Familial Clustering of Mitral Valve Prolapse in the Community

Francesca N. Delling, MD; Jian Rong, PhD; Martin G. Larson, ScD; Birgitta Lehman, RDcs; Ewa Osynip, MD; Plamen Stantchev, MD; Susan A. Slaugenhaupt, PhD; Emelia J. Benjamin, MD, ScM; Robert A. Levine, MD; Ramachandran S. Vasan, MD

Background—Knowledge of mitral valve prolapse (MVP) inheritance is based on pedigree observation and M-mode echocardiography. The extent of familial clustering of MVP among unselected individuals in the community using current, more specific echocardiographic criteria is unknown. In addition, the importance of nondiagnostic MVP morphologies (NDMs; first described in large pedigrees) has not been investigated in the general population. We hypothesized that parental MVP and NDMs increase the risk of offspring MVP.

Methods and Results—Study participants were 3679 Generation 3 individuals with available parental data in the Offspring or the New Offspring Spouse cohorts. MVP and NDMs were distinguished by leaflet displacement >2 versus ≤2 mm beyond the mitral annulus, respectively. We compared MVP prevalence in Generation 3 participants with at least 1 parent with MVP (n=186) with that in individuals without parental MVP (n=3493). Among 3679 participants (53% women; mean age, 40±9 years), 49 (1%) had MVP. Parental MVP was associated with a higher prevalence of MVP in Generation 3 participants (10 of 186, 5.4%) compared with no parental MVP (39 of 3493, 1.1%; adjusted odds ratio, 4.51; 95% confidence interval, 2.13–9.54; P<0.0001). When parental NDMs were examined alone, the prevalence of Generation 3 MVP remained higher (12 of 484, 2.5%) compared with those without parental MVP or NDMs (27 of 3009, 0.9%; adjusted odds ratio, 2.52; 95% confidence interval, 1.25–5.10; P=0.01).

Conclusions—Parental MVP and NDMs are associated with increased prevalence of offspring MVP, highlighting the genetic substrate of MVP and the potential clinical significance of NDMs in the community. (Circulation. 2015;131:263-268. DOI: 10.1161/CIRCULATIONAHA.114.012594.)

Key Words: echocardiography ■ epidemiology ■ genetics ■ mitral valve prolapse

Mitral valve prolapse (MVP) is a common disorder, affecting 2% to 5% of the general population.1-3 It is the most important cause of primary mitral regurgitation (MR) requiring surgery.4 MVP is characterized by fibromyxomatous changes leading to displacement of 1 or both leaflets into the left atrium (Figures 1A and 1B).5-8 It can lead to endocarditis, heart failure, and even sudden death.9-20

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Our knowledge of MVP inheritance is based on observations of pedigrees with familial forms of the condition, case reports in selected individuals with late systolic clicks,21,22 or reports that used older M-mode echocardiographic diagnostic criteria.23 From these studies, MVP appears to be an autosomal-dominant disorder with variable expression. The familial nature of MVP has been proposed for many years since Hancock and Cohn24 in 1966 observed systolic clicks and murmurs in members of different generations in various families.25 Subsequently, about half of first-degree relatives were reported to manifest MVP in both echocardiographic26 and echocardiographic-auscultatory studies.24 Further evidence for autosomal-dominant inheritance derives from other reports,26 including twin studies.21,22 More recently, our understanding of the 3-dimensional shape of the MV has improved the specificity of MVP diagnosis and in turn the yield of genetic studies.7,26-31 Although a genetic basis of MVP in selected patients has been described, the extent of familial clustering of MVP among unselected individuals in the community with the use of current, more specific echocardiographic criteria is unknown.
In addition, previously nondiagnostic morphologies of MVP (NDMs) have been described in the familial context. NDMs share features of excessive leaflet motion with fully affected individuals, as demonstrated by superior motion toward the left atrium, bulging of the posterior leaflet relative to the anterior (albeit not diagnostic by quantitative assessment), and coaptation asymmetry. In addition, in some NDMs, leaflet excess can also manifest itself by anterior motion and a shift of the coaptation point toward the septum and the aortic root (Figure 2). In genetic studies, NDMs shared either the complete haplotype or a major portion of the haplotype with fully diagnostic MVP. Therefore, these nondiagnostic forms may represent an early expression of MVP in genetically predisposed individuals. NDMs have also been observed in the community, but their clinical significance is unknown.

