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Report

A Locus for Autosomal Dominant Mitral Valve Prolapse on Chromosome 11p15.4

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Mitral valve prolapse (MVP) is a common cardiovascular abnormality in the United States, occurring in ~2.4% of the general population. Clinically, patients with MVP exhibit fibromyxomatous changes in one or both of the mitral leaflets that result in superior displacement of the leaflets into the left atrium. Although often clinically benign, MVP can be associated with important accompanying sequelae, including mitral regurgitation, bacterial endocarditis, congestive heart failure, atrial fibrillation, and even sudden death. MVP is genetically heterogeneous and is inherited as an autosomal dominant trait that exhibits both sex- and age-dependant penetrance. In this report, we describe the results of a genome scan and show that a locus for MVP maps to chromosome 11p15.4. Multipoint parametric analysis performed by use of GENEHUNTER gave a maximum LOD score of 3.12 for the chromosomal region immediately surrounding the four-marker haplotype D11S4124-D11S2349-D11S1338-D11S1323, and multipoint nonparametric analysis (NPL) confirms this finding (NPL = 38.59; P = .000397). Haplotype analysis across this region defines a 4.3-cM region between the markers D11S1923 and D11S1331 as the location of a new MVP locus, *MMVP2*, and confirms the genetic heterogeneity of this disorder. The discovery of genes involved in the pathogenesis of this common disease is crucial to understanding the marked variability in disease expression and mortality seen in MVP.

Originally described in the 1960s, mitral valve prolapse (MVP [MIM 157700]) is a very common Mendelian cardiovascular disorder (Barlow and Bosman 1966; Devereux et al. 1982). It is characterized by systolic displacement or billowing of the mitral leaflets into the left atrium, often accompanied by mitral regurgitation (MR). The leaflets may be thickened, show myxomatous changes with altered collagen and elastin composition, show disruption of the fibrous backbone, and show proteoglycan accumulation (Cole et al. 1984; Tamura et al. 1995). Complications include bacterial endocarditis, progressive MR, arrhythmias, and even sudden death (Devereux et al. 1987, 1989; Levy and Savage 1987; Perloff and Child 1987; Braunwald 1992; Avierinos et al. 2002), and it is the leading cause of isolated MR requiring surgical repair (Waller et al. 1982).

Familial studies of idiopathic or nonsyndromic MVP suggest an autosomal dominant mode of inheritance with incomplete penetrance (Weiss et al. 1975; Fortuin et al. 1977; Devereux et al. 1982). Additionally, sex- and age-dependent penetrance has been noted, with MVP being more prevalent in females and with increasing age (Weiss et al. 1975; Devereux et al. 1982; Strahan et al. 1983). The clinical heterogeneity observed within families is often striking, with severe valvular abnormalities seen in several patients, whereas other affected family members show only moderate or slight changes (Zuppiroli et al. 1998). MVP has been reported in association with many genetic connective-tissue disorders, including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, dominant cutis laxa, and pseudoxanthoma elasticum (Malcom 1985; Glesby and Pyeritz 1989; Struk et al. 1997; Milewicz 1998; Rubegni et al. 2000). A

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search of Online Mendelian Inheritance in Man reveals a multitude of entries for which MVP is a clinical feature, including a recent clinical and genetic study in which MVP has been proposed to be involved in panic disorder syndrome (Weissman et al. 2000). Despite the association of MVP with various connective-tissue disorders, linkage to several fibrillin and collagen genes has been excluded (Henney et al. 1989; Wordsworth et al. 1989).

