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Genetic analysis in patients with left ventricular noncompaction and evidence for genetic heterogeneity

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Abstract

Left ventricular noncompaction (LVNC) is a cardiomyopathy characterized by numerous excessively trabeculations and deep intertrabecular recesses. This study was performed to investigate Japanese LVNC patients for disease-causing mutations in a series of selected candidate genes. DNA was isolated from the peripheral blood of 79 cases including 20 familial cases and 59 sporadic cases. DNA samples were screened for mutations in the genes encoding G4.5 (*TAZ*), α-dystrobrevin (*DTNA*), α1-syntrophin (*SNTA1*), FK506 Binding protein 1A (FKBP1A or FKPB12: *FKBP1A*), and LIM Domain Binding protein 3 (Cypher/ZASP: *LDB3*), using single-strand conformational polymorphism analysis and DNA sequencing. DNA variants were identified in 6 of the 79 cases, including four familial cases and two sporadic cases. A splice acceptor mutation of intron 8 in *TAZ* (IVS8-1G>C) was identified in one family with isolated LVNC, resulting in deletion of exon 9 from mRNA. In a sporadic case of isolated LVNC and Barth syndrome (BTHS), a 158insC in exon 2 of *TAZ* resulting in a frame-shift mutation was identified. A 1876G>A substitution changing an aspartic acid to asparagine (D626N) was identified in *LDB3* in four members of two families with LVNC. A 163G>A polymorphism was identified in *LDB3*, which changed a valine to isoleucine (V55I) in one patient with isolated LVNC. In addition, in a family with nonisolated LVNC, a 362C>T mutation was identified in *DTNA*. LVNC, like other forms of inherited cardiomyopathy, is a genetically heterogeneous disease, associated with variable clinical symptoms and can be inherited as an autosomal or X-linked recessive disorder.

Keywords: Noncompaction; Cardiomyopathy; Barth syndrome; Mutation

Introduction

Left ventricular noncompaction (LVNC) is a cardiomyopathy which represents the persistence of numerous excessively prominent ventricular trabeculations and deep

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intertrabecular recesses. To date, the etiology of this disorder is postulated to be caused by an arrest of the normal process of intrauterine endomyocardial morphogenesis [1]. Although LVNC has only been recognized as an unclassified cardiomyopathy [2], two forms of this anomaly have been described, isolated LVNC which occurs in the absence of other cardiac anomalies and nonisolated LVNC in which similar myocardial anomaly is frequently reported in association with congenital heart diseases [3]. Clinical manifestations in LVNC are highly variable, ranging from no symptoms to arrhythmias, heart failure, cardiac transplantation, and death.

Both familial and sporadic cases of LVNC have been described, but the genetic causes remain unclear in many cases. We and others have identified mutations in the genes encoding α-dystrobrevin (*DTNA*), G4.5 (*TAZ*) and LIM Domain Binding protein 3 (*LDB3*/Cypher/ZASP) in patients with isolated or nonisolated LVNC [3–6]. *TAZ* is a member of the protein family called the tafazzins which are expressed primarily in heart and muscle cells, and are proposed to have acyltransferase functions within mitochondria [7,8]. Mutations in the *TAZ* result in a wide spectrum of severe infantile X-linked cardiomyopathies including isolated LVNC, Barth syndrome (BTHS) and endocardial fibroelastosis (EFE) [9]. BTHS, which was originally described in a Dutch family by Barth et al. [10] in 1983, is a complex X-linked recessive disorder associated with dilated cardiomyopathy, skeletal myopathy, neutropenia, abnormal cholesterol metabolism, lactic acidosis, elevated 3-methylglutaconic acid and 2-ethylhydracrylic acid, and cardiolipin abnormalities. *DTNA* binds dystrophin, syntrophin, and proteins of dystrophin-associated glycoprotein complex (DAPC), which is thought to play an important role in the stability and maintenance of the plasma membrane during muscle contraction and relaxation [11]. α1-Syntrophin (*SNTA1*) is one isoform of syntrophins, which are a biochemically heterogeneous group of intracellular membrane-associated DAPC, and is abundantly expressed in heart and skeletal muscle. Since it binds α-dystrobrevin we considered it a candidate gene [12]. *LDB3*, also known as ZASP, the Z-band alternatively spliced PDZ-motif protein, or Cypher, is a PDZ and LIM domain-containing cytoskeletal protein which has been shown to result in cardiomyopathy when knocked out in mice [13,14]. Shou et al. [15] reported that ablation of FK 506 Binding protein 1A (*FKBP1A*, previously known as FKBP12) resulted in noncompaction of left ventricular myocardium and congenital heart disease in mice.

