

Ebstein's anomaly may be caused by mutations in the sarcomere protein gene *MYH7*

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Published online: 21 May 2011

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Abstract Ebstein's anomaly is a rare congenital heart malformation characterised by adherence of the septal and posterior leaflets of the tricuspid valve to the underlying myocardium. Associated abnormalities of left ventricular morphology and function including left ventricular non-compaction (LVNC) have been observed. An association between Ebstein's anomaly with LVNC and mutations in the sarcomeric protein gene *MYH7*, encoding β -myosin heavy chain, has been shown by recent studies. This might

represent a specific subtype of Ebstein's anomaly with a Mendelian inheritance pattern. In this review we discuss the association of *MYH7* mutations with Ebstein's anomaly and LVNC and its implications for the clinical care for patients and their family members.

Keywords Heart defects, congenital · Ebstein anomaly · Genetics · Cardiomyopathy · Isolated noncompaction of the ventricular myocardium

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Introduction

Ebstein's anomaly is a rare congenital heart malformation affecting about 1 in 200,000 live births [1]. Associated abnormalities of left ventricular morphology and function including left ventricular noncompaction (LVNC) have been reported [2–6]. Recently, mutations in the sarcomeric protein gene β -myosin heavy chain (*MYH7*) were described in patients with Ebstein's anomaly associated with LVNC [5, 7]. Here, we will discuss this association and focus on its implications for the clinical care of patients with Ebstein's anomaly and their family members.

Ebstein's anomaly and LVNC

Ebstein's anomaly is characterised by apical displacement and adherence of the septal and posterior leaflets of the

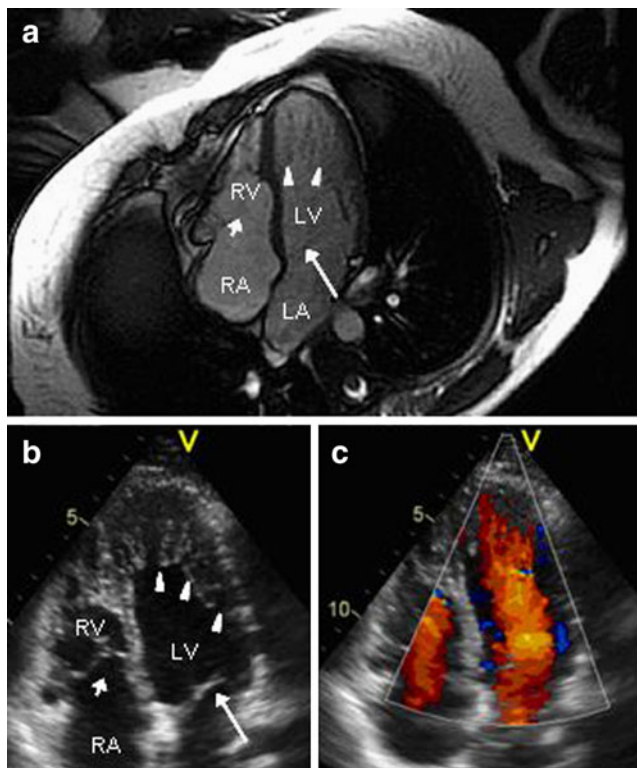


Fig. 1 Images of a 24-year-old woman with an *MYH7* mutation from the study of Postma et al. [7] This patient was a relative of one of the probands with Ebstein's anomaly, LVNC and *MYH7* mutation. She was asymptomatic and identified as a mutation carrier by family screening. **a**) MRI image, 4-chamber view; Ebstein anomaly is present (shown by apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve), as well as LVNC. **b**) Echocardiographic images, apical 4-chamber view; Ebstein's anomaly and LVNC are evident. There is also noncompaction of the right ventricle. **c**) Colour Doppler image, showing trabecularisation and recesses filled with blood in the left ventricle. Large arrow, mitral valve; small arrow, tricuspid valve; triangles, LVNC; LV, left ventricle; LA, left atrium, RA, right atrium

