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Familial Atrial Fibrillation Is a Genetically Heterogeneous Disorder

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OBJECTIVES The aims of this study were to identify and characterize familial cases of atrial fibrillation (AF) in our clinical practice and to determine whether AF is genetically heterogeneous.

BACKGROUND Atrial fibrillation is not generally regarded as a heritable disorder, yet a genetic locus for familial AF was previously mapped to chromosome 10.

METHODS Of 2,610 patients seen in our arrhythmia clinic during an 18-month study period, 914 (35%) were diagnosed with AF. Familial cases were identified by history and medical records review. Four multi-generation families with autosomal dominant AF (FAF 1 to 4) were tested for linkage to the chromosome 10 AF locus.

RESULTS Fifty probands (5% of all AF patients; 15% of lone AF patients) were identified with lone AF (age 41 ± 9 years) and a positive family history (1 to 9 additional relatives affected). In FAF 1 to 3, AF was associated with rapid ventricular response. In contrast, AF in FAF-4 was associated with a slow ventricular response and, with progression of the disease, junctional rhythm and cardiomyopathy. Genotyping of FAF 1 to 4 with deoxyribonucleic acid markers spanning the chromosome 10q22-q24 region excluded linkage of AF to this locus. In FAF-4, linkage was also excluded to the chromosome 3p22-p25 and lamin A/C loci associated with familial AF, conduction system disease, and dilated cardiomyopathy.

CONCLUSIONS Familial AF is more common than previously recognized, highlighting the importance of genetics in disease pathogenesis. In four families with AF, we have excluded linkage to chromosome 10q22-q24, establishing that at least two disease genes are responsible for this disorder. (J Am Coll Cardiol 2003;41:2185–92) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, affecting more than two million adults in the U.S. (1). The mean age of individuals with AF is 75 years; disease prevalence increases with age (2.3% age >40 years, 5.9% age >65 years) and with the presence of structural heart disease. Atrial fibrillation results in substantial morbidity, with the augmented risk of stroke being the most serious. In the elderly, the relative risk of stroke in persons with non-rheumatic AF is 4.5 times that of persons in sinus rhythm (2). Atrial fibrillation also increases the risk of mortality; the age-adjusted odds ratio for death with AF is 2.4 in men and 2.5 in women (3). While death and stroke are clearly the most serious hazards, AF can produce other complications including adverse hemodynamics, congestive heart failure, and tachycardia-induced cardiomyopathy. Thus, the morbidity and mortality of AF are substantial, as are the socioeconomic consequences of repeated hospital admissions, chronic disease management, and disabilities.

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The molecular determinants of AF are poorly understood. In the elderly, AF is often associated with underlying heart disease such as ischemic, hypertensive, myocardial, or valvular disease. By contrast, idiopathic or "lone" AF typically occurs in young and middle-aged adults (mean age at diagnosis = 44 years) (4). The prevalence of lone AF, depending on the age of the population under consideration, ranges from 3% to 11% (4,5). Among patients with lone AF, an unknown proportion have a familial form of the disease with a genetic basis. Familial AF was first reported in 1943 (6), but there has been no attempt to determine the overall prevalence of familial disease. A recent report, however, suggests that familial AF may be more common than previously recognized (7).

Identification of a gene responsible for AF will provide important insights into the etiology of familial disease. The chromosomal location of an AF gene was first reported in 1997 based on genetic mapping studies in three families from Spain who appeared to share common ancestry (8). However, the gene responsible for AF in these families has not yet been identified. Moreover, the overall importance of this locus in other families with AF is unknown. In this

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Abbreviations and Acronyms

AF = atrial fibrillation
cM = centiMorgan
DNA = deoxyribonucleic acid
ECG = electrocardiogram/electrocardiographic/electrocardiography
FAF = multi-generation families with autosomal dominant atrial fibrillation
PCR = polymerase chain reaction

study, we sought to identify and characterize familial cases of AF and to determine whether or not AF is a genetically heterogeneous disorder.

METHODS

Clinical evaluation. Between November 2000 and April 2002, patients referred to our Arrhythmia Clinic with lone AF and a positive family history documented by the primary physician, were identified. Family history data were available in the medical record in 90% of patients with AF. A more detailed family history was subsequently obtained by a study coordinator, following written informed consent under a protocol approved by the Institutional Review Board of the Mayo Clinic. When possible, first- and second-degree relatives were contacted directly to obtain medical records and review cardiac symptoms. Screening electrocardiography (ECG) and echocardiography was performed in consenting members of four families (FAF 1 to 4), if these tests had not been previously done for clinical indications.

