Parental Atrial Fibrillation as a Risk Factor for Atrial Fibrillation in Offspring

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Context Atrial fibrillation (AF) is the most common cardiac dysrhythmia in the United States. Whereas rare cases of familial AF have been reported, it is unknown if AF among unselected individuals is a heritable condition.

Objective To determine whether parental AF increases the risk for the development of offspring AF.

Design, Setting, and Participants Prospective cohort study (1983-2002) within the Framingham Heart Study, a population-based epidemiologic study. Participants were 2243 offspring (1165 women, 1078 men) at least 30 years of age and free of AF whose parents had both been evaluated in the original cohort.

Main Outcome Measures Development of new-onset AF in the offspring was prospectively examined in association with previously documented parental AF.

Results Among 2243 offspring participants, 681 (30%) had at least 1 parent with documented AF; 70 offspring participants (23 women; mean age, 62 [range, 40-81] years) developed AF in follow-up. Compared with no parental AF, AF in at least 1 parent increased the risk of offspring AF (multivariable-adjusted odds ratio [OR], 1.85; 95% confidence interval [CI], 1.12-3.06; $P=.02$). These results were stronger when age was limited to younger than 75 years in both parents and offspring (multivariable-adjusted OR, 3.23; 95% CI, 1.87-5.58; $P<.001$) and when the sample was further limited to those without antecedent myocardial infarction, heart failure, or valve disease (multivariable-adjusted OR, 3.17; 95% CI, 1.71-5.86; $P<.001$).

Conclusions Parental AF increases the future risk for offspring AF, an observation supporting a genetic susceptibility to developing this dysrhythmia. Further research into the genetic factors predisposing to AF is warranted.

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ATRIAL FIBRILLATION (AF) IS the most common cardiac dysrhythmia in the United States, affecting approximately 2.3 million adults[1] and resulting in substantial societal costs.[2] Atrial fibrillation increases the risk of stroke,[3] heart failure,[3,4] and mortality.[3,5] The prevalence of AF is increasing and is projected to affect 5.6 million Americans by 2050.[1] Known risk factors for AF include male sex, advancing age, diabetes, hypertension, heart failure, myocardial infarction, and valvular heart disease.[4,6,7]

However, much of the variability in risk for AF remains unexplained,[6] leading investigators to look for novel and genetic risk factors for AF. Rare familial forms of AF have been reported, and loci have been mapped to chromosomes 10q22-24[8] and 6q14-16.[9] A gain-of-function mutation in the *KCNQ1* gene has been implicated in a family with persistent AF.[10] Although a genetic basis of AF in selected patients has been described, it is unknown if there is a genetic component to AF in the general population. Thus, we sought to test whether documented parental AF was associated with increased risk of AF in a community-based cohort.

METHODS

Beginning in 1948, 5209 men and women aged 28 to 62 years were enrolled into the "original" (ie, "parental") cohort of the Framingham Heart Study. Offspring and their spouses (n=5124) were enrolled in the "offspring" cohort starting in 1971. The design of the study[11,12] and methods of risk factor measurement have been described in detail elsewhere.[13] Routine clinic examinations included structured interviews, physical examinations, laboratory tests, and electrocardiograms. The Boston Medical Center institutional review board approved the study, and all participants provided written informed consent.

Framingham Offspring Study participants were included for study in this investigation if they had 2 biological parents in the original cohort, were at

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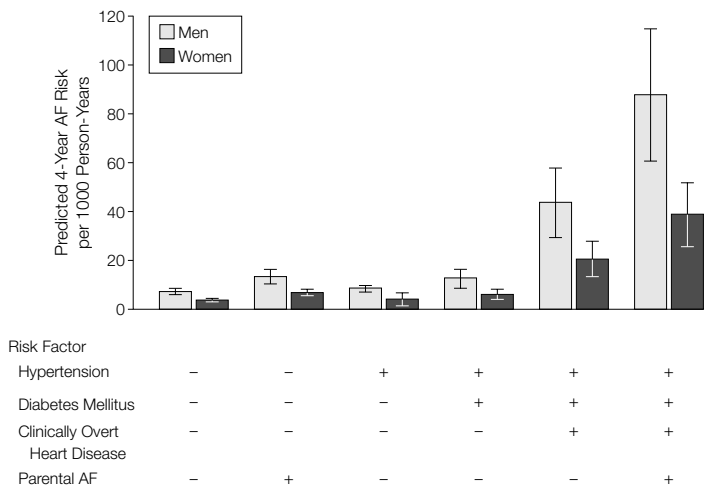
Figure. Four-Year Predicted Risk of AF per 1000 Person-Years Given Documented AF in at Least 1 Affected Parent.



