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**Familial associations of complete atrioventricular block: a national family study in
Sweden**

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Abstract

Background: Complete atrioventricular block (CAVB) is a major reason for implantation of permanent pacemakers but knowledge of CAVB inheritance is sparse. This nationwide study aimed to determine the occurrence of CAVB in first-, second-, and third-degree relatives (full siblings, half-siblings, and cousins).

Methods The Swedish multi-generation register was linked to the Swedish nationwide patient register for the period 1997-2012. All Swedish full sibling, half-sibling, and cousin pairs born to Swedish parents between 1932 and 2012 were included. Odds ratios (ORs) for CAVB were calculated for relatives (full siblings, half-siblings, cousins) of individuals who had CAVB compared with relatives of individuals without CAVB as reference. Additionally, to include competing risks and time-to-event, subdistributional hazard ratios (SHRs) according to Fine and Gray and hazard ratios (HRs) using Cox proportional hazards model were estimated using robust standard errors and considering the relatedness of relatives.

Results The study population (n=6,113 761) consisted of 5,382 928 full siblings, 1,266 391 half-siblings, and 3,750 913 cousins. In total, 6 442 (0.11%) unique individuals were diagnosed with CAVB. Of these, 4 200 (65.2%) were males. Odds ratios (ORs) for CAVB were 3.03 for full siblings (95% confidence interval: 2.54-3.63), 1.51 for half-siblings (0.55-4.13), and 3.65 for cousins (1.79-7.42) of affected individuals. Age-stratified analysis showed higher risk in young individuals born 1947-1986: OR=5.68 (4.08-7.91) for full siblings, OR=3.29 (1.05-10.34) for half-siblings, and OR=3.22 (1.42-7.30) for cousins. Similar familial SHRs and HRs were obtained without any major differences. Apart from familial relationship, CAVB was associated with hypertension (OR=1.83), diabetes (OR=1.41),

coronary heart disease (OR=2.08), heart failure (OR=5.01), and structural heart disease (OR=4.59).

Conclusions Risk of CAVB among relatives of affected individuals depends on relationship degree, being strongest in young siblings. The familial association extending to third degree relatives indicates presence of genetic components in the etiology of CAVB.

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INTRODUCTION

Complete atrioventricular block (CAVB) also known as third degree atrioventricular block is a major reason for implantation of permanent pacemakers but knowledge of CAVB inheritance is sparse.^{1,2} According to a report from the Swedish pacemaker registry in 2019, any type of atrioventricular block was the most common indication for pacemaker implant in Sweden (49.6%).³ CAVB alone accounted for 26.5% of the 7352 cases with newly implanted pacemakers.³

CAVB may be either congenital or acquired implying that incidence in a younger population is dominantly congenital, whereas in an older population CAVB is mostly acquired.¹

Congenital atrioventricular block has been defined as CAVB diagnosed *in utero*, at birth or within the neonatal period (0 – 27 days after birth).⁴ This condition consists of two groups; in the first there is a genetic mutation, while the second occurs because of the mother's pathological state (lupus and related conditions), which determines the child's development *in utero* and directly after birth, leading to a neonatal cardiomyopathy with a poor prognosis. Among adults several conditions have been implicated in CAVB.^{1,5-7} Acquired CAVB may result from infection, such as Lyme or Chagas disease, inflammatory and degenerative processes such as calcification of aortic stenosis extending into the ventricular conduction tissue, isolated scarring of the ventricular conduction system possibly auto-immune, amyloidosis, sarcoidosis, and ischemic or non-ischemic cardiomyopathy, both of which are associated with scarring in the ventricular conduction system.¹ Other causes are much less frequent although reflex atrioventricular block as a presentation in vasovagal syncope may be more common than presently accepted.⁸ It has been observed that atrioventricular block may be inherited in families.⁹ Several genes including those coding for ion channels have been associated with progressive cardiac conduction disorders such as Lenègre's disease.¹⁰ SCN5A gene encoding the alpha subunit of the cardiac sodium channel (NaV1.5) has been linked to

