

Original article

Association Between rs2200733 and rs7193343 Genetic Variants and Atrial Fibrillation in a Spanish Population, and Meta-analysis of Previous Studies



Albert Ferrán,^a José María Alegret,^b Isaac Subirana,^{a,c} Gerard Aragonès,^{b,d} Carla Lluís-Ganella,^a César Romero-Menor,^e Francesc Planas,^f Jorge Joven,^g and Roberto Elosua^{a,*}

^a Grupo de Investigación en Epidemiología y Genética Cardiovascular, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain

^b Sección de Cardiología, Hospital Universitario de Sant Joan, Grup de Recerca Cardiovascular, IISPV, Universitat Rovira i Virgili, Reus, Tarragona, Spain

^c CIBER de Epidemiología y Salud Pública, Barcelona, Spain

^d Centre for Omic Sciences, Servei de Recursos Científics i Tècnics, Universitat Rovira i Virgili, Tarragona, Spain

^e Servicio de Cardiología, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain

^f Servicio de Cardiología, Hospital Municipal de Badalona, Badalona, Barcelona, Spain

^g Unidad de Investigación Biomédica (URB-CRB), IISPV, Hospital Universitario de Sant Joan, Universitat Rovira i Virgili, Reus, Tarragona, Spain

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ABSTRACT

Introduction and objectives: The objectives of this study were to analyze the association between two genetic variants (rs2200733 and rs7193343) in a Spanish population and the risk of developing atrial fibrillation, and to carry out a systematic review and meta-analysis of these associations.

Methods: We performed a case-control study involving 257 case patients with atrial fibrillation and 379 controls. The case patients were individuals who had donated samples to the Spanish National DNA Bank; the controls were participating in a population-based cross-sectional study. Genotyping was carried out using a TaqMan assay. We conducted a systematic literature search in which 2 independent reviewers extracted the necessary information. The study involved a meta-analysis, a heterogeneity analysis, and a meta-regression analysis to identify the variables that explain the heterogeneity across studies.

Results: In our population, the presence of atrial fibrillation was found to be associated with rs2200733 (odds ratio = 1.87; 95% confidence interval, 1.30-2.70), but not with rs7193343 (odds ratio = 1.18; 95% confidence interval, 0.80-1.73). In the meta-analysis, we observed an association between atrial fibrillation and both variants: odds ratio = 1.71 (95% confidence interval, 1.54-1.90) for rs2200733 and odds ratio = 1.18 (95% confidence interval, 1.11-1.25) for rs7193343. We observed heterogeneity among the studies dealing with the association between rs2200733 and atrial fibrillation, partially related to the study design, and the strength of association was greater in case-control studies (odds ratio = 1.83) than in cohort studies (odds ratio = 1.41).

Conclusions: Variants rs2200733 and rs7193343 are associated with a higher risk of atrial fibrillation. Case-control studies tend to overestimate the strength of association between these genetic variants and atrial fibrillation.

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Asociación de los polimorfismos rs2200733 y rs7193343 con la fibrilación auricular en población española y metanálisis de la evidencia existente

RESUMEN

Introducción y objetivos: Los objetivos del estudio son analizar en población española la asociación entre dos variantes genéticas (rs2200733 y rs7193343) y el riesgo de sufrir fibrilación auricular y realizar una revisión sistemática y un metanálisis de estas asociaciones.

Métodos: Estudio de casos y controles con 257 casos de fibrilación auricular y 379 controles. Los casos eran donantes del Banco Nacional de ADN; los controles participaron en un estudio transversal de base poblacional. La genotipificación se realizó mediante pruebas TaqMan. Se realizó una búsqueda bibliográfica sistemática, dos revisores independientes extrajeron la información necesaria. Se realizó un metanálisis, un análisis de heterogeneidad y de metarregresión para identificar las variables que explicaran la heterogeneidad entre estudios.

