Original Article

Heritability of Mitral Regurgitation
Observations From the Framingham Heart Study and Swedish Population

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Background—Familial aggregation has been described for primary mitral regurgitation (MR) caused by mitral valve prolapse. We hypothesized that heritability of MR exists across different MR subtypes including nonprimary MR.

Methods and Results—Study participants were FHS (Framingham Heart Study) Generation 3 (Gen 3) and Gen 2 cohort participants and all adult Swedish siblings born after 1932 identified in 1997 and followed through 2010. MR was defined as ≥ mild regurgitation on color Doppler in FHS and from *International Classification of Diseases* codes in Sweden. We estimated the association of sibling MR with MR in Gen 2/Gen 3/Swedish siblings. We also estimated heritability of MR in 539 FHS pedigrees (7580 individuals). Among 5132 FHS Gen 2/Gen 3 participants with sibling information, 1062 had MR. Of siblings with sibling MR, 28% (500/1797) had MR compared with 17% (562/3335) without sibling MR (multivariable-adjusted odds ratio, 1.20; 95% confidence interval [CI], 1.01–1.43; P=0.04). When we combined parental and sibling data in FHS pedigrees, heritability of MR was estimated at 0.15 (95% CI, 0.07–0.23), 0.12 (95% CI, 0.04–0.20) excluding mitral valve prolapse, and 0.44 (95% CI, 0.15–0.73) for ≥ moderate MR only (all P<0.05). In Sweden, sibling MR was associated with a hazard ratio of 3.57 (95% CI, 2.21–5.76; P<0.001) for development of MR.

Conclusions—Familial clustering of MR exists in the community, supporting a genetic susceptibility common to primary and nonprimary MR. Further studies are needed to elucidate the common regulatory pathways that may lead to MR irrespective of its cause. **(*Circ Cardiovasc Genet*. 2017;10:e001736. DOI: 10.1161/CIRCGENETICS.117.001736.)**

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

Mitral regurgitation (MR) is the most common form of valve disease, affecting >2 million people in the United States.[1] MR is characterized by incomplete coaptation of valve leaflets, resulting in regurgitant flow across the valve and reduced effective cardiac output.[1] When severe, MR is associated with onset and worsening heart failure and decreased survival.[1]

See Editorial by Judge and Norris
See Clinical Perspective

MR constitutes an etiologically heterogeneous set of conditions, similar to aortic stenosis, atrial fibrillation, and heart failure. Whereas primary MR is most commonly caused by mitral valve prolapse (MVP), secondary or functional MR results from left ventricular (LV) dilation such as seen in dilated cardiomyopathies or isolated myocardial infarction causing papillary muscle displacement and leaflet tethering.[1] Recent literature demonstrates that mitral valve leaflets are not innocent bystanders in functional MR but are able to grow in response to tethering in both humans and in animal models.[2–4] Interestingly, not all patients with coronary heart disease or other causes of LV dilatation develop significant MR, suggesting genetic variability in the ability to compensate for any potential leaflet tethering. Also, similar reactivation of embryonic development pathways has been demonstrated in primary MR related to MVP.[5,6] Moreover, mild/moderate degrees of MR are often observed in clinical practice without a clear cause (absence of calcification, congenital conditions, or rheumatic involvement) and may be the result of leaflet response to subtle mechanical stress in the setting of hypertension or increased afterload.[7]

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A familial component has been described for specific causes of MR such as MVP[8,9] and reported in a recent twin study,[10] but has not been systematically studied across both primary and nonprimary subtypes of MR in whole pedigrees. We postulate that genetic susceptibility and familial clustering of MR can be identified irrespective of cause of MR in both the FHS (Framingham Heart Study) cohort and the entire Swedish population, 2 different, but complementary, data sets.

Methods

Framingham Heart Study

Participants

The FHS is a multigenerational community-based cohort study including residents of the town of Framingham, MA. Beginning in 1948, 5209 men and women were enrolled into the Original cohort.[11] Their offspring and the offsprings' spouses were enrolled into the Offspring cohort (n=5124) starting in 1971. Examination cycles were performed at ≈4- to 8-year intervals, with comprehensive echocardiograms and Doppler color flow imaging obtained at examination cycles 4, 5, 6, and 8. In our investigation, study participants included Generation 3 individuals (Gen 3; examination 1, 2002–2005) with at least 1 parent identified in the Offspring cohort (Gen 2; examination 6 or 8, 1996–1998 and 2005–2008, respectively) or in the New Offspring Spouse cohort (examination 1; Figure 1). For a separate sibling analysis, study participants included Gen 2 and Gen 3 participants with at least 1 sibling at Gen 2 examination 6 or 8, and Gen 3 examination 1, respectively (Figure 1). Participants were excluded if concomitant diagnoses of mitral or aortic stenosis (rheumatic or calcific, with or without history of surgery) were present (Gen 2/New Offspring Spouse cohort n=32; Gen 3 n=5). The study protocol was approved by the Institutional Review Board of Boston University Medical Center, and all participants provided written informed consent.

