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Familial Aggregation of Lone Atrial Fibrillation in Young Persons

Nina Øyen, MD, MPH, DrMed,*†‡ Mattis F. Ranthe, MD,* Lisbeth Carstensen, PhD,* Heather A. Boyd, PhD,* Morten S. Olesen, PhD,§ Søren-Peter Olesen, MD, DrMed,‖ Jan Wohlfahrt, MSc, DrMed,* Mads Melbye, MD, DrMed*

Copenhagen, Denmark; and Bergen, Norway

Objectives This study investigated whether an individual's risk of developing lone atrial fibrillation (AF) before age 60 years is associated with lone AF in relatives.

Background Genetic factors may play a role in the development of lone AF.

Methods Using Danish national registers, a cohort was established of ~4 million persons born between 1950 and 2008, and those with a family history of lone AF (AF without preceding cardiovascular/endocrine diagnoses) were identified. Individuals were followed up until the first diagnosis of lone AF. Poisson regression was used to estimate incidence rate ratios (IRRs).

Results In ~92 million person-years of follow-up, 9,507 persons were identified as having lone AF. The IRRs for lone AF given an affected first- or second-degree relative were 3.48 (95% confidence interval [CI]: 3.08 to 3.93) and 1.64 (95% CI: 1.04 to 2.59), respectively. IRRs were higher for men than for women but were not associated with the affected relative's sex. IRR for lone AF was 6.24 (95% CI: 2.59 to 15.0), given at least 2 first-degree relatives affected with lone AF. The IRR for lone AF in persons aged <40 years given a first-degree relative affected at age <40 years was 5.42 (95% CI: 3.80 to 7.72), and 8.53 (95% CI: 3.82 to 19.0) in persons age <30 years given a first-degree relative affected at age <30 years.

Conclusions A family history of lone AF is associated with substantial risk of lone AF, with the strongest risks associated with young age at onset, multiple affected relatives, and in first-degree relatives. These results suggest routine evaluation of the families of at least certain types of patients with lone AF. (J Am Coll Cardiol 2012;60:917–21)

The lack of known predisposing conditions and the earlier age at onset of lone atrial fibrillation (AF) is suggestive of a genetic etiology. Mutations and polymorphisms in genes coding for ion channels involved in cardiac repolarization and for connexins in the atria have been associated with the development of lone AF and have also been observed in familial cases of lone AF (1).

Epidemiologic studies show that AF in general clusters in families (2,3), but the familial aggregation specifically of lone AF has only been assessed in smaller case-control or prevalence studies (4,5), or by using young age at AF with preceding/associated cardiovascular or systemic disease as a proxy for lone AF (2,3). To our knowledge, familial aggregation of lone AF, defined as AF without predisposing cardiovascular or systemic diseases, has never been examined in a large population. This topic warrants attention, because family history of lone AF, in the absence of traditional risk factors for AF, could be an important risk factor for lone AF. In this nationwide, population-based study, we investigated whether an individual's risk of developing lone AF before 60 years of age was associated with lone AF in relatives.

Methods

The unique personal identification number used in all of Denmark's nationwide population-based registers, including the Civil Registration System (CRS), permits accurate linkage of individual-level information across registers. The CRS regularly updates vital status and kinship information

From the *Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; †Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway; ‡Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway; §Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; and the ‖Danish National Research Foundation Centre of Cardiac Arrhythmia, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark. This study was supported by the Danish Heart Foundation (10-04-R78-A2912-22619) to Dr. Øyen. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CRS = Civil Registration System
DFRD = Danish Family Relations Database
ICD = *International Classification of Diseases*
IRR = incidence rate ratio
NPR = National Patient Register
WPW = Wolff-Parkinson-White syndrome

based on official registrations of parents. The Danish Family Relations Database (DFRD) is based on parent–child links registered in the CRS. This information allows for construction of pedigrees identifying first-degree relatives (i.e., parents, siblings) and half-siblings for most persons born in Denmark in or before 1950. Second-degree relatives (i.e, grandparents, aunts/uncles, nieces/nephews) can be identified for the majority of persons born after 1985. The National Patient Register (NPR) contains information from all Danish hospitals on inpatient diagnoses since 1977 and outpatient diagnoses from 1995 onward. The Causes of Death Register contains death certificate information, including underlying and contributing causes of death, for all deaths occurring in Denmark since 1970.

The study cohort included all residents who were born in Denmark on January 1, 1950, or later and were still alive when the NPR was established or were born in Denmark on January 1, 1977, or later and had at least 1 identifiable relative in the DFRD.

