TOPICS IN REVIEW

Genetic mechanisms underlying arrhythmogenic mitral valve prolapse: Current and future perspectives

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Mitral valve prolapse (MVP) is a heart valve disease that is often familial, affecting 2%–3% of the general population. MVP with or without mitral regurgitation can be associated with an increased risk of ventricular arrhythmias and sudden cardiac death (SCD). Research on familial MVP has specifically focused on genetic factors, which may explain the heritable component of the disease estimated to be present in 20%–35%. Furthermore, the structural and electrophysiological substrates underlying SCD/ventricular arrhythmia risk in MVP have been studied postmortem and in the electrophysiology laboratory, respectively. Understanding how familial MVP and rhythm disorders are related may help patients with MVP by individualizing risk and working to develop effective management strategies. This contemporary, state-of-the-art, expert review focuses on genetic factors and familial components that underlie MVP and arrhythmia and encapsulates clinical, genetic, and electrophysiological issues that should be the objectives of future research.

KEYWORDS Mitral valve prolapse; Cardiac arrhythmia; Sudden cardiac death; Genetics; Mitral annular dysjunction

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Introduction

Mitral valve prolapse (MVP) affects an estimated 2%–3% of the general population and can be familial.[1] Pathologically, MVP is a complex entity involving the "ventriculo-mitral unit" and is characterized by myxomatous structural changes of the valve apparatus with (1) "floppy" mitral valve (MV)

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KEY FINDINGS

- There is increasing recognition of arrhythmia in mitral valve prolapse (MVP) having a familial component.
- Overlap between inheritance, ventricular arrhythmias, sudden cardiac death, and MVP has been reported.
- Understanding familial MVP and its connection to rhythm disorders can help determine patient risk and ultimately aid in the development of effective management strategies.
- Prospective evaluation of arrhythmogenic MVP not only should include multimodality imaging, electrophysiological studies, and ablation, but also should incorporate family screening and genetic evaluation.

leaflets, which have the propensity to prolapse into the left atrium leading to mitral regurgitation (MR); and (2) attenuation and elongation of the chordae tendineae, which have an increased risk of rupture.[2] The disease can be complicated with severe MR requiring operative management. Furthermore, MVP with or without MR may have the potential to lead to ventricular arrhythmia (VA) and sudden cardiac death (SCD).

The annual rate of SCD in patients with MVP (0.2%–0.4%) is approximately twice as high as in the general population (0.1%–0.2%).[3] However, estimates of the incidence of MVP-related sudden cardiac arrest in the general population vary substantially according to methodology, study population criteria, and valve morphology criteria. It has been reported that MVP occurs in 2.3% of sudden cardiac arrest patients in the general population.[4] A study showed that MVP was observed in 11.7% of patients with unexplained SCD.[5] Furthermore, a study of 13 women showed that more than one-half of those with "unexplained" SCD had MVP.[6]

Although much of the sudden cardiac arrest/SCD risk in MVP is attributed to left ventricular (LV) dysfunction occurring secondary to severe MR, life-threatening VAs still occur in MVP patients with only trivial-to-mild MR. Arrhythmogenic mitral valve prolapse syndrome (AMVPS) is a clinical entity characterized clinically by frequent, complex premature ventricular contractions (PVCs) and sustained or nonsustained ventricular tachycardia (NSVT). These arrhythmias commonly arise from one or both papillary muscles and fascicular tissue. There are some reports of outflow tract PVCs or ventricular tachycardia (VT); however, this could be ascertainment bias given the prevalence of MVP and outflow tract tachycardias.[7] The exact mechanisms are not well understood.

Despite advances in clinical knowledge, the genetic mechanisms underlying MVP and their relationship to VA risk remain elusive. Understanding familial components and genetic aspects of the disease can help improve individual risk prediction and apply precision medicine approaches to management of MVP patients. Furthermore, screening and identifying MVP early and monitoring for complications is imperative. This review summarizes the current evidence regarding familial MVP, its genetic underpinnings, and arrhythmias associated with MVP.

Table 1 Definitions

MVP	MVP is a prevalent condition affecting 2%–3% of the general population and can be familial.[1] MVP is characterized by myxomatous structural changes of the valve apparatus with (1) floppy mitral valve leaflets, which have propensity to displacement into the left atrium leading to MR; and (2) attenuation and elongation of the chordae tendineae, which have a tendency to rupture.[2]
Malignant MVP	Malignant MVP has been characterized by ventricular fibrillation, survived cardiac arrest, and SCD. One study labeled a subset of MVP patients who experienced life-ventricular arrhythmias as "malignant."[17]
Arrhythmic MVP	Arrhythmic MVP may be due to overlap of MVP and an arrhythmic syndrome, or an overlap with a specific form of cardiomyopathy.
MVP with SCD	MVP with SCD usually refers to a decedent with an SCD event or survivor of sudden cardiac arrest with MVP.
Billowing	A term sometimes used to refer to the entire body of the leaflet(s).

MR = mitral regurgitation; MVP = mitral valve prolapse; SCD = sudden cardiac death.

Methods

Literature search

A comprehensive search of the literature in Medline via PubMed was conducted. Using the MESH terms "genetic" AND "mitral valve prolapse," 577 articles were found. Of these, we excluded nonhuman studies and studies regarding syndromic MVP. Overall, we included only studies relevant to genetics and heart rhythms. We included articles with both positive and negative findings in genetics. Although they were not very common, we looked for articles that included an overlap of MVP and arrhythmias.