Initial attempts to establish a genetic basis for MVP were limited by nonspecificity of diagnosis and searches restricted to presumed candidate genes. Regarding specificity, early studies estimated MVP prevalence in the general population to be 5%–15% and even as high as 35%, but generally without clinical evidence of disease (Markiewicz et al. 1976; Procacci et al. 1976; Savage et al. 1983*a*, 1983*b*; Bryhn and Persson 1984; Warth et al. 1985; Levy and Savage 1987). Initial diagnosis relied mainly on auscultation and single-dimensional echocardiography, which could produce the diagnosis in up to 21% of otherwise normal individuals (Markiewicz et al. 1976; Gilon et al. 1999). Nonspecificity continued with two-dimensional (2D) echocardiography, as criteria were broadened to maximize diagnostic frequency (Warth et al. 1985; Levine et al. 1988). More recently, recognition of the three-dimensional (3D) saddle shape of the valve has eliminated false-positive diagnosis related to this shape (Levine et al. 1987, 1988, 1989; Perloff and Child 1989; Nidorf et al. 1993). Without loss of sensitivity, this recognition has increased specificity, with an estimated frequency of 2.4% in a recent population-based survey using the Framingham Heart Study (Freed et al. 1999, 2002*a*, 2002*b*). This has improved correspondence between noninvasive diagnosis and the recognized surgical and pathologic process (Marks et al. 1989; Nidorf et al. 1993). The phenotypic basis for genetic studies is now stronger, thereby increasing the likelihood of identifying genes involved in the pathogenesis of MVP.

Recently, the first locus for nonsyndromic MVP, *MMVP1,* has been mapped to chromosome 16p11.2-p12.1 (Disse et al. 1999) in two of four families from a surgical center. Further, X-linked myxomatous valvular dystrophy, a rare disorder with histopathological features similar to severe MVP, has been mapped to chromosome Xq28 (Kyndt et al. 1998). The purpose of the current study was to determine the chromosomal localization of an MVP locus by performing a genomewide search for linkage. Using a single large pedigree, we have identified a second MVP locus (*MMVP2*) on chromosome 11p15.4, further demonstrating genetic heterogeneity and setting the stage for the molecular identification of responsible genes. Such knowledge will increase our understanding of pathogenesis, with the ultimate potential of developing targeted therapy and possibly preventing disease progression.

This study was carried out using the pedigree shown in figure 1. The proband was identified as a volunteer in a course teaching echocardiographic imaging. The study was approved by the institutional review board at Massachusetts General Hospital, and all patients signed informed consent forms prior to enrollment. Two-dimensional echocardiograms were obtained on all available family members, using a 2.5-MHz transducer with complete parasternal, apical, subcostal, and suprasternal views and color Doppler assessment of valvular regurgitation. The echocardiograms were read separately by two readers (L.A.F. and R.A.L.) who were blind to clinical status. Currently accepted 2D echo criteria based on the 3D shape of the valve were used, and diagnosis of MVP was based on maximal superior mitral leaflet displacement during systole, relative to a line connecting the annular hinge points (Levine et al. 1987, 1988, 1989; Marks et al. 1989; Perloff and Child 1989; Nidorf et al. 1993). Anterior and posterior leaflet displacements were measured in the parasternal and apical long-axis views, which were scanned to visualize all three posterior leaflet scallops sequentially. Because the lateral scallop is the most difficult to evaluate from these views, its displacement was also measured in the apical four-chamber view (Levine et al. 1988; Shah 1994), but it was always confirmed in the long-axis scans. Mitral leaflet thickness was examined during diastasis at the midportion of the leaflet, excluding focal thickening and chordae (Chandraratna et al. 1984; Levine et al. 1988; Weissman et al. 1994).

On the basis of prior clinical and prognostic studies, subjects were classified as having MVP if displacement exceeded 2 mm. In addition, the degree of leaflet thickening was qualitatively assessed (Chandraratna et al. 1984; Nishimura et al. 1985; Levine et al. 1988; Marks et al. 1989; Perloff and Child 1989; Nidorf et al. 1993). Although borderline degrees of displacement ($\leqslant$2mm) are not associated with increased leaflet thickness, mitral regurgitation, left atrial enlargement, valve-related complications, or progression over a period of 10 years, for this study, we considered these individuals indeterminate rather than unaffected (Levine et al. 1988; Nidorf et al. 1993; Vivaldi et al. 1994).

