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GENETICS OF MYXOMATOUS MITRAL VALVE DISEASE: A SHORT REVIEW

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ABSTRACT
Myxomatous mitral valve disease (MMVD) is the most common cause of primary mitral regurgitation in developed countries and represents the main pathological substrate of mitral valve prolapse. Although traditionally considered an age-related degenerative condition, increasing evidence demonstrates that MMVD has a significant genetic component involving both rare pathogenic variants and common susceptibility alleles. Familial studies, linkage analyses, and genome-wide association studies have identified genetic abnormalities involved in valve development, extracellular matrix regulation and cytoskeletal organization. Understanding the genetic basis of MMVD has improved knowledge of disease mechanisms and may facilitate earlier diagnosis, family screening, risk stratification, and the development of future targeted therapies. Further integration of genomic, molecular, and clinical data will be essential for advancing precision medicine approaches in patients with myxomatous mitral valve disease.

KEYWORDS: Myxomatous mitral valve disease; mitral valve prolapse; mitral regurgitation; cardiovascular genetics; extracellular matrix remodeling.

INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common cause of primary mitral regurgitation in developed countries and represents the pathological basis of most cases of mitral valve prolapse (MVP). The disease is characterized by progressive structural remodeling of the mitral valve apparatus, including leaflet thickening, excessive leaflet motion, chordal elongation or rupture, annular enlargement, and accumulation of proteoglycans within the extracellular matrix (ECM). These changes lead to impaired leaflet coaptation and progressive mitral regurgitation, which may result in left ventricular dilatation, heart failure, atrial fibrillation, and, in selected patients, ventricular arrhythmias and sudden cardiac death (1,2).

Historically, MMVD was considered an acquired degenerative disorder related mainly to aging and chronic mechanical stress. However, increasing evidence from familial studies, twin analyses, linkage studies, and genome-wide association studies (GWAS) has demonstrated a strong genetic contribution. Mitral valve prolapse shows significant familial aggregation, and heritability estimates suggest that genetic factors account for approximately 40–60% of disease susceptibility (3,4). Current concepts therefore consider MMVD as a complex disease caused by interactions between inherited abnormalities in valve development, extracellular matrix regulation, and mechanical adaptation.

Genetic Architecture of Myxomatous Mitral Valve Disease

The genetic architecture of MMVD includes both rare monogenic forms and common polygenic susceptibility variants. Familial cases are usually transmitted as an autosomal dominant trait with incomplete penetrance and variable expression. Within the same family, some individuals may have mild leaflet displacement, whereas others develop severe bileaflet prolapse and significant mitral regurgitation requiring surgery at a young age (5).

Early linkage studies identified several chromosomal regions associated with familial MVP, including MMVP1 on chromosome 16p, MMVP2 on chromosome 11p, and MMVP3 on chromosome 13q (6). These discoveries demonstrated that MVP was not simply a consequence of tissue degeneration but could originate from inherited defects affecting mitral valve formation and maintenance.

More recently, next-generation sequencing has identified several genes involved in familial MMVD. These genes encode proteins involved in cell adhesion, cytoskeletal organization, developmental signaling, and mechanotransduction. In addition, GWAS have identified common genetic variants that influence susceptibility to sporadic MVP, supporting the concept that most cases represent a polygenic disorder rather than a single-gene disease (7).

FLNA: A Major Gene in Familial Mitral Valve Prolapse

The first gene clearly associated with inherited MVP was FLNA (Filamin A), located on chromosome Xq28. FLNA encodes a large cytoskeletal protein that connects actin filaments with membrane proteins and signaling molecules. Through these functions, filamin A regulates cell migration, adhesion, and response to mechanical forces.

Pathogenic FLNA variants cause an X-linked form of MVP characterized by abnormal valve development, myxomatous leaflet changes, and, in some cases, involvement of multiple cardiac valves. Human studies and experimental models have shown that altered FLNA function disrupts cytoskeletal organization and extracellular matrix remodeling, producing structural abnormalities similar to those observed in human MMVD (8).
The discovery of FLNA was important because it demonstrated that abnormalities of intracellular mechanical signaling could produce a degenerative valve phenotype. It also provided early evidence that MMVD involves defective developmental biology rather than simple age-related deterioration.