In a 2-step algorithm, we first identified all first admissions for AF/atrial flutter before age 60 years registered in the NPR or the Causes of Death Register (Table 1), assuming AF and atrial flutter as the same entity. Next, these AF cases were classified as having lone AF if there were no preceding or concurrent International Classification of Diseases (ICD) codes for cardiovascular diseases (mitral valve/aortic valve disease, ischemic heart disease, congestive heart failure, cerebral-vascular stroke, congenital heart malformation, and cardiomyopathy), or specific systemic diseases (hyperthyroidism, hypertension, and diabetes). The algorithm was validated with a clinical register of lone AF cases aged <40 years and diagnosed consecutively at 8 hospitals in the Copenhagen area from November 2007 through December 2008 (6) with our AF cases at same age and period.

Using the DFRD, relatives were identified for each cohort member and those relatives with lone AF. Family history of lone AF was considered as a time-dependent variable, with a positive family history being assigned 1 day after the first-time lone AF was registered in a relative; this action was to ensure that lone AF in the relative was diagnosed before any lone AF diagnosis in the cohort member (affected pairs in the cohort contributed to the analysis only once). If there was no AF in a cohort member's family, all of his or her follow-up time was classified as unexposed.

Cohort members were followed up from January 1, 1977, or birth, whichever came later, until the first of the following events: 1) first admission for lone AF; 2) first admission for the specific cardiovascular diseases or systemic diseases (Table 1); 3) 60th birthday; 4) death; 5) emigration; 6) designated "missing person" in the CRS; or 7) December 31, 2008 (end of follow-up).

Using log-linear Poisson regression, incidence rate ratios (IRRs) were estimated comparing the rate of lone AF in individuals with a family history of lone AF and the rate in individuals with no family history of lone AF; the IRRs can be interpreted as a measure of familial aggregation. All estimates were adjusted for attained age, cohort member sex, calendar period, and other types of relatives with lone AF (for relative-specific estimates). IRRs compared cohort members with identifiable relatives of the same type. Separate IRRs were estimated for men and women and for different age groups by inclusion of an interaction term. IRRs for different types of family history were compared by using likelihood ratio tests. The analyses were conducted using PROC GENMOD in SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Our cohort included 3,985,446 persons born in 1950 or later and followed up for 91,903,390 person-years from 1977 to 2008. Of these, 14,684 individuals were registered with an AF diagnosis before 60 years of age, and among these, 9,507 individuals had lone AF (64.7 %). Table 2 shows basic characteristics of cohort members with lone AF.

Among the 9,507 cohort members with lone AF, there were 4 twins with an affected co-twin, 269 persons who had a first-degree relative with lone AF, and 19 persons with AF in a second-degree relative.

Table 1 Lone AF* Using Data From the National Patient Register and Causes of Death Register, Denmark, 1977–2008

Disease	ICD-10/ICD-8 Codes†
AF, atrial flutter	I48.0–I48.9; 427.93, 427.94
Cardiovascular diseases	
Mitral valve disease/aortic valve disease	I05, I06, I08, I34, I35; 394–396
Ischemic heart disease	I20–I25; 410–414
Congestive heart failure	I50; 425.99, 427.09, 427.10, 427.11, 427.19, 427.99, 428.99
Cerebral-vascular stroke	I60–I64; 430–434, 436
Congenital heart malformation	Q200–Q289, Q893; 746.00–747.99, 759.00, 759.01, 759.09
Cardiomyopathy	I42, I43; 425.99, 429.00
Systemic diseases	
Hyperthyroidism	E05; 242
Hypertension	I10–I15; 400–404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00, 437.01, 437.08, 437.09, 438.09
Diabetes	E10–E14; 249, 250

*Atrial fibrillation (AF) without preceding/concurrent cardiovascular or systemic diseases at first-time AF diagnosis. †International Classification of Diseases, Eight Revision (ICD-8), for 1977 to 1993 and International Classification of Diseases, 10th Revision (ICD-10) for 1994 onward used for coding of primary diagnosis and any secondary discharge diagnoses.