Definition of MVP and mitral annular dysjunction

MVP is defined as prolapse of >1 mitral leaflets ≥2 mm above the mitral annulus on a long-axis view.[8] It should be noted that parasternal views are preferred to apical 4-chamber views because the latter may show the mitral leaflets to ascend above the annulus without distorting leaflets and may be misdiagnosed as MVP. MVP can be single or bileaflet, and it can be due to disruption or elongation of

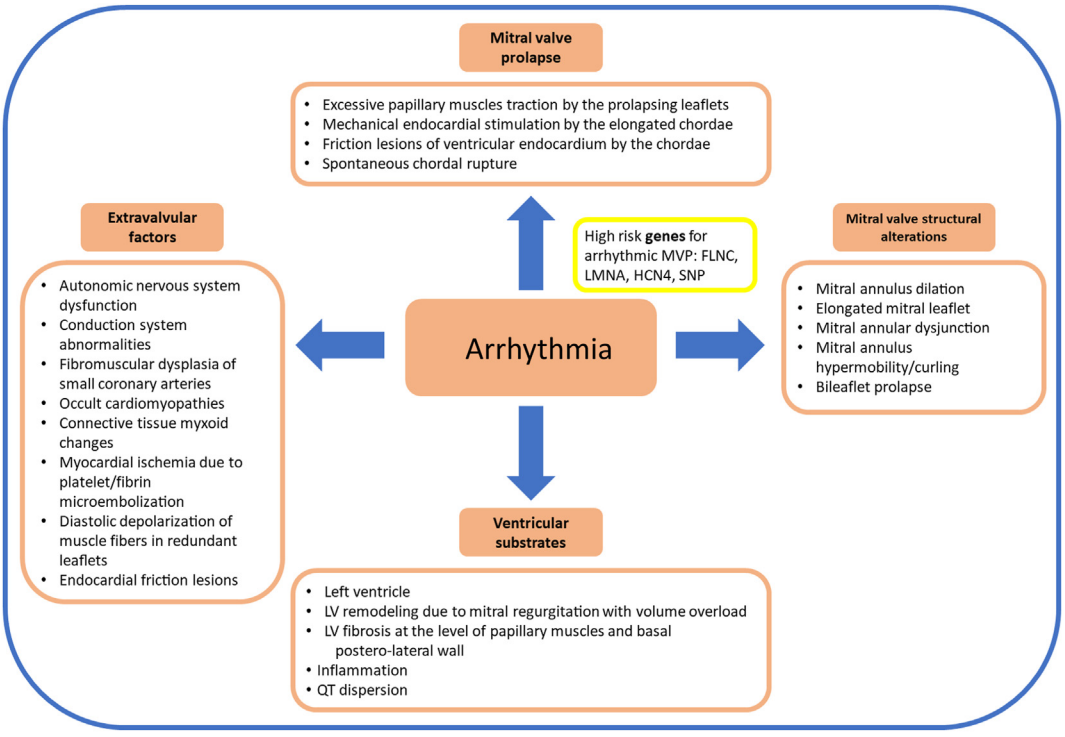

Figure 1 Associations between valve and ventricle conditions and arrhythmia. Arrhythmia has a variety of secondary effects related to mitral valve prolapse (MVP), extravalvular factors, mitral valve structural alterations, and ventricular substrates. LV = left ventricle.

leaflets, chordae, or papillary muscles. Classic bileaflet MVP with thickening ≥5 mm is defined as the Barlow valve.[9] However, MVP without MV thickening (ie, <5 mm) has also been reported. Fibroelastic deficiency with chordal thinning, elongated leaflets, and possibility of rupture with varying MVP and varying MR is the more frequent type of MVP (vs myxomatous Barlow) (Table 1).[10]

Mitral annular dysjunction (MAD) can coexist with MVP and without MVP, and it is associated with increased risk of PVCs as well as SCD.[11,12] The absence of MVP has suggested arrhythmias with MAD may indicate a separate syndrome or a common upstream antecedent before the subsequent development of MVP. MAD features an abnormal insertion of the hinge line of the posterior mitral leaflet on the atrial wall, with mitral annulus demonstrating a dysjunction between the leaflet–atrial wall junction and the crest of LV myocardium.[13]

By imaging, MAD is defined as separation ≥5 mm between the mural leaflet insertion site in the atrium and the base of the lateral LV free wall, which may be seen on echocardiography but is best identified with cardiac magnetic resonance (CMR).[11] In addition, a recent study of UK Biobank data showed MAD is nearly universal, but inferolateral MAD is more likely to be pathogenic. However, definition of apparent (or pseudo-MAD, posterior mitral leaflet inserted in diastole at the ventricular-atrial junction) vs true MAD (posterior mitral leaflet displaced on the atrial wall either in diastole or systole) may need confirmatory studies based on systematic advanced imaging analysis.[14]

Definition of AMVPS

VAs reported with MVP include both monomorphic and polymorphic PVCs, NSVT, and sustained VT, as well as ventricular fibrillation (VF) (Figure 1).[3,15,16,17] When studying malignant MVP syndrome, 1 study included patients who had histories of unexplained out-of-hospital arrest with documented cardiovascular collapse from VT or VF that required defibrillation to restore sinus rhythm.[16] However, it is important to note that the definition of malignant MVP syndrome has varied since this review. Nonetheless, despite the limited clarity on what exactly is meant by "arrhythmogenic" and "malignant," the presence of frequent arrhythmias has been termed arrhythmic MVP; and VF, survived cardiac arrest, and SCD are termed "malignant MVP syndrome." It should be noted that these definitions and terms have varied in the literature, with some (inappropriate) use of these interchangeably as synonyms. The recent consensus statement defines arrhythmogenic MVP as[13] (1) the presence of MVP (with or without MAD); (2) VAs that are [2a] PVCs ≥5% burden or [2b] complex VAs (NSVT, VT, VF); or (3) absence of other well-defined arrhythmogenic substrates. Arrhythmogenic MVP can occur with severe degenerative MR and independent of MV severity (Table 1).

