Cardiol Young 2007; 17: 124–129

ISSN 1047-9511
doi: 10.1017/S1047951107000273

Review Article

Isolated left ventricular non-compaction: the case for abnormal myocardial development

Ross A. Breckenridge,[1] Robert H. Anderson,[2] Perry M. Elliott[3]

[1]Department of Clinical Pharmacology, BHF Laboratories, [2]Cardiac Unit, Institute of Child Heath, [3]The Heart Hospital, University College, London

Abstract Isolated ventricular non-compaction is an increasingly commonly diagnosed myocardial disorder characterised by excessive and prominent trabeculation of the morphologically left, and occasionally the right, ventricle. This is associated with high rates of thromboembolism, cardiac failure, and cardiac arrhythmia. Recent improvements in understanding the embryonic processes underlying ventricular formation have led to the hypothesis that ventricular non-compaction is due to a failure of normal ventriculogenesis, leading to abnormal myocardium which may present clinically many years later. Experimental work in animal models provides several candidate transcription factors and signalling molecules that could, in theory, cause ventricular non-compaction if disrupted.

Keywords: Hypertrabeculation; molecular biology; transcription factors

Isolated left ventricular non-compaction is a myocardial disorder characterised by excessive and prominent trabeculation of the morphologically left ventricle, with frequent additional involvement of the right ventricle.

Infants and children with the disease can present with cardiac failure, often in association with somatic or other cardiac abnormalities. Older children and adults may also present with stroke, arrhythmia, and cardiac failure. Until quite recently, this condition was thought to be extremely rare in adults, and remains unclassified as a cardiomyopathy in the most recent system for classification of heart muscle disease made by the World Health Organisation. Greater awareness of the disease, and improvements in echocardiographic technology, have resulted in a dramatic increase in the frequency of diagnosis.

In most patients, isolated left ventricular non-compaction is thought to be a disorder of cardiac morphogenesis. Relatively little attention has been given, however, to the role that altered control of intrauterine cardiac development might play in the development of left ventricular dysfunction. In this review, we summarise current theories on cardiac development, and discuss potential mechanisms by which abnormal cardiac development might contribute to non-compaction.

Correspondence to: Ross A. Breckenridge, Department of Clinical Pharmacology, BHF Laboratories, 5 University Street, London WC1E 6JJ, United Kingdom. Tel: +44 (0)207 679 6205; Fax: +44 (0)208 816 2009; E-mail: rbrecke@nimr.mrc.ac.uk

Accepted for publication 3 November 2006

Clinical presentation and diagnosis

The macroscopic hallmark of the lesion is the appearance of prominent trabeculations in the luminal surface of the ventricle, with deep recesses between the trabeculations that extend into the ventricular wall, but which do not communicate with the coronary circulation (Fig. 1). Histologically, the findings are non-specific, ranging from normal myocardium to acquired fibrotic changes superimposed on the background of normal myocardium.[1]

Non-compaction can occur in association with numerous congenital cardiac malformations, including atrial and ventricular septal defects, aortic stenosis, and aortic coarctation. When no other congenital lesion is present, the lesion is said to be isolated. A male predominance has been suggested, but this has not been confirmed in recent studies.[2] Until quite recently, isolated ventricular non-compaction was thought to be extremely rare in adults. Its true prevalence remains