Resultados: En nuestra población se observa una asociación entre el rs2200733 y la presencia de fibrilación auricular (odds ratio = 1,87; intervalo de confianza del 95%, 1,30-2,70), pero no con el rs7193343 (odds ratio = 1,18; intervalo de confianza del 95%, 0,80-1,73). En el metanálisis, se observó una

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* Corresponding author: Grupo de Investigación en Epidemiología y Genética Cardiovascular, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Dr. Aiguader 88, 08003 Barcelona, Spain. Corresponding author:

E-mail address: relosua@imim.es (R. Elosua).

asociación de ambas variantes con la fibrilación auricular: *odds ratio* = 1,71 (intervalo de confianza del 95%, 1,54-1,90) para el rs2200733 y *odds ratio* = 1,18 (intervalo de confianza del 95%, 1,11-1,25) para el rs7193343. En la asociación entre el rs2200733 y la fibrilación auricular se observó heterogeneidad entre estudios, parcialmente relacionada con el diseño del estudio, con mayor magnitud de asociación en estudios de casos y controles (*odds ratio* = 1,83) que en cohortes (*odds ratio* = 1,41).

Conclusiones: Las variantes rs2200733 y rs7193343 se asocian con mayor riesgo de fibrilación auricular. Los estudios de casos y controles tienden a sobrestimar la magnitud de la asociación entre estas variantes genéticas y la fibrilación auricular.

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Abbreviations

AF: atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the arrhythmia most frequently encountered in clinical practice^{1,2} and is associated with higher risk of mortality and incidence of cardiovascular disease.³ Among the factors that increase the risk of developing AF are age, hypertension, cardiomyopathies, and valve disease. Atrial fibrillation occurring in patients < 60 years of age with no clinical or echocardiographic evidence of cardiovascular disease is referred to as lone AF, and its prognosis is good.

There is substantial familial aggregation in the development of AF, indicating the relevance of genetic factors.⁴ Familial forms, although uncommon, have been reported, and mutations have been identified on different genes, generally related to ion channels.⁴ However, in the majority of the cases of AF found in the general population, individual susceptibility is related to multiple genes, genetic variants, and environmental factors. In recent years, genome-wide association studies have identified common genetic variants associated with a higher risk of AF.^{5,6} The 2 loci that most consistently have been associated with AF are found in the 4q25 region, in linkage disequilibrium with the *PITX2* gene, where the single nucleotide polymorphism rs2200733 is of particular interest, and in the 16q22 region, associated with the *ZFHX3* gene, where the single nucleotide polymorphism rs7193343 is located. Among the limitations of studies of this type are the possible variations between different publications. Some meta-analyses have analyzed the available evidence and the existence of heterogeneity among studies, but have failed to analyze the causes.^{7,8}

The objectives of this study were as follows: a) to analyze the association between the abovementioned genetic variants, rs2200733 and rs7193343, and the probability of AF in a Spanish population, and b) to carry out a systematic review and meta-analysis of the association between these two genetic variants and the risk of AF, determining whether there was heterogeneity among the studies and, if so, its possible causes.

METHODS

Analysis of the Association Between Variants rs2200733 and rs7193343 and Atrial Fibrillation in a Spanish Population

Study Design

We designed a case-control study in which the cases corresponded to patients with AF who had donated biological

samples to the Spanish National DNA bank and from 2 hospitals participating in the project. One of the Spanish National DNA bank hubs collected samples from patients with cardiovascular disease, among them, AF. The patients from the Spanish National DNA bank were recruited in 4 hospitals between February 2007 and December 2009. In addition, we included patients with AF from 2 hospitals that recruited these individuals during 2011. The patients with AF ranged in age from 18 years to 70 years at the time of diagnosis, were Caucasian, and had AF documented in at least 1 electrocardiographic recording. Lone AF was defined as that found in patients younger than 60 years with no clinical or echocardiographic evidence of cardiovascular disease. Recruitment of these patients was performed prospectively, including all the cases of AF diagnosed during the study period, and retrospectively, in which case we contacted only those patients who had been diagnosed as having lone AF to ask them to participate in the study.

The controls were selected randomly from a population-based cross-sectional study carried out in Spain between 2000 and 2001 that included Caucasian individuals ranging in age from 19 years to 75 years.⁹ The presence of AF was ruled out on the basis of an absence of suspicious symptoms and a normal electrocardiogram.

All the case patients and controls signed an informed consent form prior to their inclusion in the study, which received the approval of the Clinical Research Ethics Committee of *Hospital Universitario Sant Joan* in Reus, a city in Catalonia, Spain, and the Scientific Committee of the Spanish National DNA Bank.

