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Review

Genetic background of mitral valve prolapse

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Abstract

Mitral valve prolapse (MVP) has a prevalence of 2–3% among the population. It involves a heterogeneous group of patients with different expressions and according to the phenotype can be further divided into fibroelastic deficiency, which is mainly considered as a degeneration due to aging, and myxomatous disease, frequently associated with familiar clusters. Thus, MVP can be present in syndromic, when part of a well-defined syndrome, and non-syndromic forms. The latter occurs more often. To the second belong both familiar and isolated or sporadic forms. On one hand, among familial forms, although X-linked transmission related to *FLNA* gene was initially identified, further studies reported also autosomal dominant mode involving *MVPP* genes, including *DCHS1*. On the other hand, genome-wide association studies (GWAS), among unrelated patients, allowed the identification of new MVP-associated genes, such as *LMCD1*, *GLIS*, and *TNS1*. Moreover, single nucleotide polymorphisms (SNPs) on metalloproteinase genes have been related to MVP. Interestingly some genes such as *DCHS1* and *DZIP1* have been reported to be involved in both familiar and isolated forms. The present review aims to illustrate the updated genetic background of MVP.

Keywords: genetics; familiar form; sporadic form; syndromic form; mitral valve disease; mitral valve prolapse; genome-wide study

1. Introduction

With its prevalence of 2% to 3% among the population, mitral valve prolapse (MVP) is the most frequent valvular heart disease [1]. The prolapse is characterized as the systolic superior displacement of almost one leaflet toward the left atrium, due to a fibro-myxomatous alteration in the valvular tissue [2,3]. Several studies have also demonstrated the association between MVP and ventricular arrhythmias and sudden cardiac death [4,5]. Using two-dimensional transthoracic echocardiography (2D TTE) at the parasternal view, MVP is defined as an abnormal displacement of one or both mitral leaflets >2 mm above the annular plane, occurring in systole [6]. MVP includes a large spectrum of heterogeneous entities and represent one of the most common valvular disease requiring surgery [7]. Pathologically, MVP is usually classified into Barlow's disease and fibroelastic deficiency (FED). In the first scenario the prolapse involves often more scallops and both leaflets, valvular tissue is redundant, thickened, and histologically affected by myxoid infiltration [8]. FED, instead, is due to deficiency of extracellular matrix (ECM) proteins, such as collagen, elastins, and proteoglycans, resulting in leaflet and chordae thinning, with increased risk of rupture [8].

MVP is encountered in various conditions. Non-syndromic (or primary) MVP, is the most common form, usually without extra-cardiac manifestations, or with only those benign [9]. The latter form can be further classified into isolated, or sporadic, and familiar. In the context of syndromic diseases, to name one Marfan syndrome (MFS), one of the multiple manifestations affecting several organs is represented by MVP (secondary MVP) [9].

Although several studies have been published so far on this topic, the genetic substrate of the disease, the prevalence of the genetic defects, and their relationship with phenotype remain to be investigated, especially in the clinical setting of sporadic forms. This manuscript summarizes the major genetic alterations and the related molecular pathways associated to date with MVP, focusing on the primary and the MFS-related forms of the disease.

2. Clinical findings and diagnosis of mitral valve prolapse

Historically, MVP was diagnosed based on cardiac auscultation and "classical" symptoms and signs, including dyspnea, chest pain, and electrocardiographic abnormalities. Nowadays through echocardiography, we can determine leaflet involvement and prolapse characteristics, such as chordal rupture, annulus dilation, and severity of regurgitation. Therefore it is considered the gold standard for diagnosis [6]. It is also well known that the "classical" MVP symptoms can be found at an equivalent rate in patients without any identifiable prolapse [1].

