causales, qui fournissent la base pour un dépistage présymptomatique de membres de la famille qui sont à risque de développer la maladie. Cela garantit un suivi clinique adéquat des porteurs de la mutation, alors que les non-porteurs peuvent en être dispensés. Cependant, avant que le test génétique puisse être utilisé pour l'évaluation du risque individuel et la prédiction du pronostic, il est important d'étudier s'il existe une relation entre l'expression clinique de l'état de la maladie (phénotype) et les mutations de gènes spécifique à la maladie (génotype).

Méthodes : Nous avons examiné la littérature se rapportant aux caractéristiques phénotypiques connues pour être associées à des

Cardiomyopathies are a group of cardiac disorders characterized by structural and functional abnormalities of the myocardium in the absence of coronary artery disease, hypertension, or valvular heart disease sufficient to cause the observed abnormality. These conditions are often hereditary and most commonly inherited by dominant transmission, which implies that affected individuals have a 50% risk of passing the disease gene on to each of their offspring.[1]

Hypertrophic cardiomyopathy (HCM) is the most studied of the conditions and is considered to be one of the commonest hereditary cardiac conditions, with a prevalence of 1 in 500 persons.[1,2] The diagnosis relies on demonstration of unexplained thickening of the left ventricle. The major clinical problems are reduced exercise capacity, risk of arrhythmia, and thromboembolic events. Sudden cardiac death may occur as the initial disease manifestation and is believed to be the most frequent cause of cardiovascular-related death in young individuals.[3] Recently, a novel risk prediction model was published to help physicians identify high-risk patients with HCM who are suitable for prophylactic implantable cardioverter defibrillator (ICD) treatment.[4]

Restrictive cardiomyopathy (RCM) is a very rare disorder characterized by increased stiffness of the ventricles, leading to compromised diastolic filling with preserved systolic function.[5] Adult patients often present with symptoms of heart failure, whereas RCM in children may present with failure to thrive, fatigue, and syncope.[6] A large number of patients die shortly after diagnosis unless they receive a heart transplant.

Dilated cardiomyopathy (DCM) is a condition characterized by unexplained left ventricular dilatation, impaired systolic function, and nonspecific histologic abnormalities dominated by myocardial fibrosis. The condition has an estimated prevalence of 1 in 2500 persons and is the commonest cause of heart failure and cardiac transplantation in the young.[7,8] Patients may experience severe disease

Received for publication April 13, 2015. Accepted June 8, 2015.

Corresponding author: Dr Jens Mogensen, Department of Cardiology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark. Tel.: +45-65-41-49-61.

E-mail: jens.mogensen@dadlnet.dk

See page 1383 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.06.015

Results: The results of this review did not identify specific genotype-phenotype relations in HCM or DCM, and cTnI appeared to be the most frequent disease gene in RCM.
Conclusions: To further explore if there is a genotype-phenotype relation, long-term follow-up studies are needed. It is essential to investigate the natural history of the condition among affected individuals and to provide clinical follow-up on disease development among healthy mutation carriers. Such information is required to provide evidence-based counselling for affected families and to elucidate if knowledge about specific genotypes can be used in future risk prediction models.

Résultats : Les résultats de cet examen ne permettent pas d'identifier les relations spécifiques génotype-phénotype pour les CMH ou les CMD, alors que la cTnI semblait correspondre au gène de la maladie le plus fréquent pour les CMR.
Conclusions : Pour explorer davantage l'existence d'une relation génotype-phénotype, des études de suivi à long terme sont nécessaires. Il est essentiel d'étudier l'histoire naturelle de la maladie chez les personnes touchées et de fournir un suivi clinique du développement de la maladie chez les porteurs sains de la mutation. Ces informations sont nécessaires pour fournir des conseils fondés sur des constatations pour les familles touchées et pour démontrer si les connaissances sur des génotypes spécifiques peuvent être utilisées dans les futurs modèles de prédiction du risque.

