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A Common Variant on Chromosome 4q25 is Associated With Prolonged PR Interval in Subjects With and Without Atrial Fibrillation

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Abstract

Single nucleotide polymorphisms (SNPs) at chromosome 4q25 (near *PITX2*) are strongly associated with atrial fibrillation (AF). We assessed whether a 4q25 tagging SNP (rs2200733) is associated with PR interval duration in patients with lone and typical AF and controls. Patients with lone (n=169) and typical (n=269) AF enrolled in the Vanderbilt AF registry and controls (n=1403) derived from the Vanderbilt DNA Biobank (BioVU) were studied. Carriage of the rs2200733 T allele (CT or TT genotype) was more common in lone (39%) than in typical (25%) AF patients or controls (21%, $P<0.01$ for both comparisons). In both AF cohorts, we observed an association between genotype and PR interval duration (median PR interval for CC, CT, and TT: 162, 178, and 176 ms for lone, $P=0.038$ and 166, 180, and 196 ms for typical, $P=0.001$). After adjustment for covariates, the association between T allele and PR prolongation persisted, with mean effect size 10.9, 12.8, and 4.4 ms for lone and typical AF patients and controls ($P<0.05$ for each comparison). We found that a common 4q25 AF susceptibility allele (rs2200733) is associated with PR interval prolongation in patients with lone and typical AF and controls with no AF. Given that prolonged PR interval is an established risk factor for AF, this observation, in the context of previously described functional effects of *PITX2* deficiency, provides further knowledge about the pathophysiological link of 4q25 variants with AF.

Introduction

Atrial fibrillation (AF) is becoming increasingly common, with prevalence in the United States projected to roughly double by the year 2050 to an estimated 6-12 million.¹⁻³ Identifying patients at high risk for developing AF, with the objective of developing strategies for prevention, is an important area of discovery.⁴ Genome-wide association studies (GWAS) have identified novel variants associated with prevalent AF.⁵ The strongest and most consistently associated locus is at chromosome 4q25 near the paired-like homeodomain transcription factor 2 (*PITX2*) gene. Prolongation of the electrocardiographic PR interval has emerged as an important independent risk factor for AF, and in some patients might represent an 'endophenotype,' or a heritable, early marker of AF.^{6,7} Recently, a 4q25 variant was associated with PR interval prolongation in patients with lone AF.⁸ Here,

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we sought to investigate the role of the rs2200733 variant at 4q25 on PR duration in three patient cohorts: those with lone AF, patients with typical AF, and controls free from AF or structural heart disease.

Methods

Patients with lone AF, typical AF, and controls with no AF were studied. Lone AF was defined as AF diagnosed prior to age 66 years in the absence of hypertension, hyperthyroidism, structural heart disease, or other predisposing cardiopulmonary disorders. Typical AF was characterized by age at diagnosis $\geq$ 66 years or the presence of hypertension, structural heart disease, or other predisposing cardiopulmonary disorders. Patients with lone and typical AF were prospectively enrolled in the Vanderbilt AF Registry and all data were entered prospectively by dedicated study nurses.⁹ Controls without AF were identified by querying the Vanderbilt University Medical Center DNA Biobank (BioVU).¹⁰ This resource consists of de-identified medical records of Vanderbilt inpatients and outpatients and DNA extracted from blood that is left over after routine laboratory testing and scheduled to be discarded. As of August 2013, BioVU included >158,000 patients with available DNA. Controls were identified in BioVU using a previously validated algorithm that includes natural language processing, billing codes, and medication records. This automated algorithm was previously created and optimized through multiple reiterations with manual review of medical records until a positive predictive value for AF >95% was achieved. Cases with AF and controls identified by the automated algorithm were previously studied to confirm known genotype-phenotype relations.¹¹ The Vanderbilt Institutional Review Board approved this study, and all participants gave written, informed consent.

Clinical comorbidities, including diabetes, hypertension, heart failure (HF), coronary artery disease (CAD), myocardial infarction (MI), and tobacco use, were prospectively entered into the AF registry using standard definitions. Use of medications was entered upon enrollment and updated periodically. In the no-AF cohort, information about comorbidities and medications was queried using previously validated computer algorithms utilizing natural language processing, laboratory values, medication records, and International Classification of Diseases-9 (ICD-9) codes.