Clinical Characteristics

Clinical variables used in the present investigation included: age, sex, and body mass index (BMI). History of smoking (using chronic obstructive pulmonary disease as a surrogate of significant tobacco use), diabetes mellitus, hypertension treatment, and systolic/diastolic blood pressure were included in the analysis as potential valve stressors that may influence the progression of MR. Risk factors for cardiovascular disease such as diet (total fat, protein, calories), physical activity index (calculated as described in a previous FHS investigation),[12] and lipid levels (total cholesterol/high-density lipoprotein) were also included among the clinical variables. Moreover, we determined whether any of the study participants had a history of heart failure or myocardial infarction to account for any potential common genetic substrate for myopathy (ischemic or nonischemic) and the development of secondary MR.

Echocardiographic Characteristics

All study participants in the Gen 3, Gen 2, 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 MR; they were stored on VHS and digitized for subsequent review. All measurements were performed with an off-line cardiac analysis system (Digiview, Houston, TX).

MR was assessed qualitatively by 2-dimensional color Doppler in a long-axis view and graded as trace, mild, moderate, moderate/severe, or severe. Gen 3 MVP was diagnosed as leaflet displacement >2 mm beyond the mitral annulus in a parasternal or apical 3-chamber long-axis view.[13] Gen 2 MVP was diagnosed using similar criteria at examination 6 or 8 (if 6 not available), and in the Offspring Spouse cohort at examination 1.

Left atrial dimension was calculated by M-mode as the anteroposterior maximal left atrium diameter in systole. LV 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. The fractional shortening percentage was calculated as (LV internal diameter in diastole−LV internal diameter in systole)/LV internal diameter in diastole×100.

Case Ascertainment

MR was defined regardless of cause as ≥ mild regurgitation on Doppler color flow imaging. Cause of MR was adjudicated as follows: if MVP was present, MR was considered primary. If no MVP was present and there was a clinical history of myocardial infarction or echocardiographic evidence of a regional wall motion abnormality or LV dilatation, MR was considered secondary and related to coronary heart disease or other cause of LV dilatation. If none of the above conditions was present, MR was classified as idiopathic.

Finally, we determined whether any of the participants with MR had asymmetric hypertrophy (as a surrogate for hypertrophic cardiomyopathy) or dilated cardiomyopathy (individuals with LV cavity dilatation but no history of myocardial infarction), as both these conditions can be inherited and cosegregate with MR.

Nationwide Swedish Hospital Registers

Participants

All subjects born after 1932 and living in Sweden in 1997 with at least 1 sibling alive in 1997 were identified from nationwide registers and included in this study (Figure 2). Siblings and spouses were

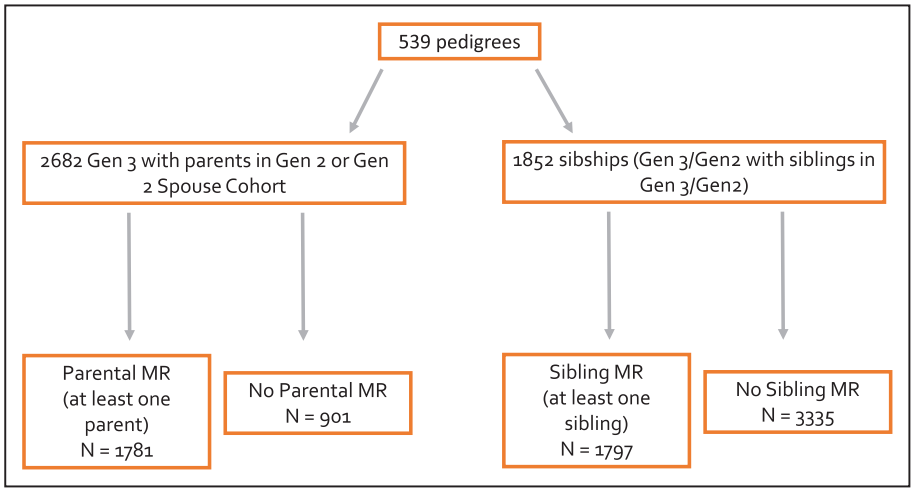

Figure 1. Schematic overview of the Framingham Heart Study cohorts according to parental or sibling mitral regurgitation (MR). Gen 2/Gen 3 indicates Generation 2/Generation 3.

identified from the Swedish Multigeneration Register.[14] We protected anonymity by replacing the personal identification number with a serial number when linking data to hospital registers. The ethics committee at Lund University approved the study.

Clinical Characteristics

Clinical variables included age, sex, history of chronic obstructive pulmonary disease, hypertension, diabetes mellitus, obesity, and coronary heart disease. Such variables were identified from the National Patient Register and *International Classification of Diseases* (ICD) diagnosis codes as described in the following section.

Case Ascertainment

Ascertainment and validity of clinical diagnoses from nationwide Swedish registers has been described previously.[15,16] All patients with a first diagnosis of MR were identified from the National Patient Register. The National Patient Register includes diagnosis codes from all hospital inpatient and outpatient visits in Sweden. Reporting to the National Patient Register is mandatory, and departmental reimbursements from the Swedish tax-financed healthcare system are based on ICD. The ninth version was used from 1987 to 1996 and the tenth version of ICD was used from 1997 and onwards. ICD definitions are shown in the Data Supplement. Individuals with a diagnosis of MR and hypertrophic or dilated cardiomyopathy were also identified using ICD codes.

