Another Chromosomal Locus for Mitral Valve Prolapse
Close but No Cigar

Robert Roberts, MD

The mitral valve forms a complex apparatus whose closing and opening with the heartbeat coordinates the flow of blood from the left atrium to the left ventricle. In an average human life span, it does a command performance to the tune of ≈3 billion heartbeats. During the life span, the leaflets experience significant wear and tear exhibited by a thickening of the outer silk lining, but performance in most individuals remains graceful and relatively undeferred. This synchronized dance to the rhythm of the heartbeat, a rhythm which changes in response to emotional, mental, and physical demands, appears effortless and relentless. Beneath this superficial and necessary display, however, lurks many opportunities for a misstep. There have been decades of statistics suggesting that abnormalities in the mitral valve are common—2% to 16%. The symptoms, when present, are vague and include dizziness, palpitations, syncope, atypical chest pain, and dyspnea. On physical examination, the presence of a click or murmur often positions the patient for multiple tests, which can be a source of great emotional concern. Once the observation came that diet pills were associated with valvular dysfunction, echocardiographic analysis demanded by lawyers from urban billboards uncovered many patients with mitral valve prolapse and lifted the diagnosis to a new level of notoriety.

In the past 10 years, improved technology and community studies rather than hospital-based studies have ascertained a prevalence of ≈2.4%. This reduced prevalence is in part the result of better understanding of the 3-dimensional architecture of the mitral valve annulus provided by 3-dimensional echocardiography. This led to standardized echocardiographic criteria for the diagnosis of mitral valve prolapse. Classic mitral valve prolapse is diagnosed if upward displacement of the leaflet exceeds 2 mm and maximal thickness is ≥5 mm; nonclassic mitral valve prolapse refers to displacement that exceeds 2 mm but maximal thickness is <5 mm. It is comforting to know that the mitral valve apparatus is not significantly affected in 97% of individuals. Nevertheless, with a 2.4% prevalence, mitral valve prolapse would be expected to be present in 7.2 million individuals in the United States and 144 million worldwide. It is also of note that the prevalence is based primarily on European and North American populations and may not be representative of other ethnic groups. Fortunately, the complications of mitral valve prolapse—heart failure, mitral regurgitation, bacterial endocarditis, thromboembolism, and atrial fibrillation—although serious, are extremely uncommon and probably affect no more than 3% of those with mitral valve prolapse. It is not surprising that mitral valve prolapse is the single most common cause for surgical repair or replacement of the mitral valve.

The dawn of molecular genetics suggested new excitement in the landscape of this disorder. It has been recognized since Barlow and Bosman’s description in the 1960s of a family with this disorder that at least a certain proportion of individuals with mitral valve prolapse is hereditary. In 1999, a crack in the armor came when a family with mitral valve prolapse segregating as an autosomal dominant trait underwent genetic linkage analysis and a locus was mapped to chromosome 16p11.2-p12.1. Genetic linkage gave maximum multipoint LOD scores of 5.4 and 5.6, indicating that this was the responsible locus. This was confirmed by haplotype analysis showing a chromosomal region of about 5 cm containing the locus (a genetic distance equivalent to 5 million DNA base pairs) was present in all affected individuals. Analysis of this family showed mitral valve prolapse exhibits age-dependent penetrance and the disease seldom appears before age 30. The investigators evaluated several candidate genes but none showed a mutation responsible for the disease. In 2003, Freed et al identified a second locus for mitral valve prolapse at chromosome 11p15.4. Genetic analysis again confirmed this to be an autosomal dominant disease with age-dependent penetrance.

In this issue of Circulation, Nesta et al from the Levine laboratory have identified a third chromosomal locus for mitral valve prolapse on chromosome 13q31.3-q32.1 with a multipoint LOD score of 3.17. This is a marginal LOD score, but haplotype analysis does show that a portion of the chromosome containing the locus is present in all affected members of the family. This chromosomal segment contains >8 million bases (the postgenome era enables us to refer to the number of DNA bases rather than a genetic distance) and thus encloses a region with multiple genes. The disease exhibits autosomal dominant inheritance with age-dependent penetrance. Current knowledge indicates that there are at least 16 known genes in the region, several of which would appear to be good candidates for mitral valve prolapse. The mapping

See p 2022

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

Reprint requests to Robert Roberts, MD, President and CEO, University of Ottawa Heart Institute, 40 Ruskin St. Ottawa, ON K1Y 4W7, Canada. E-mail rroberts@ottawaheart.ca

Circulation is available at http://www.circulationaha.org
DOI:10.1161/CIRCULATIONAHA.105.569517

1924
of the location of 3 genes on 3 separate chromosomes bodes well for chromosomal mapping of genes; however, it is only the first step in providing us the opportunity to seek the gene and identify the ultimate defect. After identification of the defect, usually functional studies are required to elucidate the pathogenesis of the disease. Given the increased rapidity to sequence DNA and identify mutations, one can soon expect a fiesta of genes for mitral valve prolapse. Once the first gene is identified, it is likely to significantly accelerate the identification of other genes. This expectation is based on the assumption that the gene belongs to a class of molecules with a similar function that would be expected to induce the phenotype of mitral valve prolapse.

It is also of note that several of the individuals in the family studied inherited the haplotype containing the defective gene and had minor nonspecific prolapse, which would not satisfy the established diagnostic criteria for classical or nonclassical mitral valve prolapse. Does this mean revised criteria are required? Until the gene and its mutations are identified, it would be premature because of the issue of having the defective gene but because of nonpenetrance, it may not be expressed. If these nonspecific minor mitral valve abnormalities are independent of the mutation, then it should remain in the benign nonspecific category. If it relates to the mutation, then a revision of the diagnostic criteria is in order.

