Evidence for a Heritable Component in Death Resulting From Aortic and Mitral Valve Diseases

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Background—Cardiac valvular diseases contribute to >42 000 deaths yearly in the United States, but the role of genetics in these deaths is unknown. This study evaluated the familiality of death resulting from aortic, mitral, and all valvular diseases using a population-based genealogy linked to death records.

Methods and Results—The Utah Population Database contains >2 million individual records with genealogy data and 250 000 linked death certificates. Nonrheumatic aortic (n=932), mitral (n=1165), and all valvular (n=2504) disease deaths and rheumatic heart disease deaths (n=4713) were studied. Familial relative risks (FRRs) were assessed for first- and second-degree relatives. Familiality was also evaluated with the genealogical index of familiality, which considers all relationships in the Utah Population Database. FRRs were increased only for mitral valve death in both first-degree (FRR, 2.55; P<0.0001) and second-degree (FRR, 1.67; P<0.0001) relatives. Genealogical index of familiality analysis showed significant excess relatedness for all groups (P<0.001). Genealogical index of familiality results (P<0.001) for early age at death cases showed higher mean relatedness, a common characteristic of heritable disorders. Excess familiality extended to distant relatives for mitral (second-degree relatives) and aortic (beyond second-degree relatives) valve death.

Conclusions—Deaths resulting from nonrheumatic mitral and aortic diseases clustered among both close and distant relatives, especially among early age at death cases, suggesting a significant genetic component in death resulting from valvular diseases. Future studies should focus on gene discovery. (Circulation. 2004;110:3143-3148.)

Key Words: databases ■ genealogy and heraldry ■ genetics ■ pedigree ■ valves

Cardiac valve diseases contribute to >42 000 deaths annually. Causes of valvular diseases include nonrheumatic diseases such as mitral valve prolapse (MVP), mitral annular calcification (MAC), and senile aortic sclerosis/stenosis (AS), as well as rheumatic heart diseases (RHDs) that are usually considered secondary to infection. Although all of these conditions may lead to death, it is often benign.

Nonrheumatic aortic and mitral valve diseases are suspected to result from pathophysiological processes containing genetic components. For example, MVP may have an autosomal dominant inheritance pattern with age- and sex-based variable expressivity. Also, linkage studies have reported loci for MVP on chromosomes 16 and 11 and a candidate gene for Marfan’s syndrome, fibrillin-1, may influence MVP. Furthermore, it has been proposed that MAC and AS result from genetic factors related to atherosclerosis, including the apolipoprotein E gene. RHD, though usually secondary to infection, may also involve genetic factors regulating patient response to infection.

Although a genetic component is suggested and death is a known, albeit rare, complication, it is unknown whether genetic factors contribute to death resulting from valve diseases. The present study used a genealogical, population-based resource linked to death records to evaluate the familiality of death resulting from cardiac valve diseases.

Methods

Evaluation of Familiality

The most common population approach to assessing familiality evaluates individuals with a phenotype of interest and the occurrence of the same phenotype in their first-degree relatives. This rate is compared with either the rate in first-degree relatives of matched controls or the phenotype’s population rate. However, such analysis cannot separate genetics from shared environment. An improved approach determines risk among both close and distant relatives because distant relatives rarely systematically share the same imme-
Categorization of Death Causes

Each death record in the UPDB contains a primary cause of death, and certificates since ~1980 also contain multiple secondary causes of death and classify individuals with each. The clinical disease phenotypes we considered were death resulting from nonrheumatic cardiac valve diseases (specifically subcategories considering aortic or mitral valve disease) and RHD death (Table 1). Because of the rarity of death caused by tricuspid or pulmonary valve diseases, these causes were not evaluated individually. RHD death was evaluated separately because it is caused primarily by an environmental exposure.

### Statistical Methods

#### Familial Relative Risk

The familial relative risk (FRR) is an implementation in the UPDB of the traditional relative risk measure for family history of disease. The FRR is the ratio of the observed disease rate among relatives of cases and the internal UPDB expected rate among individuals with a death certificate; the overall expected is the sum of the 128 cohort-specific rates. Valve deaths measured among first- or second-degree relatives of probands are expected to be rare events and thus to follow a Poisson distribution, and 95% CIs and probability values were calculated by use of a normal approximation of that distribution.

The first-degree FRR compares rates among probands’ first-degree relatives, whereas the second-degree FRR examines rates only among second-degree relatives. The second-degree FRR perhaps more cleanly represents genetic risk because environmental exposures are less shared than genetic material among second-degree relatives.