Statistical Analysis

Framingham Heart Study

Clinical and echocardiographic characteristics were compared between Gen 3 participants with and without parental MR and, in separate analyses, Gen 2/Gen 3 participants with and without a sibling with MR. We performed *t* tests to compare continuous variables and χ^2 tests to compare binary variables (Fisher exact test for binary variables with low frequencies). We used logistic regression via generalized estimating equations to estimate the associations of parental MR with the prevalence of MR in their Gen 3 offspring (pooling all causes). A similar regression model was fitted to estimate the association of MR in an individual with the prevalence of MR in a sibling in Gen 2/Gen 3. For each sibling pair, sibling 1 and sibling 2 were included twice in the analysis: once for sibling 1 as the outcome and sibling 2 as the risk factor, and once for sibling 2 as the outcome and sibling 1 as the risk factor. We used the generalized estimating equations procedure to accommodate correlated responses. Sensitivity analyses were performed (1) excluding MVP and (2) including ≥ moderate MR cases only. Multivariable models were estimated adjusting for age, sex, BMI, systolic/diastolic blood pressure, diabetes mellitus, chronic obstructive pulmonary disease and history of myocardial infarction. All analyses were conducted using R (R Core Team [2014]. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org). We also estimated additive heritability of MR in full pedigrees (n pedigrees=539, n individuals=580) using SOLAR liability threshold model. Sensitivity analyses were conducted (1) excluding MVP, (2) including ≥ moderate MR cases only, and (3) excluding MR cases with hypertrophic or dilated cardiomyopathy. Finally, separate heritability analyses were conducted for primary, secondary, and idiopathic MR. A 2-sided *P* value <0.05 was the criterion for statistical significance.

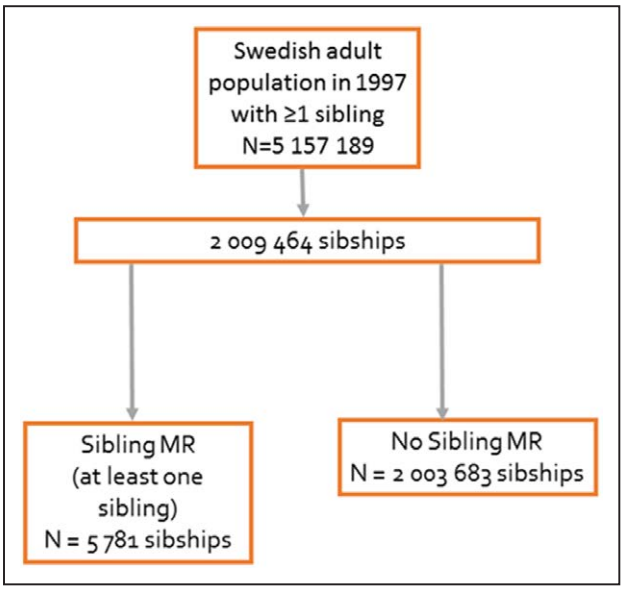

Figure 2. Schematic overview of the Swedish sibling cohort according to sibling mitral regurgitation (MR).

Nationwide Swedish Hospital Registers

Risk of MR with an affected sibling was evaluated using Cox regression, censoring at death or emigration, and with follow-up until December 31, 2010. Adjustments were performed for age, sex, family size, and cardiovascular risk factors (hypertension, diabetes mellitus, history of coronary heart disease). Two sensitivity analyses were performed, restricting sibling history to (1) siblings diagnosed with MR between 1997 and 2010 (the 10th version of the ICD was used during this time), and (2) history of surgery for MR. Variance estimation accounted for sibships using methods described previously.[17] Statistical analyses were performed in SAS version 9.3 (SAS Institute Inc, Cary, NC). As information on twins was not available in the Swedish sample, heritability of MR was estimated using tetrachoric correlations between full-siblings (n=5 157 189) and half-siblings (n=832 507). This method has been shown to generate comparable heritability estimates to twin designs in Swedish data for other diseases.[18] Similar to the FHS, a sensitivity analysis was conducted excluding MR cases with a diagnosis of hypertrophic or dilated cardiomyopathy in the MR heritability estimate. Statistical significance was defined by a 2-sided *P* value <0.05.

Results

Framingham Heart Study

There were a total of 1761 cases of MR (138 primary, 223 secondary, and 618 idiopathic) among Gen 2/Gen 3 participants regardless of availability of sibling/parental MR data. Clinical and echocardiographic characteristics of the 3679 Gen 3 participants (53.2% women, mean age 40 years) with available parental information on MR status are summarized in Table 1. Gen 3 participants with parental MR (n=1781) were slightly older, had higher diastolic blood pressure and a greater number of participants with a history of prior myocardial infarction compared with the group without parental MR (n=901). Otherwise, the 2 groups were fairly similar with regards to sex, BMI, diet, physical activity, lipid levels, diabetes mellitus, and prior heart failure. Gen 3 participants with parental MR had a higher proportion of MR cases (mostly mild) and slightly larger mean left atrial diameter. They had a higher number of primary MR cases. Otherwise, the 2 groups were similar with regards to other causes and other grading of MR. They also had similar LV dimensions.