The complete pedigree contains 41 individuals in 5 generations, with both founders of Western European descent (fig. 1). Echocardiograms and DNA were obtained on 28 subjects (11 males and 17 females) of whom 12 were diagnosed with MVP, 3 were found to have an indeterminate phenotype, and the remaining 13 were classified as unaffected. The echocardiographic characteristics of the affected patients are provided in table 1. No extracardiac manifestations of connective-tissue abnormalities or Marfan syndrome were present in any family members. Participating subjects' age ranged 3–73 years; however, the 2 unaffected individuals under the age of 6 years (25075, 25086) were excluded from the analysis.

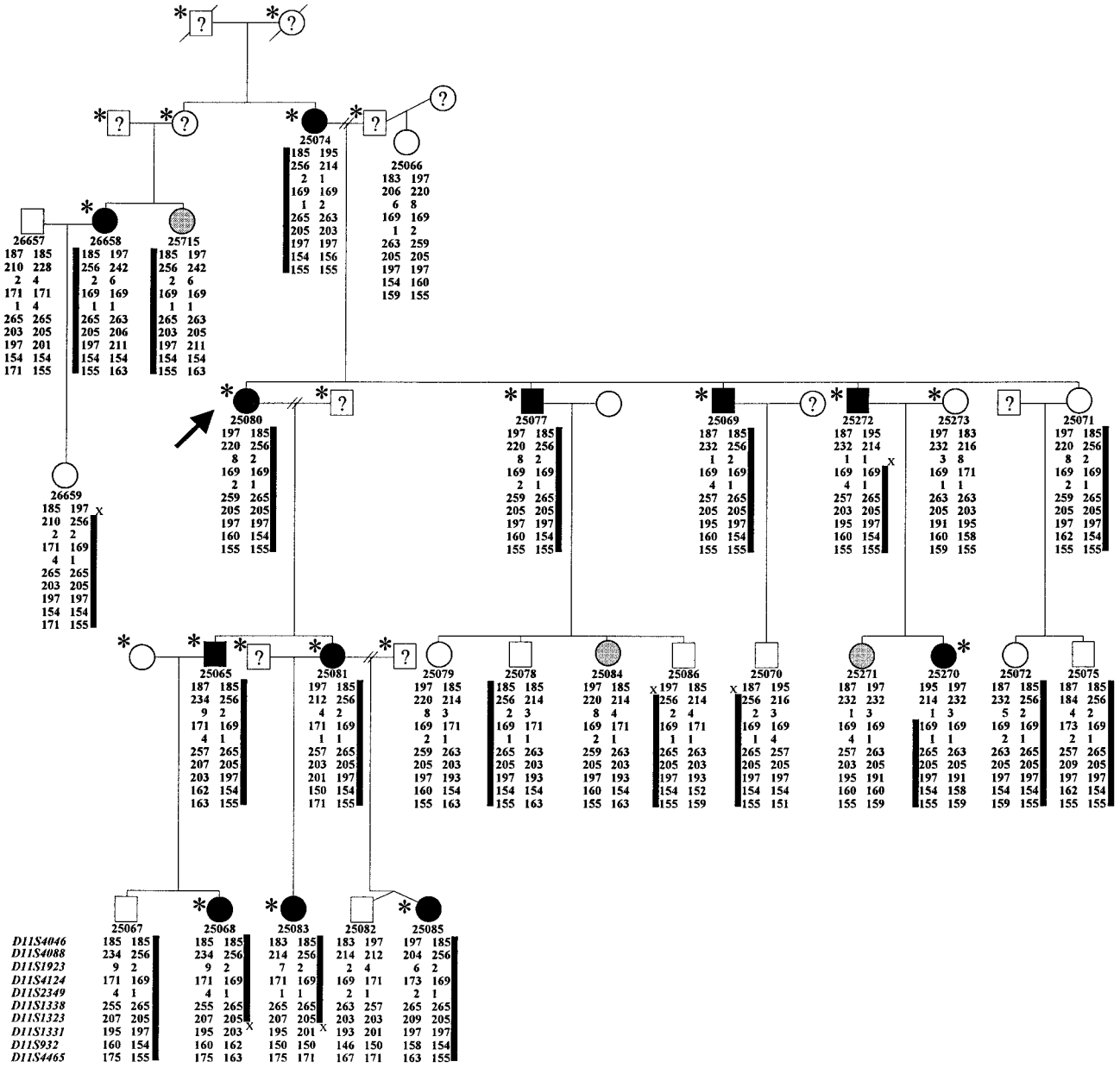

Figure 1 Pedigree of family with MVP showing chromosome 11 haplotypes. Affected, unaffected, and indeterminate individuals are shown as blackened, unblackened, and gray symbols, respectively. Patient ID codes are shown beneath the symbol. Symbols with a question mark (?) represent individuals who did not participate in the study. An asterisk (*) indicates individuals who were used in the GENEHUNTER analysis. Spouses of 25077 and 25065 were phenotyped, but DNA was unavailable. A black bar represents the disease chromosome, with the location of recombination events marked as "X." The marker order for all haplotypes is shown next to individual 25067.

Blood samples were collected on all family members at the time of echocardiography. Genomic DNA was prepared from either transformed lymphoblast cell lines (Anderson and Gusella 1984) using the SDS-proteinase K method followed by phenol extraction or directly from blood with the Nucleon II kit (Amersham). As part of the genome scan, genotyping was performed using 374 genetic markers that make up the MGH Genomics Core Facility linkage panel, the majority of which are from the ABI Prism Linkage Mapping Set v. 2 (Perkin Elmer Applied Biosystems). If additional map resolution was needed, markers from the Cooperative Human Linkage Center Weber Human Screening Set v. 8 (Research Genetics) was used. All markers were amplified according to the individual manufacturer's recommended guidelines. PCR was performed using a PE 9700 thermocycler