Although the accepted MVP definition is based on 2D TTE [6], independent studies showed that three-dimensional transesophageal echocardiography (3D TEE) offers a better characterization of prolapse in terms of segments involved than two-dimensional transesophageal echocardiography (2D TEE) [10,11]. Plus, since its measures are comparable with those surgical collected, 3D TEE is also considered the gold standard for surgical planning [10]. 2D TEE allows also the detection of both mitral annular disjunction (MAD), which is an unusual atrial displacement of the mitral valve leaflet hinge point, and, using tissue Doppler evaluation, Pickelhaube sign, a high-velocity positive systolic wave noted at lateral mitral annulus [12].

Electrocardiography and 24-hour Holter monitoring are used to detect atrial and ventricular arrhythmias; a higher probability of developing more dangerous, life-threatening arrhythmias was noticed in patients with a significant burden of premature ventricular contractions (PVCs) [13,14]. Cardiac magnetic resonance (CMR) imaging has been included in the MVP work-up by many groups, to accurately estimate left ventricular (LV) volumes and function, identify areas with late gadolinium enhancement (LGE), and improve arrhythmic risk stratification [15].

3. Methods

Two authors (NAG and PV) searched Pubmed and in October 2021 for the terms “mitral valve prolapse” and “gene”, “mutation”, “genetic”, “syndrome” between 1980 and 2021; references cited by retrieved studies were also screened. We restricted our search to studies that were published in English.

4. Non-syndromic form of mitral valve prolapse

4.1 Familiar

Genetically, non-syndromic MVP is a heterogeneous disease with two transmission modes (Fig. 1). Although MVP is widely deemed as a genetically transmittable disease, molecular abnormalities underlying its pathogenesis remain partially unclear and not suitable for diagnosis in a clinical setting [9]. In familial studies, autosomal dominant inheritance with different degree of penetrance is more frequent than the X-linked one. Gene expression seems to be influenced by gender and age, with high phenotypic variability even within the same family [16].

4.1.1 Autosomal dominant inheritance

Several studies conducted among different families pointed out that MVP was transmitted as a familial disease in >60% of cases. Soon was noticed that the expression was dependent on age and sex. Moreover, within the same family reduced penetrance and high pleiotropic variability were observed [16]. Autosomal dominant was the main heritable pattern. Therefore, MVP appeared as the most frequent Mendelian cardiovascular alteration [16]. Three loci in chromosomes 16p11.2-p12.1 (*MMVP1*), 11p15.4 (*MMVP2*) and 13q31.3-31.2 (*MMVP3*) were identified through linkage analysis in large MVP families [17–19].

In 2015, Durst *et al*. [20], by applying a targeted re-sequencing approach in a large family, identified *MMVP2* as a disease-causing gene. The analysis of the initial MVP pedigree showed a loss-of-function mutation in the *DCHS1* (Dachsous1) gene (R2513H), encoding a member of the cadherin proteins, and playing a role in planar cell polarity (PCP) [20]. Later investigations discovered another two *DCHS1* mutations (R2513H and R2330C). Although *DCHS1* variants are known to be associated with familial MVP, no *DCHS1* variants were found in any of the 95 Greek patients with isolated non-familial and non-syndromic MVP requiring surgery, studied by Boudoulas *et al*. [21]. Interestingly, Clemenceau *et al*. [22] investigated known and novel *DCHS1* mutations in a cohort of 100 subjects affected by moderate to severe organic mitral insufficiency and without neither symptoms nor familiar history of MVP. Although p.R2330C and p.R2513H mutations, tested by DNA specific sequencing assays, were not founded among these patients, *DCHS1* exome sequencing revealed 8 missense variants, of which 6 were considered as deleterious; p.A2464P, one novel variant and p.R2770Q and p.R2462Q), two rare variants, were included. These variants were predicted to be deleterious according to combined annotation-dependent depletion (CADD) scores greater than 25, which are in the same range as p.R2330C (CADD = 28.0) and p.R2513H (CADD = 24.3). Plus, 24 of 100 cases were carriers of at least one in silico-predicted deleterious missense variant in *DCHS1*, suggesting that this single gene may account for a substantial portion of cases [22]. The authors suggested that *DCHS1* could be involved also in the sporadic form of MVP [22].