Genotyping

Deoxyribonucleic acid was isolated from peripheral blood mononuclear cells using a standardized column method described elsewhere.¹⁰ The 2 genetic variants were genotyped using Taqman allelic discrimination assays (Life Technologies Ltd.; Paisley, United Kingdom) on the ABI 7900HT Real-Time PCR System (Life Technologies Ltd.).

Other Variables

Information was collected on the history of hypertension and tobacco use. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. We considered a smoker to be any individual who had smoked, on average, ≥ 1 cigarette/day during the preceding week or any ex-smoker who had been abstinent < 1 year. The weight and height of the participants were recorded and the body mass index calculated (weight in kilograms divided by height in meters squared).

We had access to the following echocardiographic data for a subgroup of AF patients: left ventricular end-diastolic and end-systolic diameters, interventricular septal thickness and left ventricular posterior wall thickness, and left atrial anteroposterior diameter. The echocardiographic studies were performed and interpreted in the hospitals in which the AF case patients had been recruited in accordance with standardized international protocols.

Statistical Analysis

Quality control of the genotype data included the analysis of Hardy-Weinberg equilibrium. The continuous variables were tested for normality. For between-group comparisons, the chi-square test was used for categorical variables and Student *t* test or analysis of variance was employed for continuous variables. Logistic regression was utilized for the multivariate analysis. The association was considered to be statistically significant when $P < .05$.

Systematic Review and Meta-analysis

Review of the Literature

Using the PubMed database, we carried out a search for articles on the subject of interest published up to 31 March 2013. The search strategy was based on the following terms: (rs2200733 or rs7193343 or 4q25 or 16q22 or PITX2 or ZFX3) and (“Atrial fibrillation” or “supraventricular arrhythmias”) and (“genetics” or “polymorphism”). We also analyzed reviews on “atrial fibrillation” and “genetics”, and the bibliography of the articles ultimately selected in order to identify any article that had not been identified in the original search.

In a first step, 2 independent reviewers (AF and RE) analyzed the title and abstract of the articles identified and selected the candidates to review the entire article. The same reviewers, independently, extracted the information necessary for the meta-analysis and for the evaluation of the quality of the evidence presented. In case of disagreement, the 2 reviewers reached a consensus decision.

In the articles that included more than one population or study, the results of each of the studies included were considered individually. In the case of studies that were dealt with in several publications, we considered only the results of the article that included the largest number of participants.

Qualitative Evaluation of the Available Evidence

The STREGA recommendations were followed for the evaluation of the quality and transparency of the information provided in the selected studies.¹¹ These guidelines define 22 items that should be described or discussed in the different sections of the manuscripts. The two reviewers assigned a 1 or a 0 depending on the presence or absence of an adequate description of each of these items. The differences of opinion were discussed and resolved by consensus. The higher the value of this indicator, the higher the quality of the information presented in the article.

Quantitative Evaluation of the Associations of Interest: Meta-analysis

From each of the selected studies, we obtained the following data: study design (case-control, cohort), type of AF (all types; lone; recurrence following ablation), number of case patients and controls included, estimate of the risk associated with each genetic variant and the 95% confidence interval (95%CI), whether or not the risk estimate was adjusted for confounding variables, frequency of the risk allele in the control population, ethnic origin, age, and the proportion of women and of hypertensive individuals.

We conducted a meta-analysis of the previously selected studies and also included the data from our study using the meta.DSL function of the R *rmeta* package, applying the random effects method of DerSimonian and Laird.¹² In addition, we analyzed sensitivity by repeating the meta-analysis and eliminating a study each time to determine whether any of those included exerted a powerful influence on the strength of the association observed. The analyses were stratified for the evaluation of total and lone AF.

Analysis of the Heterogeneity and of Its Causes: Meta-regression Analysis

The presence of heterogeneity was analyzed using the quantity I^2 , which describes the percentage of the variation across studies

Table 1

Sociodemographic Characteristics, Risk Factor History, and Genotype and Allele Frequencies of the Genetic Variants Analyzed in the Group of Patients With Atrial Fibrillation and the Control Group