PR interval duration, the study's primary endpoint, was derived from 12-lead ECGs, where it was calculated using standard automated interpretation algorithms. For patients with lone and no AF, PR interval was ascertained from the ECG recorded at the time patients were enrolled into the AF registry, unless the patient was not in sinus rhythm during this recording, in which case the first preceding ECG in which the patient was in sinus rhythm was used. In the lone AF cohort, medication records were manually reviewed to confirm that the index ECG was recorded while the patient was not currently or recently ($\geq$ 7 days) on any anti-arrhythmic drugs (AADs) or atrioventricular (AV) nodal blockers. For patients with typical AF, medical records were manually searched to select ECGs recorded prior to the diagnosis of AF and while the patient was not on AAD therapy. As many of the patients with typical AF had structural heart disease, it was not possible to exclude patients taking β -blockers. Patients with lone or no AF who were taking β -blockers were excluded from the study.

Genotyping was performed for the rs2200733 single nucleotide polymorphism (SNP), which was previously demonstrated to be an effective tagging SNP for the AF-associated 4q25 haplotype.¹² In the AF registry, genotyping was performed using Taqman[®] chemistry (Applied Biosystems, Foster City, California). Genotyping in the no-AF BioVU cohort was performed using the Human660W-Quad micro-array platform (Illumina, San Diego,

California). Laboratory personnel performing genotyping were blinded to clinical and electrocardiographic data.

Group comparisons were made using the Kruskal-Wallis test or Pearson's correlation, as appropriate, for continuous variables or Chi-squared test for categorical variables. Multivariate linear regression was used to adjust for covariates. In univariate analysis, the following variables were associated with PR interval for each group and included in the final regression model: age and β -blocker for typical AF; and age, sex, and body-mass index (BMI) for no AF. In the smaller lone AF group, no clinical variable was associated with PR interval in univariate analysis. For consistency, age, sex, and BMI were included in the multivariate model for lone AF. Nominal statistical significance was taken as a two-tailed $P \leq 0.05$. Analysis was performed using SPSS (v20, Chicago, IL).

Results

Baseline demographic and clinical characteristics are summarized in Table 1. Average age was 54.5, 66.6, and 49.5 for lone AF (n=169), typical AF (n=269), and no-AF controls (n=1403), respectively. Genotype frequencies for rs2200733 (CC, CT, and TT) were 0.61, 0.33, and 0.05 in lone AF, 0.75, 0.24, and 0.02 in typical AF, and 0.79, 0.20, and 0.01 in controls, and were in Hardy-Weinberg equilibrium. Carriage of the T allele (genotypes CT and TT) was associated with lone ($P < 0.01$) but not typical AF.

In univariate analysis, PR interval duration differed by rs2200733 genotype in lone and typical AF (Table 2). Among patients with lone AF, median [interquartile range] PR interval durations were 162 [148–184], 178 [157–196], and 176 [156–181] ms for CC, CT, and TT, respectively ($P = 0.038$, Figure 1a). In the typical AF group, PR interval durations were 166 [155–183], 180 [168–192], 196 [188–206] ms for CC, CT, and TT, respectively ($P = 0.001$, Figure 1b). In univariate analysis, PR intervals did not differ by genotype in controls (156 [144–169], 156 [144–170], and 170 [149–176] ms for CC, CT, and TT, respectively, $p = 0.4$, Figure 1c).

Multivariate linear regression was used to correct clinical variables associated with PR interval. The association between rs2200733 genotype (CC vs. CT/TT) and PR interval duration remained significant in patients with lone and typical AF (Table 3). For controls with no history of AF, adjustment was made for age, sex, and BMI, resulting in statistically significant association of T allele carriage and PR interval ($P = 0.003$).

Discussion

We found that the rs2200733 polymorphism at the 4q25 locus was associated with PR interval duration in patients with lone AF, typical AF, and controls with no history of AF. In our study, the minor allele (T), which has been associated with AF, was more common in patients with lone AF than in those with typical AF (carriage of the T allele: 39% vs. 25%, $P < 0.01$). This is in keeping with a prior report wherein carriers of the rs2200733 T allele, as compared to wild-type individuals, were diagnosed with AF at a younger age.¹² However, the largest effect size of genotype on PR interval duration in our study was seen in patients with typical (not lone) AF, where a genetic dose response relationship was evident (Figure 1). The reason for this somewhat paradoxical finding is unclear.