DCHS1 and Valve Development
A major breakthrough in MMVD genetics was the identification of DCHS1 (Dachsous Cadherin-Related 1) as a causative gene responsible for familial autosomal dominant MVP. Using positional cloning approaches, Durst and colleagues identified damaging DCHS1 variants in families with inherited MVP (9).
DCHS1 encodes a large cadherin protein involved in planar cell polarity, cell–cell adhesion, and embryonic tissue organization. During cardiac development, DCHS1 contributes to correct positioning and maturation of valve precursor cells. Loss-of-function variants interfere with normal valve morphogenesis, resulting in enlarged and redundant mitral leaflets that predispose to prolapse later in life (9).
Experimental models have confirmed the importance of DCHS1 in valve biology. Animals with impaired DCHS1 signaling demonstrate abnormal leaflet development and progressive valve dysfunction, supporting the concept that familial MMVD originates from developmental abnormalities that become clinically evident decades later.

DZIP1 and Primary Cilia Signaling
Another important gene identified in familial MVP is DZIP1 (DAZ Interacting Protein 1). DZIP1 plays a role in the formation and function of primary cilia, specialized cellular structures involved in mechanosensing and developmental signaling pathways, including Sonic Hedgehog signaling (10).
Primary cilia are increasingly recognized as important regulators of cardiac valve development because they allow cells to detect mechanical forces and coordinate tissue remodeling. Defects in DZIP1 impair ciliary signaling, leading to abnormal extracellular matrix organization and altered valve architecture. The discovery of DZIP1 expanded the understanding of MMVD genetics by linking valve disease with abnormalities in cellular mechanosensation.

Polygenic Susceptibility and Genome-Wide Association Studies
Although rare variants explain some familial cases, most MMVD occurs sporadically and results from multiple genetic factors. GWAS have identified several susceptibility loci associated with MVP, including variants near TNS1, LMCD1, and GLIS1 (11–13).
TNS1 (Tensin 1) encodes a focal adhesion protein involved in interactions between the cytoskeleton and extracellular matrix. Because mitral valve cells are continuously exposed to mechanical stress, abnormalities in focal adhesion pathways may increase susceptibility to progressive remodeling.
LMCD1 functions as a transcriptional regulator involved in cardiac development and gene expression. Altered LMCD1 activity may influence valve formation and maintenance.
GLIS1 belongs to the GLI-similar family of transcription factors and regulates developmental pathways involved in cellular differentiation. Variants affecting these genes are not sufficient alone to cause disease but contribute to the genetic background that determines individual susceptibility.

Molecular Mechanisms Linking Genetics to Disease
The genetic alterations identified in MMVD converge on several biological pathways.
Transforming growth factor-beta (TGF-β) signaling is one of the most important mechanisms involved in valve degeneration. Excessive TGF-β activation promotes fibroblast and myofibroblast activity, increases matrix turnover, and contributes to proteoglycan accumulation within valve tissue (14).
Extracellular matrix remodeling is another central process. Abnormal collagen organization, elastin degradation, and increased matrix metalloproteinase activity weaken the valve structure and promote leaflet enlargement and prolapse (15).
Endothelial-to-mesenchymal transition (EndMT), an essential process during normal valve development, may become pathologically activated in adult disease. Persistent EndMT contributes to abnormal valve interstitial cell activation and excessive matrix deposition (16).
Finally, mechanotransduction has emerged as a key concept linking genetics and biomechanics. Genes such as FLNA, TNS1, and DZIP1 regulate cellular responses to mechanical forces. Their disruption may impair the ability of valve cells to adapt to repetitive cardiac loading, accelerating myxomatous degeneration.