Risk of atrial fibrillation (AF) is displayed by the presence or absence of risk factors: high systolic blood pressure and receiving hypertension treatment, diabetes, clinically overt heart disease, or parental AF, assuming a mean offspring age of 55 years. Plus signs indicate the presence of each risk factor; minus signs refer to the absence of the risk factor. Error bars indicate SEs.

Table 1. Baseline Characteristics, by Presence or Absence of Parental Atrial Fibrillation (AF)

Characteristic	No. (%)	
	No Parental AF (n = 1562)	Parental AF* (n = 681)
Age, mean (SD), y	47 (9)	48 (9)
Women	818 (52.4)	347 (51.0)
Diabetes	62 (4.0)	19 (2.8)
Systolic blood pressure, mean (SD), mm Hg	122 (17)	123 (17)
Hypertension treatment	222 (14.2)	104 (15.3)
Valve disease by auscultation	17 (1.1)	10 (1.5)
Myocardial infarction	29 (1.9)	11 (1.6)
Congestive heart failure	4 (0.3)	2 (0.3)
Maternal AF	0	358 (52.6)
Paternal AF	0	387 (56.8)
Maternal and paternal AF	0	64 (9.4)

*Either mother or father developed AF at or prior to the participant's baseline examination; cases of first parental AF occurring after offspring AF were excluded (n = 5).

least 30 years of age, and were free of AF at the baseline examination (occurring after 1982). Because offspring participants were examined every 4 years, covariates were updated at each examination cycle, and 4-year follow-up windows between examinations were studied for development of AF. Once participants developed AF, they were censored from further follow-up.

Participants in the offspring and original cohorts were considered to have AF if either atrial fibrillation or atrial flutter was confirmed on electrocardiogram. Offspring AF cases were detected in the hospital (69%), by an outside physician (14%), at the Framingham Heart Study examination (11%), or by careful review of the participant's history only (6%), and confirmed upon review by 1 of 2 Framingham heart Study cardiologists. Parental AF had to occur temporally before the onset of offspring AF; cases of first parental AF occurring after development of AF in offspring were excluded (n=5). We accrued parental AF cases from 1949-2002 and offspring AF cases from 1983-2002. In prespecified analyses, the overall sample was restricted to parental and offspring participants younger than 75 years (ie, the median age of AF incidence[14]); the offspring sample was additionally restricted to participants without antecedent clinically overt heart disease (defined as myocardial infarction, heart failure, or clinical valve disease [identified as any diastolic murmur, or systolic murmur ≥3/6 on Framingham visit physician-administered physical examination]). Among parents who did not develop AF during the study, 83% (n=853) of mothers and 69% (n=688) of fathers were older than 70 years at death or at the end of follow-up in 2002. Similarly, 62% (n=638) of mothers and 39% (n=386) of fathers were older than 80 years at death or the end of follow-up.

Statistical Methods

Pooled logistic regression was used to examine the 4-year risk of incident offspring AF associated with documented parental AF; pooled logistic regression provides similar estimates to time-dependent Cox regression analysis.[15] Person-examination observations were pooled over a total of 4 baseline examinations, each with 4 years of follow-up; covariates and outcome status were updated every 4 years over a total of 16 years. The generalized estimating equations procedure in SAS version 8[16] was used to account for correlations among family members. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated; the referent group consisted of participants without parental AF. $P<.05$ (2-sided) was used to determine statistical significance. Models were unadjusted, age- and sex-adjusted, and multivariable-adjusted. Multivariable covariates were chosen a priori based on standard risk factors for AF[6] and included age, sex, systolic blood pressure, hypertension treatment, diabetes, and clinically overt heart disease (defined above).

To provide a visual display of the additional predictive information conferred by parental AF status in the context of known risk factors, we computed the 4-year predicted risk of AF per 1000 person-years over each follow-up interval. Sex-specific values were constructed from the original models, based on combinations of risk factor profiles (see FIGURE legend).

RESULTS

The offspring study sample included 1165 women and 1078 men free of AF at baseline (defined as the first examination attended after 1982). During the offspring study period (1983-2002), 30% (681/2243) had at least 1 parent with documented AF. Baseline clinical characteristics of offspring participants did not vary by parental AF status (TABLE 1).