Probands and their relatives were clinically classified using a consistently applied set of definitions. Atrial fibrillation was defined as replacement of sinus P waves by rapid oscillations or fibrillatory waves that varied in size, shape, and timing and were associated with an irregular ventricular response when atrioventricular conduction was intact. Documentation of AF on an ECG, rhythm strip, event monitor, or Holter monitor recording was required. "Lone AF" was defined as AF in individuals <60 years of age without hypertension or overt structural heart disease by clinical examination, ECG, and echocardiography (4). The upper limits of normal for cardiac chamber dimensions were based on age and body surface area (9). Relatives with AF occurring at any age in the setting of structural heart disease (hypertensive, ischemic, myocardial, or valvular) were classified as "uncertain" for having an inherited form of AF. The "uncertain" classification was also used when documentation of AF on an ECG tracing was lacking in relatives with symptoms consistent with AF (palpitations, dyspnea, light-headedness) or when a screening ECG and echocardiogram were not performed, regardless of symptoms. Relatives were classified as "unaffected" if they were ≥18 years of age, asymptomatic, and had a normal ECG. "Paroxysmal AF" was defined as AF lasting more than 30 s that terminates spontaneously. The AF was classified as "persistent" when it lasted more than seven days and required either pharmacologic therapy or electrical cardioversion for termination. Three classifications for familial AF were used, based on increasingly stringent definitions: "possible" familial AF, one additional first- or second-degree relative with lone AF by history alone (symptoms of AF without known structural heart disease but without confirmation of lone AF in medical records); "probable" familial AF, ≥2 additional first- or second-degree relatives with lone AF by history alone, or one additional relative with documented lone AF; "confirmed" familial AF, ≥2 additional first- or second-degree relatives with documented lone AF.

Molecular genetic studies. Whole blood for genomic deoxyribonucleic acid (DNA) extraction was obtained from the index case and consenting family members. For genotyping, we selected eight polymorphic dinucleotide repeat markers (10) spanning a previously reported locus for familial AF on chromosome 10q22-q24 (8). The marker set included the two flanking markers, D10S1694 and D10S1786, which define boundaries of the 11 centiMorgan (cM) AF locus; two markers that lie just distal to each of the flanking markers, D10S1650 and D10S1717; and four internal markers. The eight tightly linked markers (intermarker distances 1 to 3 cM) were amplified by the polymerase chain reaction (PCR) and resolved by polyacrylamide gel electrophoresis as previously described (11). Genotypes were scored and used to construct haplotypes to test for linkage. Family members phenotypically classified as "unaffected" and "uncertain" were included in these analyses to aid in construction of haplotypes. However, exclusion of linkage was based on a stringent "affecteds-only" analysis whereby lack of a shared chromosome segment among the affected members of each family was required. Similarly, markers were selected to test for linkage to two loci previously associated with familial AF and dilated cardiomyopathy. For the chromosome 3p22-p25 locus, the five markers used in the original report were used (11). For the lamin A/C gene on chromosome 1q21 (12), we identified novel polymorphic markers. This was accomplished by a "find text" search for potentially polymorphic repetitive sequences in the genomic contig harboring lamin A/C (NT_004858). Two dinucleotide repetitive sequences were found: $(TG)_5(TA)_8TG(CA)_{10,}$ 5.1 kilobases 5′ of the start codon, and $(GT)_{22}$, 2.4 kilobases 3′ of the stop codon. Oligonucleotide primer pairs were designed for PCR amplification by use of OLIGO 6.51 Primer Analysis Software (National Biosciences, Plymouth, Minnesota).

RESULTS

Clinical evaluation. Of 2,610 patients referred to the Arrhythmia Clinic during the 18-month study period, 914 (35%) had documented AF (mean age 68 ± 15 years). Lone AF was present in 325 (36%). Fifty probands (5% of all

Table 1. Phenotypic and Family Data for Patients With Familial Atrial Fibrillation