Table 2 Lone AF* Diagnosed in 9,507 Individuals Age <60 Years From a Cohort of 3,985,446 Individuals Born in Denmark in 1950 or Later and Followed-Up From 1977 to 2008

Characteristics	Lone AF* (N = 9,507) n	%
Age at diagnosis (yrs)		
0–9	54	0.57
10–19	206	2.2
20–29	1,074	11.3
30–39	2,285	24.0
40–49	3,632	38.2
50–59	2,256	23.7
Period of diagnosis		
1977–1981	87	0.92
1982–1986	134	1.4
1987–1991	299	3.2
1992–1996	887	9.3
1997–2001	2,275	23.9
2002–2006	3,704	39.0
2007–2008	2,121	22.3
Period of birth		
1950–1959	5,447	57.3
1960–1969	2,579	27.1
1970–1979	1,104	11.6
1980–1989	317	3.3
1990–1999	44	0.46
2000–2008	16	0.17
Sex		
Men	6,703	70.5
Women	2,804	29.5

*Arial fibrillation (AF) with no preceding or concurrent other cardiovascular diseases (mitral valve disease/aortic valve disease, ischemic heart disease, congestive heart failure, cerebral-vascular stroke, congenital heart malformation, or cardiomyopathy) or specific systemic diseases (hyperthyroidism, hypertension, or diabetes) at first-time AF diagnosis.

Overall, the rate of lone AF in cohort members with a history of lone AF in first-degree relatives was 3.5 times greater than the lone AF rate in cohort members without lone AF in first-degree relatives (Table 3). IRRs for lone AF were similar when comparing types of affected first-degree relatives: parents versus siblings (p = 0.65) and mothers versus fathers (p = 0.66). IRRs for lone AF were slightly higher by affected brother than by affected sister (3.89 vs. 2.09), but the confidence intervals (CIs) overlapped (p = 0.13) (Table 3).

The familial aggregation of lone AF among second-degree relatives in general (IRR 1.64) was weaker than that observed among first-degree relatives (p = 0.001). However, a history of lone AF in half-siblings yielded an IRR of 3.59. The IRRs for lone AF in paternal and maternal half-siblings were not significantly different (p = 0.68) (Table 3).

Among first-degree relatives, the IRRs stratified according to time since relative's diagnosis and calendar year were generally similar across strata (Table 4). However, having ≥2 first-degree relatives with lone AF increased the risk of lone AF (IRR: 6.24 [95% CI: 2.59 to 15.0]) more than having a single affected relative. The IRRs of lone AF for males and females were 3.77 and 2.77, respectively, given lone AF in a first-degree relative, with a male/female ratio of 1.37 (95 % CI: 1.02 to 1.82; p = 0.04). Furthermore, the association by a history of lone AF diagnosed before age 40 years in a first-degree relative and the risk of lone AF was stronger for lone AF diagnosed before 40 years (IRR: 5.42 [95% CI: 3.80 to 7.72]) than for lone AF diagnosed later (IRR: 3.19 [95% CI: 2.25 to 4.52]); p = 0.04 (Fig. 1). The risk of lone AF in younger persons became even stronger with age <30 years in the cohort member for age <30 years in first-degree relative (IRR: 8.53 [95% CI: 3.82 to 19.0]).

Patients with lone AF with Wolff-Parkinson-White syndrome (WPW) was not excluded. Among 8,756 lone AF cases followed up from 1994 to 2008, 119 (1.4%) had previous/concurrent WPW (ICD 10th Revision code I45.6), but the estimates for lone AF with WPW (IRR: 3.51 [95% CI: 3.11 to 3.97]) or without WPW (IRR: 3.53 [95% CI: 3.12 to 3.99]) were similar.

Validation of lone AF. All 138 lone AF cases from the Copenhagen clinical register were identified in our study; our algorithm correctly identified 134 (97%) as lone AF.

Discussion

The risk of lone AF was 3.5 times higher for a family history of lone AF in parents or in siblings compared with the risk in individuals without such family history.

Table 3 IRRs of Lone AF in 9,507 Individuals Age <60 Years According to Family History of Lone AF Stratified by Type and Sex of Relative With Lone AF, Denmark, 1977–2008*

Type and Sex of Relative With Lone AF	No. of Lone AF	PYRS per 1,000	IRR†‡	CI†‡
First-degree (all types)§	269	461	3.48	3.08–3.93
Parents	196	398	3.51	3.04–4.04
Father	132	289	3.44	2.90–4.09
Mother	64	110	3.46	2.71–4.43
Siblings	68	58	3.42	2.69–4.35
Brother	58	44	3.89	3.00–5.05
Sister	10	14	2.09	1.12–3.89
Second-degree (all types) ‖	19	430	1.64	1.04–2.59
Half-siblings	8	11	3.59	1.79–7.20
Paternal	6	6.6	4.37	1.96–9.77
Maternal	2	4.4	2.34	0.58–9.39
Others#	11	419	1.18	0.65–2.15