Lenègre's disease in mice - SCN5A knock-outs¹¹. However, familial associations and importance of hereditary factors in CAVB have not been explored in the general population. Determination of the familial risk of a disease in first-degree, second-degree, and third-degree relatives of affected individuals could be used to estimate the relative influences of genes and shared family environment.^{12,13} In this study, we have aimed to determine the familial incidence of CAVB by examining full siblings, half-siblings, and cousins in a large nationwide Swedish family database linked to the national patient registry.^{14, 15}

METHODS

The Swedish registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.¹⁴⁻¹⁷ This study was approved by the Regional Ethical Review Board in Lund, Sweden (Reg.no 2012/795) and later amendments in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was waived as a requirement by the ethics committee. Data for this original research article will be shared with external scientists in accordance with the Swedish law and the agreements that exist between us and the Swedish Government agencies.

Full method description is available in the Supplemental Methods included in the supplemental data.

RESULTS

Among 6,113 761 unique personal records, 6 442 patients (0.11%) with CAVB diagnosis were identified (Table 1). In total, 6069 patients (0.11 %) with CAVB were identified among full siblings, 799 CAVB patients (0.06 %) among half-siblings, and 999 CAVB patients (0.03 %) among cousins (Tables 2-4). Individuals may occur in more than one relative group. Due

to the register effect i.e. that cousins' parents were born 1932 or later (Supplemental Figure 1), cousins were younger than full siblings and half-siblings (Tables 2-4). Therefore, cousins were affected by CAVB at a relatively younger age. Males were more commonly affected by CAVB in all three cohorts (Tables 1-4). The age distributions of females and males with CAVB are shown in Supplemental Figure 2. Male CAVB patients were slightly older than females (median age 63 years versus 61 years). In Supplemental Figure 3 the age distribution of CAVB patients with and without any comorbidities (according to Supplemental Table 1) are presented. CAVB patients without comorbidities were considerably younger than those with one or more comorbidity (median age 50 years versus 64 years).

Odds ratios for incident CAVB conferred by age and sex difference, and presence of comorbidities in full sibling pairs are presented in Supplemental Table 2. Female sex (OR=0.69, 95%CI 0.66-0.71) was associated with lower risk of CAVB. Higher birth year, i.e. younger age, was also associated with lower risk (OR=0.95, 95%CI 0.95-0.95 per year). Educational level was not associated with CAVB. All comorbidities except hypothyroidism (OR=1.16) and cancer (OR=0.97) were significantly associated with increased CAVB risk: diabetes (OR=1.41), hypertension (OR=1.83), heart failure (OR=5.01), coronary heart disease (OR=2.08), myocarditis (OR=3.31), pericarditis (OR=2.34), borreliosis (Lyme disease) (OR=1.47), amyloidosis (OR=6.46), sarcoidosis (OR=4.33), hemochromatosis (OR=1.81), structural heart disease (OR=4.59), hypothyroidism (OR=1.35), neuromuscular disorders (OR=4.44), and collagenosis (OR=1.22) (Supplemental Table 2).

Familial risks

Table 5 shows, in the crude Model 1, that CAVB risk for full sibling with affected sibling was increased (OR: 8.01; 95 % CI, 6.74-9.51). In multivariable-adjusted Model 2, which also

included birth year, sex, educational attainment, the familial OR for CAVB was 3.37 (95 % CI, 2.83-4.02). After adjustment for comorbidities in Model 3, the familial OR was slightly attenuated but still significant (3.03; 95 % CI, 2.54-3.63). Among half-siblings, the familial OR in the fully adjusted Model 3 was 1.51 (95% CI, 0.55-4.13), and among cousins 3.65 (1.79-7.42). This CAVB risk in cousins was unexpectedly high and, therefore, stratified analyses according to birth year were performed as shown in Table 5. In comparison of full siblings, half-siblings, and cousins with the same birth years a clear risk gradient according to the grade of familial relationship was exhibited. Accordingly, age-stratified analysis showed high risk in young individuals born 1947-1986: OR=5.68 (4.08-7.91) for full siblings, OR=3.29 (1.05-10.34) for half-siblings, and OR=3.22 (1.42-7.30) for cousins. Very high OR of 62.25 (23.11-167.70) was observed for youngest full siblings born 1986-2012 in Model 2.