There were 1852 sibships (average sibship size 2.8, 792 sibships with at least 1 affected sibling). Similarly to participants with parental MR, Gen 2/Gen 3 participants with sibling MR (n=1797; Table 1) were slightly older, had higher blood pressure and a higher proportion of individuals with prior myocardial infarction compared with the group without sibling MR (n=3335). Diet, physical activity, and lipid levels were not significantly different between the 2 groups. The sibling MR group had a higher proportion of MR cases (mostly mild and moderate) and a slightly larger left atrial size. There were more participants with secondary MR compared with

Table 1. Baseline Characteristics of Study Subjects According to Parental or Sibling MR in the Framingham Heart Study

	Gen 3 Participants With Parental MR (n=1781)	Gen 3 Participants With No Parental MR (n=901)	*P* Value	Gen 2/Gen 3 Participants With Sibling MR (n=1797)	Gen 2/Gen 3 Participants With No Sibling MR (n=3335)	*P* Value
Clinical characteristics						
Age, mean (SD), y	41 (9)	37 (8)	<0.001	52 (13)	45 (12)	<0.001
Sex (male), n (%)	826 (46)	428 (48)	0.58	870 (48)	1550 (46)	0.19
Diabetes mellitus, n (%)	43 (2)	21 (2)	0.89	118 (7)	151 (5)	0.003
SBP, mean (SD), mm Hg	116 (14)	114 (13)	<0.001	123 (17)	119 (16)	<0.001
DBP, mean (SD), mm Hg	75 (10)	74 (9)	0.002	75 (10)	75 (10)	0.99
Hypertension treatment, n (%)	152 (9)	44 (5)	<0.001	409 (23)	440 (13)	<0.001
BMI, mean (SD), kg/m^2	26.4 (5.0)	26.3 (5.1)	0.83	27.3 (5.1)	27 (5.3)	0.08
Fat intake, mean (SD), g	76 (36)	79 (38)	0.14	78 (36)	77 (37)	0.51
Protein intake, mean (SD), g	97 (47)	100 (46)	0.14	98 (43)	98 (47)	0.95
Calories, mean (SD), kcal	2134 (893)	2190 (903)	0.15	2142 (867)	2131 (890)	0.75
Physical activity index, mean (SD)	38 (8)	38 (8)	0.84	37 (8)	38 (7.9)	0.59
Total cholesterol/HDL	3.75 (1.32)	3.75 (1.6)	0.93	3.79 (1.35)	3.76 (1.44)	0.66
Heart failure, n (%)	1 (0.06)	2 (0.2)	0.26	13 (0.7)	19 (0.6)	0.52
History of myocardial infarction, n (%)	10 (0.6)	0 (0)	0.02	46 (2.6)	51 (1.5)	0.02
Chronic obstructive pulmonary disease, n (%)	66 (4)	26 (4)	0.36	91 (6)	147 (5)	0.37
Echocardiographic characteristics						
MR (total), n (%)	262 (15)	90 (10)	<0.001	500 (28)	562 (17)	<0.001
Primary vs secondary vs idiopathic MR, n (%)	27/2/150 (2/0.1/8)	5/2/59 (0.6/0.2/7)	0.03/0.61/0.09	38/68/192 (2/4/11)	47/61/230 (1/2/7)	0.075/<0.001/<0.001
LVIDd, mean (SD), mm	4.9 (0.40)	4.9 (0.4)	0.53	4.9 (0.5)	4.9 (0.4)	0.49
LVIDs, mean (SD), mm	3.2 (0.3)	3.2 (0.3)	0.24	3.1 (0.4)	3.1 (0.4)	0.27
LADs, mean (SD), mm	3.7 (0.5)	3.6 (0.5)	0.002	3.9 (0.6)	3.8 (0.5)	< 0.001
Mild/moderate/moderate–severe/severe MR, n (%)	247/15/0/0 (14/0.8/0/0)	84/5/1/0 (9/0.6/0.1/0)	<0.001/0.41/0.36/NA	461/37/2/0 (26/2/0.1/0)	537/21/4/0 (16/0.6/0.1/0)	<0.001/<0.001/0.93/NA

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LADs, left atrial dimension in systole; LVIDd, left ventricular internal diameters in diastole; LVIDs: left ventricular internal diameters in systole; MR, mitral regurgitation; NA, not applicable; and SBP, systolic blood pressure.

Gen 2/Gen 3 participants without sibling MR. The 2 groups were similar with regards to LV dimensions.