	Controls	Cases of lone AF	Total cases of AF	P^a	P^b
Patients, no.	379	123	257		
Age, mean (SD) y	42.56 (15.15)	50.97 (8.83)	60.64 (11.51)	< .001	< .001
Women, %	49.2	34.8	42.3	.090	.007
Hypertension, %	11.90	45.54	51.22	< .001	< .001
Tobacco use, %	34.13	20.54	16.26	< .001	.006
Body mass index	26.91 (5.11)	28.45 (5.17)	28.59 (4.48)	< .001	.007
rs2200733, genotypes ^c				< .001	< .001
CC, %	71.42	53.15	55.84		
CT, %	25.61	38.74	36.80		
TT, %	2.96	8.11	7.36		
T allele frequency, %	15.77	27.48	25.76		
rs7193343, genotypes ^c				.156	.635
CC, %	69.44	64.86	61.95		
CT, %	27.88	31.53	34.07		
TT, %	2.68	3.60	3.98		
T allele frequency, %	16.62	19.37	21.02		

AF, atrial fibrillation; C, cytosine; T, thymine.

Unless otherwise indicated, data are expressed as mean (standard deviation).

^a Comparison between all case patients with atrial fibrillation and controls.

^b Comparison between case patients with atrial fibrillation aged < 60 years and controls.

^c CC: individuals homozygous for the most common genetic variant, carriers of 2 common alleles (cytosine); CT: heterozygous carriers of 1 rare allele (thymine); TT: individuals homozygous for the least common genetic variant, carriers of 2 rare alleles (thymine).

Table 2

Probability of Atrial Fibrillation Corresponding to the Different Genetic Variants Analyzed Defining an Additive Model

	Atrial fibrillation, OR (95%CI)	Lone atrial fibrillation, OR (95%CI)
rs2200733	1.87 (1.30-2.70)	2.06 (1.37-3.10)
rs7193343	1.18 (0.80-1.73)	1.03 (0.64-1.61)

95%CI, 95% confidence interval; OR, odds ratio.

Increase in the likelihood of atrial fibrillation due to the presence of each risk allele (T).

Results adjusted for age, sex, body mass index, history of hypertension, and tobacco use.

that is due to heterogeneity rather than chance.¹³ To analyze its causes, we performed a meta-regression analysis using a mixed effects model, and the factors that could explain the heterogeneity between studies were examined. The potential factors analyzed were study design (case-control vs cohort), number of case patients included ($n \geq 500$ vs $n < 500$), adjustment for confounding variables, ethnic origin, and STREGA score (median < 18 vs ≥ 18). When any variable that could explain the heterogeneity was identified, the meta-analysis was repeated with stratification for that variable.

Table 3

Differences in the Echocardiographic Characteristics of the Case Patients With Atrial Fibrillation According to Genotype

	CC [*]	CT [*]	TT [*]	P
<i>rs2200733</i>				
Patients, no.	89	49	10	
LVEDD, mean (SD), mm	48.5 (5.3)	49.3 (4.3)	50.9 (2.0)	.307
LVEDDi, mean (SD), mm/m ²	26.1 (3.0)	25.8 (2.8)	25.2 (2.6)	.661
LVESD, mean (SD), mm	30.2 (5.4)	29.6 (4.5)	33.43 (3.0)	.170
LVESDi, mean (SD), mm/m ²	16.2 (2.7)	15.6 (2.5)	16.9 (1.7)	.350
LA, mean (SD), mm	40.2 (6.4)	41.2 (5.8)	46.1 (13.1)	.033
Lai, mean (SD), mm/m ²	21.5 (3.5)	21.6 (3.5)	23.0 (6.0)	.497
EF, mean (SD), %	67.8 (8.5)	69.1 (8.9)	68.3 (6.3)	.692
PW, mean (SD), mm	9.5 (1.2)	9.8 (1.5)	9.0 (1.3)	.297
Septum, mean (SD), mm	10.6 (1.5)	10.6 (1.5)	10.6 (0.7)	.999
<i>rs7193343</i>				
Patients, no.	94	43	7	
LVEDD, mean (SD), mm	48.8 (5.1)	49.5 (4.3)	49.7 (3.8)	.664
LVEDDi, mean (SD), mm/m ²	25.9 (2.9)	26.0 (2.8)	26.7 (2.5)	.754
LVESD, mean (SD), mm	30.3 (5.4)	30.8 (3.9)	28.3 (5.0)	.455
LVESDi, mean (SD), mm/m ²	16.2 (2.9)	16.2 (1.9)	15.2 (2.5)	.621
LA, mean (SD), mm	40.6 (7.5)	41.8 (6.1)	41.1 (4.1)	.641
Lai, mean (SD), mm/m ²	21.6 (4.0)	21.9 (3.2)	25.1 (2.4)	.878
EF, mean (SD), %	67.8 (8.9)	67.8 (7.5)	75.7 (5.9)	.056
PW, mean (SD), mm	9.6 (1.4)	9.5 (1.3)	9.5 (2.0)	.877
Septum, mean (SD), mm	10.6 (1.5)	10.6 (1.4)	10.7 (1.9)	.974

