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INVITED EDITORIAL
Toward an Understanding of the Cause of Mitral Valve Prolapse

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Mitral valve prolapse (MVP [MIM 147700]) is among the most common cardiovascular abnormalities, affecting ~2%–8% of the population (Levy and Savage 1987). In fact, this abnormality is believed to affect as many as 15%–20% of young women and a significantly lower proportion (1%–3%) of men, suggesting to some clinicians that this abnormality is, in most cases, a trivial variant of normal valve architecture. However, since some adult patients ultimately require mitral valve replacement (Carpentier et al. 1980; Alpert et al. 1998) and since MVP is commonly associated with well-known clinical entities such as Marfan syndrome and Ehlers-Danlos syndrome (Glesby and Pyeritz 1989), others believe MVP to be a form of significant heart disease (Boudarias 1991).

MVP is described as excessive mitral valve tissue that leads to billowing of the mitral valve leaflets, with or without prolapse and mitral regurgitation (MR) (Frable 1969; Kern and Tucker 1972; Barlow and Pocock 1979; Virmani et al. 1987). Clinically, the diagnosis is suspected when a mid-systolic click and/or late-systolic cardiac murmur are auscultated (Barlow et al. 1963; Barlow and Pocock 1979; Perloff et al. 1986). The diagnosis is confirmed by echocardiography (Nishimura et al. 1985; Levine et al. 1988), and occasionally there is disparity in the physical exam findings and echocardiographic findings (Weiss et al. 1975). In some families, several affected individuals can be identified, with inheritance usually being autosomal dominant (Shappell et al. 1973; Weiss et al 1975; Bareiss 1976; Cooper and Abinader 1981; Strahan et al. 1983). Age dependence and sex dependence (Devereux et al. 1982) also have been noted. In addition, X-linked inheritance has been reported in a forme fruste of MVP, called "severe myxomatous valvular dystrophy," which has been mapped to Xq28 (Kyndt et al. 1998). In families with MVP, clinical heterogeneity is quite significant, with severely abnormal valves noted in some and with nearly normal valves seen in other members of the same family (Zuppiroli et al. 1998). In addition, most patients are asymptomatic, although a portion of the affected individuals have severe symptoms of congestive heart failure with severe MR. Some individuals (usually teenage girls) have a personality type that includes a high-strung style, and these individuals commonly complain of palpitations, chest pain, and dizziness (which is due to hyperventilation).

In this issue of the *Journal,* Disse et al. (1999) localize the first locus for autosomal dominant myxomatous MVP (MMVP) to chromosome 16p11.2-p12.1. This work highlights a number of important points. First, the authors have avoided issues of uncertain diagnosis, by selecting severely affected index cases in whom mitral valve–replacement surgery was required. In addition, only first-degree relatives were recruited for evaluation, and each relative underwent double-blind echocardiographic analysis, thus allowing for consistent diagnostic criteria. This approach also enabled the authors to maximally diagnose family members, avoiding the insensitivity noted when only family history is used. This point previously had been highlighted by Michels et al. (1985, 1992), who showed that the use of family history alone identified 6% of relatives of probands as having dilated cardiomyopathy (DCM), whereas echocardiograms performed on all family members irrespective of history identified 20% of these members as being affected, albeit asymptomatic in most cases.

Another important finding by Disse et al. is that, in the families studied, equal numbers of men and women were affected (i.e., there were no sex-dependent differences), a finding that differs from the female predominance reported by others. Whether clinical signs, symptoms, and outcomes differ between the sexes was not studied by Disse et al., however.