Table 1

Echocardiographic Characteristics of Affected Pedigree Members

ID No.	Age (years)	Sex	MVP Type	Leaflet Thickening	LA[a] (mm)	LVIDd[b] (mm)	EF[c] (%)	MR
25074	73	F	Bileaflet	Yes	37[d]	43[d]	68[d]	Severe
25080	52	F	Bileaflet	Yes	46	57	61	Severe
25077	48	M	Posterior	Yes	35	32	64	Mild
25069	46	M	Mild bileaflet	Yes	38	46	65	Mild
25272	44	M	Mild posterior	Yes	31	50	74	Trace
25065	32	M	Mild posterior	Yes	27	47	64	None
25081	29	F	Bileaflet	Yes	30	47	64	Trace
25068	6	F	Mild posterior	Yes	20	30	66	Trace
25083	9	F	Bileaflet	Yes	20	38	73	Trace
25085	6	F	Mild posterior	Yes	20	34	68	None
25270	11	F	Mild posterior	Yes	30	42	62	Mild
26658	51	F	Posterior	No	31	40	57	Trace

[a] LA = left atrial diameter.
[b] LVIDd = left ventricular internal diameter (diastolic).
[c] EF = ejection fraction.
[d] Individual 25074 had mitral valve replacement for bileaflet MVP with severe MR; values are postoperative.

(Applied Biosystems), and the products were run on an ABI377 automated DNA sequencing system (Applied Biosystems). GeneScan and Genotyper software packages were used for allele identification and sizing. Additional markers for fine mapping were identified from the Genome Database (GDB), and PCR was performed using a total volume of 15 μL with ~100 ng of genomic DNA; 20 pmol of each primer; 0.5 U *Taq* polymerase; 1.5 mM $MgCl_2$; 50 mM KCl; 200 μM dATP, dCTP, and dTTP; 20 μM dGTP; and 0.1 μCi $\alpha(^{32}P)$-dGTP. PCR was performed on the PTC-100 thermal cycler (MJ Research) using the following cycles: initial denaturation at 94°C for 2 min, followed by 30 cycles of 94°C for 20 s, 53°C–60°C for 20 s, and 72°C for 20 s, concluding with a final extension step of 72°C for 2 min. Annealing temperatures were optimized for each set of primers, and PCR products were electrophoresed on a 6% acrylamide gel.