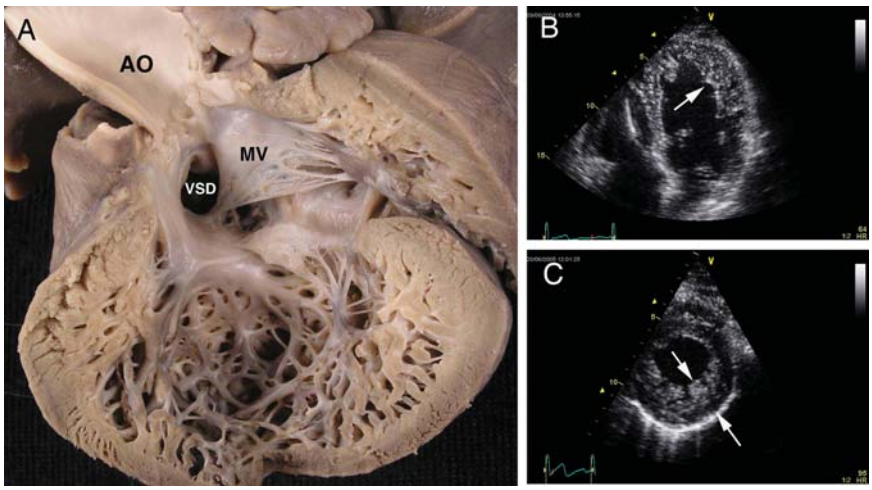

Figure 1.
*(A) Left ventricular non-compaction in the context of a ventricular septal defect (VSD) in an adult. Note the deep trabeculations extending throughout the left ventricle (AO; aorta, MV; mitral valve). (**B**) parasternal long axis transthoracic echocardiograph of an adult patient with isolated non-compaction of the left ventricle at end diastole, showing predominantly apical trabeculations (arrowed). (**C**) short axis transthoracic echocardiograph at the midcavity level showing grossly thickened trabeculated myocardium (arrowed) in a different patient.*

uncertain, with published figures varying between 0.05 and 0.24%.[1] It is almost certain that greater awareness of the disease, and continuing improvements in diagnostic techniques, have increased the frequency of the diagnosis.

Presentation with symptoms of cardiac failure and arrhythmia is described at all ages. Familial occurrence, with X-linked and autosomal dominant inheritance, is also reported.[3,4] In many instances non-compaction, when seen in children, is associated with neuromuscular abnormalities and facial dysmorphism.[5]

Several papers have suggested that afflicted patients have poor left ventricular function, with a high incidence of ventricular arrhythmias and systemic thromboembolism.[6–8] Recent studies, nonetheless, report a much lower incidence of death, stroke, or documented sustained ventricular arrhythmia, probably reflecting the increased identification of preclinical or mild cases.[9,10]

The echocardiographic criterions for diagnosis have been discussed elsewhere.[10–12] The simplest criterion for diagnosis is that the distance from the epicardial surface to the peak of trabeculations is double, or more, of the distance from the surface of the epicardium to the trough of ventricular trabeculations.[11] Other more complex echocardiographic methods have been proposed.[12] A role for echocardiographic contrast to increase the sensitivity of diagnosis has been suggested.[12] Cardiac magnetic resonance imaging has also been reported to be a sensitive tool for diagnosis of ventricular non-compaction,[13] but formal diagnostic criterions have not yet been formulated. Furthermore, discrepancies have been reported between magnetic resonance and echocardiographic appearances of the same heart.[14] This emphasises that the diagnosis of non-compaction of the ventricles on morphological grounds is sometimes problematic. Advances in imaging technology, coupled with a deeper understanding of the biology of normal and abnormal ventricular trabeculation, may be helpful in this regard in the future.

Normal development of the left ventricle

The most cogent model of ventricular development is the "ballooning" model, in which the future apical components of both ventricles are considered to grow outwards from the outer curve of the looped tubular heart.[15] Trabeculations in the embryonic heart are first evident from day 9.5 in the mouse, and at the end of the fourth gestational week of the human (Carnegie Stage 12),[16] when endocardium evaginates through the cardiac jelly to contact the adjacent myocardium. It is postulated that this process initiates the formation of myocardial trabeculations, which at this stage are finger-like projections of myocardium protruding into the ventricular lumen, when seen in section,[15] although the overall arrangement of the trabeculations may be more accurately described as "sponge-like".[17] It has been argued that this trabeculation allows oxygen to diffuse rapidly to the growing myocardium in the absence of coronary arteries. Indeed, the process of compaction, whereby these large embryonic trabeculations are remodelled, is coincident with development of the coronary arteries.[17] Rather than being a process of resorption, compaction may be a function of changes in ventricular size and shape, leaving a reduced inner layer of trabeculations, with the compacted layer then forming the ventricular walls and conduction system.[17] In hearts with non-compaction, there is an increase in the trabeculated relative to the compact layer of the ventricular walls. It is possible that this represents defective embryonic development of the ventricular walls, the effects of which are only clinically apparent many years later.