Clinical risk factors for arrhythmogenic MVP

Several markers of arrhythmogenic MVP have been reported, including T-wave inversion in the inferior leads, female sex, bileaflet myxomatous leaflets, late gadolinium enhancement

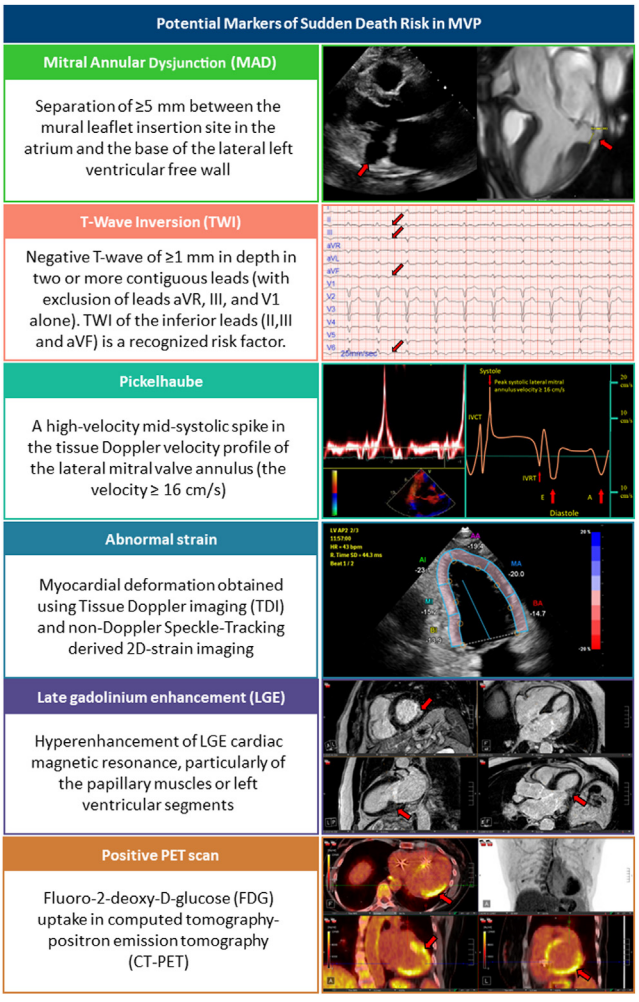

Figure 2 Possible phenotype presentations of mitral valve prolapse (MVP). There are multiple phenotypic potential presentations of mitral valve prolapse, including Pickelhaube sign, late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), inflammation on computed tomography–positron emission tomography (CT-PET), and mitral annular dysjunction (MAD) on transthoracic echocardiography and CMR. FDG = fluoro-2-deoxy-D-glucose; TDI = tissue Doppler imaging; TWI = T-wave inversion.

(LGE) on CMR, Pickelhaube sign, curling and paradoxical systolic annular expansion on echocardiography, inflammation on computed tomography–positron emission tomography, and MAD on echocardiography or CMR (Figure 2).[13] Although many findings regarding these biomarkers have not been reproduced, validated, or tested systematically, they are essential when understanding MVP risk and presentation.

Interestingly, MAD ≥9 mm is a strong predictor of NSVT, and in MVP without significant MR, the presence of MAD seems to be an independent predictor of PVCs and NSVT.[3,12] This was demonstrated in both a long-term study of a cohort of 595 MVP patients and a study of 116 MAD patients that used echocardiography and advanced CMR imaging.[3,12]

Inheritance of MVP

Landmark studies showing familial heritability

Before discussing contemporary genetic studies (Supplemental Table 1), it is important to summarize landmark studies reporting the familial aspects of MVP. In the past, studies have shown the familial component to MVP,[18] but the extent of familial clustering in the community with more specific echocardiographic criteria was unknown. Multiple studies have used loosely defined terms such as "floppy mitral valve" and "mitral valve click," which has led to inaccurate epidemiological estimates until standardized echocardiography-based studies were conducted. On imaging, MVP presents as systolic prolapse of 1 or more segments of one or both mitral leaflets into the left atrium. A more recent study from Framingham used defined echocardiographic criteria to systematically assess MVP.[19] In that longitudinal study using 3 cohorts from 3 different generations, it was determined whether MVP and nondiagnostic MVP morphologies are related to a high prevalence of MVP in offspring.[20] The participants from the 3 generations consisting of the original cohort, the offspring cohort, and generation 3 were divided into 2 groups: one without parental MVP (n = 3493) and one with at least 1 parent with MVP (n = 186). These groups were compared with respect to their clinical and echocardiographic characteristics. Results showed that both parental MVP and nondiagnostic MVP morphologies are associated with an increased chance of MVP in offspring, thus supporting the familial link to MVP.

Environmental

Familial patterns are not always the result of shared genetics, as family members often share the same environment. Th contribution of genetics and environment is often determined using twin studies. MVP has been observed in twin cases for decades.[20] A recent study assessed differences of concordance rates of diagnosed MR between monozygotic and dizygotic twins.[21] The concordance rate for monozygotic twins was found to be twice that of dizygotic twins. This indicates the importance of genetics in MVP through monozygotic studies but also environment with dizygotic studies.