Carter effect

CAVB was more common among males (Table 1-4). Sex stratification was, therefore, performed to search for a Carter effect (Supplemental Table 3). Among full siblings, the adjusted OR for female-female full siblings (OR=6.36, 95% CI, 4.44-9.12) was higher compared with male-male full siblings (OR=3.29, 95% CI 2.51-4.31) (Supplemental Table 3).

Sensitivity Analysis

Families with CAVB without ICD-10 codes or procedure codes for pacemakers were excluded in a sensitivity analysis (Supplemental Table 4). This did not substantially change the main results. Further, patients with both AF and CAVB were excluded (Supplemental Table 5): 820 full siblings, 89 half-siblings, and 42 cousins. Too few informative half-siblings remained after exclusion but for full-siblings and cousins there were no major changes in

odds ratios. For instance, age-stratified analysis after exclusion of patients with both AF and CAVB showed high risk in young individuals born 1947-1986 (in fully adjusted Model 3): OR=4.18 (2.73-6.39) for full siblings and OR=3.52 (1.55-7.98) for cousins. Very high OR of 64.47 (23.41-177.58) was observed for the youngest full siblings born 1986-2012 in Model 3 after exclusion.

Additional analyses of familial risks: subdistributional hazard ratios and hazard ratios

Additional analyses were performed using subdistributional hazard ratios (SHRs) according to Fine and Gray (competing risk) that were used to assess the association between history of CAVB in full siblings, half-siblings and cousins estimated by SHR with 95% confidence intervals (CI) and calculated with robust standard errors taking into account the relatedness of relatives (Supplemental Table 6).¹⁸⁻²² However, the results were similar to the results using logistic regression in Table 5. Cumulative incidence functions (CIF), i.e. probability of CAVB, for family history of CAVB versus no family history of CAVB were also calculated (Supplemental Figure 4). A clear difference and dose dependent association between degree of genetic resemblance and risk of CAVB is visualized in Supplementary Figure 4. We also estimated hazard ratios (HRs) using Cox proportional hazards model and 95% confidence intervals (CIs) that were calculated with robust standard errors considering the relatedness of relatives (Supplemental Table 7).^{21,22} However, the results were similar to Table 5 without any major differences. We also aggregated all individuals and included all familial relationship in the same database for calculations. Determination of SHRs, HRs, and ORs showed similar results as Table 5 without any major differences (Supplemental Table 8-10).

Familial Mortality risk

Supplemental Tables 11-16 show familial mortality (total mortality, cardiovascular mortality, and sudden or unknown death) for siblings, half-siblings and cousins calculated with logistic regression and Cox regression. The number of deaths were rather low among relatives with affected probands limiting any conclusions to be drawn from these analyses. Most associations were non-significant or only with a weakly increased effect on mortality observed for those with family history of CAVB in siblings, half-siblings or cousins. Among siblings the familial HR for total mortality in Model 3 was 1.07 (1.01-1.13) and 1.15 (1.05-1.27) for cardiovascular mortality (Supplemental Table 12). Among half-siblings the familial HR for total mortality in Model 3 was 1.04 (0.88-1.23). A slightly higher familial mortality was observed for cousins. In Model 3, HR for cardiovascular mortality in cousins was 1.73 (1.12-2.67) but only 18 mortality cases were included (Supplemental Table 16). Due to a potential register effect cousins were younger which may explain this observation. The only strong and significant association was found in the stratified analysis of siblings born 1986 < Year of birth $\leq$ 2012 with a HR of 30.46 (7.55-122.93) for cardiovascular mortality (Supplemental Table 12).