DCHS1 seems to play a role in maintaining protein stability: indeed *Dchs1* (+/-) mice are affected by prolapse in the presence of thickened mitral leaflets, eventually due to morphological alterations in valve development, with disorganized interstitial cells. *DCHS1* lacks in patients with MVP or mice results in an altered migration and cellular patterning, suggesting its involvement in the disease pathogenesis.

4.1.2 X-linked inheritance

The first evidence of X-linked inheritance MVP pattern was advanced in the later 60s by Monteleone and Fagan [23]. A large France family with the same mode of transmission was also described later [24,25]. In this context, the X-linked MVP inheritance [24,25] was genetically related to chromosome Xq28. The P637Q mutation in the *FLNA* gene was found in all members with MVP following a standard positional cloning approach. Further stud-

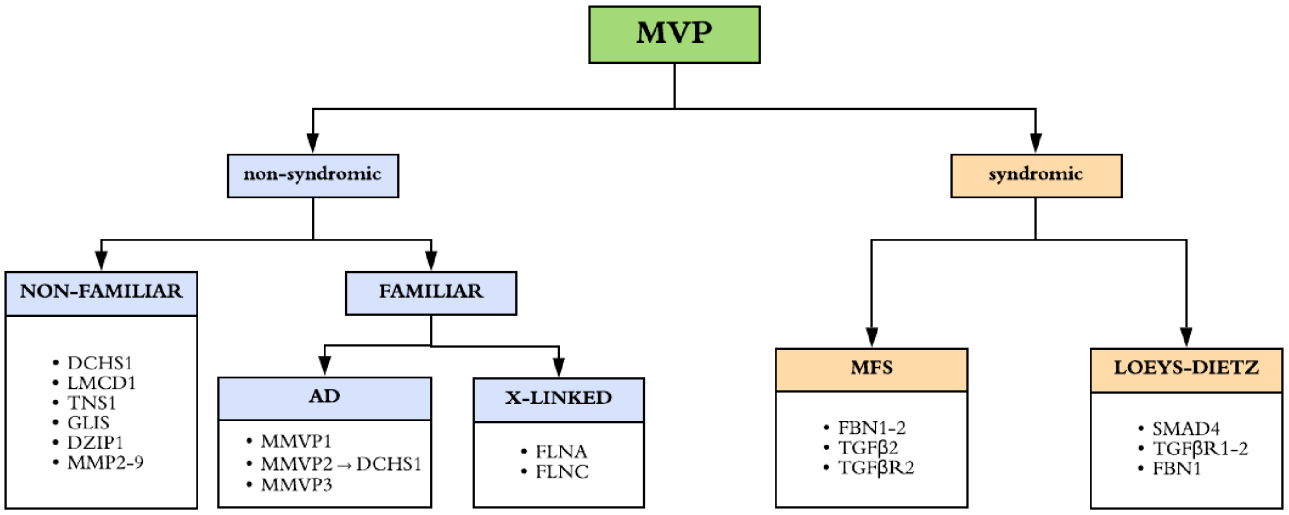

Fig. 1. The flow-chart shows the classification of the mitral valve prolapse in non-syndromic and syndromic forms; associated genetic abnormalities are shown for each form. AD, autosomal dominant; MFS, Marfan syndrome; LOEY_DIETZ, Loeys-Dietz syndrome.

ies on three *FLNA*-MVP affected, smaller, unrelated families confirmed the association of *FLNA* to X-linked myxomatous valvular dystrophy. Interestingly was observed a sex-related difference in the penetrance of the disease, as it was incomplete in women while complete in men. Recently *FLNA* mutations have been pointed out in families with an X-linked form of MVP/dystrophy [26]. Thanks to these studies, the *FLNA*-MVP phenotype is now characterized as involving both congenital and degenerative alterations of the MV apparatus, and frequent multi-valvular disease in men. Furthermore, the association between myxomatous degeneration, paradoxical restricted diastolic motion, and *FLNA* mutations makes until now *FLNA*-MVP the only genotypic-phenotypic characterization in MVP disease.

