Left Ventricular Noncompaction in a Family with Lamin A/C Gene Mutation

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Left ventricular noncompaction is a rare type of cardiomyopathy, the genetics of which are poorly understood to date. Lamin A/C gene mutations have been associated with dilated cardiomyopathy and diseases of the conduction system, but rarely in left ventricular noncompaction cardiomyopathy. This report describes the cases of 4 family members with a lamin A/C gene mutation, 3 of whom had phenotypic expression of left ventricular noncompaction. (*Tex Heart Inst J* 2015;42(1):73-6)

Left ventricular noncompaction (LVNC) is a distinct cardiomyopathy characterized by prominent trabeculations of the left ventricular (LV) myocardium. Patients with LVNC can develop progressive cardiac dysfunction that results in heart failure and increased risk of death.¹⁻³ A variety of genes, primarily those encoding cardiac sarcomeric and cytoskeletal proteins, have been identified as causes of LVNC. At least one report identifies mutations in the gene lamin A/C (also known as *LMNA*), which encodes an inner nuclear membrane protein.⁴ Lamin A/C gene mutations have been associated with dilated cardiomyopathies, with and without conduction-system disease.⁵⁻¹⁷ We present a case report involving a family, 4 members of which had a heterozygous *LMNA* gene mutation—3 of whom had a phenotypic expression of LVNC.

Case Report

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A 7-year-old boy presented with syncope that appeared to be of vasovagal origin. During his initial evaluation at another facility, an echocardiogram showed a dilated left ventricle. These findings—dilated cardiomyopathy and recurrent syncope—prompted an electrophysiologic (EP) study and diagnostic cardiac catheterization. The EP study revealed no arrhythmias, and endomyocardial biopsy results showed myocyte hypertrophy without inflammation. Additional evaluation included the implantation of a loop recorder, which again did not identify any arrhythmias.

The patient continued to have dilated cardiomyopathy with recurrent syncope and was eventually referred to us for further evaluation. During the initial visit for a second opinion, an echocardiogram showed LVNC with normal LV size, thickness, and function; the patient's LV end-diastolic dimension at that time was 4.67 cm (Z score, 1.57), his LV diastolic wall thickness was 0.7 cm (Z score, -0.50), his LV diastolic septal thickness was 0.8 cm (Z score, 0.19), and his shortening fraction was 41%.

Serial evaluations continued to reveal LVNC, with otherwise normal LV dimensions and function. Upon consultation, our cardiovascular genetics staff recommended genetic testing. A blood sample was sent to GeneDx (Gaithersburg, Md), where a panel of 27 genes known to cause dilated cardiomyopathy and LVNC was analyzed. This testing showed that the patient was heterozygous for a *LMNA* gene mutation: an amino acid substitution of arginine for cysteine (R644C) (Fig. 1). No other abnormality was identified.

We next identified at-risk family members by using cascade genetic screening and yearly follow-up clinical evaluations. Cascade genetic testing in first-degree relatives (Fig. 2) revealed that the patient's brother was genotype positive and had LVNC with normal LV size and function on echocardiography (Fig. 3), his sister was genotype positive and had no abnormalities on echocardiography (Fig. 4), his father was

genotype positive and had LVNC with normal LV size and function on cardiac magnetic resonance (CMR), and his mother was genotype negative and had no abnormalities on echocardiography. Established diagnostic criteria¹⁸ were used for the evaluation of all family members, to determine whether LVNC was present.

The genotype-positive family members have now been monitored yearly by means of either echocardiography or CMR, to determine LV function and dimensions. In addition, exercise stress tests and Holter monitoring for arrhythmia surveillance are performed yearly on the 3 family members with the mutant genotype and phenotypic expression. Given their normal LV dimensions, normal LV function, and absent evidence of dysrhythmias, none of the genotype-positive members of the family has been restricted from athletics or other activities, and none has had any clinical problems or symptoms, disease progression, or evidence of dysrhythmias during the 4 years of monitoring.