*A cohort of 3,985,446 individuals born in Denmark in 1950 or later was followed up for 91,903,390 person-years (PYRS) from 1977 to 2008. †Incidence rate ratios (IRR) compared the rate of lone atrial fibrillation (AF) given lone AF in a specific type of relative and the rate of lone AF given no family history of lone AF in same type relative (the reference was cohort members with lone AF who had the specified type of relative without lone AF). IRRs with 95% confidence intervals (CIs) were adjusted for age (1-year categories), sex, period (5-year categories), and having other type relatives with lone AF. ‡Additional adjustment for family size (categories 1, 2, 3, 4, 5, 6, 7, 8, 9, 10–14, 15+ family members) revealed an IRR of 3.48 (95% CI: 3.08 to 3.94) for lone AF by lone AF in first-degree relative, and an IRR of 1.64 (95% CI: 1.04 to 2.58) for lone AF by lone AF in second-degree relative. §The reference was cohort members (with nonaffected first-degree relatives) contributing to 90,172 PYRS per 1,000 and 8,987 lone AF. ‖The reference was cohort members (with nonaffected second-degree relatives) contributing to 52,368 PYRS per 1,000 and 5,639 lone AF. #Grandparents, grandchildren, uncle/aunts, and nephews/nieces.

Table 4 IRRs of Lone AF in 9,507 Individuals Age <60 Years According to Lone AF in First-Degree Relative for Certain Characteristics, Denmark, 1977–2008*

Characteristics	No. of Lone AF	IRR†	95% CI†
No. of affected first-degree relatives			
1 affected	264	3.45	3.05–3.90
≥2 affected	5	6.24	2.59–15.0
Sex of cohort member			
Male	207	3.77	3.28–4.33
Female	62	2.77	2.15–3.56
Time since lone AF diagnosis in relative			
<1 yr	21	3.92	2.56–6.02
≥1 yr	248	3.45	3.04–3.91
Year			
1977–1996	21	4.43	2.87–6.82
1997–2008	248	3.42	3.01–3.88

*A cohort of 3,985,446 individuals born in Denmark in 1950 or later was followed up for 91,903,390 persons-years from 1977 to 2008. †IRR with 95% confidence intervals CIs compared the rate of lone AF given lone AF in first-degree relatives and the rate of lone AF given no family history of lone AF in first-degree relative (reference), adjusted for age, sex, and period.
Abbreviations as in Table 3.

Previous family studies of lone AF (4,5) have been smaller case-control studies with self-reported family histories and small numbers of nonrepresentative controls (5) or cross-sectional studies comparing lone AF prevalence in relatives of hospitalized lone AF cases (4) with lone AF prevalence rates in populations from other studies (4). These various designs have introduced potential bias due to over-ascertainment of families with multiple lone AF cases or the use of a mixture of incident and prevalent cases. Investigating the risk of lone AF according to family history of lone AF requires a large population-based cohort with disease incidence data and pedigree information, as in our cohort study.

First- and second-degree relatives. Risks associated with lone AF in first-degree relatives were significantly higher than those associated with lone AF in second-degree relatives. Assuming that gene mutations or common gene variants inherited in traditional Mendelian fashion play a role in the etiology of some proportion of lone AF, these findings are consistent with the proportion of shared genes among different relative types. Further support for a strong genetic contribution to the etiology of lone AF was the finding that the lone AF risk was increased >6 times given a family history of at least 2 affected relatives.

The increased familial aggregation of lone AF may reflect some lone AF families in which single gene mutations associated with lone AF have been passed down in an autosomal dominant pattern but with reduced penetrance and variable phenotype expressivity, as has been demonstrated for other cardiac arrhythmias (7,8). Alternatively, familial aggregation of lone AF could be explained by some aspect of shared family environment that may trigger lone AF in several family members; suggestive factors include excessive alcohol intake (9) and vigorous sports activity (10). Interestingly, we found comparable risks of lone AF in full and half-siblings, possibly reflecting that shared environment might interact with a genetic predisposition to lone AF.

Sex. AF is known to be much more prevalent in men than in women (11), and our study population was no exception. We also found a slightly increased male/female ratio (1.37) for lone AF given a lone AF first-degree family history, lending further support for a male susceptibility to the development of lone AF. Interestingly, these associations were not related to the sex of the affected relative (mothers vs. fathers, brothers vs. sisters, or maternal vs. paternal half-siblings).