The data were analyzed assuming an autosomal dominant mode of inheritance with incomplete penetrance and a disease gene frequency of 0.005, with a phenocopy rate of 1% to account for the high incidence of sporadic MVP, as in the chromosome 16 linkage study (Disse et al. 1999). Penetrance for adults over age 15 years was set at 95% for females, 63% for males, and at 32% and 21%, respectively, for those below age 15 years, to account for sex and age differences in familial studies reported elsewhere (Devereux et al. 1982). Individuals designated indeterminate were coded as "unknown" for the analysis. We also performed nonparametric (NPL) analysis for all chromosomes using the GENEHUNTER program (Kruglyak et al. 1996). Because the memory constraints of this program cannot accommodate all members of this pedigree together, the pedigree was trimmed for analysis according to standard convention (individuals analyzed are shown in fig. 1).

A simulation study on the pedigree using all individuals with available DNA was performed using the SLINK program (Ott 1989; Weeks et al. 1990). Five hundred replicates were simulated using the above model. Two-point LOD scores between the disease and individual markers were calculated with the MLINK program of the FASTLINK 3.0P package (Cottingham et al. 1993), a faster version of the original LINKAGE package (Lathrop and Lalouel 1984; Lathrop et al. 1984, 1986). This analysis generated a maximum parametric LOD score of 3.88, suggesting that this family was sufficiently powerful to detect linkage.

Prior to the genome scan, representative markers covering the *MMVP1* region on chromosome 16 were tested for linkage. Parametric GENEHUNTER analysis across the previously reported *MMVP1* locus region on chromosome 16 using the markers D16S404-D16S3103-D16S420-D16S3133-D16S3068-D16S3080-D16S515 yielded two-point LOD scores with range -0.90–-2.81 at $\theta = 0$ and a maximum multipoint LOD score of -0.50 between the markers D16S3080 and D16S515. The maximum score achieved for the NPL analysis was -0.18 ($P = .42$) and occurred at the same position (data not shown). Evaluation of the multipoint LOD scores and haplotypes across this region effectively excluded linkage of our family to the *MMVP1* locus.

Following exclusion of linkage to *MMVP1,* the entire genome scan was performed and the data analyzed using both LINKAGE and GENEHUNTER. A two-point LOD score of 1.48 at $\theta = 0.1$ was observed for the marker D11S1338, with a corresponding NPL score of 9.29

($P = .008$), calculated under the assumption of equal allele frequencies of 0.10. D11S1338 was the only marker in the scan to yield a two-point LOD score >1.0. Two other markers (D1S2134 and D4S1539) had positive NPL scores ($P < .05$) and positive LOD scores (<1.0); however, GENEHUNTER analysis across these chromosomal regions did not support linkage. Additional markers were subsequently genotyped in the region of D11S1338, and the data were analyzed using actual allele frequencies obtained from the CEPH Genotype Database. Allele frequencies were not available for D11S2349; therefore, we genotyped 44 CEPH parents and estimated the frequencies as: 1 = 53.4%, 2 = 28.4%, 3 = 3.4%, and 4 = 14.8%. The two-point parametric LOD scores are shown in table 2*A*. The highest two-point LOD score observed was 1.48 at $\theta = 0.1$ for the marker D11S1338. Multipoint analysis across this region of the chromosome (fig. 2*A*) showed a positive region between the markers D11S1923 and D11S1331 that peaks with a LOD score of 3.12, which is highly suggestive of linkage (Lander and Kruglyak 1995). Nonparametric analysis across this interval was highly significant (fig. 2*B*), with a maximum NPL of 38.59 ($P = .000397$). The results of the parametric and nonparametric analyses support linkage of MVP in this family to a 4.3-cM region between the markers D11S1923 and D11S1331. Next, haplotypes were manually constructed for all members of the pedigree and confirmed with the haplotypes generated by GENEHUNTER (fig. 1). Examination of the haplotypes confirms the segregation of a common haplotype with MVP in this family. The haplotypes also show that eight unaffected individuals (25071, 25078, 25072, 25070, 25075, 26659, 26067, and 25086) are nonexpressing carriers of the haplotype. With the exception of one adult female (25071) and one 18-year-old male (25070), all of these individuals are below age 15 years, which is consistent with a model of age-dependent reduced penetrance. Further, two of these are under age 6 years (25075 and 25086), which we consider below the minimal age of accurate MVP detection. We therefore performed an affecteds-only parametric analysis using LINKAGE to take into account the observed age-dependent penetrance in MVP. This analysis was carried out with the same individuals used in the GENE-