Of eligible offspring participants, 70 (23 women) developed AF in follow-up, with a mean age at onset of 62 years (range, 40-81). Offspring participants with at least 1 parent with AF had an incidence rate of 4.5 per 1000 person-years, compared with 3.0 per 1000 person-years in participants without parental AF (TABLE 2).

After multivariable adjustment, offspring AF was associated with maternal AF (Table 2), particularly when the parental and offspring samples were restricted to participants younger than 75 years, as well as when further limited to offspring participants without clinically overt heart disease, defined as antecedent myocardial infarction, heart failure, or valve disease. Paternal AF was nonsignificantly associated with offspring AF (Table 2) but was significantly associated with offspring AF when the parental and offspring samples were limited to those younger than 75 years and when offspring participants with antecedent clinically overt heart disease were additionally removed.

Offspring AF was independently associated with at least 1 parent with AF, especially when the parental and offspring samples were limited to participants younger than 75 years and when offspring participants with antecedent clinically overt heart disease were excluded.

Only 5 offspring AF cases had both parents with AF. Overall, the multivariable-adjusted OR was 3.20 (95% CI, 1.15-8.91). The wide CIs reflect the very small number of cases in this group.

Results were not substantively different if cases of atrial flutter as the only documented atrial dysrhythmia (n=3) were not considered cases in the AF analyses. Similarly, when we considered smoking, body mass index, and electrocardiographic evidence of left ventricular hypertrophy as additional confounders, there were no material changes in the independent associations of parental and offspring AF.

Effect of Parental History on Predicted AF Risk

The 4-year predicted risk of AF based on the model for at least 1 affected parent in the setting of different risk factor profiles was estimated assuming an offspring mean age of 55 years (Figure). Having at least 1 affected parent

Table 2. Odds Ratios for Offspring Atrial Fibrillation Over 4 Years, According to Parental Atrial Fibrillation Status

	Parental Atrial Fibrillation Status						
		Maternal		Paternal		One or Both Parents	
	None	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*
Overall Sample							
No. of cases	42	19		14		28	
Incidence rate per 1000 person-years†	3.0 (1.8-4.2)	6.5 (4.7-8.3)		4.0 (2.6-5.4)		4.5 (3.0-6.0)	
Unadjusted	Reference	3.06 (1.78-5.27)	<.001	1.87 (1.02-3.43)	.04	2.23 (1.38-3.59)	.001
Age- and sex-adjusted	Reference	2.26 (1.29-3.98)	.005	1.75 (0.95-3.21)	.07	1.86 (1.15-3.01)	.01
Multivariable-adjusted‡	Reference	2.23 (1.25-3.98)	.007	1.76 (0.93-3.35)	.08	1.85 (1.12-3.06)	.02
Age <75 y (Both Offspring and Parent)							
No. of cases	48	13		10		20	
Unadjusted	Reference	4.44 (2.39-8.24)	<.001	2.13 (1.07-4.21)	.03	2.72 (1.61-4.60)	<.001
Age- and sex-adjusted	Reference	5.04 (2.68-9.49)	<.001	2.64 (1.31-5.31)	.006	3.36 (1.95-5.77)	<.001
Multivariable-adjusted‡	Reference	5.00 (2.67-9.36)	<.001	2.48 (1.21-5.10)	.01	3.23 (1.87-5.58)	<.001
Age <75 y (Both Offspring and Parent), Without Clinically Overt Heart Disease in Offspring							
No. of cases	37	11		7		15	
Unadjusted	Reference	4.91 (2.49-9.67)	<.001	1.93 (0.86-4.34)	.11	2.65 (1.45-4.83)	.002
Age- and sex-adjusted	Reference	5.52 (2.77-10.97)	<.001	2.36 (1.04-5.38)	.04	3.19 (1.73-5.90)	<.001
Multivariable-adjusted§	Reference	5.75 (2.96-11.18)	<.001	2.31 (1.00-5.34)	.049	3.17 (1.71-5.86)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.
*For comparison wtih "none" category.
†Age- and sex-adjusted, based on follow-up time of 30 344 person-years.
‡Adjusted for age, sex, diabetes, systolic blood pressure, hypertension treatment, and clinically overt heart disease (defined as myocardial infarction, congestive heart failure, or clinically significant valve disease determined by auscultation).
§Adjusted for age, sex, diabetes, systolic blood pressure, and hypertension treatment.

approximately doubled the risk of predicted AF when compared with models with either absent or present coexisting risk factors.

Relatedness of Offspring AF Cases

Of the 70 offspring individuals with AF, 4 pairs belonged to the same extended families. The only related pair of offspring with AF (siblings) did not have documented parental AF.

