

# Familial Aggregation of Calcific Aortic Valve Stenosis in the Western Part of France

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**Background**—Calcific aortic valve stenosis (CAVS) is the most common valvular defect in developed countries. Unlike mitral valve prolapse, there is no demonstration that a familial factor could play a role in the occurrence of this disease. The aim of this study was to demonstrate a familial aggregation for CAVS.

**Methods and Results**—We used the files of 2527 consecutive patients operated on for CAVS in our institution between 1992 and 2002 to map the distribution of operated CAVS in the western part of France. In a second step, we investigated clinically and genealogically the clusters with the highest rates of operated CAVS to detect familial forms of the disease. The geographic distribution of CAVS is highly heterogeneous, with an average frequency of operated CAVS of 1.13 per 1000 inhabitants but up to 9.38 per 1000 in specific parishes. A screening of the population from the parishes with the highest rate of operated CAVS allowed us to identify 5 families with  $\geq 3$  sibs affected by CAVS. A large genealogical analysis performed in one of these families allowed us to link 48 patients who derived from 34 nuclear families. Genealogical information could be traced to a common ancestor within 13 generations.

**Conclusions**—Identification of clusters and large families affected by a classic form of CAVS demonstrates a familial aggregation for this disease. (*Circulation*. 2006;113:856-860.)

**Key Words:** aorta ■ epidemiology ■ genetics ■ stenosis ■ valves

Calcific aortic valve stenosis (CAVS) is the most common valvular defect in developed countries. This condition increases in prevalence with advancing age, afflicting 2% of the population by 65 years of age.<sup>1</sup> It is a progressive disease, well tolerated for several years or decades until the occurrence of symptoms such as cardiac failure, angina pectoris, or syncope that mark a sudden change in its mortality rate.<sup>2</sup>

## Clinical Perspective p 860

Despite the high prevalence of this condition and the increasing morbidity and mortality, very little is known about the cellular basis of CAVS. Several risk factors are associated with calcific aortic valve disease, including hypertension, age, male sex, smoking, diabetes, hyperuremia, hypercholesterolemia, increased body mass index, and hyperparathyroidism.<sup>1,3-5</sup> Arteriosclerosis has also been evoked to play a critical role in the occurrence of aortic valve stenosis, and preliminary data are in favor of a reduction in the progression of CAVS by statin treatment. However, most patients with arteriosclerosis risk factors have a normal aortic valve.<sup>6-10</sup>

Polymorphisms in vitamin D receptor and apolipoprotein E (apoE) genes have been linked to an increased risk for CAVS,

suggesting a genetic background for the disease.<sup>11,12</sup> Familial inheritance has been demonstrated for mitral valve prolapse (MVP), the other main valvular disease, and a familial study is recommended when a case of MVP is identified.<sup>13</sup> Until now, there has been no description of familial forms of CAVS, probably because of the late onset of the disease and the frequently unknown genealogical background and health status of the proband. However, familial factors could play a role in the occurrence of the disease because a recent study has demonstrated a heritable component in death resulting from aortic disease.<sup>14</sup>

The aim of our study, as a first step in the identification of a genetic basis for the disease, was to evaluate by an epidemiological approach whether a familial factor could play a role in the occurrence of CAVS.

## Methods

### Epidemiological and Genealogical Surveys of the Disease

We used our hospital files to identify all the patients operated on for CAVS in our area. These files showed that 2527 patients were operated on for CAVS in our institution between 1992 and 2002. The place of birth for each patient was determined through the use of the