Presence of both parental and sibling MR was associated with a greater odds of prevalent MR in offspring and sibs, respectively: 14% (n=262) offspring with parental MR had MR compared with 10% (n=90) without parental MR (multivariable-adjusted odds ratio, 1.31; 95% confidence interval [CI], 0.98–1.74; *P*=0.07); and 28% (n=500/1797) of siblings with sibling MR had MR compared with 17% (n=562/3335) without sibling MR (multivariable-adjusted odds ratio, 1.20; 95% CI, 1.01–1.43; *P*=0.04). These results did not change significantly when adjusting for age and sex alone (without the covariate history of myocardial infarction) (model 1, Table 2) and after excluding MVP (model 3). Results were reinforced after restricting to ≥ moderate MR (model 4), even in nonprimary cases only (model 5).

Multivariable-adjusted heritability of MR was estimated at 0.15 (95% CI, 0.07–0.23; *P*≤0.001) in the FHS-based pedigree analysis. Heritability of MR was similar at 0.12 (95% CI, 0.04–0.20; *P*<0.001) in the sensitivity analysis excluding individuals with MVP and more prominent at 0.44 (95% CI, 0.15–0.73; *P*=0.001) when including ≥ moderate MR cases only. Multivariable-adjusted heritability of MR did not change (0.15; 95% CI, 0.07–0.23; *P*≤0.001) when we excluded the 7 participants with available parental/sibling MR data and a diagnosis of hypertrophic cardiomyopathy (n=3) or dilated cardiomyopathy (n=4). Separate multivariable-adjusted heritability estimates for the 3 MR categories were as follows: 0.47 (95% CI, 0.20 to 0.74; *P*<0.001) for primary MR, 0.18 (95% CI, −0.25 to 0.43; *P*=0.21) for secondary MR, and 0.47 (95% CI, 0.20 to 0.74; *P*<0.001) for idiopathic MR.

Table 2. Risk of MR According to Parental or Sibling MR in the Framingham Heart Study

	MR OR	95% CI	*P* Value
Parental MR			
Model 1: sex+age	1.34	1.00–1.79	0.04
Model 2: model 1+risk factors*	1.31	0.98–1.74	0.07
Model 3: model 2 excluding MVP	1.25	0.93–1.67	0.14
Model 4: model 2+≥ moderate MR only	1.42	0.97–2.06	0.07
Model 5: model 3+≥ moderate MR only	1.35	0.92–1.99	0.13
Sibling MR			
Model 1: sex+age	1.25	1.06–1.48	0.01
Model 2: model 1+risk factors*	1.20	1.01–1.43	0.04
Model 3: model 2 excluding MVP	1.23	1.02–1.48	0.03
Model 4: model 2+≥ moderate MR only	1.78	1.25–2.53	0.002
Model 5: model 3+≥ moderate MR only	1.67	1.10–2.54	0.02

CI indicates confidence interval; MR, mitral regurgitation; MVP, mitral valve prolapse; and OR, odds ratio.

*Risk factors are body mass index, systolic/diastolic blood pressure, diabetes mellitus, chronic obstructive pulmonary disease, and history of myocardial infarction.

Nationwide Swedish Hospital Registers

Between 1997 and 2010, 8628 subjects were diagnosed with MR from a population of 5 157 189 subjects from Sweden (Table 3). The proportions of MR cases with hypertrophic and dilated cardiomyopathy were 1% and 5%, respectively. The group with sibling MR (n=18 891) had larger family sizes and a nominally significant higher proportion of individuals diagnosed after 50 years of age (65%) compared with the group without sibling MR (n=5 138 298). The 2 groups were similar with regards to sex distribution and cardiovascular risk factors (including history of myocardial infarction). A sibling history of MR was present in 0.4% (18 891/5 157 189) of all Swedish individuals and 2.8% (239/8628) of MR cases. One percent (n=239/18 891) of siblings with sibling MR had MR compared with 0.2% (n=8389/5 138 298) without sibling MR, corresponding to a hazard ratio of 4.00 (95% CI, 2.48–6.44; *P*<0.001; Figure 3) adjusted for age and sex. Additional adjustment for family size and cardiovascular risk factors resulted in a slight risk attenuation (hazard ratio, 3.57; 95% CI, 2.21–5.76; *P*<0.001; Figure 3). The increased long-term MR risk in Swedish siblings in the presence of a sibling history of MR is shown in Figure 4. Results were similar in sensitivity analyses restricted to siblings diagnosed with MR between 1997 and 2010 (reflective of ICD-10 coding of MR) and siblings undergoing valve surgery for MR, respectively (Figure 3). Of 2 million Swedish families, only 2 had ≥2 affected siblings. Among the 7 subjects originating from these 2 families, 6 were diagnosed with MR. Overall, the risk of MR was driven by the majority of families with 1 affected sibling (233 MR cases among 18 891 subjects with sibling MR; hazard ratio, 3.62; 95% CI, 3.18–4.13; *P*<0.001).

Multivariable-adjusted heritability of MR was estimated at 0.52 (95% CI, 0.48–0.56) in the Swedish full-sibling and half-sibling analysis. The estimated heritability did not change after excluding individuals with hypertrophic or dilated cardiomyopathy (0.51; 95% CI, 0.48–0.56).