Table 2

Two-Point Parametric LOD Scores of Chromosome 11 Markers

A. Entire Family

		LOD Score at θ						
Marker	cM[a]	.00	.01	.05	.10	.20	.30	.40
D11S4046	2.8	−.64	−.16	.48	.72	.75	.58	.31
D11S4088	7.0	−1.59	−1.02	−.13	.31	.58	.54	.33
D11S1923	8.6	−1.87	−1.45	−.62	−.16	.21	.27	.18
D11S4124	11.1	.41	.40	.37	.32	.24	.16	.08
D11S2349	12.3	.38	.43	.55	.58	.47	.27	.09
D11S1338	12.9[b]	.93	1.07	1.38	1.48	1.34	.98	.51
D11S1323	13.0[b]	−.42	−.38	−.26	−.14	.04	.12	.11
D11S1331	13.1[b]	−2.65	−2.36	−1.67	−1.18	−.62	−.30	−.11
D11S932	14.5	−1.47	−1.19	−.53	−.12	.20	.23	.13
D11S4465	16.1	−1.55	−1.39	−.98	−.68	−.35	−.17	−.06

B. Affected Individuals Only

		LOD Score at θ						
Marker	cM[a]	.00	.01	.05	.10	.20	.30	.40
D11S4046	2.8	.31	.71	1.08	1.13	.93	.63	.30
D11S4088	7.0	.84	1.23	1.58	1.59	1.33	.92	.46
D11S1923	8.6	.34	.59	.90	.96	.83	.59	.30
D11S4124	11.1	.45	.44	.40	.35	.25	.16	.08
D11S2349	12.3	1.18	1.15	1.04	.89	.56	.24	.03
D11S1338	12.9[b]	2.76	2.71	2.50	2.24	1.70	1.11	.52
D11S1323	13.0[b]	1.91	1.87	1.69	1.47	1.03	.61	.25
D11S1331	13.1[b]	−1.65	−1.45	−.98	−.66	−.31	−.13	−.03
D11S932	14.5	−.06	.11	.47	.64	.65	.47	.21
D11S4465	16.1	−.84	−.75	−.52	−.35	−.16	−.07	−.02

[a] Marker location on the Marshfield sex-averaged linkage map.

[b] Marker order is discrepant between the Marshfield genetic map and the HGB physical map. Locations were adjusted to reflect the physical order.