COMMENT

Primary Findings

In a population-based sample, parental AF independently predicted an increased risk of offspring AF events after adjustment for standard AF risk factors, including hypertension,[17] diabetes,[18,19] and myocardial infarction,[20] which are known to have genetic components. This finding suggests that potentially unaccounted-for genetic mechanisms may contribute to the pathogenesis of AF. To our knowledge, our study is the first to demonstrate that a familial component exists for AF among unselected community-based individuals.

Because disorders with a genetic predisposition often occur at a younger age, or in the absence of major predisposing conditions, we performed analyses restricting the sample to participants younger than 75 years and subsequently eliminating those with clinically overt heart disease. Both analyses demonstrated a lack of attenuation of the increased odds of offspring AF associated with parental AF, lending further support to the hypothesis that there is a genetic predisposition to AF.

Most studies to date have focused on families with large numbers of affected individuals. Genetic linkage analyses have demonstrated logarithm of odds scores of 3.6 on chromosome 10q22-24[8] and 4.9 on chromosome 6q12-14.[9] Candidate genes associated with AF have been identified, including a gain-of-function mutation in *KCNQ1*, a gene encoding a potassium-channel subunit associated with long-QT syndrome.[10] In addition, AF has been associated with polymorphisms in *KCNE1* (a gene also involved in potassium-channel physiology)[21] and in the renin-angiotensin system.[22] Taken together, these studies suggest that AF is potentially a heterogeneous disorder with a significant genetic component.

A recent analysis of AF cases from an arrhythmia clinic found that 5% of all patients with AF, and 15% of all patients with lone AF, had a family history of this dysrhythmia.[23] We demonstrated that 30% of offspring were documented as having parents with AF. The higher prevalence of parental AF in our study likely stemmed from the prospective cohort design, which enabled us to more completely ascertain parental AF cases and allowed us to follow the parental cohort to near extinction.

Strengths and Limitations

The strengths of this study include prospective collection and validation of AF events by 1 of 2 Framingham Heart Study cardiologists in both the offspring and parents, substantially reducing any possibility of recall bias. Moreover, our sample was community-based and our participants were unselected, reducing the likelihood that our sample had a unique mechanism underlying the AF cases. It is unlikely that our results were driven by unusual families with rare genetic profiles.

Limitations of our study include a small number of offspring with AF (n=70), a predominantly white sample, and a mean age of AF onset younger than that reported in the United States.[14] Because of our sample's relatively young mean age, our AF cases have a lower prevalence of hypertension and overt heart disease than the general AF population. Despite the fact that the younger mean age limits the generalizability of our findings, it does not limit our findings to younger patients with parental AF, who are potentially the population most likely to be affected by genetic causes. Our use of validated cases of parental AF reduces misclassification in our data but potentially limits the usefulness of a parental history of AF in the clinical setting, since offspring may incorrectly identify whether their parents had AF. An additional limitation is that the effects of early family environmental influences cannot be excluded as an alternate explanation for our findings, but this appears less likely given the mean age of AF onset in our offspring sample (62 years). We were unable to account for all potential risk factors for AF that are known to have genetic components and thus may provide alternative mechanisms to explain our findings, including C-reactive protein,[24] hemostatic factors,[25] left atrial enlargement,[26] Graves disease, and use of alcohol.[27] Lastly, we were unable to account for echocardiographic features that are known to be associated with AF.[26]

Clinical and Research Implications

Parental AF increases the risk of future offspring AF events, consistent with a genetic contribution to the etiology of AF. Further research pertaining to the etiology of AF, particularly additional basic and clinical investigations into the genetic mechanisms involved in AF, is warranted. Data from animal models may be helpful in elucidating genetic underpinnings of AF, particularly now that mouse models of this dysrhythmia have been established.[28] The identification of genetic mechanisms in the pathophysiology of AF could help guide research into the causes, prevention, and treatment of AF.

Author Contributions: Dr Fox had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Fox, D'Agostino, Lloyd-Jones, Vasan, Benjamin.
Acquisition of data: D'Agostino, Wang, Levy, Wolf, Benjamin.
Analysis and interpretation of data: Fox, Parise, D'Agostino, Lloyd-Jones, Vasan, Wang, Levy, Benjamin.
Drafting of the manuscript: Fox, Vasan, Benjamin.
Critical revision of the manuscript for important intellectual content: Parise, D'Agostino, Lloyd-Jones, Vasan, Wang, Levy, Wolf, Benjamin.
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It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast. It keeps him young.
—Konrad Lorenz (1903-1989)