Table 3. Baseline Characteristics of Study Subjects According to Sibling History of MR in the Swedish Population

	No Sibling History of MR n (%)	Sibling History of MR n (%)	*P* Value
Population	5 138 298	18 891	
MR	8389 (0.16)	239 (1.2)	<0.001
Valvular surgery	2233 (0.04)	83 (0.4)	<0.001
Sex			0.51
Men	2 627 510 (51.1)	9522 (50.4)	
Women	2 510 788 (48.9)	9369 (49.6)	
Age at MR diagnosis, y			0.09
<20	836 (10.5)	25 (10.7)	
20–29	351 (4.4)	5 (2.1)	
30–39	673 (8.4)	11 (4.7)	
40–49	1509 (1.9)	41 (17.5)	
50–59	3038 (38.0)	100 (42.7)	
60–69	1579 (19.8)	52 (22.2)	
Family size			<0.001
2 children	2 433 566 (47.4)	3823 (20.2)	
3 children	1 608 473 (31.3)	5005 (26.5)	
4 children	629 813 (12.2)	3764 (20.0)	
≥5 children	466 446 (9.1)	6299 (33.3)	
Chronic obstructive pulmonary disease			0.93
No	4 968 928 (96.7)	18 007 (95.3)	
Yes	169 370 (3.3)	884 (4.7)	
Diabetes mellitus			0.71
No	4 999 508 (97.3)	17 741 (93.9)	
Yes	138 790 (2.7)	1150 (6.1)	
Obesity			0.15
No	5 081 788 (98.9)	18 683 (98.9)	
Yes	56 510 (1.1)	208 (1.1)	
Hypertension			0.12
No	4 873 515 (94.8)	16 274 (86.1)	
Yes	264 783 (5.2)	2617 (13.9)	
Coronary heart disease			0.89
No	4 998 073 (97.3)	17 135 (90.7)	
Yes	140 225 (2.7)	1756 (9.3)	

MR indicates mitral regurgitation.

Discussion

Our study demonstrates that familial clustering of MR exists in the community, supporting a genetic susceptibility common to primary and nonprimary MR. Our findings are particularly relevant, as they originate from 2 different but complementary

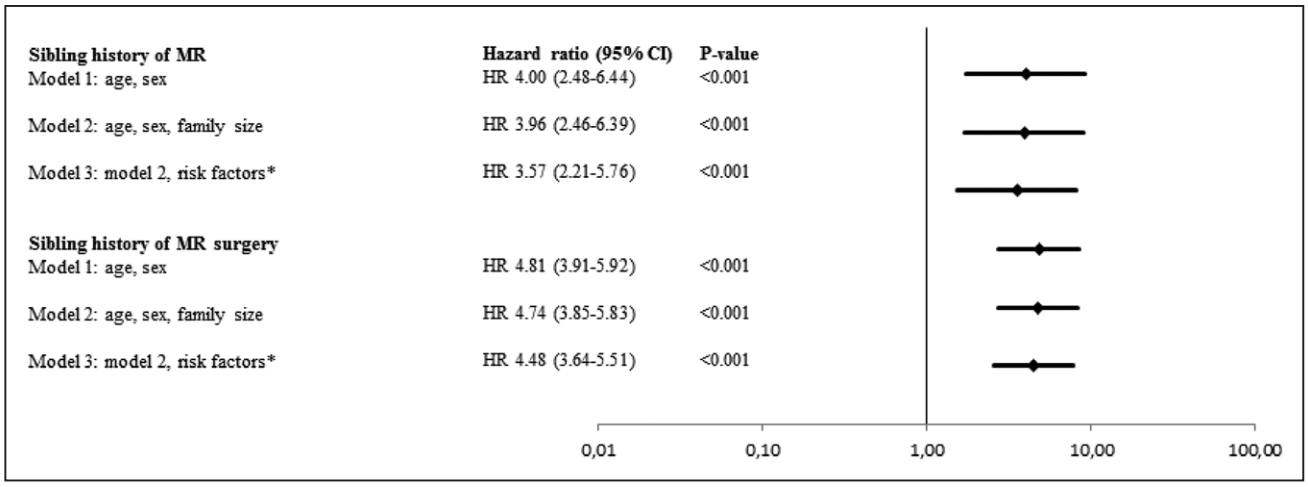

Figure 3. Sibling risk of mitral regurgitation (MR) in the Swedish population. *Risk factors are history of obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and coronary heart disease. CI indicates confidence interval.

community-based studies: the FHS and the nationwide Swedish registries. In the former, diagnosis of MR was based on routine echocardiography and comprised mostly mild/moderate MR cases. In Swedish registries, MR diagnosis was based on nationwide clinical/inpatient ICD coding and largely included moderate and severe cases. Accordingly, the risk ratios for familial clustering were lower in FHS, and considerably higher in Swedish registry data, but were comparably high in FHS sensitivity analyses restricted to at least moderate cases.