There is circumstantial evidence supporting this hypothesis. During development, Connexins

https://doi.org/10.1017/S1047951107000273 Published online by Cambridge University Press

40 and 43, molecules which are integral components of the embryonic and mature conduction systems,[18] are highly enriched in the non-compact as compared to the compact layer.[15] Later, these molecules are found in the mature conduction system, and in the compact ventricular layer, implicating the embryonic non-compact ventricular layer as a source of the cells that form the definitive conduction system during ventricular compaction. It is of note that, as mentioned earlier, a high incidence of cardiac arrhythmias has been reported in patients with non-compaction.

Defects in the coronary microcirculation have also been reported with ventricular non-compaction,[7,19] suggesting that the vascularisation of the abnormal myocardium is affected. This abnormal coronary microcirculation may not be confined to obviously non-compacted ventricular segments.[20] Given the evidence of abnormal cardiac conduction and myocardial perfusion in this condition, it is very likely that isolated ventricular non-compaction represents a failure of normal ventricular development.

Control of ventricular development

The genetic factors controlling the early development of the ventricle are not fully understood. The fact that non-compaction does not represent a catastrophic defect in ventricular formation suggests that the developmental defect may affect the later maturation process of the ventricle, rather its initial specification. It is possible to identify several processes involved in development of the ventricular myocardium which could, in theory, lead to non-compaction if disrupted.

The growth patterns of individual embryonic cardiomyocytes have been studied in chick by marking cells with replication-defective LacZ-encoding virus,[21] revealing a complex pattern of growth, whereby an individual myocyte gives rise to a cone-shaped clone of progeny myocytes reaching into the trabeculated layer, with the outer layers of cardiomyocytes exhibiting the highest rates of cell division. This fits with a model whereby the epicardium acts as a source of proliferative paracrine signalling to myocytes, which proliferate inwards. Retinoic acid and erythropoietin have been implicated as secreted epicardial factors controlling mitosis of the ventricular myocytes,[22,23] acting through their upregulation of fibroblast growth factor signalling.[24] Furthermore, experimental studies have shown that the cardiac-specific null mice for retinoic acid RXRalpha receptor exhibit dilated and thin ventricles.[25] Fibroblast growth factor, retinoic acid, and erythropoietin have not yet been implicated as genes involved in human cardiomyopathic disease, perhaps reflecting that disruption of these signalling molecules, which participate in many embryonic processes, is incompatible with a viable embryo.

Current knowledge of transcription factors controlling the early development of the ventricle is incomplete, and a full review is beyond the scope of this article. The reader is directed to several excellent recent reviews.[26–30] Mutations in several genes encoding transcription factors, nonetheless, have been shown to disrupt left ventricular formation, albeit that no single transcription factor null allele has been shown to prevent left ventricular function in isolation. This could be explained by the existence of large nuclear "transcription complexes", made up of several transcription factors, which may participate in multiple stages of ventricular development, both the initial phase of "specification", and the later "morphogenetic" phase of modelling. The hypothesis that transcription factors participate at multiple points in cardiac development is now supported by a wealth of experimental evidence.

The homeobox factor Nkx2.5, the first candidate for a "master regulator" of cardiac development, was isolated after searching for homologues of the *Drosophila* gene *tinman*. This gene, when deleted, results in absence of the dorsal vessel, the equivalent of the heart in the fly.[31,32] Nkx2.5 has been shown to associate physically with the T-box factors Tbx5[33] and Tbx20,[34] and GATA4,[35] to modulate expression of a large set of downstream genes. Nkx2.5 is a key node in the transcriptional network controlling specification of the cardiomyocytes and development of the chambers. To date, 26 mutations in Nkx2.5 causing human disease have been isolated.[36] Polymorphisms in the human Nkx2.5 gene have been associated with congenital cardiac malformations, as well as conduction defects.[28,37] As yet, no mutation in this gene has been associated with a human cardiomyopathy. Experimental evidence now suggests that Nkx2.5 could, in theory, also be a candidate gene for human cardiomyopathy. The Nkx2.5 null mouse is non-viable, and arrests early in development with an unlooped and hypoplastic heart, reflecting a role for the gene in early cardiac development.[38,39] Using a cardiac muscle-restricted null mouse circumvents the multiple developmental roles of Nkx2.5.[40] This late-stage cardiomyocyte Nkx2.5-null mouse exhibits heart block, and increased ventricular trabeculations. Interestingly, these defects were found to be progressive as the animal aged. In this respect, the model proposed by the authors was failure of recruitment of cells to the conduction system during embryogenesis, and overgrowth of cardiomyocytes throughout embryonic and adult life. Thus, Nkx2.5, or interacting/downstream factors, may be candidates for disease-causing genes in isolated ventricular non-compaction.

