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Relation of Obstructive Sleep Apnea and a Common Variant at Chromosome 4q25 to Atrial Fibrillation

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Abstract

Obstructive sleep apnea (OSA) and single nucleotide polymorphisms (SNPs) at the 4q25 locus are associated with increased risk of atrial fibrillation (AF). Whether these associations are independent of traditional risk factors for AF remains unknown. Using billing code queries and manual chart review, we assembled a cohort of adults that underwent overnight polysomnography and at least one 12-lead electrocardiogram. Case status was defined by electrocardiographic data in support of AF or documentation of AF by a staff cardiologist. Controls were defined by a lack of primary evidence of AF and absence of a diagnosis of AF in the medical record. OSA severity was categorized based on apnea-hypopnea index. Genotyping for a key 4q25 SNP (rs2200733) was performed using the Sequenom platform. Logistic regression was used to test for associations of AF with OSA category and 4q25 SNP genotype while adjusting for age, gender, body mass index, ancestry, hypertension status, and heart failure status. The cohort consisted of 674 individuals (62 ± 13 years; 44% female), including 132 patients with AF. After adjustment for established risk factors, the association between AF and OSA severity was borderline significant (OR 1.2, 95% CI 1.0–1.5). The association between AF and 4q25 SNP status remained significant in a fully adjusted model that included OSA severity (OR 1.5, 95% CI 1.3–5.7). In conclusion, OSA severity and the chromosome 4q25 SNP genotype were associated with AF status independent of clinical risk factors. Knowledge of AF-related SNPs may enhance AF risk-stratification for those undergoing polysomnography.

Keywords

obstructive sleep apnea; genotype; atrial fibrillation

INTRODUCTION

Identification of individuals at increased risk for atrial fibrillation (AF) is important because AF is associated with significant morbidity and increased mortality (1, 2). Risk-stratification may facilitate modification of contributing conditions and could potentially prevent or alter the impact of AF. Several clinical risk factors are known to influence the risk of AF (3) and predictive models incorporating these factors have been developed from the Framingham Heart Study (4) and validated in other cohorts (5). Over the past decade, the association of AF with obstructive sleep apnea (OSA) and genotype has been increasingly recognized. Furthermore, OSA and genotype can reduce the efficacy of standard therapies for AF. Individuals with OSA have a higher prevalence of AF than those without OSA (6) and OSA is more prevalent in those with AF than those without AF (7). Anti-arrhythmic drugs are less effective in those with severe OSA compared to those with mild OSA (8) and recurrence of AF is more common after electrical cardioversion and catheter ablation when OSA is present (9, 10). Genome-wide association studies have identified multiple genetic loci, including a chromosome 4q25 locus (near *PITX2*), that associate with AF (11). A specific SNP at 4q25, rs2200733, has been shown to predict recurrence of AF after electrical cardioversion (12) and catheter ablation (13, 14). Given the established relationship of 4q25 SNPs with AF and the emerging relationship of OSA to AF, we sought to assess whether the addition of OSA severity and/or rs200733 SNP status would improve the performance of a clinically-based AF prediction model. As an initial step towards this goal, we analyzed a cohort of adults with known AF status, formal overnight polysomnography, and chromosome 4q25 SNP genotype data.

METHODS

The cohort was assembled from BioVU and the Synthetic Derivative, Vanderbilt Medical Center resources linking DNA samples to de-identified electronic medical records (EMRs), which have been described in detail previously (15). Briefly, the Synthetic Derivative is an archived copy of the electronic medical record from which identifying information that could be linked to subjects and health care personnel has been removed. BioVU is a biobank containing DNA for a subset of subjects in the Synthetic Derivative that has been extracted from blood samples that would have otherwise been discarded (i.e. excess blood from routine lab testing). BioVU currently houses over 200000 DNA samples.

Using a comprehensive list of CPT codes, the Synthetic Derivative was queried to identify all adults that had a formal overnight polysomnogram (PSG) at our institution's Sleep Laboratory and at least one 12-lead electrocardiogram (EKG). Of these individuals, those that had DNA samples available in BioVU formed the cohort.

Basic demographic (age, gender, ancestry), anthropomorphic (height and weight at the time of the PSG), and clinical data were obtained from manual chart review. Race is administratively assigned in our EMR and has been shown to have high concordance with genetically determined ancestry in that context (16). Body mass index (BMI) was calculated as the mass (in kilograms) divided by the height (in meters) squared. Co-morbid conditions, such as hypertension and heart failure, were confirmed by review of clinic notes, admission

history/physicals, and discharge summaries. When available, echocardiographic information was used to support the diagnosis of heart failure; for the purposes of this study, no distinction was made between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.

Polysomnographic data were obtained from the formal PSG report, based on the interpretation of the PSG by board-certified Sleep Physicians at our institution; standard protocols for data acquisition and scoring were used, as described previously (17). Apnea-hypopnea index (AHI) was defined as the sum of apneic and hypopneic events divided by the total duration of sleep. Based on the reported AHI, OSA severity was categorized as none (< 5 events/hour), mild (5–15 events/hour), moderate (16–30 events/hour), or severe (> 30 events/hour).