Because of the large distance of the MMVP1 critical region, which now is considered to be in the 5–34-cM range, a positional candidate-gene approach has been used by Disse et al., which requires a detailed understanding of the clinical and histopathological phenotype. As these authors note, genes involved in the structure

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or development of the atrioventricular valves are obvious possibilities. Other reasonable choices are needed, however. Hints with regard to candidate-gene selection could come from successful studies of other cardiovascular disorders. My colleagues and I recently have described the "final common pathway" hypothesis of cardiovascular disease, which suggests that hereditary cardiovascular diseases with similar phenotypes and genetic heterogeneity occur because of abnormalities of genes encoding proteins either with similar functions or participating in a common pathway cascade (Towbin 1999; Towbin et al. 1999). For instance, all of the genes responsible for hypertrophic cardiomyopathy (HCM)—a cardiac disorder in which thickening of both the left ventricle and interventricular septum occurs in association with diastolic dysfunction, hypercontractile systolic function, and myofiber disarray (Maron 1997)—encode proteins composing the sarcomere (i.e., contractile units of the heart) (Thierfelder et al. 1994). In addition, all of the genes responsible for inherited forms of ventricular arrhythmias (as in the long QT syndromes and Brugada syndrome) are due to mutations in cardiac ion channels (Wang et al. 1998; Chen et al. 1998). Recently, I have suggested that abnormalities of cytoskeletal proteins will underlie the development of dilated cardiomyopathy (DCM) and that, since the sarcomere and cytoskeleton are connected via dystrophin and the actin cytoskeleton, intermediate phenotypes are likely (Towbin 1998). The identification of mutations in actin that are near the dystrophin-binding site and that cause DCM (Olson et al. 1998) and of mutations at the sarcomeric end that cause HCM (Mogensen et al. 1999) further support this hypothesis.

Taking advantage of the final common pathway hypothesis, one could evaluate previously identified genetic mutations in patients with MVP associated with other diseases. For years there has been speculation that connective-tissue abnormalities cause MVP (Glesby and Pyeritz 1989; Henney et al. 1989; Tamura et al. 1995). This speculation has been supported by a variety of studies. The fibrillin-1 gene, when mutated, causes Marfan syndrome in which MVP and aortic-root dissection are common (Glesby and Pyeritz 1989). This connective tissue–encoding gene gives rise to a wide variety of clinical phenotypes when mutated, including classic Marfan syndrome (Lee et al. 1991; Towbin and Roberts 1998), with its pleiotropic findings that include cardiac, vascular, bone/skeletal, and ocular abnormalities, to pure skeletal abnormalities, to pure cardiovascular phenotypes (i.e., aortic aneurysm) (Putnam et al. 1995; Sood et al. 1996; Furthmayr and Francke 1997). Another cardiovascular disorder associated with connective-tissue abnormalities is Williams syndrome (Williams et al. 1961; Beuren 1972; Ewart et al. 1993; Morris 1998), which is associated with mental retardation, dysmorphisms, and supravalvar aortic stenosis associated with elastin mutations. Mutations in this same gene also cause a pure cardiovascular disorder known as "familial supravalvar aortic stenosis" (Eisenbert et al. 1964; Ewart et al. 1994; Furthmayr and Francke 1997; Morris 1998). Finally, Ehlers-Danlos syndrome, with its abnormalities of the aorta and mitral valve that are associated with skeletal abnormalities (Tsipouras et al. 1986; DePaepe et al. 1997; Michalickova et al. 1998) and osteogenesis imperfecta, has associated skeletal and vascular abnormalities that are due to mutations in collagen genes (Willing et al. 1994). Thus, the common final pathway involved in aortic and mitral valve abnormalities associated with connective-tissue disorders appears to be genes encoding connective-tissue proteins. Therefore, it seems reasonable to suggest that pure MMVP could arise from abnormalities of genes encoding either members of this family of proteins or products that interact in the cascade of these connective-tissue functions. As the genes for this genetically heterogeneous disorder are identified, the utility of this common-pathway concept will become either apparent or discredited. In either case, knowledge of the affected genes should allow for a better understanding of the clinical spectrum and potentially should allow for improved clinical care of affected patients. The study by Disse and colleagues is an excellent first step.

Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for MVP [MIM 147700])

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