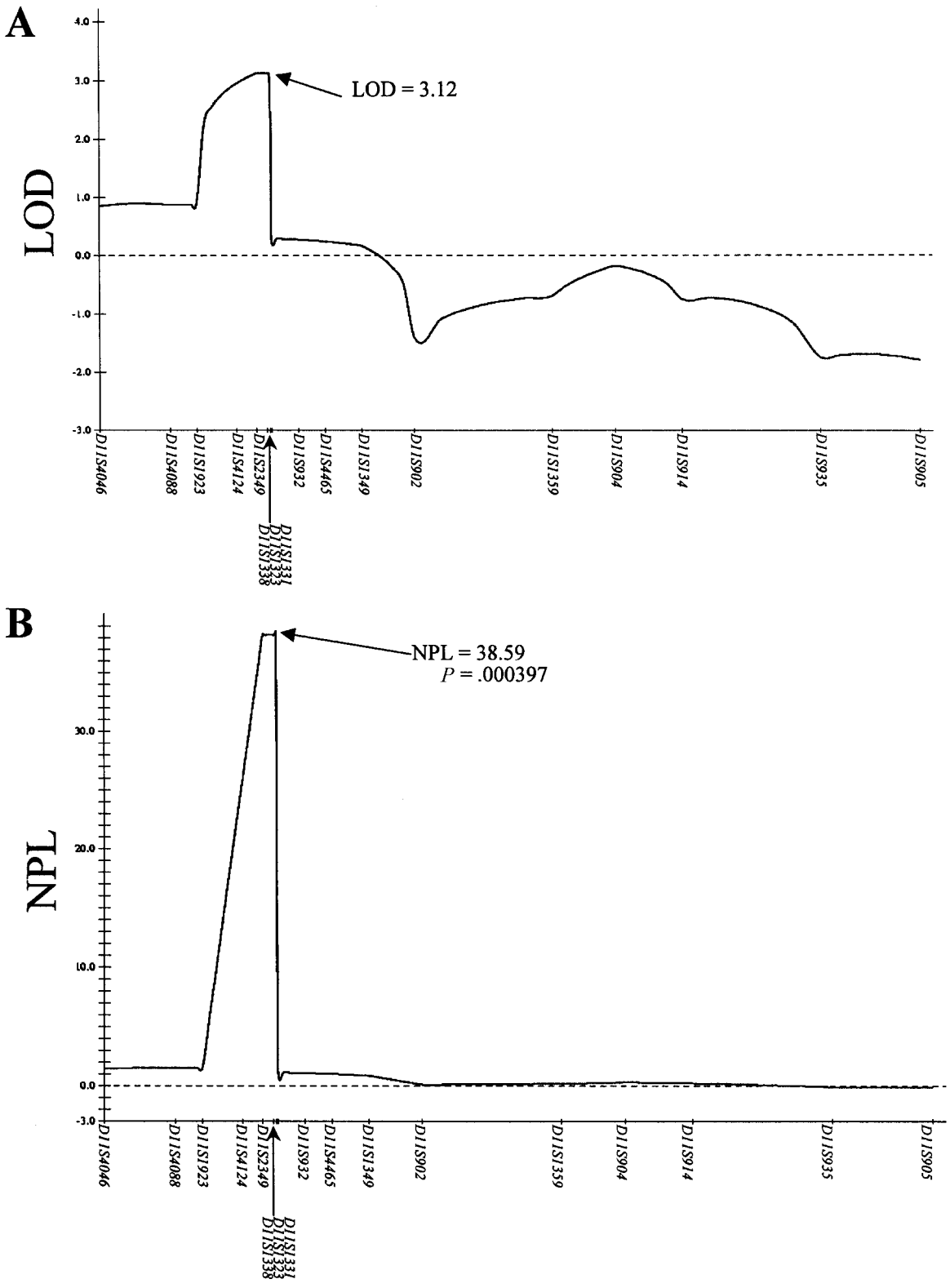

Figure 2 GENEHUNTER analysis of the *MMVP2* locus. Distances between the markers correspond to the marker map in table 1. *A*, Graph of multipoint parametric LOD scores. *B*, Graph of multipoint NPL scores.

HUNTER analysis (fig. 1). These scores, as expected, are significantly higher and are presented in table 2*B*.