Genetics

Linkage studies and candidate genes

Chromosome 16p11.2

A study from 1999 described 4 pedigrees and provided evidence for an MMVP1 locus between D16S3068 (16p11.2) and D16S420 (16p12.1).[22] No causal gene was identified. Furthermore, analysis in a more recent study did not show linkage of the family to the MMVP1 locus.[23]

Chromosome 13

By evaluating echocardiograms and blood samples from 43 individuals in a pedigree, a new locus, *MMVP3*, was found, and there was support found for the linkage on chromosome 13q31.3-q32.1.[24] Later, this study was used as groundwork

for another study in which evidence for primary cilia causing MVP was acquired.[25] Specifically, exome sequencing of certain members of the pedigree corroborated the finding that primary cilia may be involved in MVP, specifically through the cilia gene *DZIP1*.

Filamin-A

Filamin-A *(FLNA)* was studied because of the genetic linkage identified on chromosome Xq28 in a large family from Nantes, with multiple valves affected.[26] It was essential to understand the genetic causes of this linkage, and further investigation of this family revealed a P637Q mutation in the *FLNA* gene. Three other mutations were identified in smaller families.[27] In another study with 8 families, a p.G288R missense mutation in *FLNA* that was formerly identified was located in one of the families.[28]

To better understand the function of filamin-A, the role of filamin-A in MV development was studied, and a molecular mechanism was shown by which valve interstitial cells regulate matrix organization during fetal valve development. When the regulatory interactions concurrent with development are interrupted, myxomatous valve disease can occur.[29] When further studying filamin-A, by looking at the gene (*FLNA*) that produces this protein, a role of *FLNA* N-terminal repeats in small Rho-GTPases regulation was found. It was determined that the balance between RhoA and Rac1 GTPase activities was deregulated as a result of the FlnA-G288R and P637Q mutations on the actin cytoskeleton.[30] MVP-associated FlnA mutations likely end interactions between *FLNA* and PTPN12. This may be involved in the physiopathology of *FLNA*-associated MVP.[31]

Recently, a study was conducted to discern the relationships between the genotype and phenotype of *FLNA*-MVD.[32] Among 246 subjects with 3 varying *FLNA* mutations, *FLNA*-MVD was determined to be degenerative and developmental.[32]

Overall, the one successful linkage regarding chromosome Xq28 allowed for the identification of a causal filamin gene.

TGFBR1 and TGFBR2

In a study of 8 families with isolated familial MVP (5 with VAs), transforming growth factor beta receptors gene type I (TGFBRI) and II (TGFBR2) were investigated.[28] After clinical and genetic evaluation, it was determined that mutations in both of these genes likely do not underlie these MVP cases, as no mutations were found in either gene.[28]

Exome sequencing in families

Pathogenic/likely pathogenic variants in DCHS1 *and valve morphogenesis defects*

Chromosome 11p15.4

Using a pedigree, 41 individuals spanning over 5 generations were examined.[23] Analysis identified the *MMVP2* locus for autosomal dominant MVP that maps to a region on chromosome 11p15.4.[23] Members of this family were later investigated by exome sequencing, and multiple variants in the candidate gene *DCHS1* were identified.

When capture sequencing of chromosome 11 was performed in humans, a deleterious missense variant in the gene *DCHS1*, which is the human homologue of the Drosophila cell polarity gene dachsous, was identified.[33] *DCHS1* plays a role in valve morphogenesis. In the zebrafish *Danio rerio,* knockdown was performed with the goal of assessing the functional impact of the *DCHS1* variants: *dchs1a* and *dchs1b*. Whereas no cardiac phenotype was observed in knockdown of *dchs1a*, knockdown of *dchs1b* showed significant changes in cardiac morphology: reduced expression resulted in a cardiac atrioventricular canal defect. This defect was unable to be rescued by *DCHS1* mRNA with the familial mutation but could be rescued by wild-type human *DCHS1*. Knockdown of *dchs1b* also led to regurgitation of blood from the ventricle into the atrium, thus further demonstrating the role of *DCHS1* in disease pathogenesis.

To first determine whether MVP had a developmental origin, expression and functional analyses during embryonic and fetal timepoints were conducted in mice.[33] These methods also helped in determining the time in development at which the issue arises in MV formation. It was found that changes in the MV in *DCHS1*+/– occurred after embryonic development, and the phenotype exhibited in the mice was traced back to developmental errors during valve morphogenesis.

To further investigate the role of *DCHS1*, the presence and frequency of known and new variants in the gene were studied in patients with MR. Evidence was provided for the role of *DCHS1* in the pathogenesis of MVP, and variants were located that are potentially affiliated with sporadic cases of MVP. Overall, Mendelian genes and single nucleotide polymorphisms (SNPs) can be viewed on a spectrum based on their effect size and frequency (Supplemental Figure 1).

Defects in primary cilia

When studying primary cilia in the context of MVP, exome sequencing in families was combined with linkage. Defects in the genes and regulated pathways of primary cilia have the potential to lead to MVP in humans.[25] Previously, analysis of a multigenerational family with MVP showed linkage to chromosome 13. Notably, *DZIP1,* a gene associated with altered developmental processes involving primary cilia, is in the linked region. Thus, further analysis on this gene was conducted to better understand its connection to MVP.

Whole exome sequencing was conducted on 4 affected family members, and a missense variant affecting DZIP1 isoforms p.S70R and p.S24R was found. Next, a genetically accurate mouse model for nonsyndromic MVP was created, and the study showed that mice with the DZIP1 mutation develop myxomatous MVs and MVP. This animal modeling allowed for a more in-depth understanding of development. Results indicate that there is a developmental basis for MVP through regulation of extracellular matrix by cilia.

As demonstrated in this study, modeling mutations in mice provides strong evidence about the mechanism of a cilia

defect. This mouse model potentially can be used in future mechanistically focused studies.