The importance of the action of secreted signalling molecules on the developing ventricles is also now

being recognised. Bone Morphogenetic Protein 10 (BMP10) is unique among the large and widely expressed transforming growth factor beta family of secreted signalling molecules in that expression is restricted to the trabeculations of the wild-type ventricle.[41] Deletion of BMP10 in transgenic mice results in intrauterine death, with decreased proliferation of ventricular cardiomyocytes and abnormal trabeculation,[42] as does cardiac-restricted deletion of the receptor ALK3.[43] Significantly, the cardiomyocyte-restricted Nkx2.5 null mouse mentioned above exhibits raised levels of BMP10. Furthermore, driving ectopic BMP10 expression in the heart was found to result in hypertrabeculation.[40]

A secreted antagonist of type 1 receptors of transforming growth factor ß/bone morphogenetic protein, FK506 binding protein 12, has been implicated in cardiac hypertrophy.[44,45] The null mutant mouse for FK506 binding protein 12 exhibits large ventricular trabeculations, increased mitosis of myocytes, and upregulated expression of BMP10.[42] Human mutations in FK506 binding protein 12 have been sought in human pedigrees exhibiting isolated ventricular non-compaction, but as yet none have been found.[46]

None of these cardiac transcription factors or signalling molecules have yet been implicated as a gene for non-compaction in the human, although mutations in Nkx2.5 and Tbx5 have been associated with other human cardiac phenotypes.[37,40,47] Genotyping of human pedigrees exhibiting isolated ventricular non-compaction for factors such as Nkx2.5 and BMP10 is awaited.

The molecular basis of isolated ventricular non-compaction in humans

While most human disease alleles for non-compaction remain unknown, the disease has been noted to be a genetically heterogeneous condition.[48] Several genetic locuses have been found to associate with ventricular non-compaction in affected pedigrees. An example is the gene G4,5 mapping to Xq28, which encodes tafazzin, and which may be the disease allele for the Barth syndrome, an X-linked syndrome affecting skeletal and cardiac muscle.[49–52] Deletion of a segment of chromosome 5q has also been reported to result in ventricular non-compaction,[53] and most recently, a gene mapped to 11p15 has been implicated in non-compaction.[4] Additionally, ventricular non-compaction has been described as part of a number of congenital syndromes.[1]

In a minority of human pedigrees, mutations have been found in genes encoding cytoskeletal components, such as tafazzin, or dystrophin,[7] contractile proteins such as *cypher/ZASP*,[54] and nuclear envelope proteins such as *emerin*, or *lamin A/C.*[55] It is unclear as to why these mutations should cause the phenotype for non-compaction as opposed to dilated cardiomyopathy. It is possible that disruption of a putative signalling pathway involving Nkx2.5 and/or BMP10 and cytoskeletal proteins, leads to subtle alterations in ventricular morphology, and results in non-compaction.