We hypothesized that parental MVP and NDMs are both associated with a greater prevalence of offspring MVP in a community-based cohort.

Methods
Participants
Beginning in 1948, 5209 men and women were enrolled in the Original cohort. Clustered random sampling was used to select family members 30 to 59 years of age living in the same household. Two-thirds of households were sampled. Their offspring and the offspring’s spouses were enrolled in the Offspring cohort (n=5124) starting in 1971, with examination cycles performed at 4- to 8-year intervals (Figure 3). Children of the Offspring cohort were enlisted in the Generation 3 cohort (n=4095) between 2002 and 2005. Selection of the Offspring and Generation 3 cohorts was not random; it was based on participation of their parents and grandparents in the Framingham Heart Study (FHS). If the spouse of an Offspring cohort member had not enrolled in the FHS and if at least 2 of his/her biological children participated in examination 1 of Generation 3, that spouse was invited to participate in the New Offspring Spouse examination 1. Although clinical evaluations were performed at each examination cycle for each cohort, echocardiograms were obtained only at select examinations, as illustrated in Figure 3. For the purpose of this study, we selected the most recent cycles for the Offspring cohort (examination 6 or 8 between 1996–1998 or 2005–2008, respectively) on the basis of better echocardiographic image quality. Examination 1 (2002–2005) was selected for Generation 3 and the New Offspring Spouse cohort because it is the only cycle with available echocardiographic data for these cohorts.

Participants in our investigation were 3679 Generation 3 individuals (at their first examination cycle) with parents identified in the Offspring cohort (examination 6 or 8) or in the New Offspring Spouse cohort (Examination 1). Two groups were identified among our study subjects: 1 group without parental MVP (n=3493) and 1 group with at least 1 parent with MVP (n=186). We then compared the 2 groups with regard to their clinical and echocardiographic characteristics. The Boston University Medical Center Institutional Review Board approved the study, and all participants provided written informed consent.

Clinical Characteristics
At Generation 3 examination 1, attendees underwent a routine medical history, targeted physical examination for cardiovascular disease, anthropometry, and laboratory assessment of cardiovascular disease risk factors. Clinical variables used in the present investigation included age, sex, body mass index (BMI), and the presence of a murmur on auscultation (defined as systolic murmur ≥3 in any location and any diastolic murmur). Additional clinical variables such as history of smoking, diabetes mellitus, systolic and diastolic blood pressures, and treatment for hypertension were included in the analysis because these factors may be considered potential stressors on the
Clinical and echocardiographic characteristics were compared between the 2 groups (Generation 3 participants with and without parental MVP). We used t tests to compare continuous variables and \( \chi^2 \) tests to compare binary variables (the Fisher exact test for binary variables with low frequencies). We performed logistic regression to estimate the associations of parental MVP and NDM with prevalence of MVP in their children in Generation 3. Multivariable models were estimated with adjustment for age, sex, BMI, and systolic and diastolic blood pressures. We used the GLIMMIX procedure with a G-side variance components structure to accommodate correlated responses among siblings (equal correlations among all sibling pairs). All analyses were conducted with SAS version 9.3 (SAS Institute Inc, Cary, NC). A 2-sided value of \( P<0.05 \) was the criterion for statistical significance.

### Results

#### Clinical Characteristics

Clinical characteristics of the 3679 Generation 3 participants (53% women; mean age, 40±8 years) with available parental data are summarized in Table 1. The groups with (n=186) and without (n=3493) parental MVP had similar age, sex, BMI, history of smoking, congestive heart failure, myocardial infarction, diabetes mellitus, and prevalence of a murmur on auscultation (\( P>0.05 \) for all comparisons). Among the Generation 3 participants who had parental MVP, there was a lower proportion of individuals with hypertension and a lower BMI compared with those without parental MVP (\( P<0.0003 \) and \( P<0.0001 \), respectively). Sibling distribution of Generation 3 participants is detailed in Table 1 in the online-only Data Supplement.