Currently, a distinct separation between primary and secondary MR causes exists with regards to pathophysiology and genetic substrate. MVP (primary MR) is typically considered a problem of excessive leaflet growth and has a strong heritable component.[8] Recent genetic studies have identified mutations in genes involved in the organization, assembly and alignment of valvular interstitial cells and extracellular matrix into a trilaminar architecture (*filamin A*, *DCHS1*, *TNS1*, and *LCMD1*) with consequent dysregulation of extracellular matrix in functional models.[19–21] Conversely, secondary MR is the result of insufficient leaflet growth with less MR seen in tethered valves with more prominent leaflet elongation, and a similar dysregulation of extracellular matrix observed in MVP.[3] Despite the individual variability in developing MR in the setting of LV systolic dysfunction/dilatation, a genetic susceptibility to secondary MR has never been postulated. Moreover, mild/moderate MR in the absence of MVP or other primary causes and without papillary muscle displacement or leaflet tethering has traditionally been considered idiopathic and without a clear pathophysiologic or genetic background. In our study, presence of sibling MR in FHS was associated with greater odds of prevalent MR in siblings. The association with parental MR was weaker, likely because of lower statistical power to detect a significant difference compared with the no parental MR group. Full pedigree heritability analysis demonstrated that 15% of the total variation of the MR trait in the FHS sample was because of genetic variation. This proportion did not change significantly after excluding

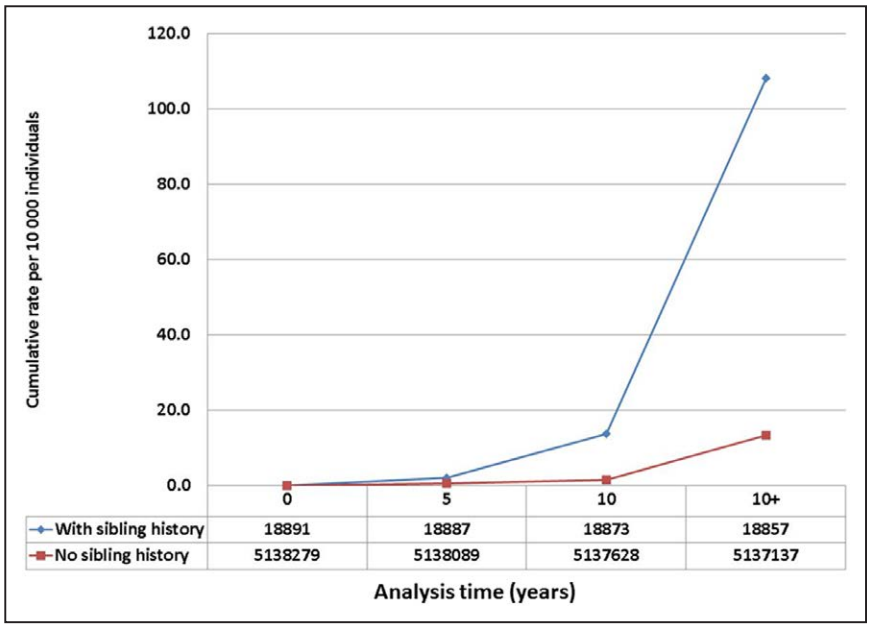

Figure 4. Risk of mitral regurgitation in Swedish siblings by sibling history.

participants with MVP in a sensitivity analysis, suggesting that familial clustering of MR is not exclusively explained by a traditionally inherited condition such as MVP. These findings were confirmed in the Swedish population (over 5 million individuals), in which the hazard of MR was almost 4× higher in the presence of a sibling history of MR. Furthermore, primary results were reinforced after restricting to individuals with ≥ moderate MR (FHS) or treated surgically (Swedish sample), suggesting a spectrum of effect of sibling MR on development of MR based on severity of disease. We found substantially higher MR heritability estimates in Sweden (52%) than in the FHS (15%). This is consistent with the greater severity of MR observed in the Swedish study design (with at least moderate severity in >75% of cases as described in a recent validation study)[16] when compared with FHS where cases were mostly mild (Table 1). Indeed, the estimate was comparable to the heritability estimate from the sensitivity analysis of FHS with ≥ moderate MR (44%). We also note that the magnitude of MR heritability in Sweden was comparable to that of other complex diseases including coronary artery disease (40%–60%),[22] atrial fibrillation (62%),[23] and venous thromboembolism (47%).[24]

Whereas multiple genetic variants have been associated with coronary heart disease,[25] genetic predisposition to the development of secondary MR (independent of coronary heart disease inheritance) has not been established. In our investigation, risk estimates of sibling MR remained statistically significant after adjusting for history of myocardial infarction in the multivariable models in both FHS and Swedish samples. On the other hand, MR heritability was not statistically significant in a separate FHS pedigree analysis that included secondary MR only. The lack of statistical significance of secondary MR heritability was likely because of a small number of cases included in the pedigree analysis (only 4 of Gen 3 participants with available parental information on MR had secondary MR, 2 with and 2 without parental MR; Table 1). As the diagnosis of secondary MR was not available in the Swedish registries, familial aggregation of secondary MR could not be explored in the Swedish sample. Larger studies in different populations are needed to better understand the heritability of secondary MR.

