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Review

Recent advancements in the molecular genetics of left ventricular noncompaction cardiomyopathy

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ABSTRACT

Left ventricular noncompaction cardiomyopathy (LVNC) is a myocardial disorder characterized by prominent and excessive trabeculations with deep recesses in the ventricular wall. Clinical manifestations of LVNC are highly variable, ranging from no symptoms to arrhythmias, heart failure, thromboembolism, or even sudden cardiac death. It is a heterogenetic disease which can be presented as an autosomal, X-linked or mitochondrial disorder. A series of candidate mutations have been identified in LVNC patients or murine models. It is generally believed that these gene mutations may share a final common pathway in the pathogenesis of LVNC, but the underlying molecular mechanisms are unknown. In this review, we discuss the gene mutations identified in LVNC patients and summarize recent advancements in the molecular genetic analysis of LVNC.

Contents

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1. Introduction

Left ventricular noncompaction cardiomyopathy (LVNC) is a rare disorder first described by Grant in 1926, characterized by prominent and excessive trabeculations with deep recesses in the ventricular wall. The World Health Organization/International and Federation of Cardiology Task Force categorized noncompacted ventricular myocardium as an "unclassified cardiomyopathy" in 1995 [1]. The American Heart Association in its scientific statement in 2006 classified it under the "genetic" section of "primary cardiomyopathies" [2]. It is a geneticall-y heterogeneous disease associated with variable clinical symptoms and can be inherited as an autosomal or X-linked disorder, mutations in the mitochondrial genome are also associated with LVNC.LVNC is the third most common cardiomyopathy after dilated and hypertrophic cardiomyopathies, and its prevalence ranges between 0.05 and 0.3% of the general population [3–5]. Dense trabecular meshwork and deep inter-trabecular recesses are seen on the ventricle wall. The etiology of LVNC is thought to be an arrest of the normal process of intrauterine endomyocardial morphogenesis [5,6].

LVNC has gained increasing attention in recent years as it is associated with high rates of mortality and morbidity in adults, including heart failure, thromboembolic events, and tachyarrhythmias. LVNC is caused by mutations in genes encoding sarcomere, cytoskeletal, ion channels, nuclear membrane, and chaperone proteins, but the underlying molecular mechanisms are unknown [6].

This review discusses the clinical manifestation, diagnosis, clinical management, and molecular genetics of LVNC, focusing on the pathogenic mutations associated with LVNC.

2. Clinical manifestations

LVNC can occur in isolation or in association with other disorders, including congenital heart defects, cardiac disorders, and musculoskeletal disorders. It can also be part of other genetic syndromes. Both sporadic and familial forms of LVNC have been described. Clinical manifestations are highly variable. Patients often present with a spectrum of disease severity ranging from no symptoms to cardiac arrhythmias, cardiac failure, thromboembolism, or even sudden cardiac death [6,7].

3. Diagnosis and clinical management

Diagnosis of LVNC relies on imaging modalities including echocardiography and cardiac magnetic resonance imaging. Echocardiography is the most frequently used first-line diagnostic tool for LVNC. Although different echocardiographic diagnostic criteria have been proposed, Jenni criteria is generally accepted [8]. (1) Bilayered myocardium with multiple, prominent trabeculations in end-systole. (2) NC/C ratio of >2:1. (3) Communication with the intertrabecular space demonstrated with color Doppler. (4) Absence of coexisting cardiac abnormalities. Recent reports suggest that cardiac magnetic resonance imaging has higher sensitivity and specificity by showing a ratio of noncompacted myocardium to compacted myocardium [9]. The MRI diagnostic criteria proposed by Petersen et al. are generally accepted [10]. (1) Visual appearance of two distinct myocardial layers-a compacted epicardial layer and a noncompacted endocardial layer. (2) Presence of marked trabeculations and deep intertrabecular recesses within the noncompacted layer. (3) Noncompacted-to compacted myocardial ratio >2.3 as measured in end-diastole. However, current diagnostic criteria are based on small cohorts and are liable to result in over-diagnosis of LVNC [11].