A key question is whether adults presenting with isolated ventricular non-compaction have developed the phenotype in adulthood, or whether a sub-clinical abnormality has been present from birth. Children with hypertrabeculated left ventricular myocardium have been identified during screening of pedigrees, but it is not yet determined whether all of these individuals will go on to develop the phenotype for ventricular non-compaction. Experimental work outlined above gives at least a theoretical basis for a molecular defect that causes development of a progressive phenotype in adulthood. Another important question is whether the lesion in human ventricular non-compaction is progressive, as in these mouse models. It has been suggested that, in ventricular non-compaction presenting during childhood, the lesion is detectable at birth, and ventricular remodelling delays clinical presentation by several years.[9] Whether this is true for disease presenting for the first time during adulthood is an open question. Interestingly, "acquired" non-compaction lesions not detected during fetal ultrasonography have been reported,[50] implying either that non-compaction could develop postnatally, or that early detection of abnormal ventricular morphology was at that time imperfect. More recently, successful detection of the non-compaction phenotype during fetal life has been reported.[56]

Transgenic mouse technology is now at the point where it is possible to limit misexpression of control molecules to a given temporo-spatial point in cardiac development, thereby facilitating experiments that can examine subtle defects in cardiac development that may result in non-compaction in man. The future identification of human genes responsible for ventricular non-compaction will also shed light on the molecular basis of the disease.

Challenges for the future

The emergence of non-compaction as a new diagnosis in clinical cardiology is presenting clinicians with many diagnostic and therapeutic dilemmas. For example, data from the families of patients with isolated ventricular non-compaction, showing that isolated ventricular non-compaction can occur with or without dilated and hypertrophic cardiomyopathy in the same family suggest that, at least in some instances, isolated ventricular non-compaction is a marker of an underlying disease process rather than its primary cause.[7]

Perhaps an even greater problem is the identification of increasing numbers of patients with prominent trabeculations not fulfilling the published criterions for isolated ventricular non-compaction. Do such individuals have normal hearts, or could they be a preclinical manifestation, or *forme fruste*, of the more extreme phenotype? Some unconfirmed reports have also suggested that the phenotype for isolated ventricular non-compaction may appear during adult life in patients with myotonic dystrophy, or as a transient phenomenon during myocarditis. At present, it would seem more appropriate to label such cases as "hypertrabeculation", rather than non-compaction, although without serial echocardiographic data it may be impossible to distinguish the two.

Conclusion

Our understanding of the development of the left ventricle is increasing. Experimental studies provide a theoretical basis for understanding non-compaction as seen in the human, and suggest a model in which subtle perturbations in embryonic ventriculogenesis result in a phenotype that does not become evident clinically until adulthood. Sequential and high resolution screening of cardiac morphology in affected pedigrees from newborn ages onwards is now possible, and will enable the testing of this hypothesis.