Genome-wide association studies analyses/meta-analyses

In 2015, Dina et al[34] conducted a meta-analysis of 2 genome-wide association studies (GWAS) that marked the identification of the first MVP risk loci. The study used consensus inclusion criteria of adult idiopathic MVP patients based on echocardiographic measurements or surgeon diagnoses. They identified multiple candidate genes, including *LMCD1* (SNP rs17408) and *TNS1* (SNP rs12465515).[34] These genes may play a role in degeneration of the valve during development. More recent analyses have built upon this study.

Polygenic/MVP polygenic risk score

In 2022, the first and primary polygenic risk score (PRS) was developed by Roselli et al.[35] They conducted a meta-analysis of 6 GWAS and defined MVP according to contemporary echocardiography society guidelines. The study identified 16 relevant genetic loci associated with MVP. Furthermore, multiple candidate MVP genes were identified. Using results from the meta-analysis, they calculated a PRS using the PRS–continuous shrinkage method. To validate their PRS, they applied it to UK Biobank data, which originally was excluded from their meta-analysis. The performance of the PRS, which is associated with 1,097,364 variants, was found. Improved MVP risk prediction was seen when combining the PRS to a model with age, sex, and clinical risk factors.[35]

Leveraging epigenetics

The use of epigenetic open chromatin maps in mitral tissue is valuable in annotating GWAS loci. For instance, in 2021 Kyryachenko et al[36] used assay for transposase accessible chromatin using high-throughput sequencing (ATAC-Seq) to further understand gene expression and regulatory elements in the MV. Open chromatin of myxomatous valves were found to play an important role in MVP, as MVP-associated variants are significantly and specifically enriched in this chromatin. Additionally, SNPs were selected from the 2015 study by Dina et al[34] at 6 MVP-associated loci and further analyzed. The results showed that rs6723013 is a potential causal variant at the *IGFBP5/TNS1* locus while rs2641440 at the *SMG6/SRR* locus is a potential regulatory SNP. Along with Kyryachenko et al, in 2022 Roselli et al[35] analyzed open chromatin regions in MV tissue. They showed that the sentinel variant at the *LMCD1* locus is located in a region of active chromatin.[35] The results using this methodology support the usefulness of genome-wide chromatin accessibility profiles in the search for relevant genes to MVP onset and must continue to be utilized.

Pathophysiology of MVP

A basic ultrastructural feature of MVP is marked proliferation of the spongiosa and the fibrosa or ventricularis. The spongiosa is the delicate myxomatous connective tissue between the atrialis (thick layer of collagen and elastic tissue that forms the atrial aspect of the leaflet), and the fibrosa is a dense layer of collagen that forms the basic support of the leaflet. Myxomatous proliferation of the acid mucopolysaccharide-containing spongiosa tissue causes focal interruption of the fibrosa, especially in older populations of patients who can also develop chordal rupture. Secondary effects of primary MVP include fibrosis of the surface of the MV leaflets, thinning and/or elongation of the chordae tendineae, and ventricular friction lesions. Fibrin deposits often form at the MV–left atrial angle.

Interestingly, a study showed that when Follistatin-Like 1 (FSTL1) is deleted from the endocardial/endothelial lineage in a mouse model, abnormal MV leaflets developed.[37]

Inheritance of arrhythmias and SCD

Risk of arrhythmias and SCD in MVP

The first descriptions by Barlow and Bosman[9] and Barlow et al[38] of MVP reported an association with VAs and SCD. Afterward, most studies reported MVP as being benign. However, around the year 2000, renewed interest based on observational data reported an association of MVP with PVCs and also SCD.[3,15,16,17] Arrhythmias were shown to develop more frequently in patients with severe MR than in the general population.[14] Consideration of these 2 risk factors is essential when studying MVP. A study of 650 young adults showed that an underestimated cause of arrhythmic SCD is MVP, as the disease was associated with 7% of the total deaths.[17] There may be a relationship between hemodynamically uncomplicated MVP and arrhythmic SCD, as suggested by the finding of MVP in SCD victims or survivors of life-threatening arrhythmias.[7]

A recent prospective study investigated the risk of arrhythmia and outcomes in 595 consecutive patients with MVP evaluated at the Mayo Clinic.[3] On 12-lead electrocardiogram, 26% of patients showed combined T-wave inversion/ST depression (details on specific leads were lacking). The frequency of VAs was common, with 43% experiencing PVCs >5%. Furthermore, although increased mortality in arrhythmic MVP syndrome was noted, the proportion that resulted from SCD was unknown. Based on this finding, chronic ambulatory heart rhythm monitoring would be beneficial in the long-term follow-up of MVP patients. In addition to the limitation of variably defined MVP criteria, this study did not look at a pure "malignant MVP syndrome population." Although there are benefits to this approach, the malignant component of MVP was not the sole focus of the study. In the future, a study focusing on the malignant component of MVP and utilizing more advanced technology such as programmed ventricular stimulation, Holter monitoring, and loop recorder may be considered.