AF cases were identified by manual chart review that yielded the following: (1) primary electrocardiographic data in support of AF (EKG, ambulatory monitoring, pacemaker/defibrillator interrogation); and/or (2) documentation of AF by a staff cardiologist. ‘Non-AF’ status was defined by a lack of primary electrocardiographic evidence of AF and absence of a diagnosis of AF in the narrative portions of the EMR. For the purposes of this study, no distinction was made between categories of AF; for completeness, the distribution of cases among AF categories was 80% paroxysmal, 16% persistent, and 4% permanent.

Genomic DNA was isolated from whole blood by a commercial kit (Purgene; Gentra Systems; Minneapolis, MN). Genotyping of the 4q25 SNP (rs2200733) was performed using real-time polymerase chain reaction (PCR), iPLEX single base primer extension, and MALDI-TOF mass spectrometry in a 384-well-format (Sequenom; San Diego, CA) as previously described (17) by laboratory personnel who had no knowledge of a given individual’s AF status.

Descriptive statistics for the study population were reported. Clinical data are reported as mean $\pm$ standard deviation for continuous variables and as counts and percentages for categorical variables. Differences between individuals without AF and patients with AF were evaluated by the non-parametric Wilcoxon rank-sum test for continuous variables and with the Pearson χ^2 test for categorical variables. Comparisons were considered statistically significant if the p value was less than 0.05 for two-tailed tests. The Pearson χ^2 test was also used to test for Hardy-Weinberg equilibrium. Due to expected low numbers of homozygous variants, it was defined *a priori* to include homozygous variants of the SNPs with their respective heterozygous variants.

Logistic regression models were constructed with AF status as the dependent variable. The baseline/clinical model included age, ancestry, gender, BMI, hypertension status, and heart failure status as co-variables (independent variables). OSA category was added to the baseline co-variables to produce the ‘sleep model’. SNP status was added to the baseline co-variables to produce the ‘genetic’ model. Addition of both OSA category and SNP status yielded the ‘combined’ model. An interaction term between OSA severity and SNP status was included in the combined model. Individual co-variate contributions to outcome prediction were assessed with point estimates and 95% confidence intervals (CI) of odds ratios (OR). To

examine the models' discriminatory ability (i.e. the ability to distinguish those with and without AF), C-statistics and their corresponding 95% CIs were calculated. To assess for model over-fitting, model validation was performed using the bootstrapping technique with 200 repetitions (18). Analyses were performed with the R statistical package (version 3.3.1; Vienna, Austria).

RESULTS

The cohort consisted of 674 adults (63 ± 13 years; 44% female; 86% Caucasian), 132 of whom had AF (20%). Approximately 1/3 of individuals with AF had either a pacemaker or ICD. As shown in Table 1, those with AF were more likely to be male, had a higher prevalence of hypertension and heart failure, and had more severe OSA compared to unaffected individuals. There were no differences in race or BMI between groups. The overall minor allele frequency (MAF) for rs2200733 was ~ 30% and the carrier rate for the minor allele was higher for subjects with AF (46% vs 25%; $p < 0.001$).

Table 2 displays the output for the baseline, sleep, genetic, and combined models. For the baseline model, age and heart failure were significant predictors of AF, whereas gender, hypertension, BMI, and ethnicity did not achieve statistical significance. This remained the case for the sleep model in which categorical AHI was also a significant predictor of AF. In the genetic model, age and HF remained significant and 4q25 SNP status was a significant addition (OR 1.7, 95% CI 1.3–5.9). Key features of the combined model include the continued significance of age, heart failure, and genotype as well as the borderline significance of OSA severity (OR 1.3, 95% CI 1.0–2.4). Ancestry was also a significant predictor of AF in this model with African-American ethnicity conferring a lower likelihood of AF compared to Caucasians. An interaction term between OSA severity and genotype status was not significant in the combined model. C-statistics for each model are also presented in Table 2. Adding OSA severity does not add much predictive capability to the baseline model. There is a larger, although still modest, effect of adding 4q25 SNP status to the baseline model. The combined model improves the ability to predict AF by a degree similar to the genetic model.

DISCUSSION

This study shows that in a cohort of individuals who underwent PSG at a tertiary medical center (1) OSA severity is associated with AF independent of traditional AF-risk factors; (2) common AF susceptibility SNP at chromosome 4q25 is associated with AF, independent of traditional AF-risk factors and OSA severity; and (3) OSA severity remains a significant predictor of AF status, even when adjusting for clinical risk factors and 4q25 SNP carrier status.