#### Echocardiographic Characteristics

Echocardiographic characteristics are compared in Table 2 on the basis of parental MVP status. Among 3679 participants, 49 had MVP (53% women; mean age, 40±9 years). Prolapse most commonly involved only the posterior mitral valve leaflet (21 of 49, 44%), followed by bileaflet (16 of 49, 33%) and anterior (11 of 49, 23%) MVP. Generation 3 participants with parental MVP had a higher prevalence of MVP (10 of 186 [5%] versus 39 of 3493 [1%]; \( P<0.0001 \)) compared with their counterparts without parental MVP and a greater prevalence of MR (mild or greater MR in 59 of 186 [32%] versus 661 of 3493 [19%]; \( P<0.0001 \)). When we evaluated the prevalence of the combination of MR and MVP, Generation 3 participants with parental MVP also had a higher prevalence of MVP-related MR (\( P<0.0001 \); Table 2). Of the 10 Generation 3 MVP individuals with parental MVP, only 4 had analogous leaflet involvement in 1 of their parents (specifically, 3 Generation 3 MVPs with posterior and 1 with bileaflet MVP). There were no significant differences in left ventricular diameters, volumes, or ejection fraction between the 2 groups (parental and nonparental MVP; Table 2).

#### Contribution of NDMs

There were 484 of 3679 Generation 3 participants with at least 1 parent with NDM (≤2-mm leaflet displacement beyond the mitral valve, acting on a genetic substrate of MVP. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment for hypertension. We also determined whether any of the study participants had a history of congestive heart failure or myocardial infarction because both of these conditions are associated with valvular heart disease (albeit nonprimary) and MR.16

### Echocardiographic Characteristics

All study participants in the Generation 3, Offspring, and New Offspring Spouse cohorts underwent standard 2-dimensional echocardiography with a commercially available system (Sonos 1000, Hewlett-Packard Medical Products, Andover, MA) that used a 2.5-MHz transducer. Images included complete parasternal, apical, and subcostal views and color Doppler assessment of valvular regurgitation; they were stored on VHS and digitized for subsequent review. All measurements were performed with an offline cardiac analysis system (Digiview, Houston, TX).

With the use of current 2-dimensional echocardiographic criteria,2,8 Generation 3 MVP was diagnosed as leaflet displacement >2 mm beyond the mitral annulus in a parasternal or apical long-axis view at end systole (Figure 1A). Echocardiograms in Generation 3 were examined by investigators blinded to parental MVP diagnosis and clinical history. Parental MVP was diagnosed with the use of criteria similar to those of the Offspring cohort at examination 6 or 8 (if 6 was not available) and in the Offspring Spouse cohort at examination 1. Parental NDM was defined as ≤2-mm leaflet displacement beyond the annulus in the same echocardiographic views (Figure 2).1,8,32 In all 3 cohorts, participants were first identified by FHS sonographers as having possible systolic displacement. The diagnosis of MVP or NDM was then confirmed by 2 cardiologists (E.J.B. and F.N.D.).1,32

Left ventricular internal diameters were obtained in diastole and systole by use of a leading-edge technique and averaging of M-mode measurements from at least 3 cardiac cycles. Left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes were derived from M-mode measures by the Teichholz method, and left ventricular ejection fraction was defined as \( 100 \times (\text{LVEDV}−\text{LVESV})/\text{LVEDV} \).37

Correlation coefficients among observations made by the same reader on different occasions or among different observers reading the same images were derived from a previous FHS publication1 to estimate interobserver and intraobserver variabilities for mitral leaflet displacement and degree of MR. These correlations have previously been shown to exceed 0.97 in 20 participants of the Offspring cohort.1,32