Because 24 comparisons were performed in evaluating FRR, the Bonferroni correction was used with the critical probability value for nominal significance at \( P = 0.001 \) (1-sided test).

#### Genealogical Index of Familiality

The GIF, a statistic based on the Malécot kinship coefficient, was designed specifically to examine average relatedness among disease cases in the UPDB. It examines relatedness of all disease cases in the entire genealogy across large distances of relationship and multiple generations. The GIF has previously been described in studies evaluating the familiality of cancer and aneurysm.
similar statistic has recently become a method of choice for evaluation of the 11-century Icelandic database developed and used by DeCode Genetics.29–31 Briefly, the GIF compares the average relatedness of a set of individuals with a disease (cases) using the average coefficient of kinship (case GIF). Randomly selected controls are matched to cases by sex, 5-year birth cohort, and whether or not they were born in Utah to form a control group of the same size as the case group. The average relatedness is then computed for 1000 control sets, and the resulting GIFs are averaged (control GIF). A significant excess relatedness in cases versus controls represents a familial effect.

The coefficient of kinship measures the probability that randomly chosen copies of a gene from 2 individuals are shared identically by descent, ie, the same inherited copy from a common ancestor. Specifically, for a list of n individuals with the disease, 

$$\text{GIF} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \sum_{j=1}^{n} S_{ij} D_{ij}^{1/2}$$

where $S_{ij}$ is the number of distinct genealogical paths linking individuals i and j, and $D_{ij}$ is the path length for the kth path between i and j. It is also possible to evaluate the excess relatedness at each path length, which indicates the strength of the genetic contribution at each distance. For GIF values in which most excess relatedness is found for only low path lengths (ie, first-degree relatives), the effects of shared environment and shared genes cannot be separated.

Bonferroni correction for 8 GIF comparisons set the critical probability value at $P=0.006$ (2-sided test). Probability values for the GIF are from an empirical test of significance comparing the case GIF to the results of 1000 control GIFs. For both the FRR and GIF, secondary analyses were undertaken to evaluate the familiality of death among early age at death cases (age <65 years).

### Results

#### Description of Cases

Demographics for each death category are shown in Table 1. There were 932 cases of death resulting from aortic valve disease, 1165 mitral valve deaths, and 2504 deaths resulting from disease in any valve (ie, in addition to the aortic and mitral, 407 deaths caused by tricuspid, pulmonary, or unspecified valve, with “unspecified” comprising most of these). Average age at death from aortic valve disease was observed to be significantly older than for mitral valve disease ($P<0.001$) and RHD ($P<0.001$). No appreciable differences in ages at death were found between men and women in any death category.

#### Familial Relative Risk

Overall FRR results are shown in Table 2. Although RR estimates for all groups were $>1.0$, after correction for multiple testing, a significant risk to first-degree relatives was observed for each category except aortic valve death. Significantly elevated risk to second-degree relatives was demonstrated only for mitral valve disease (FRR, 1.67; $P<0.0001$). RR estimates were generally higher but conclusions were similar when the analysis was restricted to early age at death (Table 3).

We also examined associations between the valve groups by analyzing excess risk between the aortic, mitral, and RHD groups. For these analyses, 1 phenotype was used to define probands, and then the observed rates of the other phenotypes were estimated in the first- and second-degree relatives of these probands. For example, we estimated the risk of mitral death among relatives of aortic probands, observing 58 mitral deaths though expecting 59 (FRR, 0.99; CI, 0.75 to 1.28; $P=0.56$). All associations tested were not significant, suggesting that these phenotypes do not cosegregate.

#### Genealogical Index of Familiality

GIF analysis showed significant excess relatedness among cases for all death categories (Table 4). The average relatedness (GIFs) among controls was consistent across all categories (range, 2.62 to 2.69 for valves, 2.77 for RHD). Inspection of the path lengths (the Figure) contributing to the case GIF scores showed excess relatedness for aortic and mitral death beyond second-degree relatives (path length $>3$) and for all valvular deaths up to second-degree relatives. In contrast, for RHD, the excess relatedness was most apparent among siblings (path length, 2).