							Echocardiography			Relatives	
Gender	Age at Evaluation (yrs)	Age at Onset (yrs)	Rhythm	Treatment	HR (beats/min)	ECG	LA and LV Size	EF (%)	Comment	# Affected	Age at Onset (decade)
Possible familial AF											
M	57	55	PersAF	AAD, RFA	66	normal	normal	65		1	5
M	60	42	PAF	AAD, AVNA, PPM	40	normal	normal	60	CVA	1	5
M	54	40	PAF	AAD, RFA	64	normal	LAE	40	2°CM	1	5
M	50	39	PAF	AAD, RFA	75	normal	BAE	65		1	4
M	46	42	PAF	AAD, RFA	74	normal	LAE	50		1	4
M	60	40	PAF	AAD, RFA	72	normal	LAE	65		1	4
M	43	30	PAF	AAD, RFA	81	IVCD	LAE	65		1	4
M	53	43	PAF	AAD, RFA	78	normal	LAE	60		1	5
M	57	44	PAF	AAD, RFA	72	IVCD	LAE	60		1	5
Probable familial AF											
M	49	25	PAF	AAD, RFA	109	normal	BAE	65		2	5,6
M	57	50	PAF	AAD, RFA	60	IVCD	normal	61		1	4
M	46	41	PAF	AAD, RFA	51	1°AVB	BAE	60		3	4,5,5
F	57	40	PAF	AAD, RFA	68	normal	LAE	60		3	4,4,5
M	50	45	PersAF	AAD, RFA	140	normal	normal	NA	CVA	2	4,5
M	46	43	PAF	AAD, RFA	71	1°AVB	LAE	65		3	4,4,4
M	47	41	PAF	AAD, RFA	75	IVCD	LAE	60		3	4,4,4
M	35	31	PAF	AAD, RFA	66	IVCD	RAE	74		1	4
M	55	31	PersAF	AAD, RFA	54	IVCD	BAE	65		1	4
M	47	43	PAF	AAD, RFA	61	normal	LAE	60		2	4,4
M	53	49	PersAF	AAD, AVNA, PPM	130	normal	LAE, LVE	37	2°CM	2	4,4
M	46	28	PAF	AAD, RFA	74	1°AVB, RBBB	LAE	65		3	4,4,5
M	59	54	CAF	AAD, RFA	65	RBBB, QTc	normal	37	2°CM	1	4
M	38	36	PAF	AAD, AVNA, PPM	51	IVCD	normal	65		2	4,5
M	54	25	PAF	AAD, RFA	92	IVCD	normal	NA		2	4,5
M	50	38	CAF	AAD, RFA	110	normal	RAE, LVE	29	2°CM	1	5
F	58	38	PAF	AAD, RFA	54	normal	normal	65		2	4,5
M	38	27	PAF	AAD	74	normal	BAE	55		2	3,4
M	52	48	CAF	AAD	78	normal	LAE	65		3	4,5,5
M	48	44	PAF	AAD	68	normal	normal	65		1	4
M	61	52	PAF	AAD	114	normal	normal	60		2	4,5
M	55	48	CAF	AAD	97	normal	normal	66		3	4,4,5
M	58	48	CAF	AAD, RFA	82	QTc	LAE	63		3	2,3,4
Confirmed familial AF											
M	59	54	PersAF	AAD, RFA	61	IVCD	RAE	40	2°CM	2	4,5
M	29	25	PAF	AAD, RFA	74	IVCD	normal	65		2	3,3
M	51	25	PAF	AAD	57	1°AVB, IVCD	normal	65		2	3,4
M	39	34	PAF	AAD, RFA	88	normal	normal	60		7	3,4,4,5,5,5,5
M	54	48	PAF	AAD	78	1°AVB	LAE	65		3	4,4,4
M	51	38	PAF	AAD, RFA	66	1°AVB, IVCD	normal	63		3	4,4,4
M	38	24	PersAF	AAD	117	normal	normal	60		2	4,5
M	65	45	CAF	AAD, AVNA, PPM	40	LBBB	LAE	68		4	4,4,5,5
F	52	37	PersAF	AAD, RFA	74	IVCD	LAE	65		4	4,4,4,4
F	54	44	PAF	AAD, RFA	74	normal	LAE	68	WPW in 2 relatives	4	3,3,4,4
M	55	49	PersAF	AAD, ICD	55	normal	LAE	60		4	4,4,4,4
M	62	50	CAF	AAD	71	normal	normal	65		3	4,4,4
F	41	39	PAF	AAD, RFA	81	normal	normal	65		2	3,4
M	57	40	CAF	AAD, AVNA, PPM	70	normal	BAE	65		3	3,3,4

AAD = antiarrhythmic drugs; AF = atrial fibrillation; 1°AVB = first-degree atrioventricular block (PR > 0.20 s); AVNA = atrioventricular node ablation; BAE = biatrial enlargement; CAF = chronic atrial fibrillation; 2°CM = secondary cardiomyopathy; CVA = cerebrovascular accident; ECG = electrocardiogram; EF = ejection fraction; HR = heart rate (on drug therapy); ICD = implantable cardioverter defibrillator; IVCD = intraventricular conduction delay (QRS: 0.10 to 0.12 s); LA = left atrial; LAE = left atrial enlargement; LBBB = left bundle-branch block, LV = left ventricular; LVE = LV enlargement; NA = not available; PAF = paroxysmal atrial fibrillation; PersAF = persistent atrial fibrillation; PPM = permanent pacemaker; QTc = corrected QT interval >500 ms; RAE = right atrial enlargement; RBBB = right bundle-branch block; RFA = radiofrequency ablation of focal atrial fibrillation; WPW = Wolff-Parkinson-White syndrome.