Overlap between inheritance, rhythms/SCD, and MVP

Given the high prevalence of MVP in the general population, the question arises as to whether the reported frequency of

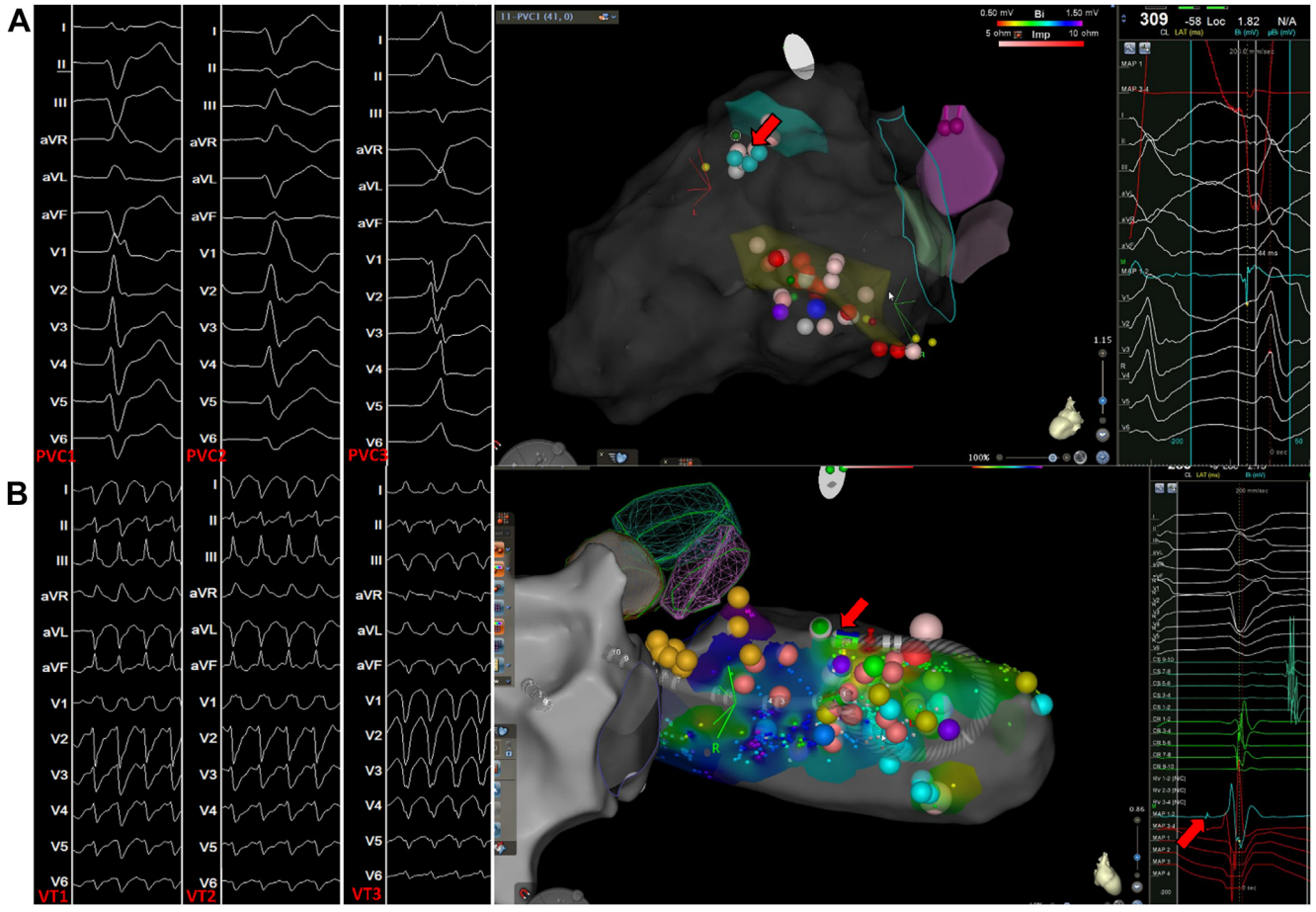

Figure 3 Clinical cases with premature ventricular contractions (PVCs) from papillary muscle and fascicular ventricular tachycardia (VT) ablated. **A:** Case 1. Best ablation site for PVC 2 on anterolateral papillary muscle *(arrow)*. **B:** Case 2. Sharp Purkinje potential very early to mid-diastolic during VT1 *(arrows)*.

MVP in SCD populations is a genuine "signal" or "noise" due to ascertainment bias. If the association is real and MVP is the cause, then deciphering the pathophysiological mechanisms is crucial because this could be a target for prevention.

Mechanisms of arrhythmia in MVP

Prolongation of the QT interval[38] and repolarization abnormalities with T-wave inversion in the inferolateral leads are reported as associations with arrhythmic MVP.[9,17,39] PVCs from papillary muscles, Purkinje fibers, outflow tracts, and fascicular systems have been reported (Figure 3).[7,40] Mechanisms may include regional stretch from mechanical forces resulting in PVCs either directly at the site of leaflet insertion into the papillary muscle or due to contact of prolapsing leaflet with ventricular myocardium in diastole. Furthermore, LGE has been seen in papillary muscles and basal inferolateral LV, consistent with reports of fibrosis on postmortem studies.[17] It has been demonstrated that myocardial stretch can result in shortening of action potential, decreased resting diastolic potential, and increased stretch-activated early afterdepolarizations. Additionally, invasive electrophysiological studies have shown Purkinje potentials commonly precede VF.[40]

Abnormal Ca^{2+} handling may lead to delayed afterdepolarizations. Autonomic changes include increased sympathetic, decreased vagal, and increased catecholamine levels.[9] Thus, the "perfect storm" leading to VF and SCD may involve substrate (fibrosis), a proarrhythmogenic state (such as QTc prolongation), and delayed afterdepolarization inducing arrhythmias.[7] Furthermore, as a new paradigm to evaluate MVP, rare and common genetic variation plays a role in creating a "susceptible" myocardium that reacts maladaptively to an inherent MVP-related cardiomyopathy vs MVP-induced direct/indirect mechanical trauma.

