The Genetics of Mitral Valve Prolapse

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Introduction

Mitral valve prolapse (MVP) is one of the most common forms of valvular heart disease.

It has long been recognized as an auscultatory phenomenon. It was not until 1966 that Barlow discovered the reason for the often-heard midsystolic click [1, 2]. Shortly afterwards, the introduction of echocardiography led to large numbers of patients diagnosed with MVP. Due to incorrect echocardiographic definitions and selection bias of studied populations, prevalences of up to 35% were reported in the 1970s and early 1980s [3]. A redefinition of echocardiographic criteria due to improved knowledge of mitral valve architecture provided a more accurate insight into the extent of the problem. Currently, the prevalence of MVP is known to range from about 0.5 to 3% in the general population [3–7]. It is equally distributed between men and women, yet patients with MVP tend to have a leaner stature [6].

Mitral valve prolapse (MVP) is defined as the billowing of one or both mitral valve leaflets across the plane of the mitral valve annulus into the left atrium during systole. By definition, the leaflets should reach more than 2 mm above the annular plane on the parasternal long axis view with echocardiography (Figs. 25.1 and 25.2).

The clinical presentation can be very diverse, ranging from an incidental finding within asymptomatic patients to dramatic cases with severe mitral regurgitation, heart failure, bacterial endocarditis, and in rare cases sudden cardiac death.

MVP may present as part of a systemic or syndromic disorder or as a solitary phenomenon. It may occur more frequently in connective tissue disorders such as Marfan syndrome, Loeys Dietz syndrome, and Ehlers Danlos syndrome. However, in most cases, it presents as a solitary entity; only a small minority, up to 1–2% of all patients with MVP have a connective tissue disorder or syndrome. This chapter focuses on the solitary forms that appear to be one of the most common Mendelian cardiovascular abnormalities in humans and it discusses the epidemiologic aspects of MVP, its pathophysiology, and the current status of genetic knowledge of this intriguing valvular disorder.

Clinical Presentation, Diagnostics, Complications, and Pathophysiology of Mitral Valve Disease

The solitary forms of mitral valve disease are referred to as the classical prolapse, with the valve leaflet thickness exceeding 5 mm on echocardiography, and the nonclassical form, with leaflet thickness of less than 5 mm (both in the presence of a systolic upward displacement of 2 mm). Leaflet thickening or myxomatous degeneration is characterized by expansion of the spongiosa layer due to accumulation of proteoglycans. Also, structural alterations of collagen in all components of the valvular system and chordae can be found. It is thought that the mechanism underlying the expansion of the spongiosa layer is the result of a dysregulation of the balance between matrix protein synthesis and degradation [6]. From the pathologic anatomical point of view, accumulation of proteoglycans (myxomatous mitral valve) is the most common cause of MVP, leading to leaflet thickening and redundancy, chordeal elongation and interchordal hookings, and annular dilatation [7].

The clinical presentation of MVP is extremely heterogeneous, and to date hardly any specific set of predictors for disease progression has been identified (see Section "Ventricular Arrhythmias and Sudden Cardiac Death in MVP").

The diagnosis is in most cases made by physical examination. Typically, a midsystolic click is heard, often followed by a late systolic murmur [3]. The diagnosis is confirmed by two-dimensional echocardiography. MVP generally has a