Because aortic death appeared to be underestimated before the general availability of 2D echocardiogram ($\approx$1975), with 696 aortic deaths (75%) after 1975, an additional GIF analysis excluded aortic deaths before 1975. This analysis did not

### Table 2: FRR Estimates

<table>
<thead>
<tr>
<th>Cause of Death Category</th>
<th>Relatives, n</th>
<th>Deaths Observed, n</th>
<th>Deaths Expected, n</th>
<th>FRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>4407</td>
<td>24</td>
<td>13.8</td>
<td>1.74 (1.12–2.59)</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>9695</td>
<td>28</td>
<td>24.9</td>
<td>1.13 (0.75–1.63)</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>6722</td>
<td>83</td>
<td>32.6</td>
<td>2.55 (2.03–3.16)$^*$</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>17 065</td>
<td>112</td>
<td>67.2</td>
<td>1.67 (1.37–2.01)$^*$</td>
</tr>
<tr>
<td>All valvular diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>13 030</td>
<td>150</td>
<td>105.3</td>
<td>1.43 (1.21–1.67)$^*$</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>28 753</td>
<td>270</td>
<td>248.1</td>
<td>1.09 (0.96–1.23)</td>
</tr>
<tr>
<td>RHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>23 763</td>
<td>619</td>
<td>355.4</td>
<td>1.74 (1.61–1.88)$^*$</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>44 470</td>
<td>623</td>
<td>573.8</td>
<td>1.09 (1.00–1.17)</td>
</tr>
</tbody>
</table>

$^*$P<0.0001 (Bonferroni threshold for significance: $P<0.001$).
appreciably reduce the excess relatedness for aortic death (case GIF, 3.30; control GIF, 2.62 ± 0.29; \( P = 0.009 \)), although exclusion of grandparents and great-grandparents of cases may have reduced the study power.

When the early age at death cases were evaluated, GIF values were found to be higher for all categories (Table 5), especially among aortic and all valvular deaths.

### Discussion

#### Valve Disease and Genetics

Nonrheumatic valve diseases include the more common AS,² MAC,³,⁵ and MVP⁴,⁶ and less frequent disorders such as bicuspid aortic valve,¹³,¹⁴ supravalvular AS,¹⁵,¹⁶ and pulmonary valve stenosis.¹⁷ Development of these diseases is suspected to have a genetic component. MVP,⁷,⁸ bicuspid aortic valve,¹³,¹⁴ and supravalvular aortic stenosis¹⁵ cluster in families, whereas MVP,¹¹ AS,¹² supravalvular AS,¹⁶ and pulmonary valve stenosis¹⁷ are associated with candidate genes. Genome scans report loci linked to MVP on chromosome 16⁹ and 11¹⁰ in 2 and 1 small pedigrees, respectively.

The present study used population-based mortality data to demonstrate a significant familial component to aortic and mitral valve death across distant relationships, suggesting a genetic component.

#### Genealogical Approach to Population Genetics

Coronary heart disease and its complications are known to cluster among first-degree relatives.³² Such clustering may indicate a genetic contribution and is a common method for assessing a “family history” of disease. However, such clustering in first-degree relatives may simply result from a shared environmental exposure that is not separable from a genetic effect.

An improved method for measuring aggregation of inherited risk uses population-based data and genealogy. Such analysis permits separation of the effects of shared environmental exposures from common genetic factors by examining not only first-degree relatives but also distant relatives who likely systematically share only genetic factors. Environmental exposures in distant relatives are expected to be randomly distributed compared with a proband’s exposures.)

Familial risk has been examined by such methods, including in the Utah resource, for cancer and aneurysm¹⁸–²⁰,²⁷,²⁸ and in Iceland’s genealogy for a variety of diseases,²⁹–³¹ attesting to the usefulness of the method.

### Table 3. FRR Estimates Among the Early Age at Death Cases

<table>
<thead>
<tr>
<th>Cause of Death Category</th>
<th>Relatives, n</th>
<th>Deaths Observed, n</th>
<th>Deaths Expected, n</th>
<th>FRR (95% CI) for Age &lt;65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve disease (n=202)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>959</td>
<td>10</td>
<td>2.5</td>
<td>4.02 (1.93–7.4)*</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>2274</td>
<td>8</td>
<td>7.2</td>
<td>1.11 (0.48–2.18)</td>
</tr>
<tr>
<td>Mitral valve disease (n=579)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>3658</td>
<td>47</td>
<td>16.8</td>
<td>2.80 (2.05–3.72)†</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>8384</td>
<td>62</td>
<td>35.7</td>
<td>1.74 (1.33–2.23)†</td>
</tr>
<tr>
<td>All valvular diseases (n=852)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>4856</td>
<td>71</td>
<td>39.0</td>
<td>1.82 (1.42–2.30)†</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>11 144</td>
<td>115</td>
<td>98.7</td>
<td>1.17 (0.96–1.40)</td>
</tr>
<tr>
<td>RHD (n=2717)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>13 095</td>
<td>392</td>
<td>201.6</td>
<td>1.94 (1.76–2.15)†</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>25 560</td>
<td>356</td>
<td>317.8</td>
<td>1.12 (1.01–1.24)</td>
</tr>
</tbody>
</table>

*\( P < 0.001 \) (significant after Bonferroni correction); †\( P < 0.0001 \).