complications, including thromboembolic events and sudden death from ventricular arrhythmia. Recent developments in medical treatment and biventricular pacing modalities have diminished symptoms and improved prognosis considerably.[8] The etiology is very heterogeneous, including viral infections, autoimmune diseases, and toxic substances.[8] A familial appearance of the condition has been recognized for > 25 years, and several studies of close relatives of patients with DCM have found a dominant mode of inheritance in as many as 30%-50% of cases.[9]

Genetics

Within the past few decades, our knowledge about cardiomyopathies has increased considerably because of numerous clinical and genetic investigations of individual patients (probands) or affected families.[10] Thereby, it has been possible to establish that the hereditary forms of HCM, RCM, and DCM are frequently caused by mutations in proteins of the contractile unit of the myocardium, also known as the sarcomere, which is composed of thick and thin filament proteins.[11] The gene encoding one of the thin filament proteins, cardiac troponin I, (cTnI; *TNNI3*), was first identified as a disease gene in HCM by Kimura et al.[12] in 1997. It is well known that the major sensor of the intracellular Ca^{2+} level is the troponin complex, which is composed of 3 subunits, cTnI, troponin C, and troponin T. Their primary function is to control the interaction between the thick and thin filaments during muscle contraction and relaxation. cTnI has an inhibitory effect, which is reversed by troponin C after binding of Ca^{2+}, which subsequently introduces conformational changes in the entire troponin complex, leading to muscle contraction. Mutations in the troponin complex introduce alterations in Ca^{2+} affinity and protein-protein interactions, which may ultimately lead to the development of cardiomyopathy. The mechanisms by which cTnI mutations affect the contractility of the sarcomere have recently been reviewed in depth by Tardiff.[13]

Besides increasing our knowledge about basic pathophysiological mechanisms in the development of cardiomyopathies, genetic investigations are useful in a clinical setting to identify causative mutations and subsequently provide presymptomatic testing of relatives who are at risk for the development of the same disease at a later stage. This process of cascade screening of family members ensures adequate clinical surveillance of mutation carriers and allows noncarriers to be discharged from clinical follow-up.[14] However, before genetic testing can be used for individual risk assessment and prediction of prognosis, it is necessary to investigate if there is a relation between the clinical disease expression (phenotype) of the condition and mutations in specific disease genes (genotype).

This article reviews the phenotypic features associated with all published mutations in the gene for cTnI to elucidate if there is a specific genotype-phenotype relation, which may be used in the context of individualized risk assessment.

Methods

Literature search and frequency of troponin I sequence variants

PubMed/MEDLINE was searched up to March 2015 for "troponin I," "TNNI3," or cTnI, combined with "mutations," "disease expression," "phenotype," or "genotype," each combined with "hypertrophic cardiomyopathy" or "HCM," "dilated cardiomyopathy" or "DCM," "restrictive cardiomyopathy" or "RCM," "noncompaction cardiomyopathy" or "LVNC" (left ventricle noncompaction cardiomyopathy). Only English-language human studies were selected that reported on genetic investigations of the gene for troponin I in addition to phenotypic features of mutation carriers. Furthermore, the Human Genome Mutation Database and the database for Online Mendelian Inheritance of Man were searched for cardiac troponin I mutations and corresponding articles.[15,16] All reference lists of articles retrieved were searched for missing studies. The frequencies of cardiac troponin I sequence variants reported in the articles retrieved were investigated in the Exome Aggregation Consortium database, which harbor exome-sequencing data of more than 60,000 individuals.[17]

A total of 55 articles were identified reporting on cTnI mutations in hypertrophic cardiomyopathy (38 studies), dilated cardiomyopathy (10 studies), and restrictive cardiomyopathy (7 studies). No articles were identified that reported on a systematic investigation of cTnI in LVNC.

All articles were included in this review. We systematically recorded available clinical data, including (1) genotype, (2) sex