The 4q25 locus, particularly the rs2200733 variant, has been associated with AF in multiple GWAS, with representative odds ratios of 1.7 for lone AF in carriers of the minor T allele.¹² While this effect size does not rise to the level of an “actionable” genetic variant, wherein carriage of the variant would dictate a specific clinical measure, there is much hope that

discovering the role of the 4q25 locus in AF will improve our understanding of the pathophysiology of this complex and heterogeneous disease.

The identified gene nearest rs2200733, *PITX2*, encodes the transcription factor Pitx2c. The 4q25 SNP most strongly associated with AF, rs2200733, is approximately 150,000 base pairs “upstream” from the gene. While the functional implications of 4q25 variants are poorly understood, the proximity of the locus to *PITX2* presents an intriguing potential pathophysiological link to AF. Candidate mechanisms include that the 4q25 SNPs are linked to coding or regulatory variants within the gene, or that the 4q25 SNPs themselves are in a regulatory region.

Given that *PITX2* is likely the candidate gene modulated by the 4q25 susceptibility variants, its role in AF pathophysiology has not completely been defined. Mommersteeg and colleagues demonstrated in a *PITX2* deficient mouse model that the transcription factor was critical for right-left patterning in the atria by inhibiting the default program for sinoatrial node formation on the left.¹³ Later, these investigators showed that the transcription factor was crucial for embryonic development of the pulmonary myocardium in mice.¹⁴ Wang et al. showed that *Pitx2c* deficient mice had increased expression of *HCN4*, *TBX3*, and *SHOX2*, all important for sinoatrial node formation. They concluded that through the increased expression of these crucial developmental factors, Pitx2c deficiency leads to an arrhythmogenic substrate in the left atrium, and they showed that, indeed, deficient mice were more prone to atrial arrhythmias with programmed stimulation.¹⁵ Chinchilla et al. showed that adult *PITX2* deficient mice demonstrated electrophysiological findings including AF, complete AV block, a more depolarized atrial resting membrane potential, and a lower amplitude atrial action potential; increased left atrial dimensions; and decreased atrial expression of *SCN5A*, *SCN1B*, *KCNJ2*, *KCNJ4*, and *KCNJ12*, as compared to control mice. They concluded that *PITX2* deficiency plays an important role in atrial anatomic and electrophysiological properties.¹⁶ Taken as a whole, these studies suggest a plausible role of *PITX2*, and by extension 4q25 SNPs, in AF pathophysiology, with candidate mechanisms including altered development of the pulmonary myocardium, ion channel expression, and right-left atrial patterning.

Even less is known about the potential mechanism by which 4q25 variants are associated with the endophenotype of prolonged PR duration, but candidate mechanisms include altered atrial ion channel expression,¹⁶ perturbed cell to cell signaling via altered gap junctions,¹⁷ and altered autonomic regulation of the AV node, perhaps through interactions with the Nav1.8 channel (encoded by *SCN10A*), which is expressed in cardiac nerve bundles.¹⁸ Previous studies showed that prolonged PR interval is an independent risk factor for AF.^{6,7} We propose that the pathophysiology of 4q25 variant-associated AF likely includes Pitx2c-determined changes that are manifested by the endophenotype of PR interval prolongation.

Goodloe and colleagues studied the electrocardiographic characteristics of 219 subjects with lone AF (age<60 and no history of hypertension or structural heart disease) who had been genotyped for the rs2200733 variant.⁸ They made the intriguing discovery of a graded allelic dose response for PR interval prolongation associated with the T allele. Our present study, while confirming this finding, makes several unique and important contributions. First, we showed an association between rs2200733 genotype and PR interval duration not only in patients with lone AF, but also in those with the more common typical form of AF. Second, we demonstrated that the association between rs2200733 genotype and PR interval persisted after adjustment was made for potential confounders. Finally, for the first time, we showed that, although the rs2200733 T allele was more common in lone than in typical AF patients, carriage of the T allele was actually associated with a larger effect on PR interval in typical

AF patients (adjusted mean effect size 19.7 [10.5–29] ms vs. 11.8 [2–21.6] ms). This finding supports a potential important role of 4q25 genetic variants in the much more common, typical form of AF.