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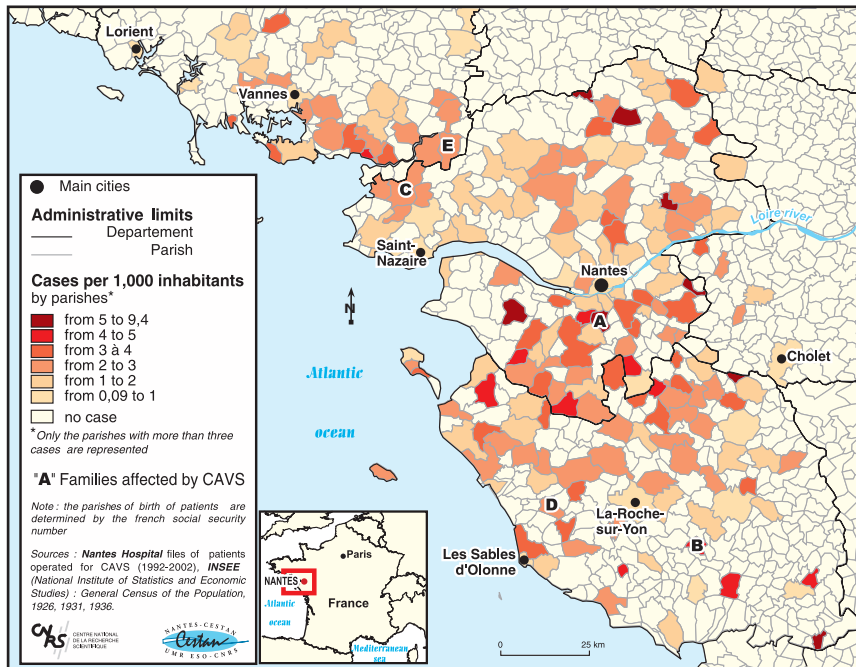
From l'Institut du thorax, Service de Cardiologie, Nantes (V.P., A.L., P.J., H. L. M.); Institut du Thorax, INSERM U533, Nantes (V.P., S.L.S., A.C., H.L.M., J.-J.S.); CNRS CESTAN, Nantes (V.J.); PIMESP, Centre Hospitalier Universitaire de Nantes, Nantes (J.-M.N.); and Laboratoire D'étude de Génétique des Populations, Université de Bordeaux, Bordeaux (A.C.), France.

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**Figure 1.** Map of the repartition of operated CAVS in the western part of France. Disease frequency was calculated for each parish by comparing the number of native cases of operated CAVS to the population living in the village. Population was estimated from the mean of the censuses performed in 1926, 1931, and 1936. This map shows an obvious spatial heterogeneity. Two clusters of high frequency can be described, 1 on the northern part of the map and 1 between the southern part of Nantes and La Roche-sur-Yon and between the Atlantic coast and Cholet, corresponding to a well-known isolate called “vendee-choletaise.” The letters represent parishes in which familial aggregation of the disease has been identified.

French social security number coding system, specifying the place of birth for each individual. We took advantage of this coding system to trace all operated patients. The frequency of the disease was calculated for each parish by comparing the number of native cases of operated CAVS with the population living in the parish. The population was estimated from the mean of the censuses performed in 1926, 1931, and 1936, corresponding to the average period of birth for the patients who underwent an aortic valve replacement. To prevent a bias in small parishes with 1 or 2 cases of CAVS, only the parishes with  $>2$  cases have been considered in the analysis.

The map was constructed with the MapInfo software (MapInfo Corp).

As a first approach, we focused on the parishes with high incidence of CAVS (frequency of operated CAVS,  $>3$  per 1000 inhabitants) and at least 2 operated patients sharing a common family name. Patients sharing the same family name and originating from the same parish were contacted; if the interview revealed a third affected member, an extended familial study was performed.

This method led to the identification of a large family in 1 parish. To extend the size of this family, we looked in our hospital files for patients operated on for CAVS who originated from this parish, and we performed a systematic screening of the population  $>60$  years of age who originated from this parish. For this screening, a nurse examined the inhabitants in the parish using an electronic stethoscope (Littmann model 4000), allowing the heart sounds of the subjects to be recorded. All the recordings were reevaluated by 2 investigators, and an echocardiography was proposed for all patients with an abnormal auscultation. A genealogical study was performed for all the affected subjects identified in this parish to find an ancestor in common with the initial family.