Fig. 1 The DNA sequence analysis of genomic DNA in the patient's proband reveals a C-T transition in the LMNA gene at cDNA position c.1930 (arrow), which resulted in amino acid substitution of arginine for cysteine (R644C).

Fig. 2 The patient's (P) pedigree and age of family members at most recent follow-up.

Discussion

Left ventricular noncompaction is a distinct cardiomyopathy with established, albeit imperfect, diagnostic criteria.¹⁸ When LVNC is not associated with congenital heart disease, it can be subdivided into dilated, hypertrophic, mixed (dilated/hypertrophic), restrictive, and isolated (normal LV dimension and function). Recent studies have stratified patients in accordance with their increased risk of death. Patients with LVNC are reportedly at risk of sudden death if they also have one of the following: LV dysfunction, LV dilation (LV end-diastolic dimension, >2 Z-scores), LV hypertrophy, or arrhythmias.¹ Reports of genetic mutations in LVNC remain uncommon,^{19,20} and only one previous case report to our knowledge has shown a LMNA gene mutation in a patient with LVNC.⁴

The causal role (for LVNC) of the R644C mutation in the LMNA gene described in our family members is

Fig. 3 Echocardiogram (parasternal short-axis view at the mid left ventricle) of the patient's brother, who is genotype and phenotype positive, shows a wide trabeculated region along the posterior and lateral free walls (between arrows) on the left. Color-flow Doppler imaging (right), shows flow into the deep trabeculae (arrow) during systole.

Fig. 4 Echocardiogram of the patient's sister, who is genotype positive but phenotype negative, shows a smoother appearance of the endocardial surface and the lack of trabeculations, in comparison with Figure 3. Therefore, color-flow Doppler (right) during systole reveals no abnormal flow.

uncertain. It is possible that an unidentified gene not tested for in this family caused, or at least contributed to, the disease state; however, our findings link a gene known to cause abnormalities in the myocardium—dilated cardiomyopathy and conduction-system abnormalities—to a family multiple members of which display clear phenotypic expression of LVNC. Although the population frequency of the R644C *LMNA* gene mutation has not been fully characterized, it appears to be exceedingly low. Muntoni and colleagues²¹ found no R644C mutations in 250 healthy control subjects drawn from the general population. The exact mechanism by which *LMNA* defects cause LVNC is difficult to know and was in any event beyond the scope of our foregoing case study. However, as Hermida-Prieto and colleagues⁴ concluded, *LMNA* is very possibly causal in the setting of LVNC, and our report adds anecdotal evidence in support of that position. Certainly future studies aimed at characterizing the myocardium at a microscopic and molecular level will be helped by the growing evidence.

We should note that one family member from our series had the *LMNA* gene mutation and no identifiable cardiac abnormalities on testing, or by history and examination. This can be explained by a few hypotheses. First, the penetrance of this mutation is not 100%, and is actually very low, according to previous reports.^{21,22} Therefore, although the girl in the family carries the heterozygous gene mutation, she has no phenotypic expression. Second, phenotypic expression can be quite variable, even among family members with the same mutation.²² Therefore, she might manifest a phenotypic disease different from that of other family members. We do not think that she will develop LVNC de novo, but she is at risk of dilated cardiomyopathy or cardiac conduction system disease—just with no phenotypic expression to date. For this reason, we have opted to continue monitoring her by means of periodic testing in our clinic.

As with all cardiomyopathies, identifying gene mutations can be important in further characterizing at-risk family members and in providing insight into disease pathogenesis and future therapies. In this study, we identified at-risk family members by using cascade genetic screening and yearly follow-up clinical evaluations, with the goal of preventing the high-risk outcomes that can affect patients with LVNC. Ongoing evaluation of patients with LVNC and associated *LMNA* gene mutations will be important in the understanding of the risk profile for this unique cardiomyopathy.