References

1. Freedom RM, Yoo S-J, Perrin D, Petersen S, Anderson RH. The morphological spectrum of ventricular noncompaction. Cardiol Young 2005; 15: 345–364.
2. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. Circulation 2004; 109: 2965–2971.
3. Sasse-Klaassen S, Gerull B, Oechslin E, Jenni R, Thierfelder L. Isolated noncompaction of the left ventricular myocardium in the adult is an autosomal dominant disorder in the majority of patients. Am J Med Genet 2003; 119A: 162–167.
4. Sasse-Klaassen S, Probst S, Gerull B, et al. Novel gene locus for autosomal dominant left ventricular noncompaction maps to chromosome 11p15. Circulation 2004; 109: 2720–2723.
5. Stollberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 2002; 90: 899–902.
6. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000; 36: 493–500.
7. Ichida F, Hamamichi Y, Miyawaki T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 1999; 34: 233–240.
8. Rigopoulos A, Rizos IK, Aggeli C, et al. Isolated left ventricular noncompaction: an unclassified cardiomyopathy with severe prognosis in adults. Cardiology 2002; 98: 25–32.
9. Pignatelli RH, McMahon CJ, Dreyer WJ, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 2003; 108: 2672–2678.
10. Murphy RT, Thaman R, Blanes JG, et al. Natural history and familial characteristics of isolated left ventricular noncompaction. Eur Heart J 2005; 26: 187–192.
11. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of the ventricular myocardium. A study of eight cases. Circulation 1990; 82: 507–513.
12. Jenni R, Oechslin E, Schneider J, Jost CA, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001; 86: 666–671.
13. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005; 46: 101–105.
14. Stollberger C, Finsterer J, Kopsa W. Magnetic resonance imaging does not always confirm left ventricular noncompaction. Int J Cardiol 2007; 114: E48–9.
15. Moorman AF, Lamers WH. Development of the conduction system of the vertebrate heart. In: Harvey RP, Rosenthal N (eds). Heart Development. Academic Press, San Diego, 1999, pp. 195–207.
16. Sedmera D, Pexieder T, Vuillemin M, Thompson RP, Anderson RH. Developmental Patterning of the Myocardium. Anat Rec 2000; 258: 319–337.
17. Sedmera D, Thomas PS. Trabeculation in the human heart. Bioessays 1996; 18: 607.
18. Miquerol L, Dupays L, Thevenau-Ruissy M, et al. Gap junctional connexins in the developing mouse cardiac conduction system. Novartis Foundation Symposia 2003; 250: 80–98.
19. Junga G, Kneifel S, Von Smekal A, Steinert H, Bauersfeld U. Myocardial ischaemia in children with isolated ventricular noncompaction. Eur Heart J 1999; 20: 910–916.
20. Jenni R, Wyss CA, Oechslin EN, Kaufmann PA. Isolated ventricular noncompaction is associated with coronary microcirculatory dysfunction. J Am Coll Cardiol 2002; 39: 450–454.
21. Mikawa T, Borisov A, Brown AM, Fischman DA. Clonal analysis of cardiac morphogenesis in the chicken embryo using a replication-defective retrovirus: I. Formation of the ventricular myocardium. Dev Dyn 1992; 193: 11–23.
22. Chen J, Kubalak SW, Chien KR. Ventricular muscle-restricted targeting of the RXRalpha gene reveals a non-cell-autonomous requirement in cardiac chamber morphogenesis. Development 1998; 125: 1943–1949.
23. Stuckmann I, Evans S, Lassar AB. Erythropoietin and retinoic acid, secreted from the epicardium, are required for cardiac myocyte proliferation. Dev Biol 2003; 255: 334–349.
24. Lavine KJ, Yu K, White AC, et al. Endocardial and epicardial derived FGF signals regulate myocardial proliferation and differentiation in vivo. Dev Cell 2005; 8: 85–95.
25. Sucov HM, Dyson E, Gummeringer CL, Price J, Chien KR, Evans RM. RXR alpha mutant mice establish agenetic basis for vitamin A signalling in heart morphogenesis. Genes Dev 1994; 8: 1007–1008.
26. Bruneau BG. The developing heart and congenital heart defects: a make or break situation. Clin Genet 2003; 63: 252–261.
27. Brand T. Heart development: molecular insights into cardiac specification and early morphogenesis. Dev Biol 2003; 258: 1–19.
28. Harvey RP, Lai D, Elliott D, et al. Homeodomain factor Nkx2-5 in heart development and disease. Cold Spring Harb Symp Quant Biol 2002; 67: 107–114.
29. Olson EN, Schneider MD. Sizing up the heart: development redux in disease. Genes Dev 2003; 17: 1937–1956.
30. Olson EN. A decade of discoveries in cardiac biology. Nat Med 2004; 10: 467–474.
31. Lints TJ, Parsons LM, Hartley L, Lyons I, Harvey RP. Nkx-2.5: a novel murine homeobox gene expressed in early heart progenitor