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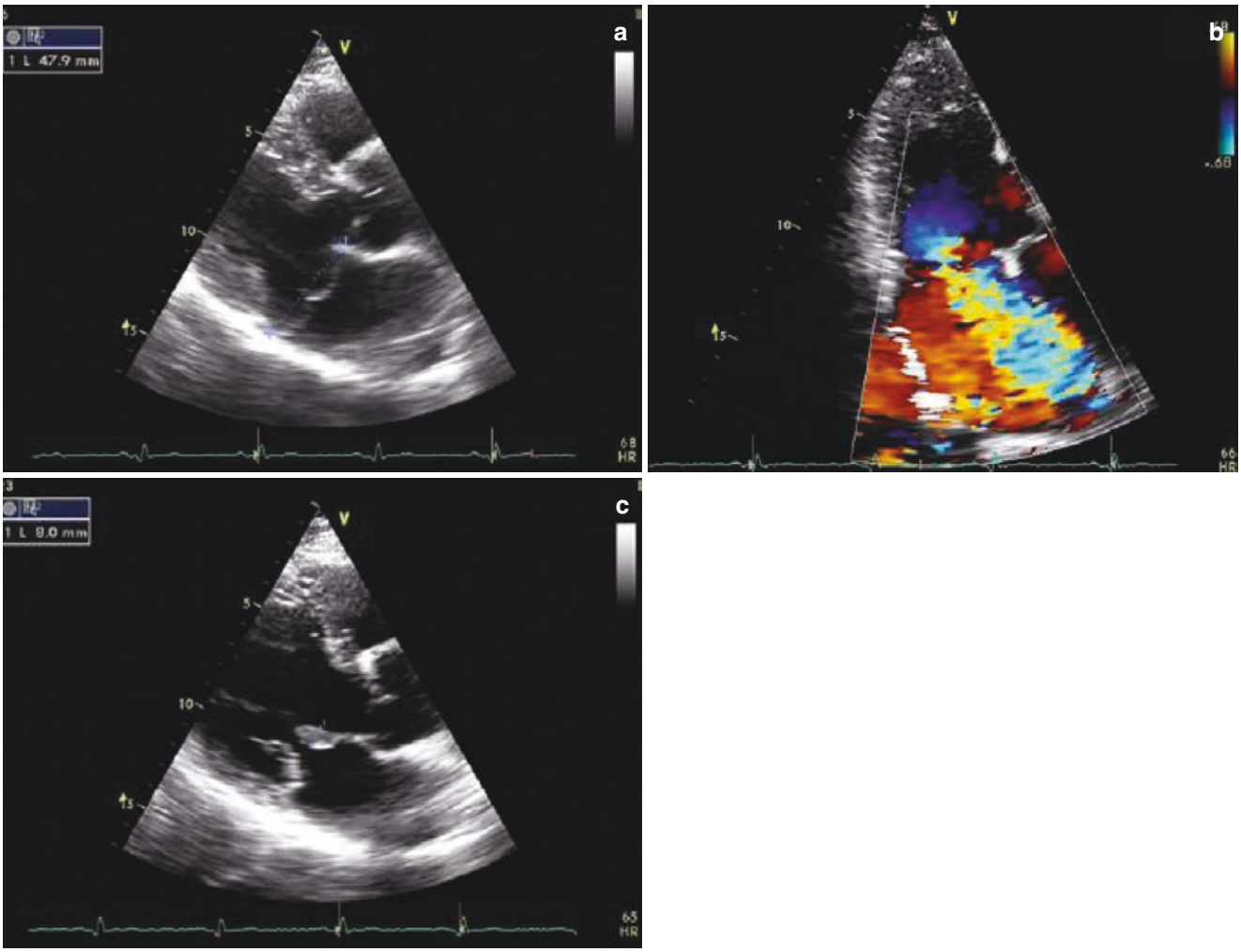


Fig. 25.1 (**a**) Parasternal long axis echocardiography showing classical mitral valve prolapse. Both posterior and anterior myxomatous mitral valve leaflets are billowing up to 6.5 mm in the left atrium during systole. (**b**) Apical three-chamber echocardiography with color Doppler flow measurement showing moderate to severe mitral regurgitation in the same patient. The left atrium is enlarged. (**c**) Parasternal long axis demonstrating myxomatous tips of both anterior and posterior mitral valves measuring 8 mm

good prognosis, however, in 25% of patients, MVP may progress to significant mitral regurgitation [9].

Complications such as severe mitral insufficiency, heart failure, thromboembolic complications, and sudden cardiac death are rare, especially in patients with nonclassical prolapse. Freed and coworkers, from the Framingham study group, found that these complications affected only 3% of all patients with MVP [6]. However, patients with classical prolapse carry a higher risk for complications [10]. It is not surprising that patients above 50 years who have a decreased left ventricular function, moderate to severe mitral regurgitation, and atrial fibrillation exhibit a high complication rate.

The risk for infective endocarditis was found to be raised; in a population study (Olmsted USA) where nearly 900 MVP patients were identified and followed up, the 15-year cohort risk of infectious endocarditis after MVP diagnosis was $1.1 \pm 0.4\%$ [11]. However, current guidelines for infectious endocarditis no longer advocate the use of prophylactic antibiotics in patients with MVP. Only patients who are known to have had endocarditis should receive infective endocarditis prophylaxis when appropriate [12].