### Statistical Methods

Clinical and echocardiographic characteristics were compared between the 2 groups (Generation 3 participants with and without parental MVP). We used t tests to compare continuous variables and \( \chi^2 \) tests to compare binary variables (the Fisher exact test for binary variables with low frequencies). We performed logistic regression to estimate the associations of parental MVP and NDM with prevalence of MVP in their children in Generation 3. Multivariable models were estimated with adjustment for age, sex, BMI, and systolic and diastolic blood pressures. We used the GLIMMIX procedure with a G-side variance components structure to accommodate correlated responses among siblings (equal correlations among all sibling pairs). All analyses were conducted with SAS version 9.3 (SAS Institute Inc, Cary, NC). A 2-sided value of \( P<0.05 \) was the criterion for statistical significance.
annulus without diagnostic criteria for MVP). Of these 484, 12 had MVP, a higher prevalence (2.5%) compared with Generation 3 individuals without parental MVP or NDM (27 of 3009, 0.9%).

**Association of MVP in Generation 3 Participants With Parental MVP Status**

As shown in Table 3, compared with the absence of parental MVP, the presence of MVP in 1 or both parents was associated with greater odds of prevalence of MVP in their children in Generation 3 (multivariable-adjusted odds ratio, 4.51; 95% confidence interval, 2.13–9.54; *P*<0.0001). The association remained statistically significant even when paternal MVP and maternal MVP were considered separately (multivariable-adjusted odds ratio, 4.96; 95% confidence interval, 1.81–13.57; *P*=0.001; and odds ratio, 5.13; 95% confidence interval, 2.07–12.74; *P*=0.0004, respectively). In addition, when parental NDM was examined alone, the prevalence of Generation 3 MVP was higher compared with those without MVP or NDM in their parents (multivariable-adjusted odds ratio, 2.52; 95% confidence interval, 1.25–5.10; *P*=0.01).

**Discussion**

**Primary Findings**

In our community-based sample, parental MVP was associated with a higher prevalence of MVP in Generation 3 after adjustment for several risk factors, including age, sex, body size, and hypertension. Prior studies on MVP inheritance have focused on observations of pedigrees, case reports in selected individuals with late systolic clicks, or investigations that used older M-mode echocardiographic diagnostic criteria for the condition. To the best of our knowledge, our study is the first to demonstrate that a familial component exists for MVP among unselected individuals in the community using current and more specific echocardiographic criteria for this valvulopathy. Interestingly, NDMs previously described among gene carriers in large pedigrees were associated with increased prevalence of Generation 3 MVP in our community-based study. Thus, mild parental MVP expression may potentially represent more than just an echocardiographic subtlety in the community. Familial clustering of MVP motivates additional studies to elucidate the genetic determinants of this condition.

To date, 3 loci for autosomal-dominant, nonsyndromic MVP have been described on chromosomes 11, 16, and 13.24–30 Whereas filamin A has been identified as causing an X-linked form of MVP,31,38 the genes for the more common form of autosomal-dominant MVP are unknown. Nevertheless, discovery of multiple loci suggests that MVP is a heterogeneous disease and represents an important step toward gene discovery.

There was no statistical difference between Generation 3 participants with and without parental MVP with regard to the prevalence of smoking, diabetes mellitus (potential metabolic stressors to the mitral valve), or other cardiac pathologies (myocardial infarction and congestive heart failure) associated with MR, indicating that these factors (which also have a familial basis) did not contribute to the familial clustering of MVP. Of note, Generation 3 participants with parental MVP had a lower BMI and less hypertension. Hence, inheritance of MVP may be associated with the same favorable metabolic and hemodynamic profile previously observed in Offspring parents with MVP.3 Finally, the 2 groups (with and without parental MVP) had similar small numbers of individuals with a murmur on auscultation (diastolic or systolic), highlighting that the prevalence of clinically detectable valvular disease from all causes was low and could not adequately identify people with familial MVP.
On echocardiography, Generation 3 participants with parental MVP had a higher prevalence of MVP and MVP-related MR, suggesting that the familial basis for MVP includes clustering of a clinical component (MR). As previously observed in selected pedigrees, variation of leaflet involvement and morphological heterogeneity were also observed among related individuals in our community-based study. This spectrum of valvular abnormalities may represent variations in disease expression, stage of progression, or modifying factors within FHS families. Finally, similar left ventricular dimensions in the 2 groups (with and without parental MVP) suggest that MVP was likely not a consequence of a small, hyperdynamic left ventricle. Similarly, there was no difference in left atrial size between the 2 groups; hence, the degree of MR observed was associated with the primary valve disease, not with dilated cardiac chambers.