Table 1 Families with *MYH7* mutation segregating with Ebstein's anomaly and LVNC

Family	Mutation	Mutation carriers with LVNC (n)	Mutation carriers partially affected with LVNC (n)	Mutation carriers with normal echocardiogram (n)	Mutation carriers with undetermined echocardiogram (n)	Mutation carriers with Ebstein's (n)	Other heart disease in mutation carriers (n of individuals)	Reference
DU-11	Arg281Thr	9	–	–	–	4	ASD (4)	Budde et al. [5]
I110.647	Tyr283Asp	4	–	–	–	2	ASDII (1), Perimembranous VSD (1)	Postma et al. [7]
I110.240	Asn1918Lys	4	–	–	1	1	Coa/BAV (1)	Postma et al. [7]
I09.787	Glu1573Lys	–	1 ^b	–	–	1	Perimembranous VSD (1)	Postma et al. [7]
I6875	Tyr283Asp	2	–	–	–	1	Pulmonary artery hypoplasia/ASDII (1)	Postma et al. [7]
I	Leu301Gln	9	–	–	–	1	Peripartum cardiomyopathy (1) ^c	Hoedemaekers et al. [18]

LVNC left ventricular noncompaction; SCD sudden cardiac death; ASD atrial septal defect; VSD ventricular septal defect; BAV bicuspid aortic valve

^a Partially affected: documented apical thickening (<18 mm) due to noncompaction with a ratio of noncompacted/compacted myocardium <2

^b ratio of noncompacted/compacted myocardium <2

^c Mutation analysis not performed

tricuspid valve to the underlying myocardium, thereby displacing the functional tricuspid orifice apically and dividing the right ventricle into two portions [1]. The main haemodynamic abnormality leading to symptoms is tricuspid valve incompetence. The clinical spectrum is broad; patients may be asymptomatic or experience right-sided heart failure, cyanosis, arrhythmias and sudden cardiac death (SCD) [1]. Many Ebstein's anomaly patients have an interatrial communication (secundum atrial septal defect (ASD II) or patent foramen ovale). Other structural anomalies may also be present, including bicuspid aortic valve (BAV), ventricular septal defect (VSD), and pulmonary stenosis [1, 8]. The genetic aetiology of Ebstein's anomaly is largely unknown. Most cases are sporadic and familial Ebstein's anomaly is rare. Genetic, environmental and reproductive factors are all believed to be contributing [9]. Patients with non-syndromic Ebstein's anomaly are generally thought to have a small risk (a few percent) of transmitting heart disease to their offspring [10]. Rare mutations in the transcription factor gene *NKX2.5* have been described in a variety of patients with congenital heart disease (CHD) including Ebstein's anomaly [11], while chromosomal abnormalities have also been reported [12, 13]. Among the nongenetic causes of Ebstein's anomaly are intrauterine infections or exposure to lithium [14].

An association between Ebstein's anomaly and left ventricular noncompaction (LVNC) has been reported in several studies [2–6]. LVNC is classified as a primary cardiomyopathy with a genetic aetiology [15], featuring a thickened two-layered myocardium with a thin, compact, epicardial layer and a severely thickened endocardial layer with a 'spongy' appearance due to prominent trabeculations and intertrabecular recesses [16]. Clinical features are variable and include heart failure, arrhythmias and thromboembolism, but patients can also be asymptomatic [17, 18]. Up to 64% of isolated LVNC has been reported to be familial, mostly consistent with an autosomal dominant mode of inheritance [18]. Mutations in several genes coding for sarcomeric proteins have been described in LVNC, such as β -myosin heavy chain (*MYH7*), cardiac myosin-binding protein C (*MYBPC3*), α -cardiac actin

(*ACTC1*), cardiac troponin T (*TNNT2*), α -tropomyosin (*TPMI*) and cardiac troponin I (*TNNI3*) [18–21]. *MYH7* has been reported to be the most frequent disease gene in LVNC in the absence of CHD [18, 19].