Mitral regurgitation may, among other things, lead to atrial arrhythmias including atrial fibrillation and therefore to thromboembolic complications. Antithrombotic medication, on the other hand, should be given only if classical risk factors unrelated to MVP are present. Mitral valve reconstruction or replacement is advocated when severe mitral regurgitation leads to symptoms. In asymptomatic patients, when left ventricular (LV) abnormalities are present (LVEF $\leq 60\%$ or LVESD ≥ 45 mm), surgery is indicated. Atrial fibrillation or pulmonary hypertension in asymptomatic patients with preserved LV function are reasons to consider surgery [13].

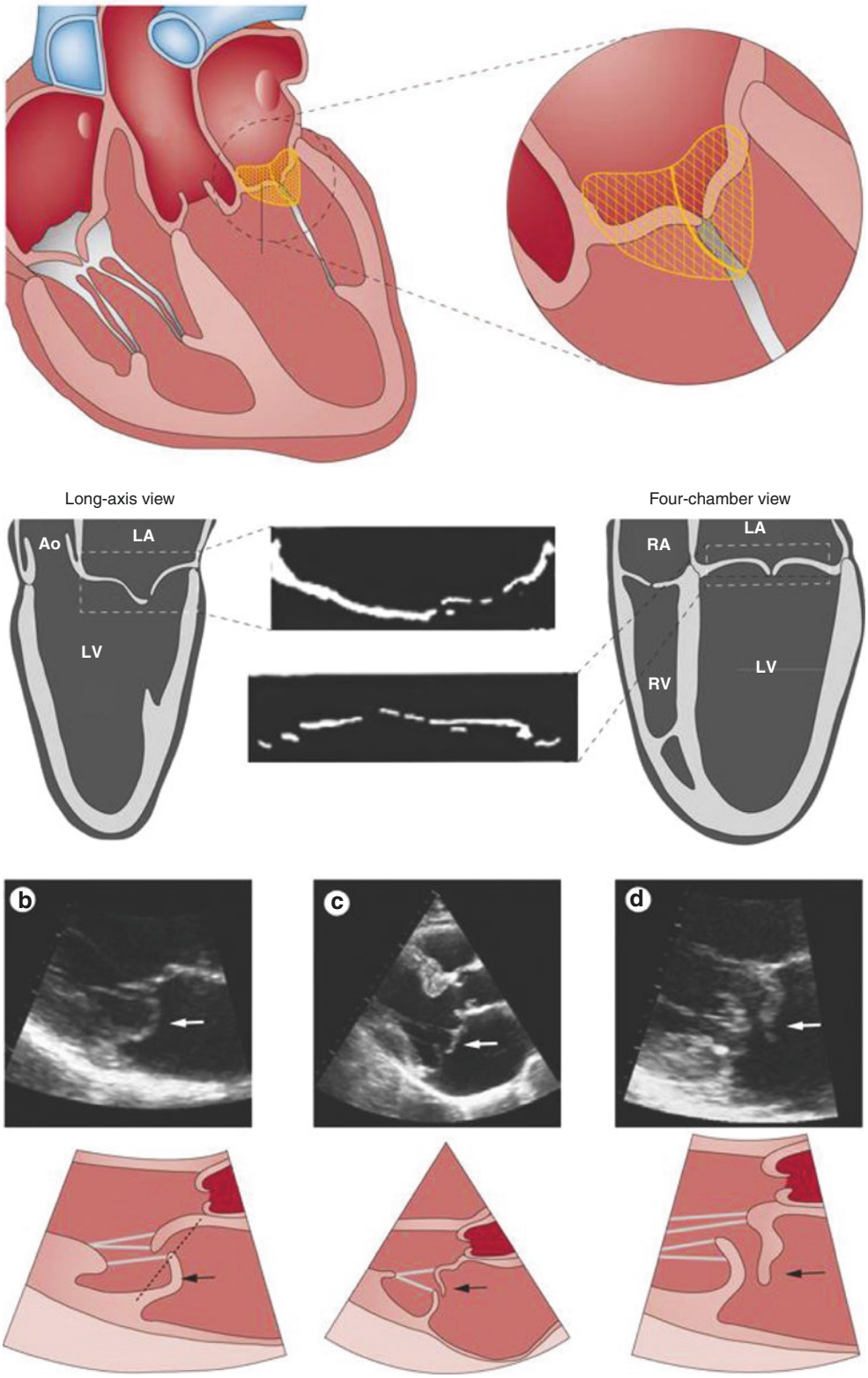


Fig. 25.2 Echocardiographic diagnosis of mitral valve prolapse. (**a**) Diagnosis of mitral valve prolapse must take into account the normal saddle shape of the valve and annulus, which produces opposite leaflet–annular relationships in perpendicular views. Mitral valve prolapse is most specifically diagnosed by leaflet displacement above the annular high points, imaged in long-axis views; and by leaflet misalignment at their point of coaptation. (**b**) Parasternal long-axis echocardiographic view of posterior leaflet prolapse (arrows) beyond the annular hinge points (dashed line). (**c**) Anterior leaflet prolapse and partial flail (partial eversion of the leaflet tip into the dilated LA; arrows) relative to the posterior leaflet, which is restricted, tethered by the dilated LV. These opposite leaflet displacements increase the regurgitant gap between the leaflets. (**d**) Patient with extensive leaflet thickening and anterior leaflet flail (arrows). *Ao* aorta, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle. From Levine et al. [8]

Ventricular Arrhythmias and Sudden Cardiac Death in MVP

Sudden cardiac death occurs twice as often in patients with myxomatous valve disease/MVP as compared to the general population, with sudden death rates of 0.2–0.4% per year [10, 14]. SCD is found more often in patients with impaired left ventricular function, moderate to severe mitral regurgitation, and redundant chordae [15]. Interestingly, in a series of 200 victims of sudden cardiac death younger than 35 years, mitral valve prolapse was the only cardiac abnormality that could be found in as many as 10% of cases [16]. In a SCD series <40 years of age, recently studied by Basso et al., 7% of cases (13% females) had MVP as a sole anomaly [17]. This might be age dependent; in a recent Sudden Unexplained Death Syndrome general population study (mean age 70 ± 15 years) MVP was observed in 2.3% of individuals prior to the sudden cardiac arrest event [18]. This percentage is similar to, e.g., the Framingham Heart offspring study (2.4%) [6].