4.1.3 Filamin proteins

Filamin families involve isoforms A, B, and C. Bains *et al.* [27] reported about a 51-year-old man with bileaflet mitral valve prolapse, MAD, mild regurgitation, and ventricular arrhythmias (835 PVCs/h and NSVT). CMR showed modest delayed enhancement in the inferior and inferolateral LV wall. The proband was symptomatic for palpitations and pre-syncopal episodes. Electrophysiologic mapping of LV revealed PVC originating from the left anterior fascicle and postero-medial papillary muscle; catheter ablation was ineffective in eliminating VAs. Interestingly, many patient's relatives (older brother, mother, and maternal aunt) had MVP, MAD, frequent PVCs or NSVT, and mild to moderate LV enlargement as well. Whole exome sequencing was performed. A novel truncating variant (p.Trp34*-*FLNC*) was identified in the cardiomyopathy-causative *FLNC*-encoded filamin C, which co-segregated with the disease. These observations provided the first evidence of genetic substrate (*FLNC* haploinsufficiency mediated weakening of cell-cell adhesion) associated with cases of arrhythmogenic mitral valve prolapse syndrome [27].

4.2 Non-familiar forms

The first Genome-wide association (GWAS) study in MVP patients was performed by Dina *et al.* [28], among 1412 sporadic MVP cases and 2439 controls. The study pointed out three loci at 2q35, 17p13, and 22q12 genome-wide significant associated with MVP. Analyzing the genes related to relevant haplotypes, the Authors identified *LMCD1* (*LIM* and cysteine domain transcription factor) [28]; the latter seems to be involved in mitral and tricuspid valve abnormalities causing insufficiency, as demonstrated by morpholino knock-down in zebrafish [28]. The same effect was observed in the *TNS1* (Tensin1) knock-down [28]. *TNS1*, which is involved in focal adhesion control, and *LMCD1* regulates cell migration and replication and takes part in MVP, eventually acting on valve growth.

In 2019, another GWAS study found mutation 1p32.3 in *GLIS* family zinc finger 1 (*GLIS1*) located on chromosome 1, encoding *GLI*-related Kruppel-link zinc finger protein. The latter acts as a positive/negative transcription regulator [29]. Since *GLIS1* is expressed by endothelium and mesenchymal cells of the murine mitral valve and its knock-down in zebrafish models determine valvular insufficiency in developing hearts, it could play an important role in MVP pathogenesis [29].

A recent updated meta-analysis of GWAS for MVP by Yu *et al.* [30], using an improved case-control sample and dense imputation coverage, replicates the association on Chr2 as the top association signal near *TNS1*. Plus, a new risk locus on Chr1 (*SYT2*) and 2 suggestive risk loci on chromosome 8 (*MSRA*) and chromosome19 (*FBXO46*), all driven by common variants, were discovered. These genes

and loci seem to be extremely significant to MVP degeneration, mainly during valvular evolution [30].

4.2.1 DAZ Interacting Zinc Finger Protein

Toomer *et al*. [31] have recently investigated the role of the cilia in MVP development using different methods, discovering that primary cilia expression is finely modulated during cardiac valves evolution and is involved in ECM modifications. The normal expression of primary cilia avoids a consistent trigger of ECM gene pathways in the anterior leaflets, especially in the early phase of myxomatous degeneration; the authors also observed ECM expansion and histological disarray, leading to mature myxomatous valve disease comparable to the one found in patients with MVP.

