Genetic Heterogeneity of Left Ventricular Noncompaction Cardiomyopathy

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ABSTRACT

Isolated noncompaction of the ventricular myocardium (INVM), sometimes referred to as spongy myocardium, is a rare, congenital, and also acquired cardiomyopathy. It appears to divide the presentation into neonatal, childhood, and adult forms, of which spongy myocardium and systolic dysfunction is the commonality. The disorder is characterized by a left ventricular (LV) hypertrophy with deep trabeculations, and with diminished systolic function with or without associated LV dilation. In half or more of the cases, the right ventricle is also affected. The sporadic type, however, in some patients, may be due to chromosomal abnormalities and the occurrence of familial incidence. Isolated noncompaction of the LV myocardium in the majority of adult patients is an autosomal dominant disorder. The familial and X-linked disorders have been described by various authors. We describe here the genetic background of this disorder: some of the most mutated genes that are responsible for the disease are (G4.5 [tafazzin gene]: α-dystrobrevin gene [DTNA]; FKBP-12 gene; lamin A/C gene; Cypher/ZASP [LIM, LDB3] gene); and some genotype-phenotype correlations, (i.e., Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, or Barth syndrome [BTHS]) based on the literature review.

Key words: ventricular noncompaction cardiomyopathy, *G4.5* (tafazzin gene), α-dystrobrevin gene (DTNA), FKBP-12 gene, lamin A/C gene, Cypher/ZASP (LIM LDB3), gene

Background

Isolated noncompaction of the ventricular myocardium (INVM), sometimes referred to as spongy myocardium, is a rare, congenital, and also acquired cardiomyopathy.[1,2] It appears more often in children than in adults. Isolated noncompaction of the ventricular myocardium may manifest itself from infancy through young adulthood with a high mortality rate. However, the rates of complications are different in adult, childhood, and neonatal forms; some neonatal forms resolve spontaneously.[3] Both sexes are affected.[4,5] The disorder may be associated with facial dysmorphism and familial recurrence.[5] Isolated noncompaction of the ventricular myocardium occurs in the absence of other structural heart diseases and, hypothetically, it is due to the arrest of myocardial morphogenesis.[4] The disorder is characterized by left ventricular (LV) hypertrophy with deep trabeculations, and with diminished systolic function, with or without associated LV dilation. In half or more of the cases, the right ventricle is also affected.[4,6,7] This disease is accompanied by depressed ventricular function, systemic embolism and ventricular arrhythmia.[5–7] Noncompaction of the ventricular myocardium can be present with a variety of symptoms, but usually includes signs of LV systolic dysfunction, even to the point of heart failure.[7–9] Left ventricular noncompaction (LVNC) may be isolated or associated with congenital heart anomalies such as ventricular septal defects, pulmonic stenosis, and atrial septal defects.[10] Typical symptoms of INVM have also been described in a patient with Becker muscular dystrophy, and INVM was suggested as a part of this systemic myopathy.[11] The familial, as well as the sporadic form of INVM, may coexist with dysmorphic facial appearance such as prominent forehead, strabismus, gothic palate, or micrognatia.[5] The sporadic type, however, in some patients may be due to chromosomal abnormalities and the occurrence of familial incidences. Isolated noncompaction of the LV myocardium in the majority of adult patients is an autosomal dominant disorder.[12] The familial and X-linked disorder have been described by Chin et al.,[5] Hamamichi et al.,[13] Bleyl et al.,[14] Ritter et al.,[15] Matsuda et al.[16]

Genes Responsible for the Disease

The first gene responsible for INVM, tafazzin (G4.5) is localized on chromosome Xq28, and expressed at high levels in cardiac and skeletal muscle; plays a role in the maintenance of mitochondria, is involved in maintaining levels of cardiolipin, promotes differentiation and maturation of osteoblast cells, and prevents adipocytes from maturing.[17] This localization is in the proximity of other genes responsible for myopathies such as Emery-Dreifuss muscular dystrophy or Barth syndrome.[18]

Bleyl et al.[18] screened the G4.5 gene for mutations in a family with isolated noncompaction of LV myocardium by single-stranded conformation polymorphism (SSCP) analysis and direct sequencing, and found a novel glycine-to-arginine substitution at position 197 of the tafazzin gene.