Table 2. Phenotypic Data for Affected Family Members in FAF 1 to 4

Pedigree Number	Age at Evaluation (yrs)	Age at Onset (yrs)	Rhythm	Treatment	Electrocardiogram				Echocardiogram				Comment
					HR (beats/min)	PR Interval (ms)	QRS Interval (ms)	QTc (ms)	LA Size (mm)	LVSD (mm)	LVDD (mm)	EF (%)	
FAF-1													
2.2	77	42	PAF	BB, AC	63	194	110	460	38 (48)	24 (35)	48 (59)	78	
3.2	52	41	PAF	—	74	130	100	420	37 (42)	28 (34)	53 (58)	72	
4.2	31	31	CAF	BB, DZ	95	—	90	410	**51** (42)	**44** (35)	**61** (59)	53	2°CM
	32				62	148	100	400	NA	NA	NA	65	
FAF-2													
2.2	deceased	50s	CAF	BB, AC	NA	NA	NA	NA	NA	NA	NA	NA	CVA
2.5	71	58	CAF	BB, AC	87	—	100	410	**55** (50)	32 (36)	52 (55)	66	
3.2	47	36	PAF	PPM, AC	70	186	Paced	Paced	33 (45)	34 (42)	51 (54)	60	
3.3	42	42	PAF	BB, AC	98	—	80	400	41 (46)	34 (37)	**56** (55)	55	2°CM
	45				60	180	85	410	42 (46)	34 (37)	53 (55)	60	
FAF-3													
2.4	deceased	45	PAF	BB, AC	NA	NA	NA	NA	NA	NA	NA	NA	
2.5	80	55	CAF	AC	68	—	96	460	50 (52)	NA	42 (48)	65	
2.6	74	60s	CAF	Dig, AC	73	—	80	400	**48** (45)	**34** (32)	47 (49)	55	CVA
2.7	77	45	CAF	Dig, AC	87	—	84	360	**51** (44)	NA	NA	81	
2.9	73	30	CAF	Dig, AC	63	—	110	380	NA	NA	NA	59	
2.12	69	60	PAF	BB, FL	46	200	80	420	40 (43)	27 (33)	47 (50)	65	CVA
2.14	63	55	PAF	Sot, AC, RFA	66	200	90	410	**58** (46)	29 (36)	48 (55)	67	
3.8	38	27	CAF	BB, Dig	80	—	85	415	NA	NA	NA	NA	
FAF-4													
2.2	61	58	PAF	AC	70	160	80	420	**44** (41)	**41** (33)	**56** (49)	50	
	72		AJR	AC	64	—	115	**520**	**51** (44)	**34** (32)	**61** (49)	50	
2.4	62	42	PAF	AC	60	—	110	440	NA	NA	NA	NA	
	67		JR	AC	45	—	110	470	39 (43)	28 (39)	49 (49)	65	
2.5	56	36	PAF	AC	80	—	100	470	46 (46)	34 (36)	**61** (55)	50	
	66		JR	AC	45	—	**140**	**500**	**51** (50)	**40** (36)	**66** (55)	50	RBBB, LAFB
3.1	47	43	PAF	FL, AC RFA	64	160	120	430	NA	NA	NA	60	
3.3	38	37	PAF	PP, AC	110	160	115	450	41 (42)	32 (37)	**54** (53)	55	
	41		AJR	PP, AC	66	—	120	460	41 (43)	**39** (34)	**54** (53)	50	
3.6	45	30	PAF	Dig, AC	65	175	90	430	NA	NA	NA	NA	
3.8	41	32	PAF, JR	AC, PPM	40	—	115	460	**47** (46)	**40** (39)	**64** (56)	55	
3.10	29	28	PAF	AC	77	145	84	410	40 (45)	36 (40)	56 (57)	50	
	41		CAF	AC	65	—	440	440	**48** (46)	39 (40)	56 (57)	50	
3.12	36	34	PAF	PP, AC	73	162	85	480	**46** (43)	**38** (37)	**54** (53)	55	
3.13	34	34	PAF	FL, AC	54	115	80	440	42 (43)	30 (35)	46 (53)	60	

Values in parenthesis indicate upper limits of normal for age and body surface area (9). **Bold font** indicates abnormal values. Heart rates (HR) were measured on drug therapy.