Based on the clinical observation of autosomal dominant polycystic kidney disease, a classic example of ciliopathy, and MVP comorbidity (about 25% of patients affected also have MVP [32,33]), Toomer *et al*. [31] suggested that cilia could contribute to mitral valve disease in humans. They verified their assumptions through three different experiences: first, starting from Dina *et al*. [28] GWAS study, they carried out a gene set enrichment analysis of the 278 genes involved in primary cilia biology, finding a modest but significant enrichment of MVP-associated variants in this cilia gene set. Furthermore, they found out throughout immunohistological examination of *DCHS1* and *FLNA* knock-out mice a significant reduction of MV primary cilia length. Toomer *et al*. [31] also analyzed a large family with autosomal dominant transmitted MVP, earlier associated with chromosome 13. Of 43 family members studied, 11 patients had a full clinical diagnosis for MVP, 2 individuals presented moderate to severe mitral insufficiency, and 1 needed surgical intervention due to chordal rupture. All MVP-affected members did not present any syndromic feature. Recently in the linked region *DAZ* Interacting Zinc Finger Protein 1 (*DZIP1*), involved in ciliogenesis and/or in cilia signaling, was found. Therefore, a whole-exome sequencing of four MVP presenting family members was performed disclosing a single heterozygous missense variant leading to a serine-to-arginine switch in already known *DZIP1* isoforms (p.S70R and p.S24R), which was further demonstrated with Sanger sequencing. Within the linkage interval that segregated with disease phenotype the only coding change recognized was this *DZIP1* variant. Sequencing on further 15 sporadic patients with MVP by whole-exome sequencing revealed rare *DZIP1* variants with possible pathogenic meaning in two of them [31].

4.2.2 Single nucleotides polymorphisms (SNPs)

Several single SNPs in genes implicated in ECM, collagen turnover, renin-angiotensin-aldosterone system, and beta-1 adrenergic receptor polymorphisms have also been associated with MVP [34–37]. Metalloproteinase (*MMP*) polymorphisms, *MMP2* rs2285053, *MMP2* rs243865, and *MMP9* rs3918242 in patients with MVP have been reported [36,37]. Balistreri *et al*. [37] performed a prospective case-control study to assess eventual associations of some functional SNPs in *MMP-2* and *MMP-9* genes with the mitral valve degeneration (MVD) risk, symptom severity, and short- and long-term (4.8 years) complications. For this purpose, 90 patients requiring MV surgery in the settings of myxomatous degeneration and two control groups (one with no MVP at enrolment but developing the disease 4.8 years later, and a healthy one), were genotyped for rs3918242 *MMP-2*, and rs2285053 *MMP-9* gene SNPs. Associations between these SNPs and symptom severity and short- and long-term (4.8 years) complications were evaluated. Interestingly, rs3918242 *MMP-9* and rs2285053 *MMP-2* SNPs, when recessive, were significantly more represented in cases than in the two control groups and were associated with a higher MVP occurrence risk at 4.8 years (OR for recessive rs3918242 *MMP-9* and rs2285053 *MMP-2* SNPs vs healthy control 3.71 and 2.44, respectively). Furthermore, 20% of controls carriers of the identified genotypes, developed MVP at a 4.8-year follow-up [37].

5. Syndromic forms of mitral valve prolapse

5.1 Marfan related mitral valve prolapse

MFS is a rare connective tissue disorder affecting 1 in 5000 patients, with autosomal dominant transmission [38]. MFS manifestations are different and tend to result in a pleiotropic presentation. Therefore, the diagnosis is clinically established with Ghent criteria [39]. Further, genetic and molecular tests are available to confirm the diagnosis in patients suspected of having MFS and fitting Ghent criteria [39,40]. Many MFS patients have coexistent MVP, accounting for a median prevalence of 56.7% (range 21.9%–100%) [41]. Although the presence of MVP in MFS has minor relevance, Ghent criteria included MVP in the score [42].