The histological hallmark of mitral valve prolapse is myxomatous degeneration of the leaflet. The essence of the functional defect is redundancy and leaflet elongation, which leads to a “billowing” of the leaflet with the potential to prolapse into the atrium and induce mitral regurgitation. An analysis of the chemical composition of the leaflets should suggest potential candidates for genetic defects. The normal mitral valve has 2 leaflets, 1 end attached to the base of the annulus fibrosis and their free edges to their chordae tendineae. The posterior leaflet is narrower than the anterior and is often the one most affected in myxomatous mitral valve prolapse. The leaflets are composed of 4 layers: auricularis, fibrosa, ventricularis, and spongiosa. The auricularis is composed of collagen and elastic tissue and forms the contact for the atrial aspect of the leaflet and is continuous with the endocardium of the left atrium. The fibrosa is the basic support of the leaflet and is composed of thick collagen. This layer is continuous with the fibrosis of the annulus and the chordae tendineae. The ventricularis is a thin layer of collagen and elastic tissue that covers the ventricular aspect and is continuous with the left ventricular endocardium. The spongiosa or fourth layer is situated between the auricularis and the fibrosa layers and is formed of delicate myxomatous connective tissue. One may assume that some defect in the basic support of the leaflet results from the genetic defect, which together with normal wear and tear leads to stretching and elongation of the leaflet and gives rise to the clinical phenotype. Major components of the normal leaflet are collagen, elastin fibers, and a high density of proteoglycans. The primary abnormality in mitral prolapse appears to occur in the spongiosa layer, which is characterized by deposition of proteoglycans. This disposition invades the other layers, particularly the fibrosa, and disrupts the normal support of the leaflet, which could enable the hemodynamic forces to mechanically stretch and derange the leaflet. The collagen content of the normal mitral valve leaflet is \( \approx 74\% \) type I, 24\% type 3, and 2\% type 5. In mitral valve prolapse, the collagen is significantly increased, particularly type 3, which increases up to 53\%. A second abnormality consistently observed in mitral valve prolapse is the increase in proteoglycans, which are thought to play a role in the assembly of collagen fibrils.

In a study by Rabkin et al, previous observations of excessive collagen degradation, elastin fragmentation, and proteoglycan accumulation were confirmed. The predominant resting cell of the leaflet is a fibroblast-like cell that synthesizes collagen, elastin, and proteoglycans. In myxomatous valves, myofibroblasts are present, which in addition to collagen are known to secrete collagenase (matrix metalloproteinase-1 [MMP-1] to MMP-13), gelatinase (MMP-2, MMP-9), cysteine proteases (cathepsin C and M), and interleukin-1\( \beta \), a cytokine that induces secretion of proteolytic enzymes. These investigators concluded that the synthesis of collagen is normal, but degradation is increased with an accumulation of breakdown products that weaken the fibroskeleton of the leaflets. It was observed in valves removed from patients with mitral valve prolapse at the time of surgery that there was increased content of proteoglycans, primarily chondroitin, dermatan sulfate, and keratan sulfate. This together with increased accumulation of water gives the leaflet its myxomatous appearance and also the floppy gelatinous nature so characteristic of the pathology. The genes encoding for all of these compounds are potential candidates for mutations leading to this disorder. All attempts to identify mutations in the collagen genes (most likely candidates) have failed.

Included in the chromosomal region of the recent locus on 13 are several important candidates. The gene referred to as ITR is a G protein-coupled receptor that is increased in intimal thickening and could play a role in the pathogenesis. A more exciting group of candidate genes are the so-called glypican family of genes, of which GPC5 and 6 are located on chromosome 13 in the region of 13q. This family of genes encode for the cell surface heparin sulfate proteoglycans, which serve as ligands for adhesion and several growth factors including fibroblast growth factor, heparin-binding epidermal growth factor, hepatocyte growth factor, and Wnts. Identification of several genes will not immediately provide elucidation of the pathogenesis but will be a significant step forward.

In the broad picture, why is the search for genes responsible for mitral valve prolapse significant? It is unlikely to add to our knowledge of the pathogenesis of atherosclerosis, the number 1 killer of Americans. If one becomes obsessed with finding the holy grail, however, then few research studies would in themselves be significant. It is the series of discoveries, each of which may appear insignificant, that leads to the big bang. The discovery of the receptor for cholesterol opened up a world that led to the development of statin therapy. A major operation today is that of replacement or repair of the mitral valve, done primarily for mitral valve prolapse. There is extensive research ongoing to improve on valves made from tissue. It is highly likely that identifying the
genes involved with the growth and maintenance of the valve will help in this quest. In an era in which there is hope the whole heart can be regenerated, we must also be prepared to regenerate such structures as valves. Identifying the genes may be a prerequisite if we hope to generate cardiac valves in culture. Understanding the factors that control collagen, elastin, and proteoglycans such as heparan sulfate have significance not only in terms of valve leaflets but also for blood vessels and other organs composed of these structures. Having identified 3 chromosomal loci for mitral valve prolapse does not in itself load the train with genes, but it does suggest that the caboose is waiting to hitch it. Let us hope that with our ability today to rapidly sequence DNA and evaluate new candidate genes we will enable the train to leave the station soon.

References

Key Words: Editorials ■ heart failure ■ valves ■ genetics ■ mitral valve
Another Chromosomal Locus for Mitral Valve Prolapse: Close but No Cigar
Robert Roberts

Circulation. 2005;112:1924-1926
doi: 10.1161/CIRCULATIONAHA.105.569517

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/13/1924

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/