AJR = accelerated junctional rhythm; AC = anticoagulation; BB = beta-blockers; Dig = digoxin; DZ = diltiazem; FAF = family with autosomal dominant atrial fibrillation; FL = flecainide; JR = junctional rhythm; LAFB = left anterior fascicular block; LVDD = left ventricular diastolic dimension; LVSD = left ventricular systolic dimension; PP = propafenone; Sot = sotalol; other abbreviations as in Table 1.

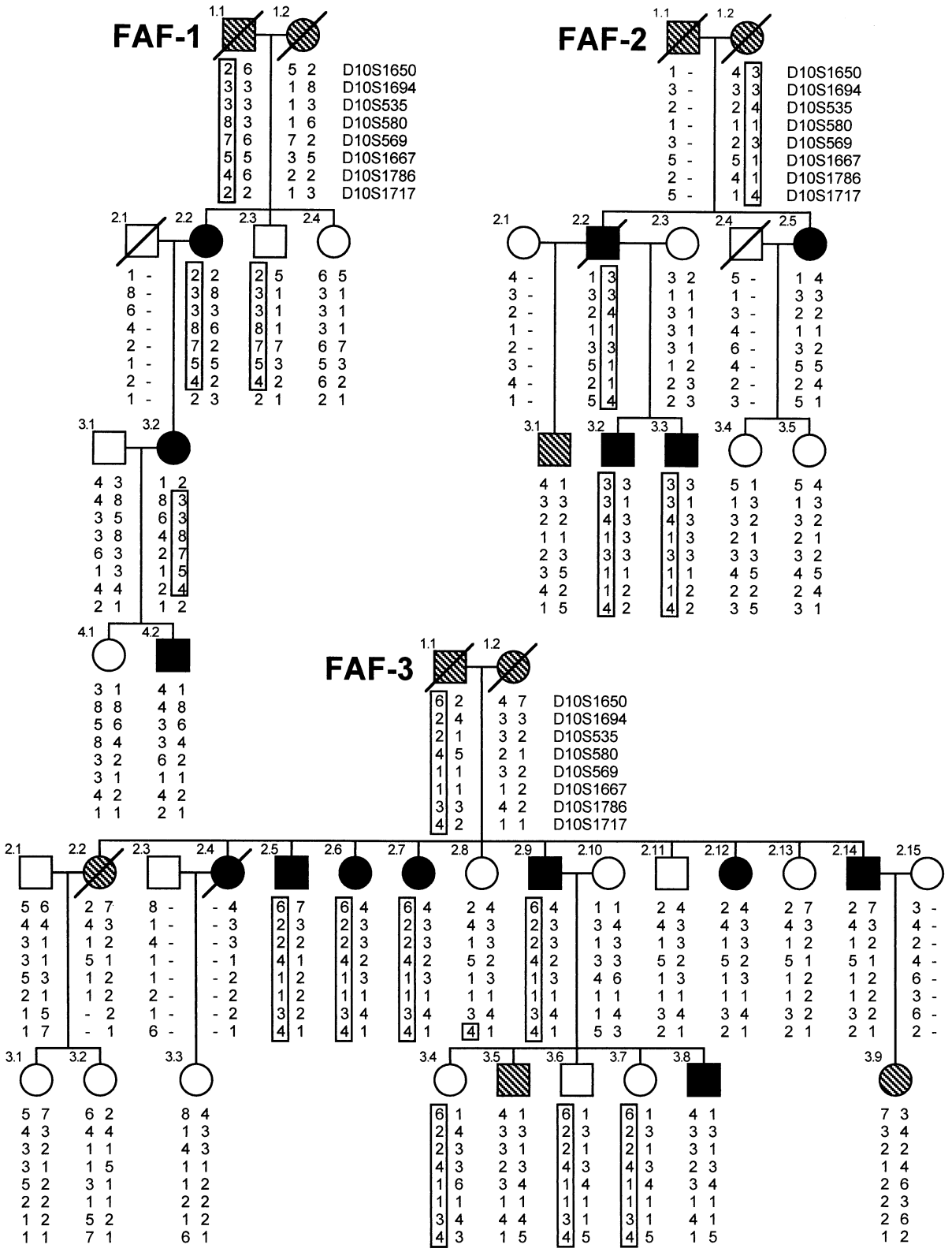

Figure 1. Haplotype analyses of three pedigrees with familial atrial fibrillation (AF). Pedigree symbols represent the following traits: **circles** = females; **squares** = males; **diagonal lines** = deceased; **filled** = AF; **hatched** = uncertain; **empty** = asymptomatic and no documented AF. Haplotypes are comprised of genotypes for eight tightly linked markers spaced 1 to 3 centiMorgans (cM) apart. D10S1694 and D10S1786 define the centromeric and telomeric boundaries, respectively, of a previously reported familial AF locus on chromosome 10q22-q24. Double recombination events between adjacent markers were assumed not to have occurred, and haplotypes of deceased individuals were inferred when possible. The patriarchal or matriarchal haplotype inherited by the majority of individuals with AF within each family is **boxed,** illustrating at least one affected individual who does not inherit this haplotype. These data exclude a disease gene for familial AF at this locus. FAF = multi-generation families with autosomal dominant atrial fibrillation.