The involvement of two leaflets might also contribute to life-threatening arrhythmias and sudden cardiac death: in a series of 24 otherwise unexplained OHCA cases, 42% had bileaflet MVP. In addition to these abnormalities, patients with life-threatening arrhythmias were (mainly) females, more often demonstrated T wave abnormalities (biphasic, or inverted T-waves) and complex ventricular ectopy (multiform premature ventricular complexes, ventricular bigeminy, VT or VF) [19, 20]. Also, at a population level, bileaflet MVP was associated with a higher level of VTs as compared to single leaflet MVP and controls [19]. These individuals with bileaflet MVP, however, did not appear to portend a poor prognosis when compared to single leaflet MVP or controls. Interestingly, bileaflet MVP was associated with a lower rate of all-cause mortality [19]. These data suggest that bileaflet MVP may in a subset of cases be associated with structural changes that predispose to VT, but also reassure that, at least at the population level, incidentally noted MVP does not signal an elevated risk of fatal arrhythmias or mortality.

Although patients with MVP more often exhibit atrial and ventricular arrhythmias during Holter monitoring, the exact mechanism for pro-arrhythmia in MVP is not yet completely understood [21]. Mechanical stress on the papillary muscles resulting in fibrosis may contribute. On MRI late gadolinium enhancement suggesting fibrosis can be found in the papillary muscles and the inferobasal wall in MVP patients with complex ventricular arrhythmias [22]. These findings and additional pathological evidence of myocardial fibrosis in one or both papillary muscles and adjacent LV free wall and the inferobasal wall were recently described [17, 23].

Endocardial friction lesions from mechanical contact from the relapsing leaflets may also play a role; not only in inducing fibrosis but also in triggerring premature contractions resulting in ventricular arrhythmias [24]. So a combination of substrate-related fibrosis and mechanical effects may trigger premature contractions that subsequently may predispose to ventricular arrhythmias. In line with these observations, a common phenotype characterized by syncope, frequent, and repetitive premature ventricular contractions (PVCs) originating from the posterior papillary muscle was found in patients with “severe myxomatous MVP disease” (i.e. the combination of bileaflet prolapse, myxomatous mitral valve with thickened leaflet, and mitral annular disjunction) after aborted SCD [25].

These different observations and additional literature reviews suggest that there is a specific subgroup of MVP patients that may be at particular risk for SCD; i.e., young adult female, with bileaflet MVP, biphasic or inverted T waves in the inferior leads, and frequent complex ventricular ectopic activity with documented ventricular bigeminy or (polymorphic/RBBB morphology complex) ventricular tachycardia (VT) and premature ventricular contractions (PVCs) configurations of outflow tract alternating with fascicular or papillary muscle origin [17, 20, 26–28].