Strengths and Limitations
The strengths of our investigation include the unique availability of multigenerational clinical and echocardiographic data, a well-characterized phenotype using a contemporary definition, and the ability to evaluate NDMs systematically. In contrast, a self-report of MVP or a family history of MVP would likely be more susceptible to ascertainment bias. In addition, MVP was diagnosed by investigators blinded to parental MVP status, and risk factors potentially contributing to MVP risk (blood pressure, age, sex, BMI, etc) were systematically and routinely ascertainment. Finally, our sample was community based and our participants were unselected, reducing the likelihood that our sample was enriched for rare genetic variants that may contribute to a familial basis for MVP.

Our study has several limitations. First, our analysis was limited to a single sample of European ancestry, and the results may not be generalizable to other populations. Second, the parental MVP sample size was small; hence, some of the nonsignificant comparisons (between the groups with and without parental MVP) may have been statistically underpowered. Third, because data on Generation 3 were available at only a single time point, we could not assess the association of parental MVP with longitudinal progression of MVP in offspring. Fourth, the true prevalence of familial MVP within and across generations in the FHS could not be assessed comprehensively. Specifically, the number of participants with prevalent MVP in Generation 3 and available parental information was low. There was a limited number of siblings with MVP (3 sib pairs, 0 triplets). However, this may be considered a relative strength because our results are not driven by unusually large pedigrees with rare genetic profiles. Fifth, there was a lack of data on grandparental MVP status in the original FHS cohort (parents of Offspring cohort participants). Current diagnostic criteria for MVP were not implemented at the time of the acquisition of echocardiographic data for the Original cohort. In addition, 2-dimensional echocardiographic studies were obtained for Original cohort attendees at examination cycle 20, at which time most participants were >75 years old and many had died. Moreover, we did not assess the risk of developing NDMs in Generation 3 on the basis of parental MVP (or parental NDM). We focused on MVP as a primary outcome because this phenotype is better characterized from a prognostic perspective. Although our study has increased our knowledge about the potential clinical significance of NDMs by linking them to the risk of developing MVP, the potential of NDMs to progress to fully diagnostic MVP or significant MR remains unknown. Finally, no systematic assessment of Marfan syndrome (another genetic condition associated with MVP) was conducted during the clinical examinations of the FHS.

Clinical and Research Implications
Parental MVP is associated with greater odds of MVP in the offspring, an observation consistent with a genetic contribution to MVP. Prior studies of large pedigrees have suggested that there are rare penetrant alleles that cause MVP, and given the discovery of multiple loci associated with such familial disease, they also inform us of the locus heterogeneity of this disease. Familial clustering of MVP in the community is consistent with the potential contribution of both rare alleles (with strong effect size) and common variants to MVP occurrence in families. Although MVP prognosis is overall benign in the FHS community, there is a minority of individuals who progress to severe MR. Parental MVP may be an important determinant of MVP progression, and further studies are needed to identify the genetic determinants (either susceptibility or modifier genes) and the environmental factors involved in the progression of MVP to significant clinical sequelae. Familial clustering of MVP also raises the possibility of screening clinically silent, unaffected family members. This premise warrants more careful examination in future cost-effectiveness studies, perhaps in a referral-type population with a more severe MVP phenotype.

Conclusions
Parental MVP and NDMs are both associated with a higher prevalence of MVP in their offspring. Such familial clustering of MVP motivates additional studies to elucidate the genetic determinants of this condition and to investigate the potential role of screening of clinically silent family members of affected individuals.

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Disclosures
None.

References
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**Supplemental Table.** Range of number of siblings from the same family and frequency of families with a specific sibling count in Generation 3 study participants.

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<th>Sibling count</th>
<th>Family frequency (%)</th>
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<tr>
<td>1</td>
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<td>537 (33)</td>
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