Clinical Implications and Future Perspectives
Syndromic Forms and Connective Tissue Disorders
Myxomatous mitral valve disease may occur as an isolated cardiac disorder or as part of inherited connective tissue syndromes. These syndromic conditions have contributed substantially to understanding the molecular pathways involved in mitral valve degeneration.
The most recognized example is Marfan syndrome, caused by pathogenic variants in FBN1, the gene encoding fibrillin-1. Fibrillin-1 is a major component of elastic microfibrils and regulates extracellular matrix integrity and transforming growth factor-beta (TGF-β) signaling. Abnormal fibrillin-1 function results in excessive TGF-β activation, contributing

to connective tissue remodeling and cardiovascular manifestations, including mitral valve prolapse and aortic root disease (17).

Similarly, Loeys–Dietz syndrome, caused by mutations affecting the TGF-β signaling pathway (including TGFBR1, TGFBR2, SMAD2, SMAD3, and related genes), may present with mitral valve abnormalities. These disorders highlight the importance of developmental signaling pathways in maintaining normal valve structure and demonstrate that abnormal regulation of extracellular matrix biology can lead to progressive valvular degeneration (18).

Although syndromic forms represent a minority of MMVD cases, their molecular characterization has provided important insights into pathways also implicated in isolated nonsyndromic disease.

Clinical Implications of Genetic Discoveries

The identification of genetic contributors to MMVD has changed the clinical approach to patients with mitral valve prolapse. A detailed family history should be obtained, particularly in patients with early-onset disease, severe myxomatous degeneration, bileaflet prolapse, or a family history of mitral valve surgery or sudden cardiac death.

Echocardiographic screening of first-degree relatives may be considered in families with multiple affected individuals. Early identification of valve abnormalities allows long-term surveillance and may facilitate intervention before irreversible ventricular remodeling occurs.

At present, routine genetic testing is not recommended for all patients with isolated MMVD because most cases result from a complex interaction of multiple genetic variants rather than a single pathogenic mutation. However, genetic testing may be valuable in selected situations, including:

- familial clustering of MVP or severe mitral regurgitation;
- diagnosis at an unusually young age;
- presence of systemic connective tissue features;
- suspected syndromic disease;
- involvement of multiple cardiac valves.

When a pathogenic variant is identified, genetic counseling and targeted screening of relatives may help identify individuals at increased risk.

Limitations of Current Genetic Knowledge

Despite major advances, several challenges remain. The majority of genetic studies have focused on European populations, and the contribution of ancestry-specific variants remains incompletely understood. Furthermore, the relationship between genotype and clinical phenotype is complex. Patients carrying similar genetic variants may develop very different degrees of valve disease, suggesting important roles for modifier genes, epigenetic regulation, inflammation, aging, and mechanical stress.

Another limitation is that many identified genetic variants are associated with increased risk but are not directly causal. Functional validation in experimental models is required to determine whether these variants alter valve biology.

Future studies combining whole-genome sequencing, transcriptomics, proteomics, and single-cell analyses will likely identify additional genes and regulatory pathways involved in MMVD progression.

Future Perspectives

The ultimate goal of genetic research in MMVD is to move from risk prediction toward disease modification. Current treatment remains largely surgical or interventional, with repair of the diseased valve being the standard therapy for severe symptomatic mitral regurgitation. However, surgery does not address the biological mechanisms that initiated disease development.

Genetic risk prediction models may eventually identify individuals likely to develop rapidly progressive disease, allowing personalized surveillance strategies. Integration of genomic information with advanced imaging techniques, including three-dimensional echocardiography and cardiac magnetic resonance imaging, may improve risk stratification.

CONCLUSION

Myxomatous mitral valve disease is increasingly recognized as a genetically influenced disorder rather than a simple degenerative consequence of aging.

Genetic discoveries have provided important insights into why some individuals develop severe mitral valve disease while others remain asymptomatic. Although clinical genetic testing currently has a limited role, continued advances in genomic medicine are expected to improve family screening, risk prediction, and eventually the development of targeted therapies.

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