DISCUSSION

In this national family study, the results indicate that there is a hereditary component of CAVB. Especially strong familial association was observed among young subjects though higher risks were also observed for older individuals. Such high odds ratios suggest that major genes may be involved in CAVB inheritance. The familial association was independent of several traditional CAVB risk factors such as presence of structural heart disease. The strongest aggregation of CAVB was observed in pairs of full siblings, whereas this association, although significant, was distinctly attenuated in half-siblings and cousin pairs of the same age. As the familial risk factors and associations correlated with genetic

resemblance, we hypothesize that genetic factors are of importance in the familial aggregation of CAVB. The higher risk in young individuals also suggests a genetic basis. Moreover, males demonstrated higher CAVB incidence than females across all different levels of family relationships. This resulted in higher familial risks for females, which fits with a Carter effect. A high familial cardiovascular mortality was observed for young individuals with a sibling history of CAVB, though the mortality analysis was limited due to a low number of deaths. Most familial mortality rates were much lower or insignificant.

In general, CAVB carries a poor prognosis without permanent cardiac pacing²³⁻²⁶. After pacing the prognosis depends on the cause of AV block. In those with isolated ventricular conduction tissue disease the prognosis is better. It must be stated that data on adult onset CAVB before the advent of pacing is sparse but implies up to 50% one-year mortality.²³⁻²⁵ Two studies reported survival rates prior to availability of pacing; the first of 50 patients in 1944 gave a six-year survival of 34%,²³ whereas in 68 unpaced cases of CAVB, survival was 68% at one year (68%) and 37% at 5 years (37%).²⁵ If the cause is coronary disease or cardiomyopathy, less good figures are expected.^{24, 26} Thus, CAVB is an uncommon disease, but it presents significant healthcare burdens.

In a recent population-based cohort study from Finland the following conditions were associated with CAVB: older age, male sex, history of myocardial infarction, heart failure, increased blood pressure, and increased fasting glucose levels.⁷ We could confirm these observations, adding history of peri- and myocarditis, amyloidosis, sarcoidosis, and neuromuscular disorders as other important factors. It deserves noting that there are other causes of acquired CAVB block, one of which is aortic stenosis. CAVB due to aortic stenosis has become more common in the recent years due to treatment of the stenotic valve by transcatheter aortic valve implantation (TAVI) in older patients²⁷. However, the role of

heredity in prediction of CAVB in this patient group has not been explored yet and one may expect a multifactorial impact on CAVB risk in post-TAVI patients. On the other hand, a simple question about the history of conduction problems and pacemaker implantation among closest relatives might add a unexpensive value to the preoperative AV block risk evaluation in patients waiting for TAVI procedure.

The systematic approach to identification of genetic determinants in complex diseases should involve studying family aggregation of phenotype and the pattern of aggregation.²⁸ The family relationship studies offer the unique possibility to explore associations of genetic and nongenetic familial factors by observing first-degree, second-degree, and third-degree relatives and occurrence of specific phenotypes. First-degree relatives share 50% of their genes, in addition to environmental exposure common to their family. Second-degree relatives (e.g., half-siblings) share 25% of their genes, and third-degree relatives (e.g., first cousins) share 12.5% of their genes.²⁹ In this study, the probability of CAVB among relatives of affected individuals followed a pattern of increasing grade of relationship, being highest in full siblings. Moreover, third degree-relatives usually do not share a household environment. Thus, our observations support the idea of CAVB heredity, although the underlying genetic mechanisms appear to be complex and remain to be determined. The observed Carter effect is an argument in favor of polygenic inheritance of CAVB,³⁰ though the high OR among young individuals suggests that major genes may be also involved.