## Clinical Evaluation of CAVS

The study was conducted according to the French guidelines for genetic research and was approved by the ethics committee of Nantes University Hospital. Informed written consent was obtained for each patient who agreed to participate in the study. Clinical investigation included a review of medical history, a physical examination, a 12-lead ECG (Mac Vu Marquette Inc), and a transthoracic echocardiography (Hewlett-Packard Sonos 5500) with a 3.5-MHz probe. Data were recorded according to the criteria of the American Society of Echocardiography.<sup>15</sup> Examinations were stored for further analysis. The aortic valve area (AVA) was calculated by means of the

continuity equation.<sup>16</sup> The mean aortic valve gradient was obtained by tracing the continuous-wave flow velocity across the aortic valve.

Patients were considered to be affected by CAVS if they underwent an aortic valve replacement for aortic valve stenosis or if the echocardiography revealed an aortic valve stenosis with an AVA  $<1.2$  cm<sup>2</sup>. For the operated patients, a careful anatomic examination was performed to confirm that the aortic valve was tricuspid and that there was no lesion indicative of rheumatic fever. Patients with AVA  $>1.2$  cm<sup>2</sup>, aortic stenosis without obstruction of the left ventricular outflow, and significant aortic valve regurgitation were considered undetermined. Patients with any abnormalities in favor of a history of rheumatic fever (ie, calcifications of the mitral valve) or bicuspid valves also were considered undetermined.

Blood samples for all participating individuals were collected for serum and genetic analyses.

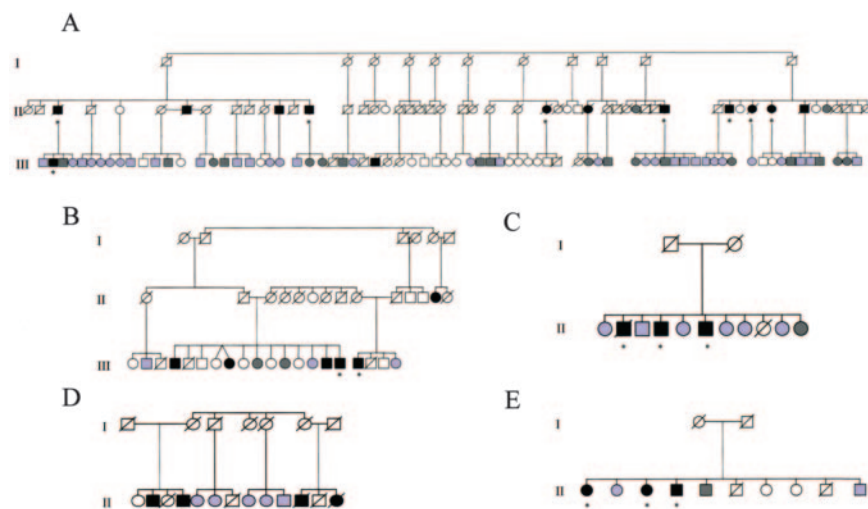
## Statistical Analysis

The heterogeneity of the prevalence of operated CAVS in the parishes was tested with a  $\chi^2$  test. Clinical data are expressed as mean  $\pm$  SD. The levels of cholesterol and creatinine were compared by use of the Student *t* test. A value of  $P < 0.05$  was considered significant. The distribution of the alleles for vitamin D receptor and apoE genes between affected and nonaffected family members was compared by use of a  $\chi^2$  test.

## Results

Starting from hospital records of patients operated for CAVS, we were able to trace the city of birth for each individual using the French social security number.

The map of the frequency of CAVS in the native population shows a clear spatial clustering (Figure 1). The average frequency of operated CAVS in the western part of France between 1992 and 2002 is 1.13 per 1000 inhabitants. In the parishes with the highest rate of operated CAVS, this level is up to 9.38 per 1000 inhabitants. On the contrary, in the main city, the frequency is 0.93 operated CAVS patients per 1000 inhabitants. A  $\chi^2$  test showed a significant ( $P < 0.001$ ) difference between the observed and expected number of CAVS between the geographic



**Figure 2.** Partial pedigrees of the families. Circles denote female family members; squares, male family members. Patients represented in black are affected by severe CAVS; gray symbols depict patients affected by nonsevere CAVS; and blue symbols identify patients with an undetermined phenotypic status because they did not reach the critical age of 65 years or have not been examined. Open symbols represent unaffected patients >65 years of age. Stars indicate patients operated on for CAVS.

clusters. The results showed a nonrandom distribution of CAVS, reflecting clusters of patients with the same disease.