As with all cross-sectional studies, ours is subject to bias and confounding. Steps were taken during the design, conduction, and analysis of the study to minimize these limitations. Genotyping was performed by personnel blinded to clinical and electrocardiographic data. PR interval duration was measured using automated, commercially available software, although the timing of ascertainment of PR interval and diagnosis of AF was not standardized, which might confound the relationship between genotype and PR interval. Although patients in the lone and no AF cohort who were on beta-blocker therapy were excluded, the typical AF cohort included many patients on beta-blockers for concomitant structural heart disease. Linear regression was used to adjust for beta-blocker therapy and other potential confounders of rs2200733 genotype and PR interval duration. Although the study was large, it was likely underpowered to detect statistically significant differences among patients with lone AF with different rs2200733 genotypes via an additive effect (n=8 for TT genotype).

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Figure 1a.

Figure 1b.

Figure 1c. **Figure 1.**

Box and whisker plots for median [interquartile range] electrocardiographic PR interval duration by rs2200733 genotype. **a)** Lone AF: 162 [184–148], 178 [157–196], and 176 [156–181] ms for CC, CT, and TT, respectively. **b)** Typical AF: 166 [155–183], 180 [168–192], 196 [188–206] ms for CC, CT, and TT, respectively. **c)** No AF: 156 [144–169], 156 [144–170], and 170 [149–176] ms for CC, CT, and TT, respectively. P-values derived with the Kruskal-Wallis test.

Table 1

Baseline demographics and clinical characteristics by rs2200733 genotype.

	Total	CC	CT	TT	P-value
Lone Atrial fibrillation	(N=169)	(n=103)	(n=58)	(n=8)	
Age (years)	54.5±13.3	55.4±13	54±12.6	62±7	0.53
Men	115 (68%)	73 (71%)	36 (62%)	6	0.58
Body-mass index (kg/m ²)	28.9±6.2	28.2±6.3	30.2±6.3	32.1±4.1	0.24
Ejection Fraction	57±7%	57±7%	57±7%	55±5%	0.62
Left atrial diameter	39±7mm	39±6mm	38±8mm	46±2mm	0.03
Typical Atrial fibrillation	(N=269)	(n=201)	(n=64)	(n=4)	
Age (years)	66.6±10.5	66.6±11	66.4±9.6	74±3.2	0.30
Men	207 (77%)	158 (79%)	46 (72%)	3	0.54
Body-mass index (kg/m ²)	28.3±7	28.6±5.4	28.9±7.5	30.6±8.3	0.98
Ejection fraction	43±15%	42±15%	46±14%	50±14%	0.07
Left atrial diameter	45±8mm	45±9mm	44±6mm	44mm	0.93
Heart failure	70 (26%)	55 (27%)	15 (23%)	0	0.43
Diabetes	99 (37%)	78 (39%)	19 (30%)	2	0.40
Coronary artery disease	145 (54%)	110 (55%)	34 (53%)	1	0.49
Beta-blockers	167 (62%)	124 (62%)	41 (64%)	2	0.83
Smoking	44 (16%)	28 (14%)	14 (22%)	2	0.06
No Atrial fibrillation	(N=1403)	(n=1110)	(n=276)	(n=17)	
Age (years)	49.5±14.7	47.6±15	49±15	42.4±18	0.67
Men	639 (46%)	520 (47%)	113 (41%)	6(35%)	0.15
Body-mass index (kg/m ²)	28.8±7.8	28.7±8.5	28.7±8.5	23.5±5.3	0.50

Table 2

Median [interquartile range] electrocardiographic PR interval duration (milliseconds) based on rs2200733 genotype.

	Total	CC	CT	TT	P-value
Lone atrial fibrillation	168 [152–188]	162 [148–184]	178 [157–196]	176 [156–181]	0.038
Typical atrial fibrillation	171 [156–187]	166 [155–183]	180 [168–192]	196 [188–206]	0.001
No atrial fibrillation	156 [144–170]	156 [144–169]	156 [144–170]	170 [149–176]	0.4

Table 3

Multivariate analysis of the association of rs2200733 T allele carriage with PR interval duration (CC versus CT or TT).

	Beta [standard error]	P-value
Lone atrial fibrillation (n=169)	10.9 [5]	0.031
Typical atrial fibrillation (n=269)	12.8 [3.8]	0.001
No atrial fibrillation (n=1403)	4.4 [1.5]	0.003