Strengths and Limitations

The large size and nationwide coverage of the study sample is a strength. Another important strength is the use of validated national hospital discharge data,¹⁵ which allows for elimination of recall bias. Further, Swedish registers such as the national statistical register and the Swedish Hospital Discharge Register have high coverage and high data validity.¹⁵

Despite a large number of individuals in the study, in some subgroups the number of familial cases were few, which limits any conclusions to be drawn for these subgroups. A strength is the consistency of results whatever method used, i.e., aggregated or non-aggregated data and logistic regression, competing risk according to Fine and Gray, and Cox regression with robust standard errors. A limitation is that individuals who died before the study period (1997-2012) were not included, which may underestimate mortality conferred by inheritance. Another limitation is that the ICD-10 I442 has not been specifically validated. However, linking I442 to pacemaker codes with approximately 9 of 10 patients being implanted with pacemaker suggests a high validity of the CAVB code. A further limitation is the lack of biomarkers and genomic information. For instance, in familial studies there is always an issue of assurance of paternity. In some populations a fair number of offspring have been genetically proven not to be descendants of their fathers. However, a recent Swedish study shows that among offspring born 1950 and later the frequency of misattributed paternity in Sweden is low (1.7%) and has decreased to 1% in recent years.³¹ Another limitation is that the study was limited to Sweden. However, the Swedish population resembles many other Caucasian populations of European origin.

In conclusion, risk of CAVB among relatives of affected individuals depends on the degree of relationship, being strongest in young full siblings and half-siblings but still significant in third-degree relatives. This suggests genetic components of CAVB susceptibility. Further studies on identification of specific hereditary CAVB components are indicated.

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Conflicts of interest

AF has received speaker fees from Medtronic Inc. , Biotronik, and Finapres Medical Systems.

RS is a consultant to Medtronic Inc., a member of the speakers bureau of Abbott (SJM) Laboratories Corp. and a shareholder in Edwards Lifesciences Corp. and Boston Scientific Corp.

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Table 1. Characteristics of patients with complete atrioventricular block (CAVB) and the whole study sample (all unique individuals).

	All individual n=6 113 761 (100%)	No CAVB n = 6 107 319 (99.89%)	CAVB n = 6 442 (0.11%)
Sex			
Male	3 131 673 (51.22)	3 127 473 (51.21)	4 200 (65.20)
Female	2 982 088 (48.78)	2 979 846 (48.79)	2 242 (34.80)
Education			
Unknown or < 9 y	750 886 (12.28)	748 811 (12.26)	2 075 (32.21)
9-11 y	2 741 142 (44.84)	2 738 427 (44.84)	2 715 (42.15)
>11 y	2 621 733 (42.88)	2 620 081 (42.90)	1 652 (25.64)
Year of birth			
Mean (SD)	1974 (22)	1974 (22)	1949 (16)
Median (IQR)	1973 (1956-1992)	1973 (1956-1992)	1944 (1938-1954)
(Range)	(1932-2012)	(1932-2012)	(1932-2012)
Age at end follow-up			
Mean (SD)	38 (21)	38 (21)	62 (16)
Median (IQR)	38 (20-56)	38 (20-56)	67 (57-73)
(Range)	(0-80)	(0-80)	(0-80)
Age at CAVB onset			
Mean (SD)	NA	NA	58 (17)
Median (IQR)	NA	NA	62 (52-69)
(Range)	NA	NA	(0-80)
Comorbidities (%)			
Diabetes	(2.89)	(2.87)	(18.94)
Hypertension	(5.90)	(5.87)	(37.38)
Heart failure	(0.82)	(0.79)	(24.82)
Coronary Heart Disease	(2.44)	(2.41)	(27.96)
Myocarditis	(0.09)	(0.08)	(0.57)
Pericarditis	(0.15)	(0.15)	(0.99)
Borrelia (Lyme disease)	(0.43)	(0.43)	(0.70)
Amyloidosis	(0.02)	(0.02)	(0.62)
Sarcoidosis	(0.16)	(0.16)	(1.29)
Hemochromatosis	(0.05)	(0.05)	(0.17)
SHD	(0.56)	(0.55)	(15.71)
Hyperthyroidism	(0.48)	(0.48)	(1.04)
Hypothyroidism	(0.98)	(0.98)	(2.98)
Neuromuscular disorders	(0.10)	(0.10)	(0.71)
Collagenosis	(1.30)	(1.30)	(4.46)
Cancer	(5.34)	(5.32)	(17.04)