In a first step, to test whether this geographic clustering of CAVS reflected a potential familial aggregation, we looked to find common family names in the parishes with highest incidences of CAVS. In the parishes with at least 2 patients with the same name, we performed a familial study to detect other family members affected by CAVS who were not yet identified. This approach led to the identification of 5 different families (Figures 1 and 2).

Family A was a large family made up of 135 members, 83 of whom were still alive (Figure 2A). Thirteen patients were clearly affected by severe CAVS (mean age,  $81 \pm 7$  years). Of them, 9 were still alive at the time of the study. Eight underwent an aortic valve replacement for symptomatic CAVS associated in 2 cases with a coronary artery bypass surgery (patients II-3, II-14, II-28, II-39, II-41, II-43, II-44, and III-2). The mean age for aortic valve replacement was  $73 \pm 8$  years. Five other patients were diagnosed with a severe CAVS with an average AVA of  $0.8 \pm 0.2$  cm<sup>2</sup> (patients II-7, II-12, II-32, II-45, and III-30). Three patients >80 years of age were clearly unaffected (individuals II-5, II-42, and II-46). Clinical status for patients from generation I could not be ascertained. Twenty other family members were diagnosed with aortic valve abnormalities not severe enough to allow them to be classified as affected. These family members were younger than patients with severe CAVS ( $58 \pm 10$  versus  $81 \pm 7$  years;  $P < 0.001$ ). Most of them originated from affected patients, suggesting that these abnormalities should be the first manifestation of CAVS. The aortic valve abnormalities were aortic valve insufficiency (3 patients), aortic valve sclerosis with moderate aortic valve stenosis (15 patients), and aortic valve insufficiency associated with moderate aortic valve stenosis (2 patients).

Family B was composed of 40 members (Figure 2B). Among them, 6 were affected by severe CAVS (patients II-13, III-4, III-8, III-15, III-16, and III-17). Patients III-16 and III-17 underwent an aortic valve replacement. The average AVA in the other affected patients was  $0.7 \pm 0.1$  cm<sup>2</sup>. Patient III-13 had a grade 1 mitral insufficiency. Patients III-10 and III-12 were classified as undetermined because of nonsevere CAVS (AVA,

$1.5$  cm<sup>2</sup> and  $1.4$  cm<sup>2</sup>, respectively). Nine other family members were unaffected.

Family C was made up of 13 members (Figure 2C). Of them, 3 were affected by CAVS (patients II-2, II-4, and II-6), 2 still alive at the time of the study. All 3 underwent surgery for severe symptomatic CAVS at  $71 \pm 4$  years of age. Patient II-11 was classified as undetermined because we found a nonsevere CAVS. The 6 other alive family members were unaffected.

Family D had 20 members (Figure 2D). Of the 20, 4 were affected by CAVS (patients II-2, II-4, II-11, and II-13), 2 still alive at the time of the study. Three of them have been operated on for severe symptomatic CAVS at  $72 \pm 1$  years of age (patients II-2, II-4, and II-11). A fourth patient refused surgery and died of severe symptomatic CAVS at 72 years of age. The other 6 family members were unaffected.

Family E was composed of 12 members (Figure 2E). Among them, 3 were affected by CAVS (patients II-1, II-3, and II-4). All of them have been operated on for severe symptomatic CAVS at  $68 \pm 4$  years of age. Patient II-5 was classified as undetermined because of nonsevere CAVS. The 4 other sibs were unaffected.