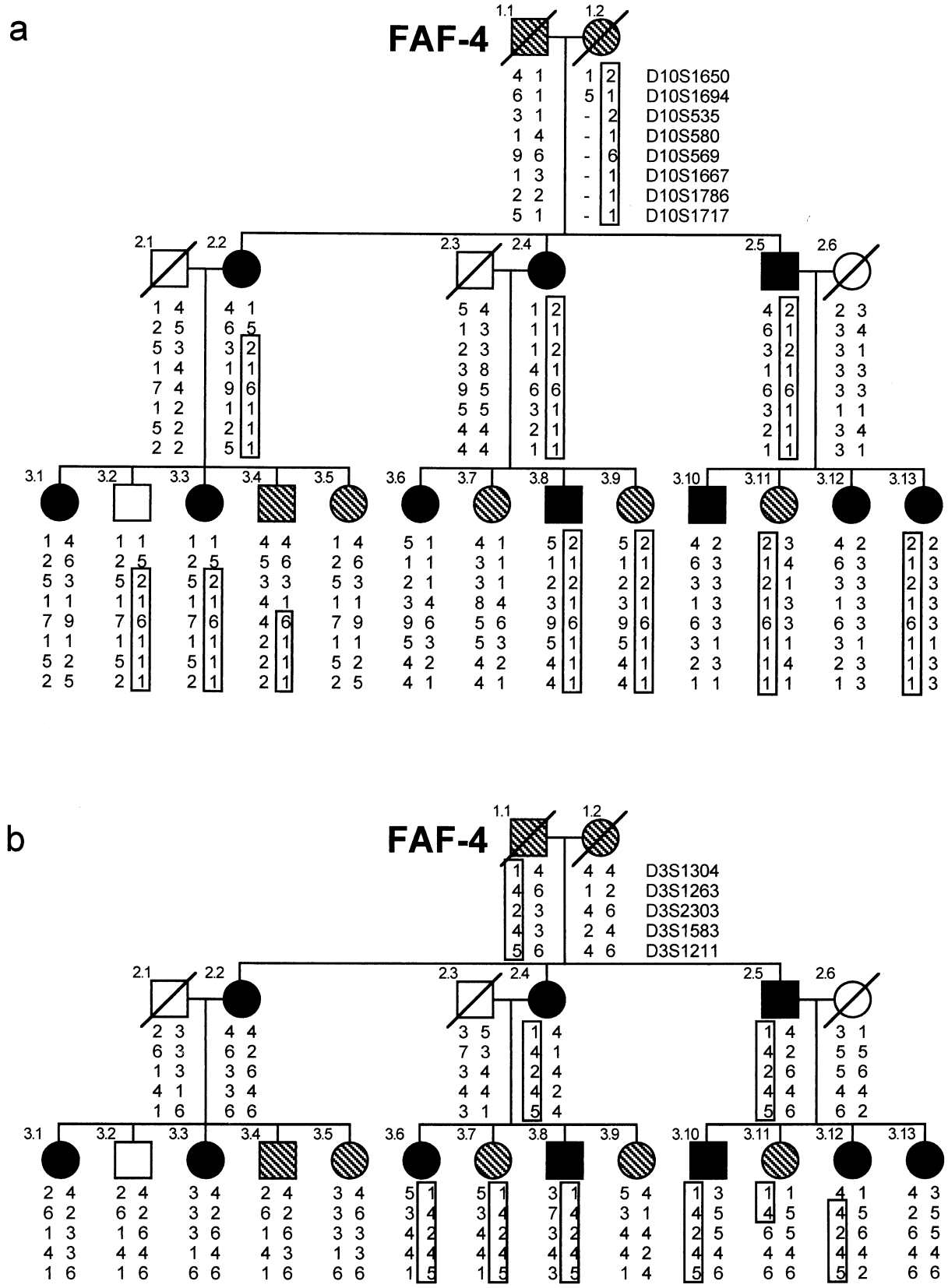

Figure 2. Haplotype analyses of a pedigree with familial atrial fibrillation (AF) and early features of dilated cardiomyopathy. Haplotypes were constructed at a locus for familial AF **(a)** and loci for familial dilated cardiomyopathy, sinus node dysfunction, conduction system disease, and AF on chromosomes 3p22-p25 **(b)** and 1q21 **(c)**, where the lamin A/C gene is located. The affected individuals do not inherit the same haplotype, excluding a disease gene at these loci. FAF = multi-generation families with autosomal dominant atrial fibrillation. *Continued on next page*

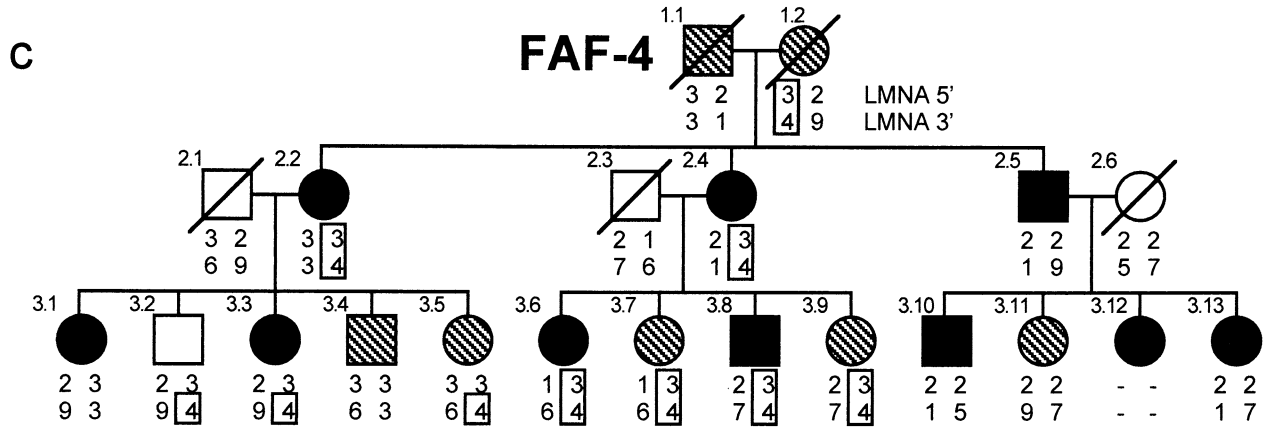

Figure 2 Continued.

patients with AF; 15% of patients with lone AF) were identified with lone AF (mean age at onset 41 ± 9 years, range 25 to 55 years) and a positive family history (one to nine additional relatives affected). Phenotypic and family history data for 46 of the probands are shown in Table 1.

Among the 50 cases of familial AF, four multi-generation families were identified in which AF appeared to segregate as an autosomal dominant trait (FAF-1 to -4; Table 2). Phenotypic data and DNA samples were ascertained from a sufficient number of relatives to enable testing for linkage at the chromosome 10q22-q24 locus. The mean age at onset of AF in FAF-1 to -4 was 38 ± 6, 51 ± 10, 43 ± 13, and 37 ± 9 years, respectively. The disease phenotype in FAF-1 to -3 was similar; the majority of affected family members presented with symptomatic paroxysmal AF associated with rapid ventricular response. Two had tachycardia-induced cardiomyopathy (FAF-1: 4.2; FAF-2: 3.3), which improved with rate control or maintenance of sinus rhythm (serial echocardiographic data shown in Table 2). Also notable, stroke occurred at young ages in these families. An individual in FAF-2 (2.2) had a stroke at the age of 52 years. In FAF-3, two individuals (2.6 and 2.12) had strokes at 48 and 52 years of age, respectively.