Evidence of a genetic link between arrhythmias and MVP

Case studies

A 51-year-old man with AMVPS had multiple family members who also exhibited the disease, prompting pedigree-based exome sequencing/variant filtering. This sequencing revealed a variant in *FLNC* gene (p.Trp34*-FLNC), believed to contribute to the development of AMVPS in this small

kindren.[41] This novel finding was the first evidence that a heritable proarrhythmic genetic substrate may underlie some AMVPS cases. This case study provides evidence of a possible genetic link between MVP and VAs.

A case from 2023 further demonstrated a potential role of *FLNC*. A 58-year-old woman with bileaflet MVP and multiple types of arrhythmias was evaluated. Familial evaluation revealed SCD in her paternal grandfather and grandmother. The patient underwent genetic testing, which showed a frameshift and truncating pathogenic variant in *FLNC c.4926_4927insACGTCACA (p.Val1643Thrfs*26).*[42]

In a recent case study, echocardiography in a 28-year-old man revealed that he had MVP associated with moderate mid-late systolic MR.[43] He was also diagnosed with PVCs, an apical mid-to-late systolic murmur, LV dilation, and MAD. Multiple members of his family were previously diagnosed with cardiac disease. Specifically, his father had MVP and developed advanced heart failure. Genetic testing of the patient showed the existence of a novel frameshift and truncating variant of *LMNA* gene [1q22; NM_170707.3(LMNA): c.590_596del (p.Leu197Profs*2)]. Previously, this mutation was seen in association with a malignant dilated cardiomyopathy phenotype from VAs. This case demonstrates a potential relationship between MAD and MVP through genetics.

An association of arrhythmia, primarily sinus bradycardia, LV noncompaction, and MVP was demonstrated in multiple studies.[44] The cause was revealed as mutations and dysfunction of the hyperpolarization-activated cyclic nucleotide channel 4 *(HCN4).* Although this breakthrough finding demonstrates an association between arrhythmia and MVP, how the mutations in the ion channel led to this fatal phenotype is unclear.

A patient who suddenly collapsed and later found to be in VF was studied.[45] She had a history of a heart murmur and was diagnosed with bileaflet MVP as well as LV dysfunction and LV inferobasal wall fibrosis. She was found to have *LMNA* (c.1556 C>T, Thr519Ile) *and SCN5A* (c.3392 C>T, Thr113Ile) mutations. Whole exome molecular autopsy series provide additional evidence beyond case studies, showing that MVP with LV fibrosis may be a cause of an unexpected number of sudden unexplained deaths in the young patients. One study demonstrated a statistical increase in pathogenic/likely pathogenic variants in strong evidence channelopathy/cardiomyopathy genes.[46]

Despite the association shown in these case studies (Supplemental Table 2), further research is necessary to investigate the link between MVP, arrhythmia, and sudden death. There is potential for bias in these reports; however, using the current state of knowledge, it can be inferred that there is a likely causal relationship or a shared common cause, genetic or other. This will be particularly helpful in discerning whether arrhythmic MVP, also seen in families, is due to an underlying genetic arrhythmia or cardiomyopathy gene. It also is plausible that the MVP itself is familial and mechanisms leading to arrhythmia (described earlier) cluster because of the mechanism of MVP. This has value because the presence of what are considered high-risk genes, such as *FLNC, LMNA, RMB20, PLN,* truncating *TTN,* and *DSP,* may provide support for the implantation of primary prevention implantable cardioverter-defibrillators.

Challenges and opportunities

Although the familial and inherited components of MVP are well recognized, there is increasing recognition of arrhythmia in MVP also having a familial component. The overlap between inheritance, VAs, SCD, and MVP has been reported in multiple cases and families thus far. The presence of MAD and LGE by CMR have generally been regarded as secondary and indicative of increased risk. Interestingly, the presence of MAD in the absence of MVP associated with arrhythmias has challenged this concept. Studies reporting pathogenic variants in genes associated with nonischemic cardiomyopathy and ion channel disease have directed research in a new unrecognized direction: arrhythmic MVP syndrome may be due to overlap of MVP and an arrhythmic syndrome or an overlap with a specific form of cardiomyopathy. Whether MVP itself is a phenotype in these conditions remains to be determined. These reports are hypothesis-generating and underscore the importance of multicenter studies investigating arrhythmic MVP syndrome with well-matched nonarrhythmic controls. These participants should undergo deep phenotyping with multimodality imaging and electrophysiological studies to identify the origin of PVCs and mechanisms of arrhythmia, as well as autonomic testing. Genetic testing is now affordable and could be justified for arrhythmic MVP syndrome. Multimodality imaging is beneficial for diagnosis. Echocardiography can reveal the patient's leaflet involvement (single or bileaflet), degree of MR and LV remodeling, MAD, Pickelhaube sign, basal hypertrophy, and exaggerated posterior annular displacement (curling). CMR provides information on LV function, thinning of mid-inferolateral segment, LGE, and MAD extension, as well as the presence of diffuse interstitial fibrosis by T1 mapping techniques. Electrocardiographic monitoring helps identify PVC burden, and electrophysiological study will reveal information on induction of arrhythmia, the origins of PVCs, and role of the Purkinje system. Exercise stress testing allows for testing of suspected exercise-induced arrhythmia. It is important to know whether a patient has these arrhythmias. Although asymptomatic MR patients often can exercise at regular capacity, those with MR with exercise-induced complex arrhythmias should not participate in competitive or leisure sports. Nonetheless, low-intensity aerobic exercise can improve prognosis for these patients.

It is important to note that although some fascicular VTs and certain PVCs from the conduction system may be genetically linked to MVP, the majority of cases likely are not linked to MVP. The occurrence of short-coupled PVCs/VF in isolation of MVP argues for an (at least) in part independent basis. However, currently there are not sufficient data to support either side, and future research should focus on understanding this relationship.