Ichida et al.[10] identified a cys118-to-arg (C118R) missense mutation in the exon 4 of the tafazzin gene in a 5-month-old male with isolated LVNC associated with a dilated, mildly hypertrophic heart with poor systolic function on echocardiogram, and clinical heart failure. Neutropenia and 3-methylglutaconicaciduria were also identified. The mother was healthy but was found to be heterozygous for the same

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mutation along with a splice donor mutation (IVS10+2T →A) in intron 10. In a family with cardiomyopathies ranging from Barth syndrome (BTHS), or fatal infantile cardiomyopathy to asymptomatic dilated cardiomyopathy (DCM), a splice acceptor mutation in exon 2 of G4.5 (398-2 A→G) was identified, and a 1-bp deletion in exon 2 of *G*4.5, resulting in a stop codon after amino acid 41, was found in a sporadic case of BTHS.[10]

Chen et al.[19] identified a novel splice acceptor site mutation of intron 8 of G4.5 in a family with severe infantile X-linked LVNC, without the usual findings of BTHS. This mutation results in deletion of exon 9 from the mRNA, and is predicted to significantly disrupt the protein product.[19] Genotype–phenotype correlation of G4.5 mutations in all 38 cases that were reported in the literature up-to-date revealed that there was no correlation between a location or a type of mutation, and either cardiac phenotype or disease severity. They suggested that males linked with cardiomyopathy, particularly during infancy, even in the absence of the typical signs of Barth syndrome, should be evaluated for mutations in G4.5.[19]

Kenton et al.[20] identified a splice site acceptor mutation in intron 10 of G4.5 resulting in the deletion of exon 10 from the mRNA. The 13 mutations affiliated with G4.5 have so far been reported.[21]

The second gene responsible for INVM is called α-dystrobrevin, which is a cytoskeletal protein found in the dystrophin-associated glycoprotein complex (DAPC)[10] and localized in 18q12.1-q12.2 by in situ hybridization.[22]

Ichida et al.[10] screened the α-dystrobrevin gene in a Japanese family in which members of 4 generations were affected, 5 of them with LVNC associated with congenital heart defects, and 1 with isolated LVNC. The missense mutation in the DTNA gene, P121L, was found. A 362C>T mutation was also identified in this gene in a family with nonisolated LVNC.[23]

Furthermore, isolated noncompaction of LV myocardium is observed in mice, among the FK506-binding protein 1A gene (FKBP1A), has been 'knocked out' by embryonic stem cell technology. The FKBP1A gene maps to 20p13.[24]

The fourth gene associated with LVNC is lamin A/C gene related sequence mapped to human chromosomes 1q12.1-q23 and 10.[25] The human LMNA gene, when mutated, has been shown to cause at least 7 human diseases: a dilated cardiomyopathy, an Emery-Dreifuss muscular dystrophy, a limb girdle muscular dystrophy, a familial partial lipodystrophy, Charcot Marie tooth disease type II, mandibuloacral dysplasia, and a Hutchinson-Gilford Progeria.[26] The human LMNA gene mutations have been associated with familial or sporadic dilated cardiomyopathy (DC), with or without conduction system disease.[26,27]

Hermida–Prieto et al.[27] studied the LMNA gene in 67 consecutive patients with DC. Two disease-causing mutations were found in 2 families. In family A, a novel R349L mutation was present in the mother and her identical twin daughters. In family B, the R190W mutation was present in 2 cousins with DC and without conduction system disease, and in 2 of their sons. One of the carriers fulfilled diagnostic criteria for isolated LV noncompaction. These data which associate with the R349L and R190W mutations in LMNA have severe forms of familial DC.[27] The human LMNA gene mutations should be taken into consideration during the genetic screening of patients with familial DC without conduction system disease. Isolated LV noncompaction may be part of the phenotypic spectrum of the laminopathies.[27]

Forissier et al.[28] found a new LMNA mutation (1621C >T, R541C) in 2 members of a French family with a history of ventricular rhythm disturbances and an uncommon form of systolic LV dysfunction. The 2 patients: the proband and his daughter, were affected and exhibited an atypical form of dilated cardiomyopathy with an unexplained LV aneurysm revealed by ventricular rhythm disturbances without atrio-ventricular block.[28]

Charniot et al.[29] found a missense mutation (R377H) in the lamin A/C gene that cosegregated with the disease in the family. Sebillon et al.[30] found a new missense (E161K) mutation in a family with an early atrial fibrillation, and a previously described (R377H) mutation in another family with a quadriceps myopathy associated with DCM. Arbustini et al.[31] identified five novel LMNA mutations (K97E, E111X, R190W, E317K, four base pair insertion at 1,713 cDNA) in 5 cases of familial autosomal dominant DCM with AVB (5/15: 33%). The LMNA expression of the myocyte nuclei was reduced or absent.[31]