Fibrillins seem to be involved in MFS pathogenesis. They are a high molecular weight ECM with structural and signaling activity. Despite mutations within Fibrillin-2 (*FBN-2*) have been shown to cause MFS, Fibrillin-1 (*FBN1*) mutations are mainly responsible for disease occurrence within patients with MFS [43]; MFS is also associated with variants of transforming growth factor-β2 (*TGFβ2*) and its receptor (*TGFβR2*). In the retrospective cohort by Détaint *et al*. [44], on 965 patients with *FBN1* mutations, the probability of developing MVP raised from 43% (95% CI: 40–47%) at 30 years of age to 77% (95% CI: 72–82%) at 60 years of age. In the same way, the probability of manifesting mitral regurgitation increased from 24% (95% CI: 21–28%) at 30 years of age to 61% (95% CI: 53–69%) at 60 years of age. Mitral regurgitation required surgery only in 3% (95% CI: 2–5%) and 13% (95% CI: 8–21%) of the patients at 30 and 60 years, respectively [44]. Most of the cardiovascular characteristics were not significantly different between patients with different types of mutations. Patients

with mutations altering a cysteine were noticed to have a higher probability of aortic annulus dilatation, aortic event, and MVP. Mutations within exons 24–32 were associated with a higher probability of all the cardiovascular features [44].

A retrospective single-center study by Demolder *et al*. [45] described a cohort of 142 patients with MFS and MVP [45]; 48 patients also had MAD. Patients with MAD more often had MVP, compared with those without (34 of 48 [71%] vs 14 of 94 [15%]; $p < 0.001$), PVCs (14 of 33 [42%] vs 15 of 70 [21%]; $p = 0.03$), and NSVT (13 of 33 [39%] vs 12 of 70 [17%]; $p = 0.01$). During the follow-up, 5 patients with arrhythmic events and 7 patients undergoing MV surgery were present in the group with MAD, and none in the group without it. However, in MFS the presence of MAD was independent of any type of *FBN1* variant and was not associated with predicted haploinsufficiency or a dominant-negative effect at the protein level [45]. Genotype-MAD phenotype remains to be investigated.

5.2 Other syndromic forms

Many previously reported disease associations are not supported by enough available data to assess the accurate prevalence of MVP or were described before the adjustment of new guidelines for its clinical diagnosis. Therefore, the association between MVP and several diseases: Down syndrome, fragile X syndrome, osteogenesis imperfecta, and Pseudoxanthoma elasticum, to name a few, might be over-reported [46]. However, strictly established genotype-phenotype associations turned our gaze to alteration of the connective structure molecular pathway. Trisomy 18, Loeys-Dietz syndrome (*TGFßR1-2*, *FBN1* gene mutations), Juvenile polyposis syndrome (*SMAD-4*, *BMPR1A*), aneurysm-osteoarthritis syndrome (*SMAD-3*), Williams-Beuren syndrome (*ELN*), Ehlers-Danlos syndrome (*collagen I, III, V, XI*), pseudoxanthoma elasticum (*MRP6*), osteogenesis imperfecta, *HCN4* mutations are syndromes associated with MVP. *FBN1*, *TGFβR1*, *TGFβR 2*, and *SMAD-4* genes are all involved in the TGFβ signaling network. Concerning the Loeys-Dietz syndrome, MV involvement was rarer in *TGFβR2* compared with *FBN1* patients: MVP was found in 21% vs 45% of patients ($p = 0.001$), MR in 35% vs 56% ($p < 0.0001$), and *TGFβR2* patients were seldom referred to MV surgery [47].

6. Molecular pathways

Nowadays, it is widely accepted that leaflet's degeneration is linked with the accumulation of myxoid ECM, the disarray of collagen, and elastin leading to myofibroblastic interstitial cells activation. However, the peculiar signaling pathways and molecular characters implicated are still uncertain. On one hand, mutations in the gene encoding the structural ECM protein *FBN1*, causing MFS, brings out the crucial function of the *TGF-β* signaling pathway in MVP. *FBN1* mutations are the major disease-causing variants within patients with MFS, although also other mutations within *FBN2* have been identified [43].

Fibrillins are a high molecular weight ECM protein playing structural and transcriptional functions. Structurally, they are part of microfibrils, ensuring mechanical and elastic support to the connective tissues [48]. Transcriptionally, fibrillins inhibit the action of a large latent *TGF-β* binding complex which regulates the level of *TGF-β* activity in the ECM [49]. In mice expressing mutant *FBN1* valvular leaflets were longer and thicker than in wild-type animals. *TGF-β* neutralizing antibodies have been seen to prevent these alterations [50].