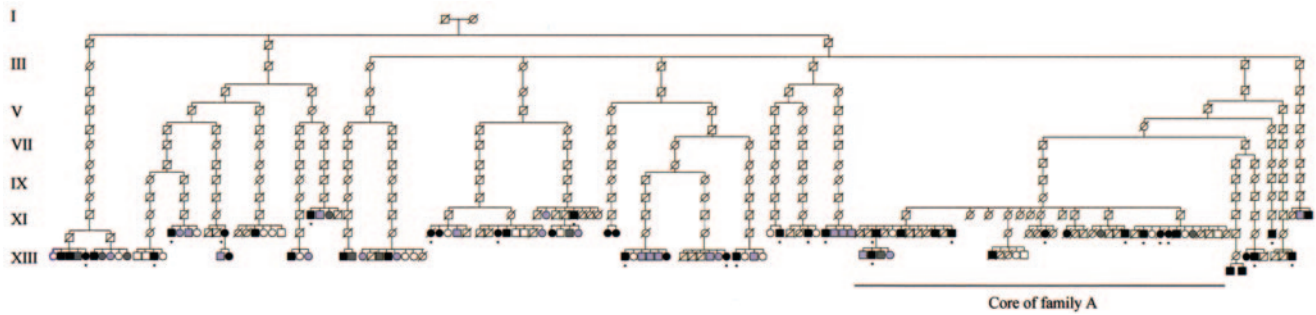
In all these families, blood exams revealed no familial history of renal insufficiency or hypercholesterolemia.

To increase the size of family A, we looked in our hospital files to detect patients who originated from the parish of family A and were operated on for CAVS. We identified 15 additional patients operated on for CAVS who originated from the same parish. We also performed a systematic screening of the population >60 years of age who originated from the parish of family A. During this screening, we examined 199 individuals. This screening allowed us to detect 53 patients with an abnormal auscultation. An echocardiography was proposed for all of these patients and accepted by 45. The echocardiography showed that 20 patients were affected by severe CAVS. A nonsevere CAVS was also identified in 11 other patients.

We hypothesized that all affected patients could be related. We then performed a genealogical analysis for these patients for >400 years and found a unique common ancestor born in 1650, 13 generations before (Figure 3).

To ensure that CAVS is not due to familial hypercholesterolemia or renal insufficiency in this pedigree, we compared the cholesterol and creatinine levels of affected family members





**Figure 3.** Pedigree of the family A showing 48 patients with severe CAVS. Patients with CAVS (solid symbols), previously thought to be largely unrelated, could be traced to a common ancestor within 13 generations. Circles denote female family members; squares, male family members. Stars indicate patients operated on for CAVS (25 patients). Patients in black are affected by severe CAVS; patients in white are unaffected and >65 years of age; patients in blue have an undetermined phenotypic status because they did not reach the critical age of 65 years or have not been examined; patients in gray are affected by a nonsevere CAVS.

with 20 nonaffected family members belonging to the same sibs who were >65 years of age. The mean cholesterol levels were  $5.7 \pm 1.2$  mmol/L in the affected patients and  $5.43 \pm 1.3$  mmol/L in nonaffected family members ( $P=NS$ ). Fifteen patients were treated with cholesterol-lowering drugs in the affected group, whereas 9 patients were treated in the nonaffected group ( $P=NS$ ). The creatinine level was significantly higher in the affected group ( $97.4 \pm 26$  versus  $77.8 \pm 18$  mmol/L;  $P=0.006$ ). Among the 25 patients who underwent an aortic valve replacement in the affected group, 5 also underwent a coronary artery bypass surgery.

Testing vitamin D receptor and apoE genes did not reveal an association between vitamin D receptor B allele or apoE 4 allele in CAVS patients.<sup>11,12</sup>

In this cluster, systematic screening of the first-degree relatives of patients affected by CAVS allowed us to identify 11 severe CAVS patients of 33. The first-degree familial recurrence of the disease in this cluster could then be estimated to be 33%.

The analysis of this pedigree provides us with several lines of evidence for a major genetic trait causing CAVS. X-linked transmission of the disease could be excluded with the identification of 1 demonstrated father-to-son transmission (patient II-3 to III-2 in Figure 2A) and 18 potential father-to-son transmissions even if the clinical status of the deceased father was not determined. Recessive transmission should also be excluded because 3 clinical records of both parents revealed monoparental affection. In patients of family A >50 years of age (Figure 2A), echocardiographies performed on offspring of affected members identified 10 of the 25 individuals with aortic valve stenosis or sclerosis. Finally, despite the late onset of the disease, it appears that the disease segregates in a 50:50 ratio, strongly suggesting an autosomal dominant mode of inheritance.