The disease phenotype in FAF-4 was different from that in FAF-1 to -3 (Table 2). Asymptomatic AF was more common (2.5, 3.6, 3.10, and 3.13 were all asymptomatic), and AF was first diagnosed in two relatives (3.10 and 3.13) during family screening for the current study. Atrial fibrillation in FAF-4 was typically associated with a slow ventricular response and, consequently, most individuals did not require rate control therapy. With disease progression, junctional rhythm with no retrograde atrial conduction developed in 4 of 10 individuals, including 1 who initially presented with AF and a rapid ventricular response (3.3). In one individual (3.8), serial electrophysiologic studies suggested an atrial myopathy, with fractionated atrial electrograms progressing to an electrically silent right atrium. He ultimately required implantation of a permanent pacemaker for symptomatic junctional bradycardia. Left ventricular enlargement with low-normal ejection fraction developed in 5 of 10 individuals. Lack of a rapid ventricular response during AF suggests that the cardiomyopathy in these individuals is not tachycardia-induced. In summary, AF, atrial conduction disease, and cardiomyopathy characterize the phenotype in FAF-4.

Molecular genetic studies. In FAF-1 to -4, phenotypic characterization and DNA sample collection were sufficient to test for linkage to the previously reported AF locus on chromosome 10. In each family, genotypes were scored and haplotypes were constructed to determine if there was co-segregation of this locus with AF. The results of haplotype analyses are shown in Figures 1 and 2a. These data revealed lack of a shared haplotype among all affected individuals within each family, excluding linkage of AF to the chromosome 10 locus. Thus, at least one additional gene for familial AF exists. Similarly, in the family with a unique phenotype (FAF-4), linkage was excluded at two loci associated with AF and cardiomyopathy (Figs. 2b and 2c).

DISCUSSION

Atrial fibrillation is not generally regarded as a heritable disorder, and only a few families with this condition have been described in the literature (6,8,13). The identification of a genetic locus for autosomal dominant AF established that, in some cases, AF is a single gene disorder (8). Although a recent report suggests that familial AF may be more common than previously recognized (7), there is no documentation of the overall prevalence of familial AF.

In our clinical practice, we found that at least 5% of all patients with AF and 15% with lone AF had a positive family history. Referral bias likely resulted in a disproportionate number of patients with lone AF evaluated in our subspecialty Arrhythmia Clinic (36% vs. 2% to 11% in population studies) (4,5), and our findings may not reflect the true prevalence of familial disease in patients with AF. Moreover, the frequency of familial AF could have been overestimated because a diagnosis of lone AF was not confirmed in ≥2 relatives in the "possible" and "probable" subclassifications of familial disease and some may have had

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a non-inherited form of AF secondary to underlying structural heart disease. Mitigating this possibility, however, is the relatively young age at onset for AF among the 50 probands and their relatives classified with familial disease, similar to age at onset for lone AF reported in population-based studies (4) and suggesting a unique substrate for AF that differs from those with more common, acquired AF developing later in life. Alternatively, we may have underestimated the true frequency of familial AF. A standardized initial approach to elicit family history was not applied in this study, and even a detailed family history may not be a sensitive marker for inherited cardiovascular diseases (14). Moreover, systematic clinical screening for occult disease in first-degree relatives was performed in only 4 of the 50 families. Indeed, lone AF develops as a paroxysmal disorder that may be clinically silent and/or difficult to document in individuals with symptomatic disease (15). Determining the true prevalence of familial AF in patients with AF would require prospective, longitudinal epidemiologic studies.

In four families with autosomal dominant AF, we have excluded linkage to the previously identified AF locus on chromosome 10q22-q24. In one family with AF and cardiomyopathy, linkage was also excluded to the chromosome 3p22-p25 and lamin A/C loci, which have been associated with familial AF, sinus node dysfunction, conduction system disease, and dilated cardiomyopathy (10,11). These data indicate that familial AF is genetically heterogeneous and that at least two disease genes are responsible for this disorder. Similar to familial cardiomyopathies, the genetic substrate for familial AF may be quite diverse. This would be consistent with proposed mechanisms for AF, ranging from a purely electrical disease to an interaction with an abnormal morphologic substrate (16–18).

Our findings suggest that familial AF is not uncommon, family history is an important component of a complete medical evaluation, and lone AF should raise suspicion of an inherited form of disease. Because AF is associated with significant morbidity and mortality, recognition of familial disease and early identification of affected family members will allow the initiation of therapies that may prevent or attenuate some of these complications. Furthermore, identification of large multi-generation families with AF will facilitate identification of additional genetic loci for AF. The ultimate discovery of AF genes will clarify molecular mechanisms responsible for familial forms of the disease and may also provide insight into the pathogenesis of more common, acquired forms of AF. These insights may lead to improved risk assessment and therapeutic strategies.

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