MYH7 mutations in Ebstein's anomaly associated with LVNC

Although an association between Ebstein's anomaly and LVNC has been suggested by previous studies, a common genetic origin was not elucidated until recently. In 2007 Budde et al. [5] investigated a large three-generation family with 12 affected patients with LVNC. Four family members had Ebstein's anomaly with or without ASD in addition to LVNC, and one patient had an ASD with LVNC. In total, 24 family members were assessed and genome-wide analysis showed linkage to chromosome 14ptel-14q12. One of the genes sequenced in this locus was *MYH7*, and a previously unknown heterozygous missense mutation was found, segregating with the condition within the family. The authors thereby detected a new phenotype that had not been known to be related to *MYH7* before. These findings by Budde et al. [5] led our group to further investigate the association between Ebstein's anomaly and *MYH7* mutations. We performed mutational analysis using next generation sequencing and direct DNA sequencing of *MYH7* in a cohort of 141 unrelated Ebstein's anomaly patients [7]. We identified heterozygous mutations in 8 of 141 patients (6%). In 6 of 8 probands LVNC was identified in addition to Ebstein's anomaly, one proband had partially penetrant LVNC and in another proband LVNC was uncertain. The probands' families were studied, and familial CHD and/or LVNC was present in 3 of 5 families that were available for study. In these kindreds *MYH7* mutations segregated with LVNC and CHD (Fig. 1). Familial Ebstein's anomaly was present in one family, while several other types of CHD were encountered in the probands and their relatives, including ASD II, perimembranous VSD, pulmonary artery hypoplasia and coarctation of the aorta with BAV (Table 1). Most of the family

Table 2 Sporadic cases with *MYH7* mutation and Ebstein's anomaly

Individual	Mutation	Phenotype	Reference
AO	1220delGlu	Ebstein's anomaly, LVNC	Postma et al. [7]
DB	Tyr350Asp ^a	Ebstein's anomaly, LVNC	Postma et al. [7]
BT	Leu390Pro	Ebstein's anomaly, LVNC, PFO	Postma et al. [7]
AD	Lys1459Asn	Ebstein's anomaly, left ventricular morphology undetermined	Postma et al. [7]

LVNC left ventricular noncompaction; PFO patent foramen ovale

^a De novo mutation

members shown to have LVNC, as well as the relative with Ebstein's anomaly, were not known to have cardiac disease before family screening. No *MYH7* mutations were found in the remaining 133 Ebstein's probands, in whom LVNC had not been reported. Recently, Hoedemaekers et al. also reported a family with an *MYH7* mutation segregating with LVNC and one individual also having Ebstein's anomaly [18]. An overview of the reported families and sporadic patients with *MYH7* mutations and Ebstein's anomaly is given in Tables 1 and 2, respectively.

The results of these studies suggest that there is a specific subtype of Ebstein's anomaly, with LVNC and an autosomal dominant inheritance pattern, caused by mutations in *MYH7*. The Ebstein's anomaly phenotype is not fully penetrant though, as only a minority of mutations carriers have Ebstein's anomaly. Additionally, other CHD may be part of the condition as well. This variable expression suggests that other genetic or environmental factors probably play a role in the establishment of the final phenotype. How mutations in *MYH7* can produce Ebstein's anomaly should be subject of further study. LVNC is thought to result from altered regulation in cell proliferation, differentiation and maturation during ventricular wall formation [22], and an arrest in directional growth may play a role in the association of Ebstein's anomaly and LVNC [23, 24].

With the identification of *MYH7* mutations in Ebstein's anomaly with LVNC, the spectrum of phenotypes with a defect in a structural protein has been broadened. While sarcomeric mutations are well-known causes of cardiomyopathies, it was not until recently that several of these genes were found to play a role in various forms of CHD. Mutations in *MYBPC3*, *ACTC1* and α -myosin heavy chain (*MYH6*) have been implicated in septal defects [25–27], while mutations in *ACTA2* and *MYH11*, genes encoding sarcomeric proteins of smooth muscle cells, can lead to aortic aneurysm with patent ductus arteriosus [28, 29]. How these sarcomeric mutations contribute to the development of CHD is unclear and should be subject to further research.

