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

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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; LV, left atrium, RA, right atrium)

| 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) | Other heart disease in mutation carriers (n of individuals) | Reference |
|--------|----------|-------------------------------|----------------------------------|-----------------|-------------------|-----------------|---------|
| DU-11  | Arg281Thr | 9                             | 3                               | 2               | 2                 | 4               | Budde et al. [5] |
| 110.647| Tyr283Asp | 4                             | 2                               | 1               | 1                 | 1               | Postma et al. [7] |
| 110.240| Asn1918Lys| 4                             | 1                               | 1               | 1                 | 1               | Postma et al. [7] |
| 109.787| Glu1573Lys| –                             | –                               | –               | –                 | –               | Postma et al. [7] |
| 16875  | Tyr283Asp | 2                             | 2                               | 1               | 1                 | 1               | Postma et al. [7] |
| 1     | Leu301Gln | 9                             | 3                               | 2               | 2                 | 1               | Hoedemaekers et al. [18] |

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

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

Mutation analysis not performed

Full noncompaction: LVNC with ratio of noncompacted/compacted myocardium of either <2 or not quantifiable
Several studies have shown that left ventricular noncompaction (LVNC) has been reported in association with intrauterine infections or exposure to lithium. 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. 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. 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. Rare mutations in the transcription factor gene NKX2.5 have been described in several genes coding for sarcomeric proteins have been described in LVNC. One of the genes sequenced in this locus was MYH7, which has been known to be related to familial Ebstein’s anomaly with or without ASD in addition to 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 14q11-14q12. 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. 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. We identified heterozygous mutations in 8 of 141 patients (6%). In 6 of 8 probands LVNC was identified in addition to 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 *    | 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

*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 [28, 29]. 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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