Conclusion

Although *LMNA* gene mutations have been associated with dilated cardiomyopathies and conduction-system disease, they have rarely been reported in the presence of LVNC. Ongoing investigation of the frequency of

LMNA mutations in LVNC is important, for it might further expand our knowledge of the disease process and aid us in identifying at-risk first-degree relatives of LVNC patients.

References

1. Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. *Circulation* 2013;127(22):2202-8.
2. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003;108(21):2672-8.
3. Towbin JA. Left ventricular noncompaction: a new form of heart failure. *Heart Fail Clin* 2010;6(4):453-69.
4. Hermida-Prieto M, Monserrat L, Castro-Beiras A, Laredo R, Soler R, Peteiro J, et al. Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with lamin A/C gene mutations. *Am J Cardiol* 2004;94(1):50-4.
5. Arbustini E, Pilotto A, Repetto A, Grasso M, Negri A, Diegoli M, et al. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. *J Am Coll Cardiol* 2002;39(6):981-90.
6. Taylor MR, Fain PR, Sinagra G, Robinson ML, Robertson AD, Carniel E, et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations [published erratum appears in *J Am Coll Cardiol* 2003;42(3):590]. *J Am Coll Cardiol* 2003;41(5):771-80.
7. Sebillon P, Bouchier C, Bidot LD, Bonne G, Ahamed K, Charron P, et al. Expanding the phenotype of *LMNA* mutations in dilated cardiomyopathy and functional consequences of these mutations. *J Med Genet* 2003;40(8):560-7.
8. Sylvius N, Bilinska ZT, Veinot JP, Fidzianska A, Bolongo PM, Poon S, et al. In vivo and in vitro examination of the functional significances of novel lamin gene mutations in heart failure patients. *J Med Genet* 2005;42(8):639-47.
9. Karkkainen S, Reissell E, Helio T, Kaartinen M, Tuomaninen P, Toivonen L, et al. Novel mutations in the lamin A/C gene in heart transplant recipients with end stage dilated cardiomyopathy. *Heart* 2006;92(4):524-6.
10. Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, Peterson A, et al. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. *Am Heart J* 2008;156(1):161-9.
11. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;341(23):1715-24.
12. Brodsky GL, Muntoni F, Micioc S, Sinagra G, Sewry C, Messtroni L. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation* 2000;101(5):473-6.
13. Becane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* 2000;23(11 Pt 1):1661-6.
14. Jakobs PM, Hanson EL, Crispell KA, Toy W, Keegan H, Schilling K, et al. Novel lamin A/C mutations in two families with dilated cardiomyopathy and conduction system disease. *J Card Fail* 2001;7(3):249-56.
15. Hershberger RE, Hanson EL, Jakobs PM, Keegan H, Coates K, Bousman S, Litt M. A novel lamin A/C mutation in a

- family with dilated cardiomyopathy, prominent conduction system disease, and need for permanent pacemaker implantation. *Am Heart J* 2002;144(6):1081-6.
16. MacLeod HM, Culley MR, Huber JM, McNally EM. Lamin A/C truncation in dilated cardiomyopathy with conduction disease. *BMC Med Genet* 2003;4:4.
 17. Pethig K, Genschel J, Peters T, Wilhemi M, Flemming P, Lochs H, et al. LMNA mutations in cardiac transplant recipients. *Cardiology* 2005;103(2):57-62.
 18. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001;86(6):666-71.
 19. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy--a Heart Failure Society of America practice guideline. *J Card Fail* 2009;15(2):83-97.
 20. Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? *Eur Heart J* 2011;32(12):1446-56.
 21. Muntoni F, Bonne G, Goldfarb LG, Mercuri E, Piercy RJ, Burke M, et al. Disease severity in dominant Emery Dreifuss is increased by mutations in both emerin and desmin proteins. *Brain* 2006;129(Pt 5):1260-8.
 22. Rankin J, Auer-Grumbach M, Bagg W, Colclough K, Nguyen TD, Fenton-May J, et al. Extreme phenotypic diversity and nonpenetrance in families with the LMNA gene mutation R644C. *Am J Med Genet A* 2008;146A(12):1530-42.