Clinical implications

LVNC is a familial disease with potentially severe complications, including severe arrhythmias, heart failure and thromboembolism [17, 18, 30]. These complications may be prevented by early diagnosis and timely treatment of high-risk patients, such as anticoagulants in patients at risk for thromboembolism [17] and implantation of an implantable cardioverter defibrillator in those at risk for life-threatening arrhythmias [30]. ACE inhibitors, β -blockers and diuretics can be of use in patients with left

ventricular dysfunction [17]. We therefore recommend detailed clinical evaluation of all Ebstein's anomaly patients to identify possible additional LVNC. If LVNC is identified, genetic counselling of the patient as well as his or her relatives should be carried out [18, 31]. Genetic counselling should be performed by trained professionals in a multidisciplinary environment, ideally in a centre specialised in cardiogenetics [31]. In patients with Ebstein's anomaly and LVNC, we recommend initiating genetic testing with *MYH7*, and other genes implicated in LVNC to be screened if no mutation in *MYH7* is found. If a disease-causing mutation is established, apparently healthy relatives at risk for the disease can subsequently be identified reliably. Relatives who carry the mutation should have regular medical follow-up to detect cardiac abnormalities at an early stage. In the absence of an identified genetic cause of LVNC, or when relatives decline genetic testing, regular medical follow-up is also warranted. Predictive genetic testing of asymptomatic family members should only be performed after counselling about potential benefits (e.g. medical benefits of early diagnosis) as well as about possible adverse implications (insurance, employment, psychological consequences) [18, 31].

Conclusions

Recent studies have identified *MYH7* mutations as a cause of Ebstein's anomaly associated with LVNC and other CHD. This condition might represent a specific subtype of Ebstein's anomaly. The inheritance pattern is autosomal dominant, though with a variable penetrance and phenotype, some family members showing only partially penetrant LVNC and others having LVNC with additional CHD. We recommend patients with Ebstein's anomaly to be carefully evaluated for LVNC, and if present, early treatment of patients at risk for complications of LVNC. Moreover, genetic counselling and genetic testing should be performed by trained professionals, preferably in a multidisciplinary setting in a centre specialised in cardiogenetics. Subsequently, genetic counselling and cardiological evaluation of relatives or, if a mutation is found in the proband, genetic testing of relatives is warranted. Further studies are needed to investigate if mutations in other (sarcomere) genes than *MYH7* can also lead to Ebstein's anomaly with or without LVNC.