Vatta et al.[32] evaluated the role of the fifth gene Cypher/ZASP (LIM, LDB3) in the pathogenesis of dilated cardiomyopathy with or without isolated noncompaction of the LV myocardium. By polymerase chain reaction (PCR) and radiation hybrid analysis, Faulkner et al.[33] localized the ZASP gene to 10q22.2-q23.3. Vatta et al.[32] determined that the LDB3 gene consists of 16 exons and spans approximately 70 kb. By screening a muscle complementary deoxyribonucleic acid (cDNA) library using a muscle expressed sequence tag (EST) sequence as the probe, Faulkner et al.[33] obtained cDNAs encoding mouse and human ZASP. Northern blot analysis detected a major 1.9-kb ZASP transcript that was most abundant in skeletal muscle and heart but absent in other tissues tested. RT-PCR analysis detected wide expression of ZASP, with weak or undetectable expression in liver, pancreas, and spleen. Western blot analysis showed expression of 32- and 78-kD proteins in heart and muscle.[34]

Vatta et al.[32] evaluated the role of Cypher/ZASP in the pathogenesis of dilated cardiomyopathy with or without isolated noncompaction of the LV myocardium. They screened 100 probands with LV dysfunction and found 5 mutations in 6 probands (6%). By in vitro studies, they showed cytoskeleton disarray in cells transfected with mutated Cypher/ZASP. In a 40-year-old man with dilated cardiomyopathy associated with mild LV hypertrophy and a

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trabeculated left ventricle on echocardiogram, Vatta et al.[32] identified heterozygosity for a 587C-T transition in exon 4 of the LDB3 gene, resulting in a ser196-to-leu (S196L) substitution. Four other family members were affected: the proband's 68-year-old mother, his 2 brothers, 1 of whom died with severe dilated cardiomyopathy at age 41 years, and the deceased brother's 7-year-old daughter, who presented with a mildly dilated left ventricle. The mutation was only identified in affected family members.[32]

In a 15-month-old Latin-American male with profound bradycardia, atrial ventricular block, and depressed ventricular function with mild LV dilation, Vatta et al.[32] identified a 638C-T transition in exon 4 of the LDB3 gene, resulting in a thr213-to-ile (T213I) substitution. Thr213 is conserved in mouse and rat. Neither parent had the substitution.

In 2 unrelated sporadic cases of dilated cardiomyopathy withLVNC, Vatta et al.[32] identified a 349G-A transition in exon 6 of the LDB3 gene, resulting in an asp117-to-asn (D117N) mutation. One patient was a 44-year-old female, diagnosed at 41 years of age with DCM, heart failure, left bundle branch block, and dilated left ventricle with deep trabeculations. The other was a 33-year-old male, diagnosed with DCM at 30 years of age during a family echocardiographic screening after sudden death had occurred within the family. Echocardiographic and MRI screening identified both left and right ventricular trabeculations, with an intraventricular conduction delay and ventricular bigeminy on electrocardiogram, as well as echocardiographic evidence of borderline systolic function and a dilated left ventricle. In the other family members, neither DCM nor isolated noncompaction of the LV myocardium was identified.[34]

In 2004, Sasse-Klaassen et al.,[35] discovered novel gene locus for autosomal dominant LVNC. They have mapped a locus for autosomal dominant LVNC to a 6.8-megabase region on human chromosome 11p15. Identification of the disease gene will allow genetic screening and provide fundamental insight into the understanding of myocardial morphogenesis.[35]

Conclusion

This statement is in agreement with that of Stollberger et al.[36] In this review it is stated that: (i) left ventricular hypertrabeculation (LVHT) has a higher prevalence than previously thought, and the prevalence of LVHT seems to increase with the improvement of cardiac imaging; (ii) because LVHT is most frequently diagnosed primarily by echocardiography, echocardiographers should be aware and trained to recognize this abnormality; (iii) LVHT is frequently associated with other cardiac and extracardiac, particularly neuromuscular disorders; (iv) there are indications that the cause of LVHT is usually genetic and quite heterogeneous; and (v) controversies exist about diagnostic criteria, nomenclature, prognosis, origin, pathogenesis, and the necessity to classify LVHT as a distinct entity and cardiomyopathy by the World Health Organization.[36]

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