Treatment of Ventricular Arrhythmias in MVP

The ESC guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death do not mention how to treat this specific group of patients. Assuming that the mechanism of ventricular arrhythmias is caused by a focus from the papillary muscles, then symptomatic patients with papillary muscle tachycardia should be treated with beta-blockade, Verapamil, or sodium channel blockers (class IC agents). If this treatment fails or the patient refuses using medication, catheter ablation should be considered [29]. A subset of patients with malignant ventricular arrhythmias like in bileaflet MVP syndrome may benefit from ablation therapy having less symptoms and less ICD shocks [20, 30]. An ICD is generally indicated as secondary prevention; however, data on the recurrence of cardiac arrest are still lacking [31].

Genetic Aspects of Mitral Valve Disease

Mitral valve prolapse has for many years been known to be familial in a subset of cases with an autosomal dominant mode of inheritance with reduced penetrance, influenced by age and sex [32–35]. Most patients with MVP present with a

family history of valvular disease. MVP was found in 46% of first-degree relatives over 20 years, whereas only 16% of patients below that age were affected, suggesting progressive disease with age-dependent penetrance [36]. A recent population study showed that parental MVP is associated with an odds ratio of about 5 for MVP in offspring, also suggesting a genetic contribution to MVP.

Therefore, cardiac screening of first-degree family members may be considered in patients with MVP. When conducting family studies, echocardiography should be performed. Holter monitoring can be performed in the presence of complaints or a family history of sudden cardiac death.

Until today, three loci for genetic myxomatous autosomal dominant MVP have been identified, on chromosomes 16p11.2-p12.1, 11p15.4, and 13q31.3-q32.1 (MMVP1 [37], MMVP2 [38], and MMVP3 [39]). The genes underlying MMVP2 and MMVP3 have been identified so far. The gene in MMVP2, *DCHS1*, was identified in a large family and its role was confirmed in two smaller families [40]. a recent follow-up study showed that rare in silico predicted pathogenic variants in *DCHS1* can also be frequently identified in sporadic cases of MVP [41]. One has to be aware that the presence of a rare in silico predicted variant does not automatically implicate an explanation for the disease, as determining pathogenicity can be a challenge (see Chaps. 1 and 2). Extensive functional analysis has suggested a role for the DCHS1 protein in the development of cardiac valves [40].

The gene underlying MMVP3 was recently discovered in a single large family [42]. The gene, *DZIP1*, regulates the genesis of cilia protein and/or cilia signaling. Cilia are microtubule containing structures that are largely used to propel fluid or gametes, and also function to transduce mechanical, electrical, and chemical signals in a tissue-specific and time-dependent context. They relay information from the microenvironment to influence cell survival, differentiation, and tissue organization. The proportion of *DZIP1* in MVP cases still has to established, but this observation further opens the possibility that MVP may turn out to be a disease of valvular cilia defects [42].

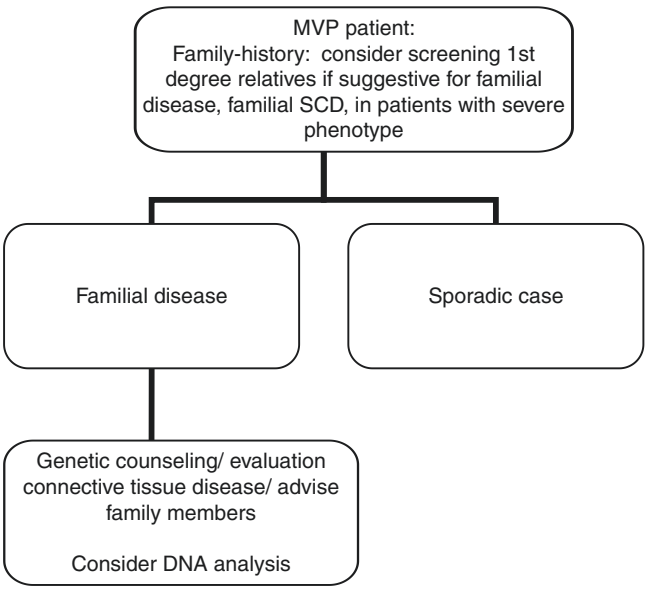
The gene encoding Filamin A (*FLNA*) has been identified in X-linked myxomatous mitral valves in different unrelated families [43, 44]. Males carrying FLNA mutations exhibit a severe phenotype, often manifesting at young age (neonatally-40 years) with polyvalvular involvement, while females (heterozygotes) show milder manifestations of the disorder [45, 46]. The mitral valve degenerative lesions worsen over time, with a substantial lifetime risk (75%) of valve surgery in men [45]. Furthermore, a paradoxical restricted motion in diastole can be seen, which is unique in MVP diseases. Also, other structural cardiac abnormalities like atrial and ventricular septal defects and aortic root dilatation can be found in mutation carriers. Filamin A is an actin binding protein that plays a pivotal role in cell motility and membrane stability. Filamin A may contribute to the development of myxomatous changes of the cardiac valves by regulation of transforming growth factor-β (TGF-β) signaling through its interaction with Smads activated by TGF-β receptors [46, 47]. Defective signaling cascades that involve members of the TGF-β superfamily have been described in impaired remodeling of cardiac valves during development. A clear role for mutations in the *TGF-β* gene and its receptors in MVP has not yet been proven [44, 48].