In addition to focusing on more cases and families, large-scale, genetic, case-control studies of arrhythmic MVP vs nonarrhythmic MVP should be conducted. These can help identify either novel genetic variants or SNPs. Ample controls have been studied for SNPs and GWAS for MVP in general, but fewer cases with both MVP and arrhythmia exist. Thus, we must increase the sample size, which can be achieved by collaborating with investigators across the world. Additionally, it is of great importance to carefully interpret genetic results and understand how a structured and systematic approach to clinical phenotyping is central to the interpretation of genetic test results, variant classification, and reinterpretation. This will ensure more accurate conclusions.

Recommendations for family screening for MVP should be followed. For patients with Marfan or other Mendelian connective tissue disease and MVP, screening should be performed on at least all first-degree relatives (FDRs). For patients who have MVP with nonischemic cardiomyopathy, we also propose screening all FDRs. Family members of SCD patients who are identified as having MVP should undergo evaluation, but the frequency and modality are unclear based on current evidence (Supplemental Table 3).[17] Although there is a recognized familial pattern for isolated MVP, guidelines are vague on screening family members, likely because of the mostly polygenic nature of the disease. Importantly, because 20 arrhythmogenic MVP may have an underlying Mendelian cause, despite the lack of evidence in the literature, we recommend at least all FDRs be screened.

The ethical, legal, and social implications (ELSI) of this screening should be considered. ELSI aims to provide protection of human rights while balancing the development of economic, commercial, and research advancements in the genetics and genomics field. To better define the ELSI risks in our rapidly evolving genomic testing world, there needs to be an internationally harmonized criterion to lessen the risk of harm to the patient.

Searching for acquired causes of arrhythmias in MVP may help elucidate their relationship. Arrhythmias are not uncommon in patients with heart inflammation diagnosed with myocarditis, pericarditis, or endocarditis. In fact, in the differential diagnosis of SCD in myocarditis, the potentially malignant tachy- and bradyarrhythmias are of utmost importance. Understanding heart inflammation in the context of MVP can provide potential evidence for the link between MVP and heart rhythm. Endocarditis, pericarditis, and myocarditis have been seen in patients with MVP. Specifically, a study of a population-based cohort from Minnesota reported a strong association between MVP and infective endocarditis.[47] Uncovering the potential role of heart inflammation in the link between MVP and arrhythmias can help patients with any of these heart diseases. A study of dogs demonstrated that the process of myxomatous MV disease can be associated with oxidative stress and inflammation.[48] A recent study showed an association between MVP and focal-on-diffuse uptake, a surrogate for myocardial inflammation.[49] It has also been indicated that nonuniform LV remodeling with LV fibrosis is essential to SCD development in MVP patients. In isolated MVP and SCD patients, a significant endocardial-to-epicardial gradient of cardiac fibrosis within the lateral and posterior walls was observed, which is comparable to other disorders that are responsible for cardiac remodeling.

In addition to the commonality of heart inflammation in MVP patients and arrhythmia patients, fibrosis is associated with both issues. Recent research demonstrates that LV replacement myocardial fibrosis in MVP patients is associated with VA. A study of SCD victims with MVP and trivial MR showed a high prevalence of myocardial fibrosis and overall changes in the myocardium that may be involved in arrhythmic MVP.[50] Increasing our understanding of the plausible contribution of fibrosis to the relationship between MVP and arrhythmia is essential.

Along with fibrosis and inflammation as potential bridges between MVP and arrhythmia, recent research has identified a link between facioscapulohumeral muscular dystrophy and both MVP and arrhythmia. One study showed that MVP is present in 9% of facioscapulohumeral muscular dystrophy patients without significant MR, and atrial fibrillation or flutter is present in 5% of patients. Such data further highlight clinical and genetic heterogeneity in MVP.

It has been shown that MV repair surgery can abate (although not necessarily cure) VAs. A retrospective study of 4477 MV surgery patients identified 8 patients with an implantable cardioverter-defibrillator before and after surgery. The 5 patients who had an arrhythmia before surgery experienced decreased adverse effects after surgery.[51] It is imperative to further study this relationship because it will help to facilitate the understanding of the mechanistic links between MVP and VAs. Additionally, understanding the outcomes of repair surgery in reducing the risk of life-threatening arrhythmic events will help determine optimal timing for surgical intervention.

The potential for heart inflammation, fibrosis, and other disorders to play a role in the relationship between MVP and arrhythmias requires further research. Additionally, the search for mutations linked to MVP must continue. Future research is necessary to identify more causative rare mutations and search for target genes that play a role in the disease. Specifically, evaluating the extent to which the rs1558666 risk allele carriers are more prone to MV degeneration compared to noncarriers is essential.

In the future, we propose further genomic research on arrhythmic MVP syndrome. It is imperative that patients be screened early and that family history of MVP, arrhythmias, and SCD be kept in mind. In addition, we suggest state-of-the-art multimodality imaging, future genetics studies, and multicenter collaboration.

Conclusion

MVP is a complex entity of the whole ventriculo-mitral unit. MVP is recognized as potentially familial, whether with or without arrhythmia. The genetics of MVP alone suggest

multifactorial, although in connective tissue disease they can be monogenic. Several studies of families with arrhythmic MVP syndrome suggest FLNC, LMNA, SCN5A, and HCN4 as possible effect modifiers. This may suggest that the dominant paradigms of mechanical stretch and calcium handling are not the only mechanisms and warrant further multicenter studies.

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Appendix

Supplementary data

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