Abbreviation: SD=standard deviation; IQR=interquartile range; NA=not applicable; CAVB =Complete Atrioventricular Block; SHD=Structural heart disease.

Age at end of follow-up: death, emigration or end of study period on December 31, 2012, whichever came first.

Table 2. Characteristics of the study sample in full siblings.

	All full siblings n=5 382 928 (100%)	No CAVB n = 5 376 859 (99.89%)	CAVB n = 6 069 (0.11%)
Sex			
Male	2758678 (51.25)	2754722 (51.23)	3956 (65.18)
Female	2624250 (48.75)	2622137 (48.77)	2113 (34.82)
Education			
Unknown or < 9 y	677707 (12.59)	675712 (12.57)	1995 (32.87)
9-11 y	2371467 (44.06)	2368944 (44.06)	2523 (41.57)
>11 y	2333754 (43.35)	2332203 (43.37)	1551 (26.56)
Year of birth			
Mean (SD)	1973 (22)	1973 (22)	1948 (15)
Median (IQR)	1972 (1954-1991)	1972 (1954-1991)	1944 (1938-1953)
(Range)	(1932-2012)	(1932-2012)	(1932-2012)
Age at end follow-up			
Mean (SD)	39 (21)	39 (21)	63 (15)
Median (IQR)	40 (21-57)	40 (21-57)	67 (59-73)
(Range)	(0-80)	(0-80)	(0-80)
Age at CAVB onset			
Mean (SD)	NA	NA	58 (16)
Median (IQR)	NA	NA	63 (53-69)
(Range)	NA	NA	0-80
Comorbidities (%)			
Diabetes	(3.03)	(3.01)	(19.10)
Hypertension	(6.32)	(6.28)	(38.05)
Heart failure	(0.88)	(0.85)	(24.98)
Coronary Heart Disease	(2.64)	(2.61)	(28.49)
Myocarditis	(0.08)	(0.08)	(0.58)
Pericarditis	(0.16)	(0.15)	(0.96)
Borreliosis (Lyme disease)	(0.44)	(0.44)	(0.72)
Amyloidosis	(0.02)	(0.02)	(0.63)
Sarcoidosis	(0.16)	(0.16)	(1.27)
Hemochromatosis	(0.06)	(0.06)	(0.18)
SHD	(0.60)	(0.58)	(15.77)
Hyperthyroidism	(0.49)	(0.49)	(1.07)
Hypothyroidism	(1.01)	(1.00)	(2.98)
Neuromuscular disorders	(0.10)	(0.10)	(0.69)
Collagenosis	(1.36)	(1.36)	(4.42)
Cancer	(5.73)	(5.72)	(17.45)

Abbreviation: SD=standard deviation; IQR=interquartile range; NA=not applicable; CAVB =Complete Atrioventricular Block; SHD=Structural heart disease.

Age at end of follow-up: death, emigration or end of study period on December 31, 2012, whichever came first.

Table 3. Characteristics of the study sample in half-siblings.