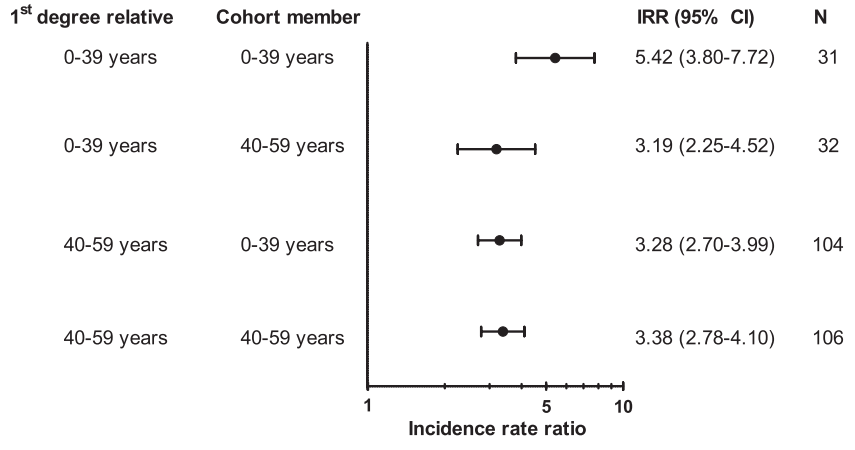

Figure 1 Risk of Lone AF According to Age at Onset and First-Degree Family History

Incidence rate ratios (IRRs) of lone atrial fibrillation (AF) given lone AF in first-degree relative, by cohort member attained age (0 to 39 years, 40 to 59 years) and first-degree relative age at diagnosis (0 to 39 years, 40 to 59 years). A total of 3,985,446 persons born in Denmark in 1950 or later were followed up for 91,903,390 person-years from 1977 to 2008 and contributed to 9,507 cases of lone AF. CI = confidence interval.

Age at diagnosis. The risk of lone AF increased >5 times when both the relative and cohort member were diagnosed with lone AF before 40 years of age and >8 times when both relative and cohort member were diagnosed with lone AF before 30 years of age. The increased lone AF risk associated with an early age at onset suggests a strong genetic contribution to early-onset lone AF.

Study limitations. Because we were unable to review 14,000 medical records of patients with AF, including electrocardiographic/echocardiographic findings, underreporting of cardiovascular or systemic diseases in the NPR predisposing to AF could have led to an inflated number of cases classified as lone AF. But the registration of several of these diseases (acute myocardial infarction [12], stroke, or heart failure) in the NPR has previously been validated against project-based clinical registers. In the present study, 13.7% of AF was excluded because of hypertension. Although not exactly comparable, 18.9% of the participants aged 20 to 65 years in the Copenhagen City Heart Study from 1991 to 1994 had blood pressure ≥140/90 mm Hg (13). The potential misclassification by including WPW among lone AF did not affect the IRR estimates of lone AF by lone AF family history. Finally, we evaluated our algorithm using the Copenhagen clinical register of lone AF (6), in which medical history, clinical records, blood samples, and electrocardiographic and echocardiographic images had been reviewed independently of our study. Our 2-step algorithm with a sensitivity of 97% was in fact slightly conservative with respect to the lone AF definition. Overall, we do not think there was substantive misclassification of lone AF. We acknowledge the limitation combining AF and atrial flutter as 1 entity.

There were few cases with affected second-degree relatives and cases with ≥2 affected first-degree relatives due to the construction of the DFRD with shorter follow-up of certain family members. We did not have information on nonpaternity, which could have reduced the offspring risk through the paternal line compared with the maternal line. However, on a population level, the potential bias introduced by including an estimated 1% nonpaternity families is negligible.

Finally, our findings may not be generalized to other races/ethnicities.

Study strengths. The Danish CRS allowed for nearly complete follow-up of our cohort. Because health care in Denmark is free and easily accessible, the registration of AF should be virtually complete in the NPR. Given the large number of AF cases, our strategy defining lone AF phenotypes by using a 2-step algorithm was the optimal approach. The DFRD made it possible to identify pedigrees without having to contact cohort members and their families, which ensured the absence of differential misclassification of disease due to self-reported family histories. IRRs only compared cohort members with identifiable relatives of the same type to reduce bias from incomplete identification of relatives. Finally, our cohort size yielded the largest and most comprehensive study of familial lone AF, which we explored in detail.

Conclusions

A family history of lone AF signals a familial predisposition to lone AF in white Europeans, which most likely is genetic. Family history should be considered in evaluations aimed at identifying younger persons at risk of lone AF.

Reprint requests and correspondence: Dr. Nina Øyen, Statens Serum Institut, Ørestads Boulevard 5, DK-2300 Copenhagen S, Denmark. E-mail: noy@ssi.dk.

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