cells and their myogenic descendants. Development 1993; 119: 969.
32. Komuro I, Izumo S. Csx: a murine homeobox-containing gene specifically expressed in the developing heart. Proc Natl Acad Sci U S A 1993; 90: 8145–8149.
33. Bruneau BG, Nemer G, Schmitt JP, et al. A murine model of Holt-Oram syndrome defines roles of the T-box transcription factor Tbx5 in cardiogenesis and disease. Cell 2001; 106: 709–721.
34. Takeuchi JK, Mileikovskaia M, Koshiba-Takeuchi K, et al. Tbx20 dose-dependently regulates transcription factor networks required for mouse heart and motoneuron development. Development 2005; 132: 2463–2474.
35. Durocher D, Nemer M. Combinatorial interactions regulating cardiac transcription. Dev Genet 1998; 22: 250–262.
36. Kasahara H, Benson DW. Biochemical analysis of eight NKX2.5 homeodomain missense mutations causing atrioventricular block and cardiac anomalies. Cardiovasc Res 2004; 64: 40–51.
37. Schott JJ, Benson DW, Basson CT, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science 1998; 281: 108–111.
38. Biben C, Harvey RP. Homeodomain factor Nkx2.5 controls left-right expression of bHLH gene eHAND during murine heart development. Genes Dev 1997; 11: 1357–1369.
39. Lyons I, Parsons LM, Hartley L, et al. Myogenic and morphogenic defects in heart tubes of murine embryos lacking the homeobox gene Nkx2-5. Genes Dev 1995; 9: 1654–1666.
40. Pashmforoush M, Lu JT, Chen H, et al. Nkx2-5 pathways and congenital heart disease; loss of ventricular myocyte lineage specification leads to progressive cardiomyopathy and complete heart block. Cell 2004;117:373–86.
41. Neuhaus H, Rosen V, Thies RS. Heart specific expression of mouse BMP-10 a novel member of the TGF-beta superfamily. Mech Dev 1999; 80: 181–184.
42. Chen H, Shi S, Acosta L, et al. BMP10 is essential for maintaining cardiac growth during murine cardiogenesis. Development 2004; 131: 2219–2231.
43. Gaussin V, Van de Putte T, Mishina Y, et al. Endocardial cushion and myocardial defects after cardiac myocyte-specific conditional deletion of the bone morphogenetic protein receptor ALK3. Proc Natl Acad Sci U S A 2002; 99: 2878–2883.
44. Sato Y, Ferguson DG, Sako H, et al. Cardiac-specific overexpression of mouse cardiac calsequestrin is associated with depressed cardiovascular function and hypertrophy in transgenic mice. J Biol Chem 1998; 273: 28470–28477.
45. Xin HB, Senbonmatsu T, Cheng DS, et al. Oestrogen protects FKBP12.6 null mice from cardiac hypertrophy. Nature 2002; 416: 334–338.
46. Kenton AB, Sanchez X, Coveler KJ, et al. Isolated left ventricular noncompaction is rarely caused by mutations in G4.5, alpha-dystrobrevin and FK Binding Protein-12. Mol Genet Metab 2004; 82: 162–166.
47. Bruneau BG, Logan M, Davis N, et al. Chamber-specific cardiac expression of Tbx5 and heart defects in Holt-Oram syndrome. Dev Biol 1999; 211: 100–108.
48. Digilio MC, Marino B, Bevilacqua M, Musolino AM, Giannotti A, Dallapiccola B. Genetic heterogeneity of isolated noncompaction of the left ventricular myocardium. Am J Med Genet 1999; 85: 90–91.
49. Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nat Genet 1996; 12: 385–389.
50. Bleyl SB, Mumford BR, Brown-Harrison MC, et al. Xq28-linked noncompaction of the left ventricular myocardium: prenatal diagnosis and pathologic analysis of affected individuals. Am J Med Genet 1997; 72: 257–265.
51. Bleyl SB, Mumford BR, Thompson V, et al. Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am J Hum Genet 1997; 61: 868–872.
52. Chen R, Tsuji T, Ichida F, et al. Mutation analysis of the G4.5 gene in patients with isolated left ventricular noncompaction. Mol Genet Metab 2002; 77: 319–325.
53. Pauli RM, Scheib-Wixted S, Cripe L, Izumo S, Sekhon GS. Ventricular noncompaction and distal chromosome 5q deletion. Am J Med Genet 1999; 85: 419–423.
54. Vatta M, Mohapatra B, Jimenez S, et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. J Am Coll Cardiol 2003; 42: 2014–2027.
55. Hermida-Prieto M, Monserrat L, Castro-Beiras A, et al. Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with lamin A/C gene mutations. Am J Cardiol 2004; 94: 50–54.
56. Guntheroth W, Komarniski C, Atkinson W, Flinger CL. Criterion for fetal spongiform cardiomyopathy:restrictive pathophysiology. Obstet Gyneacol 2002; 99: 882–885.