	All half-siblings n=1 266 391 (100%)	No CAVB n = 1 265 592 (99.94%)	CAVB n = 799 (0.06%)
Sex			
Male	646286 (51.03)	645775 (51.03)	511 (63.95)
Female	620105 (48.97)	619817 (48.97)	288 (36.05)
Education			
Unknown or < 9 y	160556 (12.68)	160322 (12.67)	234 (29.29)
9-11 y	682087 (53.86)	681712 (53.87)	375 (46.93)
>11 y	423748 (33.46)	423558 (33.47)	190 (23.78)
Year of birth			
Mean (SD)	1979 (18)	1979 (18)	1958 (18)
Median (IQR)	1980 (1965-1993)	1980 (1965-1993)	1953 (1944-1970)
(Range)	(1932-2012)	(1932-2012)	(1932-2012)
Age at end follow-up			
Mean (SD)	33 (18)	33 (18)	54 (18)
Median (IQR)	32 (19-47)	32 (19-47)	58 (42-67)
(Range)	(0-80)	(0-80)	(0-80)
Age at CAVB onset			
Mean (SD)	NA	NA	49 (19)
Median (IQR)	NA	NA	54 (35-64)
(Range)	NA	NA	(0-80)
Comorbidities (%)			
Diabetes	(2.17)	(2.16)	(16.65)
Hypertension	(3.56)	(3.54)	(29.54)
Heart failure	(0.47)	(0.45)	(25.53)
Coronary Heart disease	(1.33)	(1.31)	(24.03)
Myocarditis	(0.10)	(0.10)	(1.13)
Pericarditis	(0.15)	(0.15)	(1.50)
Borreliosis (Lyme disease)	(0.39)	(0.39)	(0.13)
Amyloidosis	(0.01)	(0.01)	(0.50)
Sarcoidosis	(0.15)	(0.15)	(1.13)
Hemochromatosis	(0.04)	(0.04)	(0.13)
SHD	(0.34)	(0.33)	(14.52)
Hyperthyroidism	(0.44)	(0.44)	(0.88)
Hypothyroidism	(0.88)	(0.09)	(2.63)
Neuromuscular disorders	(0.09)	(0.09)	(1.13)
Collagenosis	(1.04)	(1.04)	(4.13)
Cancer	(3.05)	(3.05)	(11.39)

Abbreviation: SD=standard deviation; IQR=interquartile range; NA=not applicable;
CAVB =Complete Atrioventricular Block; SHD=Structural heart disease.

Age at end of follow-up: death, emigration, or end of study period on December 31, 2012, whichever came first.

Table 4. Characteristics of the study sample in full cousins.

	All cousins n=3 750 913 (100%)	No CAVB n = 3 749 914 (99.97%)	CAVB n = 999 (0.03%)
Sex			
Male	1927119 (51.38)	1926536 (51.38)	583 (58.36)
Female	1823794 (48.62)	1823378 (48.62)	416 (41.64)
Education			
Unknown or < 9 y	211579 (5.64)	211470 (5.64)	109 (10.91)
9-11 y	1690827 (45.08)	1690351 (45.08)	476 (47.65)
>11 y	1848507 (49.28)	1848093 (49.28)	414 (41.44)
Year of birth			
Mean (SD)	1985 (15)	1985 (15)	1977 (14)
Median (IQR)	1986 (1973-1997)	1986 (1973-1997)	1975 (1965-1988)
(Range)	(1947-2012)	(1947-2012)	(1949-2012)
Age at end follow-up			
Mean (SD)	27 (15)	27 (15)	35 (14)
Median (IQR)	26 (14-39)	26 (14-29)	37 (24-46)
(Range)	(0-65)	(0-65)	(0-65)
Age at CAVB onset			
Mean (SD)	NA	NA	29 (15)
Median (IQR)	NA	NA	31 (17-41)
(Range)	NA	NA	(0-60)
Comorbidities (%)			
Diabetes	(1.08)	(1.08)	(3.80)
Hypertension	(1.13)	(1.13)	(9.61)
Heart failure	(0.11)	(0.10)	(14.51)
Coronary Heart Disease	(0.24)	(0.24)	(5.41)
Myocarditis	(0.10)	(0.10)	(1.50)
Pericarditis	(0.12)	(0.12)	(2.20)
Borrelia (Lyme disease)	(0.39)	(0.39)	(1.10)
Amyloidosis	(0.01)	(0.01)	(0.40)
Sarcoidosis	(0.11)	(0.11)	(0.90)
Hemochromatosis	(0.03)	(0.03)	(0.10)
SHD	(0.16)	(0.16)	(12.91)
Hyperthyroidism	(0.31)	(0.31)	(0.90)
Hypothyroidism	(0.66)	(0.66)	(2.60)
Neuromuscular disorders	(0.08)	(0.08)	(1.20)
Collagenosis	(0.64)	(0.64)	(2.00)
Cancer	(1.26)	(1.26)	(3.40)