We next examined the haplotypes of the affected pedigree members to determine the boundaries of the linked region. All affected members in our family share a four-marker core haplotype of 169-1-265-205 for the markers D11S4124-D11S2349-D11S1338-D11S1323. A recombination event in individual 25272 between markers D11S1923 and D11S4124 defines the proximal boundary of the linked region. Likewise, two independent and informative recombination events between D11S1323 and D11S1331 in individuals 25068 and 25083 strongly establish the distal boundary of the candidate region. The region between the linked markers D11S1923 and D11S1331 is located between 3.58 Mb and 8.03 Mb on chromosome 11p15.4 of the June 2002 freeze of the Human Genome Browser (HGB). This 4.45-Mb span, which still contains several large gaps in sequence coverage, contains 46 known genes. Further, examination of the UniGene clusters suggests the presence of as many as 90 additional transcripts. The preponderance of genes in this region, coupled with the lack of any obvious functional candidates, suggests that narrowing the interval by analysis of a more detailed haplotype is crucial to the efficient identification of the gene responsible for MVP in this family.

Our analysis demonstrates that a second locus for autosomal dominant MVP maps in a 4.3-cM region between the markers D11S1923 and D11S1331 on chromosome 11p15.4. This locus has been designated "*MMVP2*" and the symbol approved by the Human Genome Organization (HUGO) Gene Nomenclature Committee. Further, our results confirm the genetic heterogeneity of MVP, which had been suggested by linkage of the chromosome 16 locus in only two of four families studied by Disse et al. (1999). In contrast with prior negative studies (Henney et al. 1989; Wordsworth et al. 1989), the identification of two MVP loci on chromosomes 11 and 16 demonstrates the strength of the current approach, which combines new and more-specific diagnostic criteria for MVP with systematic genome scanning.

Genetic heterogeneity provides the opportunity to explore the relationship between various genetic defects and differences in disease expression, natural history, and mortality, as has been shown for familial hypertrophic cardiomyopathy (Solomon et al. 1990; Coonar and McKenna 1997; Maron et al. 1998; Seidman and Seidman 1998; Tesson et al. 1998). Analogous to familial hypertrophic cardiomyopathy, the noninvasive diagnosis of disease requires criteria of variable sensitivity and specificity for such measures as septal thickness or mitral leaflet displacement, established by correlation with concomitant echocardiographic and clinical abnormalities. In the hypertrophic condition, it has been found that the familial context successfully permits the use of more sensitive criteria without sacrificing specificity (Tesson et al. 1998). In the MVP context, it is hoped that genetic studies can also lead to a better understanding of clinical and echocardiographic observations. For example, patients with MVP and thick leaflets are much more likely to manifest regurgitation and related complications when compared with patients with MVP and thin leaflets (Nishimura et al. 1985; Marks et al. 1989; Nidorf et al. 1993), although the same family may contain a spectrum of leaflet thickness (Zuppiroli et al. 1998). This may represent two stages in disease development, variable expression, or perhaps genetic heterogeneity.

Genetic localization of MVP loci will lead to the identification of mutations in genes that underlie the molecular basis of the disorder. Not only will this result in increased diagnostic accuracy, which will in turn reduce the well-documented anxiety that often accompanies the diagnosis of MVP (Scordo 1998; Benjamin 2001), but it may also uncover genotype-phenotype relationships that will advance treatment by allowing for prediction of disease-progression patterns. This is important because the disease often manifests clinically in the 5th or 6th decade of life through presentation as a severe cardiac event. Earlier targeted intervention to reduce leaflet stresses in genetically susceptible individuals, as in the case of aortic dilatation in Marfan syndrome (Shores et al. 1994), could potentially prevent the progression and complications often associated with mitral valve prolapse.

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Electronic-Database Information

URLs for data presented herein are as follows:

CEPH Genotype Database, http://www.cephb.fr/cephdb/
Genome Database (GDB), http://www.gdb.org (for the Marshfield Map location of markers)
Human Genome Organization, http://www.gene.ucl.ac.uk/hugo/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for MVP)

UCSC Human Genome Browser, http://genome.ucsc.edu

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