### Table 4. Genealogical Index of Familiarity

<table>
<thead>
<tr>
<th>Cause of Death Category</th>
<th>Case GIF</th>
<th>Control GIF</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve disease</td>
<td>3.44</td>
<td>2.62 ± 0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>4.44</td>
<td>2.69 ± 0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All valvular diseases</td>
<td>3.14</td>
<td>2.63 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RHD</td>
<td>3.40</td>
<td>2.77 ± 0.07</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Study Evidence

Using such methods, this study found evidence for a familial and genetic component in death caused by aortic and mitral valve diseases. This evidence included increased risk to both first- and second-degree relatives (ie, FRR) for mitral death and excess relatedness (ie, GIFs) extending to distant relationships. The data also showed that aortic cases were not as closely clustered as mitral cases, perhaps because of lower penetrance, because of a different mode of inheritance, or because aortic valve disease occurs in old age and some who would have died as a result of aortic disease were censored, having died earlier of other causes. Interestingly, GIFs for both aortic and mitral death were higher than those previously published for most cancers, including several for which this Utah genealogical resource was used to discover genes suggesting that it may also be useful for discovering valve disease genes.

The failure to show increased risks for aortic compared with mitral deaths may suggest distinct pathophysiological processes and predisposition genes. The large difference in age at death for aortic and mitral cases supports this conclusion. Although all valvular deaths clustered significantly, the effect was smaller and likely resulted primarily from heterogeneous combination of aortic and mitral cases. Increased risk for RHD death was also noted, but in both FRR and GIF analyses, this increased risk was primarily among first-degree relatives, suggesting a strong environmental rather than a genetic effect, as expected from its primarily infectious origin.

All categories showed higher average relatedness when early age at death cases were considered separately. The excess relatedness for aortic, mitral, and all valves was greater than in the overall analysis. This characteristic is often noted for diseases with a strong heritable component and suggests that genetic studies may be best served by restricting ascertainment to early-onset forms of the disease.

Whether the findings from this study represent the genetics of valvular factors or of associated comorbidities is uncertain. Senile AS and MAC are associated with all-cause and cardiovascular death but are also associated with hypertension, congestive heart failure, stroke, and acute myocardial infarction, diseases known to independently lead to death. Thus, although valvular genetic factors may lead directly to death, it may be that valve problems aggravate other diseases that lead to death. If so, the genetic effects measured here may represent the genetics of other valve-associated cardiovascular diseases.

Study Strengths and Limitations

Inaccuracy in death certificate coding may introduce errors into this study and could cause biases of ascertainment in death reports. However, such errors are unlikely to be systematically based on family relationships but instead randomly distributed between study groups. Use of death certificates may, however, provide a less biased method of disease status determination than patient reports of family histories of disease. Furthermore, imprecision in coding death causes is a limitation, with the potential for error and cross-contamination (eg, RHD and nonrheumatic codes being used interchangeably).

Changes over time in ICD codes, disease understanding, clinical training, ability to diagnose disease, and treatment modalities may also have affected this study, although these errors are also likely to be randomly distributed across the genealogy. This study was also potentially limited by the lack of specific pathophysiological descriptions; the results appear to demonstrate differing pathophysiology for aortic and mitral death, but the specifics were unknown.

Because the study population is primarily white, the results presented here may not be generalizable to nonwhite ethnic groups. Further studies of other ethnic groups are required.

A study strength was the use of the GIF, a familiality metric that measures risk beyond first-degree relatives. The GIF allowed examination of the genetic component of disease and, with the increased power of a large genealogy, was able to, for example, detect familiality for aortic death across distant relationships when traditional methods did not. Another study strength may be the homogeneous geographic or social environment shared across the study population that may provide a consistent rate of sporadic cases regardless of family membership and thus give improved resolution for genetic findings.

Conclusions

Death resulting from nonrheumatic aortic and mitral valve diseases clustered among both close and extended relatives, suggesting a significant genetic effect on death caused by valvular diseases. Restriction to early age at death cases produced even more striking results. Although a familial effect was found for RHD death, it was primarily among first-degree relatives and thus probably was an environmental exposure, as expected. Finally, this study provides evidence that death resulting from aortic and mitral valve diseases are disparate processes, a finding with potential clinical and pathophysiological importance. Future investigation should focus on gene discovery.

Acknowledgments

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References

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