The exact role of monogenic MVP still has to be elucidated: the larger pedigrees studied suggest that rare, highly penetrant genes may indeed underlie the disease phenotype, while familial clustering in the population may be due to either highly penetrant rare alleles with a strong effect size or (multiple common) variants with smaller effect sizes. GWAS studies have indicated risk loci for MVP in *LMCD1* (LIM and cysteine domain transcription factor) and *TNS1* (encoding the focal adhesion protein tensin 1) genes and a SNP in a metalloproteinase gene, *MMP2*, are associated with disease [49, 50].

Molecular Diagnostics

The role of molecular genetics in MVP is limited because only three genes have been identified so far. The selection for targeted screening of one of those genes can be based upon family history or the results of clinical evaluation of family members. These genes may also be included in larger panels that are generally designed to evaluate generalized connective tissue diseases like marfan and ehlers-danlos syndromes that may also be associated with MVP. The specific clinical features of these disorders can, however, in most cases, also be recognized by careful clinical evaluation. Clinical genetics centers often offer special clinics for diagnosing these patients.

Family Screening and Follow-Up in Relatives



Summary

Mitral valve prolapse is the most common valvular disorder with a strong genetic contribution. The course of disease is benign in most cases, but serious complications such as heart failure, severe mitral regurgitation, bacterial endocarditis, ventricular arrhythmias, and sudden cardiac death occur, especially in patients with myxomatous degenerated valves. Bileaflet involvement, female sex, and substrate-related fibrosis and mechanical effects may trigger premature contractions that predispose to ventricular arrhythmias in a minority of patients. Until now, three chromosomal loci have been identified in autosomal dominant nonsyndromal MVP with *DCHS1* and *DZIP1* as the sole genes identified in dominant disease. Filamin A (*FLNA*) has been identified in X-linked myxomatous MVP, suggesting an underlying mechanism in the regulation of the valvular cytoskeleton. More genetic as well as clinical research is warranted to more precisely define patients at risk for this potentially lethal condition. First-degree relatives of patients with classical MVP and/or a history suggestive for familial disease (including signs of connective tissue disease such as aorta abnormalities) and/or SCD should undergo cardiac screening. In familial disease (MVP or connective tissue disease) or male patients with severe MVP or SCD, genetic screening should be considered.

Take Home Message

- MVP is a common, generally benign valvular disorder, with a familial character in a subset of cases
- Syndromal forms with MVP are rare and mainly consist of connective tissue disorders
- Sudden cardiac death rates are 0.2–0.4%/year
- Malignant arrhythmias infrequently occur: preliminary studies suggest that the substrate for arrhythmias seems related to fibrosis and mechanical effects that trigger premature contractions.
- Female patients with MVP, in particular those with bileaflet disease or posterior myxoid degeneration, repolarization abnormalities on ECG, and/or polymorphic/RBBB morphology complex ventricular arrhythmias may be at risk for SCD
- Cardiac screening should be considered in first-degree family members; particularly if a family history is positive for mitral valve disease, connective tissue disease, and/or sudden cardiac death
- Genetic screening/clinical genetic evaluation should be considered in males with severe (myxomatous) disease, X-linked pedigrees, or clear familial cases

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