The performance of these models compares favorably to the Framingham model, upon which our baseline model was based. Although they were part of the Framingham model, PR interval and age at which an important murmur developed were not feasible for us to include in our analysis. However, unlike the original Framingham cohort, our study population contained a significant number of African-Americans (~ 15%, similar to one of

the Framingham derivation cohorts [5]). The emergence of ancestry as a significant predictor of AF in the combined model suggests that interactions between OSA status, genotype, and AF status may differ between African-Americans and Caucasians. These interactions, which are likely complex, may play a role in the paradoxical lower prevalence of AF in African-Americans despite a higher concentration of traditional risk factors (19).

While the C-statistic for the Framingham derivation cohort (0.78, 95% CI 0.76–0.80) (4) was equal to or higher than any of our models, the C-statistic of our baseline model is slightly higher than those found in the Framingham validation studies (5). The incremental improvements in C-statistic are modest, but they do suggest that the addition of OSA severity and 4q25 SNP status to the baseline model do result in additional predictive capability for AF. The lack of interaction between OSA severity and 4q25 SNP genotype in the combined model suggests that the impact on AF of the SNP evaluated in this study does not vary with OSA severity. In the context of our prior work, which suggested a potential role of genotype in modulating the impact of OSA on anti-arrhythmic drug treatment of AF (17), this finding may suggest that the propensity for AF and the response to anti-arrhythmic drugs for established AF are not determined by identical factors.

Our findings should be interpreted in the context of the study's limitations, namely the small sample size, single-center design, and retrospective nature. Larger multi-center prospective studies are needed to validate these findings. In addition, the selection process for the study (i.e. the use of CPT codes to identify those with PSGs, limiting the study population to those with DNA samples in BioVU) could potentially introduce bias, although it is relatively unlikely that the prevalence of AF was systematically different based predominantly on entry criteria. Despite these limitations, the MAF and the OR for AF of the 4q25 SNP are similar to those found in the seminal GWAS study (11) and in a prior study from our institution that investigated the risk of AF post-cardioversion (12). Only one SNP was included in these models, primarily to preserve statistical power and avoid overfitting the predictive models. Larger studies would afford the opportunity to evaluate additional SNPs, including others associated with AF (20, 21), OSA (22), and genes involved with inflammation, a mediator that has been implicated in the pathogenesis of both OSA and AF (23, 24). Strengths of the study include robust ascertainment of OSA severity from formal overnight polysomnograms performed in a university Sleep Laboratory and a rigorous definition of AF based on primary electrocardiographic data and clinical expert determination. Despite the refined AF definition, we acknowledge the reliance on clinical recognition and EMR documentation means that the true prevalence of AF could be underestimated due to incomplete ascertainment. Furthermore, if the results are further validated, the 'sleep' model could be applied readily to patients undergoing PSGs in a clinical setting, thus providing an estimate of AF risk as part of the PSG report. A recent randomized trial of OSA treatment did not show a reduction in incident AF with positive-pressure therapy compared to standard care, despite a high burden of OSA and prevalent cardiovascular disease in the study population (25). This result raises the possibility that additional data, perhaps including genotype, may be needed to identify those who would benefit from OSA treatment to reduce the likelihood of developing AF.

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Table 1

Cohort characteristics

Characteristic	Overall (n = 674)	Atrial Fibrillation		P-value
		No (n = 542)	Yes (n = 132)	
Age (years)	63 ± 13	62 ± 12	67 ± 13	< 0.001
Gender (Female)	44%	46%	32%	0.004
Ethnicity (Black)	14%	15%	11%	0.38
Body Mass Index (kg/m ²)	34 ± 9 (16–78)	34 ± 9 (16–78)	35 ± 9 (19–69)	0.71
Hypertension	68%	66%	77%	0.02
Heart failure	14%	11%	29%	< 0.001
Severe OSA	31%	30%	38%	0.058
Minor allele frequency	29%	25%	46%	< 0.001

Table 2

Logistic regression model output

ORs are 75th percentile vs 25th percentile for continuous co-variables; male vs female for gender; African-American vs Caucasian for ancestry; presence vs absence of condition for hypertension and heart failure; 'severe' vs 'none' for sleep apnea severity; variant vs wild-type for 4q25 single nucleotide polymorphism genotype

Co-variate	Model					
	Baseline		Sleep		Genetic	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	4.3	2.3–7.8	4.4	2.4–8.0	4.0	2.1–7.5
Gender	1.4	0.9–2.2	1.2	0.7–1.9	1.3	0.8–2.1
Ethnicity	0.7	0.4–1.3	0.7	0.4–1.3	0.5	0.3–1.1
Body Mass Index	1.3	0.8–2.3	1.2	0.7–2.1	1.2	0.7–2.2
Hypertension	1.3	0.8–2.2	1.3	0.8–2.1	1.4	0.8–2.3
Heart failure	2.8	1.7–4.7	2.9	1.7–4.8	2.9	1.7–5.0
Sleep apnea severity	NA	NA	1.2	1.0–1.5	NA	NA
4q25 single nucleotide polymorphism	NA	NA	NA	NA	1.7	1.3–5.9
C-statistic (95% CI)	0.72 (0.67–0.77)		0.73 (0.68–0.78)		0.77 (0.73–0.82)	