Abbreviation: SD=standard deviation; IQR=interquartile range; NA=not applicable; CAVB =Complete Atrioventricular Block; SHD=Structural heart disease.

Age at end of follow-up: death, emigration or end of study period on December 31, 2012, whichever came first.

Table 5. Odds ratio (OR) of complete atrioventricular block (CAVB) in family members by degree of relationship (full siblings, half-siblings, and cousins) and documented history of CAVB among proband relatives. Reference=unaffected relative. Stratified results according to birth years is also shown, i.e. relatives born $1947 \leq \text{Year of birth} \leq 1986$ or $1986 < \text{Year of birth} \leq 2012$.

Predictor	Model 1	Model 2	Model 3	Cases / persons at risk [£]
Proband status	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Reference	1.00	1.00	1.00	12545/9557915
Affected full sibling	8.01 (6.74-9.51)***	3.37 (2.83-4.02)***	3.03 (2.54-3.63)***	132/12677
$1947 \leq \text{Year of birth} \leq 1986$	9.53 (6.97-13.03)***	6.19 (4.53-8.47)***	5.68 (4.08-7.91)***	40/5509
$1986 < \text{Year of birth} \leq 2012$	68.51 (25.48-184.19)***	62.25 (23.11-167.70)***	61.58 (22.38-169.38)***	4/403
Reference	1.00	1.00	1.00	1668/2603647
Affected Half-sibling	3.74 (1.40-9.99)**	1.61 (0.60-4.30)	1.51 (0.55-4.13)	4/1672
$1947 \leq \text{Year of birth} \leq 1986$	3.95 (1.27-12.28)*	2.90 (0.93-9.01)	3.29 (1.05-10.34)*	3/1198
$1986 < \text{Year of birth} \leq 2012$	NA	NA	NA	NA
Reference	1.00	1.00	1.00	6662/23662059
Affected cousin	4.27 (2.13-8.54)***	3.67 (1.84-7.34)***	3.65 (1.79-7.42)***	8/6670
$1947 \leq \text{Year of birth} \leq 1986$	3.53 (1.59-7.84)**	3.26 (1.47-7.27) **	3.22 (1.42-7.30)**	6/4761

1986< Year of birth ≤ 2012	6.12 (1.54-24.39)*	5.61 (1.40-22.47)*	6.33 (1.58-25.37)**	2/1909
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Model 1=crude model; Model 2= adjusted for sex, year of birth and education; and Model 3= adjusted further for sex, year of birth and education and comorbidities: Diabetes, Hypertension, Heart failure, Coronary Heart Disease, Myocarditis, Pericarditis, Borreliosis, Amyloidosis, Sarcoidosis, Hemochromatosis, SHD=structural heart disease, Hyperthyroidism, Hypothyroidism, Neuromuscular disorders, Collagenosis and Cancer.

£ Based on double entry.

Significance levels: * p<0.05, ** p<0.01, * p<0.001**

Swedish Family Register (1932-2012) n=6,113,671

Complete atrio-ventricular block (CAVB) incidence (1997-2012) n=6,442

Cumulative incidence
(CIF) of CAVB stratified
by presence or
absence of CAVB in
siblings, half-siblings,
and cousins.

Distribution of age at
CAVB diagnosis
stratified by gender and
presence or absence of
comorbidities