When we assessed the proportion of cases of MR based on cause, the majority of Gen 3 subjects with either parental or sibling MR were classified as idiopathic. In a separate analysis assessing the heritability of idiopathic MR alone, heritability estimates were as high as those for primary (MVP related) MR. In vitro studies have demonstrated histological changes in mitral valves in response to increased blood pressure or afterload.[7] The ability of human mitral leaflets to grow in response to valve leaflet stressors (ie, blood pressure, smoking, or diabetes mellitus) and whether this ability is genetically determined remains to be determined.

Strengths and Limitations

The strengths of the FHS investigation include the unique availability of multigenerational clinical and echocardiographic data allowing detailed phenotyping and pedigree analysis. In addition, MR was diagnosed blinded to parental or sibling MR status, and risk factors potentially contributing to MR risk (blood pressure, age, sex, BMI, history of heart failure or myocardial infarction, etc.) were routinely ascertained. The limitations of the FHS are as follows: first, our analysis was limited to a single sample of European ancestry and the results may not be generalizable to other races/ethnicities. Second, the parental MR sample size was small; hence, some of the statistically nonsignificant comparisons may have been underpowered. Third, not all siblings and parents were included in the FHS so there may be some misclassification of presence versus absence of MR in pedigrees. In the analysis of association between sibling MR and MR, a sibling may not have been recruited if he/she refused enrollment, moved out of town, or died. Among the mechanisms of missing data, death could be related to MR status. However, the relationship between MR and death may be substantially weakened after adjusting for age, sex, BMI, systolic/diastolic blood pressure, and history of myocardial infarction. A residual relationship between MR and death may be present despite adjusting for such risk factors. In this case, it is more likely that healthy siblings were ultimately included in the study, thus reducing the number of affected sibling pairs, and causing underestimation of the odds ratio. Fourth, as data on Gen 3 was available at only a single time point, we could not assess the association of parental or sibling MR with longitudinal development of MR in FHS offspring or siblings, respectively. Hence, survival analysis was not used in the FHS sample.

The major strengths of the Swedish population registries are the large sample size (>5 million individuals) facilitating detection of small differences in effect size between comparison groups. Whereas the diagnosis of MR was based on routine echocardiography in the FHS, in the Swedish population, ICD-9 and ICD-10 coding included more severe, clinically apparent cases. Therefore, our study results were consistent across 2 different epidemiological settings with different MR disease severities. Among the limitations of Swedish registries was the lack of detailed phenotyping as diagnoses were based on ICD-9 and ICD-10 coding. The Swedish population is largely of European ancestry and is characterized by unique lifestyle and climate. Hence, findings may not be generalizable to individuals of other ancestries or with different environmental conditions. Finally, some diagnoses such as obesity or hypertension may not be routinely coded using ICD-9 and ICD-10 codes, hence their prevalence may be underestimated in Swedish registries.

Clinical and Research Implications

Our study demonstrates familial clustering of MR irrespective of its cause. Upstream, genetically determined regulatory mechanisms able to influence either excessive (primary MR) or insufficient (secondary MR) leaflet growth, may be postulated and investigated in further studies. Similarly to other inherited cardiovascular conditions, we established that only a portion of variation in the MR phenotype is because of genetic variation. The role of environmental factors and the interaction between genes and environment in MR expression remains to be determined. Moreover, establishing heritability of MR in the community may clarify the use and cost-effectiveness of screening family members, which to date has not been performed on a routine basis.

Conclusions

Familial clustering of MR exists in the community, supporting a genetic susceptibility common to primary and nonprimary MR subtypes, which represents a novel finding. Further

studies are needed to elucidate common regulatory pathways that may lead to MR irrespective of cause.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Mitral regurgitation (MR) is the most common form of valve disease, affecting >2 million people in the United States. A familial component has been described for specific causes of MR such as mitral valve prolapse leading to primary MR. However, it has not been systematically studied across both primary and nonprimary subtypes of MR. We demonstrate that familial clustering of MR can be identified irrespective of cause of MR in both the Framingham Heart Study cohort and the entire Swedish population, 2 different but complementary data sets. In the former, diagnosis of MR was based on routine echocardiography and comprised mostly mild/moderate MR cases. In Swedish registries, MR diagnosis was based on nationwide clinical/inpatient ICD coding and largely included more severe cases. Establishing heritability of MR in the community may clarify the use and cost-effectiveness of screening family members, which to date has not been performed on a routine basis.

Heritability of Mitral Regurgitation: Observations From the Framingham Heart Study and Swedish Population

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SUPPLEMENTAL MATERIAL

Definitions of mitral regurgitation based on International Classification of Diseases (ICD) codes in the Swedish population.

Study population with mitral regurgitation
I34.0 Mitralisinsufficiens
Q23.3 Medfödd mitralisinsufficiens

Sibling with mitral regurgitation (1987-2010: ICD9 and ICD10)
I34.0 Mitralisinsufficiens (ICD10)
Q23.3 Medfödd mitralisinsufficiens (ICD10)
424A Mitralisklaffel (ICD9)
746G Medfödd mitralisinsufficiens (ICD9)

Surgery for mitral regurgitation (1987-2010)
Diagnosis code as above + surgery code simultaneous or later:
Op6: 3060, 3061, 3109, 3106, 3107, 3064
KKÅ97: F