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References

1. Attenhofer Jost CH, Connolly HM, Dearani JA, et al. Ebstein's anomaly. *Circulation*. 2007;115:277–85.
2. Attenhofer Jost CH, Connolly HM, Warnes CA, et al. Non-compacted myocardium in Ebstein's anomaly: initial description in three patients. *J Am Soc Echocardiogr*. 2004;17:677–80.
3. Attenhofer Jost CH, Connolly HM, O'Leary PW, et al. Left heart lesions in patients with Ebstein anomaly. *Mayo Clin Proc*. 2005;80:361–8.
4. Sinkovec M, Kozelj M, Podnar T. Familial biventricular myocardial noncompaction associated with Ebstein's malformation. *Int J Cardiol*. 2005;102:297–302.
5. Budde BS, Binner P, Waldmuller S, et al. Noncompaction of the ventricular myocardium is associated with a de novo mutation in the beta-myosin heavy chain gene. *PLoS One*. 2007;2:e1362.
6. Bagur RH, Lederlin M, Montaudon M, et al. Images in cardiovascular medicine. Ebstein anomaly associated with left ventricular noncompaction. *Circulation*. 2008;118:e662–4.
7. Postma AV, van Engelen K, van de Meerakker JBA, et al. Mutations in the Sarcomere Protein Gene MYH7 in Ebstein's Anomaly. *Circ Cardiovasc Genet*. 2011;4:43–50.
8. Frescura C, Angelini A, Daliento L, et al. Morphological aspects of Ebstein's anomaly in adults. *Thorac Cardiovasc Surg*. 2000;48:203–8.
9. Correa-Villasenor A, Ferencz C, Neill CA, et al. Ebstein's malformation of the tricuspid valve: genetic and environmental factors. The Baltimore-Washington Infant Study Group. *Teratology*. 1994;50:137–47.
10. Firth HV. Congenital heart disease. In: Firth HV, Hurst JA, Hall JG, editors. *Oxford desk reference clinical genetics*. Oxford: Oxford University Press; 2006. p. 84–7.
11. Benson DW, Silberbach GM, Kavanaugh-McHugh A, et al. Mutations in the cardiac transcription factor NKX2.5 affect diverse cardiac developmental pathways. *J Clin Invest*. 1999;104:1567–73.
12. Yang H, Lee CL, Young DC, et al. A rare case of interstitial del(1)(p34.3p36.11) diagnosed prenatally. *Fetal Pediatr Pathol*. 2004;23:251–5.
13. Miller MS, Rao PN, Dudovitz RN, et al. Ebstein anomaly and duplication of the distal arm of chromosome 15: report of two patients. *Am J Med Genet A*. 2005;139A:141–5.
14. Siebert JR, Barr Jr M, Jackson JC, et al. Ebstein's anomaly and extracardiac defects. *Am J Dis Child*. 1989;143:570–2.
15. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113:1807–16.
16. Jenni R, Oechslin E, Schneider J, et al. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart*. 2001;86:666–71.
17. Aras D, Tufekcioglu O, Ergun K, et al. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail*. 2006;12:726–33.
18. Hoedemaekers YM, Caliskan K, Michels M, et al. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. *Circ Cardiovasc Genet*. 2010;3:232–9.
19. Klaassen S, Probst S, Oechslin E, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation*. 2008;117:2893–901.
20. Monserrat L, Hermida-Prieto M, Fernandez X, et al. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. *Eur Heart J*. 2007;28:1953–61.
21. Dellefave LM, Pytel P, Mewborn S, et al. Sarcomere mutations in cardiomyopathy with left ventricular hypertrabeculation. *Circ Cardiovasc Genet*. 2009;2:442–9.
22. Chen H, Zhang W, Li D, et al. Analysis of ventricular hypertrabeculation and noncompaction using genetically engineered mouse models. *Pediatr Cardiol*. 2009;30:626–34.
23. de Lange FJ, Moorman AF, Anderson RH, et al. Lineage and morphogenetic analysis of the cardiac valves. *Circ Res*. 2004;95:645–54.
24. Meilhac SM, Esner M, Kerszberg M, et al. Oriented clonal cell growth in the developing mouse myocardium underlies cardiac morphogenesis. *J Cell Biol*. 2004;164:97–109.
25. Ching YH, Ghosh TK, Cross SJ, et al. Mutation in myosin heavy chain 6 causes atrial septal defect. *Nat Genet*. 2005;37:423–8.
26. Lekanke Deprez RH, Muurling-Vlietman JJ, Hruda J, et al. Two cases of severe neonatal hypertrophic cardiomyopathy caused by compound heterozygous mutations in the MYBPC3 gene. *J Med Genet*. 2006;43:829–32.
27. Matsson H, Eason J, Bookwalter CS, et al. Alpha-cardiac actin mutations produce atrial septal defects. *Hum Mol Genet*. 2008;17:256–65.
28. Zhu L, Vranckx R, Van Khau KP, et al. Mutations in myosin heavy chain 11 cause a syndrome associating thoracic aortic aneurysm/aortic dissection and patent ductus arteriosus. *Nat Genet*. 2006;38:343–9.
29. Guo DC, Pannu H, Tran-Fadulu V, et al. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nat Genet*. 2007;39:1488–93.
30. Oechslin EN, Attenhofer Jost CH, Rojas JR, et al. 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.
31. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2010;31:2715–26.