Up to now, there are no guidelines for treatment of LVNC. Therapy for LVNC is largely dictated by concomitant clinical findings associated with myocardial dysfunction or significant arrhythmias, or both, or congenital heart disease. Patients with evidence of systolic or diastolic dysfunction should be managed on the basis of existing recommendations [12]. Advanced pacing strategies, such as cardiac resynchronisation, are also used, and result in improvement in some patients [13]. Ventricular assist devices and cardiac transplantation are possibilities for patients with end-stage disease.

Although genetic testing is not yet a first-line diagnostic method for LVNC nor does it change the clinical management of the patient, it may help identify potential patients in LVNC families so that they can get proper clinical treatment in time.

4. Molecular genetics identified in humans

LVNC is a heterogenetic disease associated with highly variable clinical symptoms ranging from no symptoms to arrhythmias, heart failure, thromboembolism, or even sudden cardiac death. Autosomal dominant, X-linked, and mitochondrial inheritance patterns have been described, yet it most commonly presents as an autosomal dominant trait. A series of candidate mutations have been identified in LVNC patients or murine models. However, genetic testing suggests the lack of a specific genotype–phenotype association.

4.1. Mutations causing autosomal ventricular noncompaction

4.1.1. Mutations in sarcomere genes

Sarcomere gene mutations are thought to be pivotal cause of hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). Additionally, sarcomere mutations have been identified in association with more complex cardiac phenotypes, including restrictive physiology and left ventricular non-compaction. Different variants within the same sarcomere gene can result in both overlapping and divergent clinical manifestations. The penetrance and expressivity is considerably variable not only across unrelated families, but even within the same family [14].

In a study by Klaassen S et al., heterogeneous mutations in MYH7, ACTC1, and TNNT2 accounted for 17% of cases of isolated LVNC in adult patients [15]. In a study by Hoedemakers et al., mutations in 11 genes (among them, six sarcomere genes) in 41% of patients with LVNC were identified [16]. In a study by Probst S et al., mutations in eight sarcomere genes (MYBPC3, TPM1, MYH7, ACTC1, TNNT2, TNNI3, MYL2, and MYL3) resulted in a total of 18 (29%) heterozygous mutations in 63 probands [17]. In adult LVNC patients, mutations in MYH7 were the most frequent defects (Hoedemakers et al., nine of 57 probands (16%); Probst S et al., eight of 63 probands (13%)), followed by MYBP3 (Hoedemakers et al., 8%; Probst S et al., 5%) [17,18]. A research carried out at Fuwai Hospital (by Tao Tian et al.) reported a lower prevalence of sarcomere gene variants in a Chinese cohort with LVNC, suggesting the divergent genetic background of the disease among races [19]. However, the presence or absence of sarcomere gene mutation in LVNC does not predict the clinical phenotypes. There is no murine model suggesting the pathogenic effect of sarcomere mutations to LVNC.

4.1.2. Mutations in cytoskeletal genes

Mutations in the genes encoding α-dystrobrevin(DTNA),LIM Domain Binding protein 3 (LDB3/Cypher/ZASP) and Lamin AC (LMNA) have been identified in patients with isolated or nonisolated LVNC.DTNA binds dystrophin, syntrophin, and proteins of dystrophin-associated glycoprotein complex (DAPC), playing an important role in the stability and maintenance of the plasma membrane during muscle contraction and relaxation [20]. In 2001, Ichida et al. identified a heterozygous mutation (p.Pro121Leu) in the Dystrobrevin (DTNA) gene segregating with LVNC in a 3-generation Japanese family with CHD and LVNC [21]. LDB3 is a relevant candidate for LVNC.LDB3, also known as ZASP, the Z-band alternatively spliced PDZ-motif protein, or Cypher, is a cardiac and skeletal muscle-specific Z-line protein that is expressed in the cytoplasm, co-localizing with actin. Matteo Vatta et al. screened Cypher/ZASP gene in 100 probands with left ventricular dysfunction. Five mutations in six probands (6% of cases) were identified in patients