On the other hand, also mechano-transductional pathways seem to play a role in MVP development, as shown in the case of *FLNA* and *DCHS1*. The protein encoded by *FLNA* is known to be an actin-binding protein that links actin filaments to the membrane glycoproteins. *FLNA* protein is involved in remodeling the cytoskeleton into changes in cell shape and migration and orchestrates many signaling pathways including mechano-transduction [51]. Mutations in this gene are associated with several non-cardiac syndromes. However, MVP-causing mutations are all clustered only in a structural unit located in the N-terminal region of the protein. Alterations in this region destabilized the interactions of *FLNA* both with the small *GTP*ases *RhoA* and *Rac1* (involved in actomyosin complex regulation and mechano-transduction pathway) and with the tyrosine phosphatase *PTPN12* (linked with numerous mechano-transduction and integrin signaling pathway actors) [51,52].

Furthermore, *DCHS1* is a member of the cadherin family expressed in fibroblasts. It seems to play a role in planar cell polarity and in morphogenesis coordinating cytoskeletal rearrangements and cell migration [20]. Larger and thicker leaflets were noticed in mice with lower expression of *DCHS1*; a missense *DCHS1* mutation segregated with MVP in a large family pedigree [20]. Although MVP is often considered as an age-dependent degenerative disease, developmental defects were also identified in homozygous FLNA-deficient mice and in zebrafish knocked down for *DCHS1*, as well as the *TNS1* and *LMCD1* genes [20,28,53]. However, how the decreased *DCHS1*, *TNS1*, and *LMCD1* expression affects mitral valve genesis and development remains unknown.

Le Tourneau *et al*. [9] suggested that the impact of hemodynamic and mechanical stresses on the function of mutant *FLNA* and *DCHS1* proteins may explain why patients specifically develop MVP despite the pleiotropic expression of the mutant proteins in other organs.

Balistreri *et al*. [37] underlined the potential involvement of *MMP*s genes in MVP development. This is also confirmed by surgically excised human myxomatous tissues presenting an increased *MMP*s release, and down-expression of related inhibitors (*TIMP*s), responsible for the disarray of collagen and elastin elements [54,55].

7. Conclusions

Identification of several genetic alterations in patients with mitral valve prolapse opens the field to a better understanding of the disease. However, to date, the precise pathogenetic mechanism of MVP development is still partly unknown. Also, the prevalence of genetic characterization of large populations is not available. Rare genotype-phenotype correlations are emerging, referring exclusively to hereditary contexts. Genetic predisposition to the development of arrhythmias is still one of the less characterized elements, however, recent evidences showed the association between arrhythmic mitral valve prolapse and *FLNC*-encoded filamin C haploinsufficiency mediated weakening of cell-cell adhesion.

Evidence of MVP as a familial disease in >60% of cases is an important finding, that pushes towards the inclusion of familiar screening and genetic counseling in the clinical evaluation of MVP patients. However, the prevalence of the genetic defects and their relationship with phenotype remain to be investigated, especially in the clinical setting of sporadic forms. MVP is a very frequent cardiac condition, therefore the routine application of genetic tests in sporadic forms would not be cost-effective. In familial and syndromic forms, in patients with significative arrhythmic burden related, or with severe mitral insufficiency, genetic tests might improve our understanding of the disease and help to identify genotype-phenotype characterization. We hope that these findings could represent the basis of a patient tailor medicine, in terms of diagnostic screening, monitoring and therapy.

Author contributions

NAG designed the research study and performed the research; MDB contributed to editorial changes in the manuscript, read and approved the final manuscript; CDR contributed to editorial changes in the manuscript, read and approved the final manuscript; GA contributed to editorial changes in the manuscript, read and approved the final manuscript; OA contributed to editorial changes in the manuscript, read and approved the final manuscript; FM contributed to editorial changes in the manuscript, read and approved the final manuscript; PV designed the research study and performed the research.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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