Here, we report the analysis of the *TAZ*, *DTNA*, *SNTA1*, *FKBP1A*, and *LDB3* genes in a large cohort of Japanese patients with LVNC and demonstrate that this disease is genetically highly heterogeneous, as seen in the other forms of inherited cardiomyopathies.

Methods

Subjects

Blood was obtained from 103 Japanese LVNC patients after informed consent. Lymphoblastoid cell lines were established and then genomic DNA was isolated using QIAamp DNA extraction kits (Qiagen: Valencia, CA). Two hundred ethnicity-matched normal controls were recruited and DNA was isolated in an identical manner. The study was approved by the Research Ethics Committee of Toyama Medical and Pharmaceutical University Hospital.

Clinical diagnostic criteria

LVNC was diagnosed by echocardiographic criteria, including: (1) LV hypertrophy with deep endomyocardial trabeculations in $\geqslant 1$ ventricular wall segments, (2) reduced LV systolic function, (3) a two-layered endocardium with a noncompacted to compacted ratio of >2.0, and (4) deep recesses filled with blood from the ventricular cavity visualized on color Doppler imaging (Fig. 1) [3,16]. The clinical evaluation of the proband included physical examination and echocardiography (2D, M-

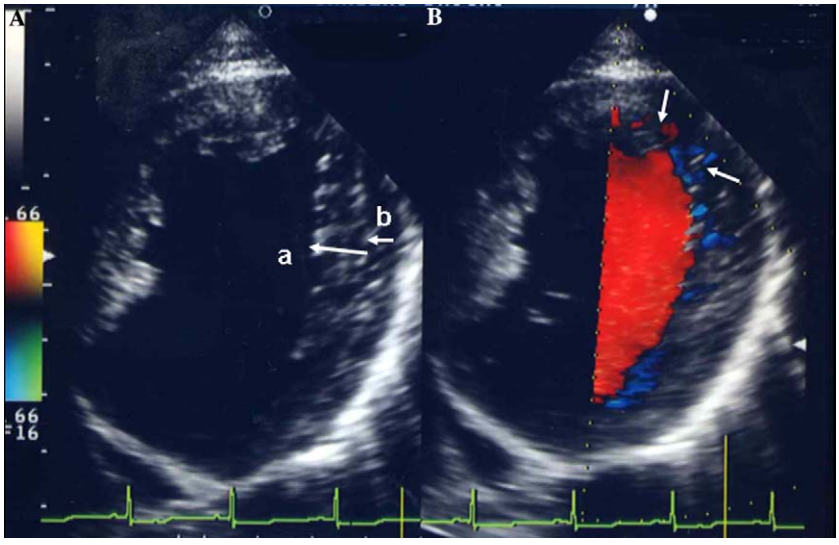

Fig. 1. (A) Two-dimensional echocardiogram of a patient with LVNC demonstrating the two-layer structure of noncompacted (a) and compacted (b) layers, a/b > 2.0. (B) Color Doppler echocardiogram of a patient with LVNC demonstrating flow within deep intertrabecular recesses (arrow) in continuity with the left ventricular cavity.