## Discussion

In this study, we evaluated the contribution of familial factors to CAVS by performing an epidemiological and a genealogical investigation to identify families affected by CAVS.

Probably because of the late onset of the disease, there is no description of large pedigrees for this disease, and familial factors are not considered to play a role in the occurrence of the disease. Genealogical approaches in isolated populations have shown their efficiency in identifying genetic contributions for common diseases.<sup>17–19</sup> We hypothesized that be-

cause the population in our area has a low geographic mobility, if a hereditary factor is present for CAVS, the frequency of this disease must be higher in certain areas corresponding to geographic isolates in which an ancestor has transmitted the disease to his offspring. To demonstrate the familial aggregation of CAVS, we took advantage of 2 major characteristics of our area in the western part of France. First, our cardiology center is the only referring hospital for cardiac surgery for >2 millions inhabitants, leading to a comprehensive view of operated CAVS in the area. Second, a part of this population originates from a geographic isolate in which the population is very sedentary. For example, in the parish of the family A, 97% of the population born in this parish before 1945 are still living in the parish today.

In the clusters with the highest rates of CAVS, we have identified 5 cases of familial aggregation of the disease. A large genealogical study performed in the cluster of the largest family allowed us to determine that all the patients detected to be affected by a severe CAVS in this area are related to the same common ancestor, suggesting that a major genetic trait is involved in the disease. In this cluster, all the affected patients are >65 years of age, and anatomic examination or echocardiography confirmed that the aortic valve was tricuspid. The disease affecting this cluster should then be considered a classic form of CAVS.

The ascertainment of the mode of inheritance cannot be evaluated easily because only patients in generation XIII fulfill the clinical criteria for CAVS diagnosis (Figure 3). However, in this cluster, we also identified 20 family members affected by minor abnormalities of the aortic valve. These family members were younger than patients with severe CAVS ( $58 \pm 10$  versus  $81 \pm 7$  years;  $P<0.001$ ). Most of them were the offspring of affected patients, suggesting that these abnormalities should be the first manifestation of CAVS. A periodic evaluation of the evolution of the AVA in these patients should confirm this hypothesis. Once these undetermined patients reach the critical age, our dominant-transmission hypothesis will be formally clarified.

The 2 largest families (families A and B) that we identified originated from a historic geographic isolate where the frequency of the disease is high. The complete isolation of this area for centuries should facilitate the anchoring of a potential genetic disease and then make possible the identi-

fication of a familial factor for the disease. An opposing view is that common environmental factors in an isolated population also could contribute to the disease. These factors cannot be formally excluded. However, the identification of related and unrelated strictly unaffected individuals >70 years of age sharing the same environment and the detection of 1 affected patient (patient XIII-45; Figure 2A) living outside the parish but belonging to family A are in favor of a low environmental contribution to the disease.

### Conclusions

This study demonstrates for the first time a familial aggregation of CAVS. The factors responsible for this familial aggregation and its frequency in the general population are still to be determined. This study is the first step toward the identification of a genetic defect in this disease.

### Acknowledgments

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The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

### Disclosures

None.

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### CLINICAL PERSPECTIVE

Calcific aortic valve stenosis (CAVS) is the most common valvular defect in developed countries. Despite its high prevalence and the increasing morbidity and mortality, very little is known about the pathophysiology of CAVS. Several risk factors have been associated with CAVS; however, most of the patients with risk factors have a structurally normal aortic valve. Familial inheritance has been demonstrated for mitral valve prolapse and for bicuspid valve disease but not for CAVS. The present study describes for the first time a familial aggregation of CAVS indicating genetic inheritance for this disease. Although the causative genes and the frequency in the general population are still to be determined, this study constitutes the first step toward the identification of a genetic defect and the understanding of the pathophysiology in this disease. Today, the only cure for this degenerative condition is replacement of the calcified valve when the patients become symptomatic. Ideally, less invasive and preventive therapeutic approaches will become available once the pathophysiology is better elucidated and “at-risk” patients are identified. Familial screening for CAVS is still not warranted as for mitral valve prolapse, but the practicing clinician should be aware of a possible hereditary component in CAVS.