C, cytosine; EF, ejection fraction; LA, left atrial anteroposterior diameter; Lai, left atrial anteroposterior diameter indexed to body surface area; LVEDD, left ventricular end-diastolic diameter; LVEDDi, left ventricular end-diastolic diameter indexed to body surface area; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; PW, posterior wall thickness; SD, standard deviation; Septum, septal thickness; T, thymine. Unless otherwise indicated, data are expressed as mean (standard deviation).

* CC: individuals homozygous for the most common genetic variant, carriers of 2 common alleles (cytosine); CT: heterozygous carriers of 1 rare allele (T: thymine); TT: individuals homozygous for the least common genetic variant, carriers of 2 rare alleles (thymine).

RESULTS

Analysis of the Association Between Variants rs2200733 and rs7193343 and Atrial Fibrillation in a Spanish Population

The sociodemographic characteristics, risk factor history, and genotype and allele frequencies of the genetic variants analyzed in the group of patients with AF (total and lone) and the control group are presented in Table 1. Table 2 shows the findings concerning the association between rs2200733 and rs7193343 and the presence of AF (total and lone); a statistically significant association was observed between rs2200733 and AF, but not between rs7193343 and AF. We analyzed a subsample of case patients ($n = 150$) and controls ($n = 150$), matched for age and sex, and the results were similar to those observed in the total sample.

In the subgroup of patients with AF and echocardiographic data for left atrium ($n = 148$), we found an association between rs2200733 and the anteroposterior diameter, demonstrating that the AF risk allele was also associated with an enlarged left atrium (Table 3). This association lost statistical significance when the atrial diameter was indexed to body surface area. We observed no association between rs7193343 and the echocardiographic variables recorded.

Systematic Review, Meta-analysis, and Meta-regression Analysis

With the literature search criteria utilized, 41 articles were selected in a first stage, and were ultimately reduced to 14. A flow chart of the result of the literature search and article selection performed for this study is shown in Figure 1. Of the 14 studies selected, 10 analyzed the association between AF risk and rs2200733^{14–23} and 4 analyzed the AF risk associated with rs7193343.^{6,24–26} These 14 articles included a total of 27 different studies, 19 that analyzed rs2200733 and 8 that focused on rs7193343; 22 were case-control studies and 5 were cohort studies.

The scores resulting from the qualitative evaluation of the studies based on the STREGA guidelines ranged between 15 points and 21 points; those corresponding to each study are presented in Figures 2 and 3.

Figure 2 shows that the results of the meta-analysis demonstrated a statistically significant association between rs2200733 and AF (odds ratio [OR] = 1.71; 95%CI, 1.54–1.90). These findings were corroborated by the sensitivity analysis in which studies were eliminated one by one (OR between 1.62 and 1.75). For the analysis of lone AF, we included 6 studies, and the strength of the association was greater (OR = 2.16; 95%CI, 1.85–2.51). In the sensitivity analysis, as studies were eliminated one at a time, the OR ranged from 2.03 to 2.25.

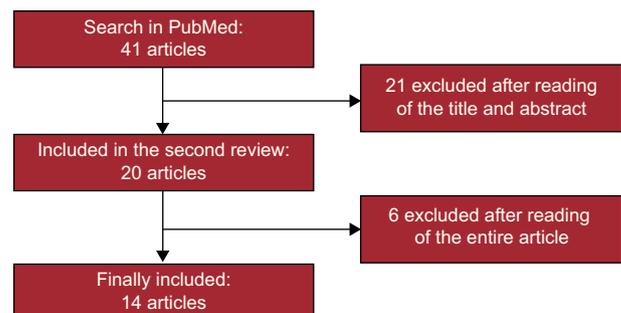


Figure 1. Flow chart illustrating the systematic review performed and final selection of the articles included in the meta-analysis.

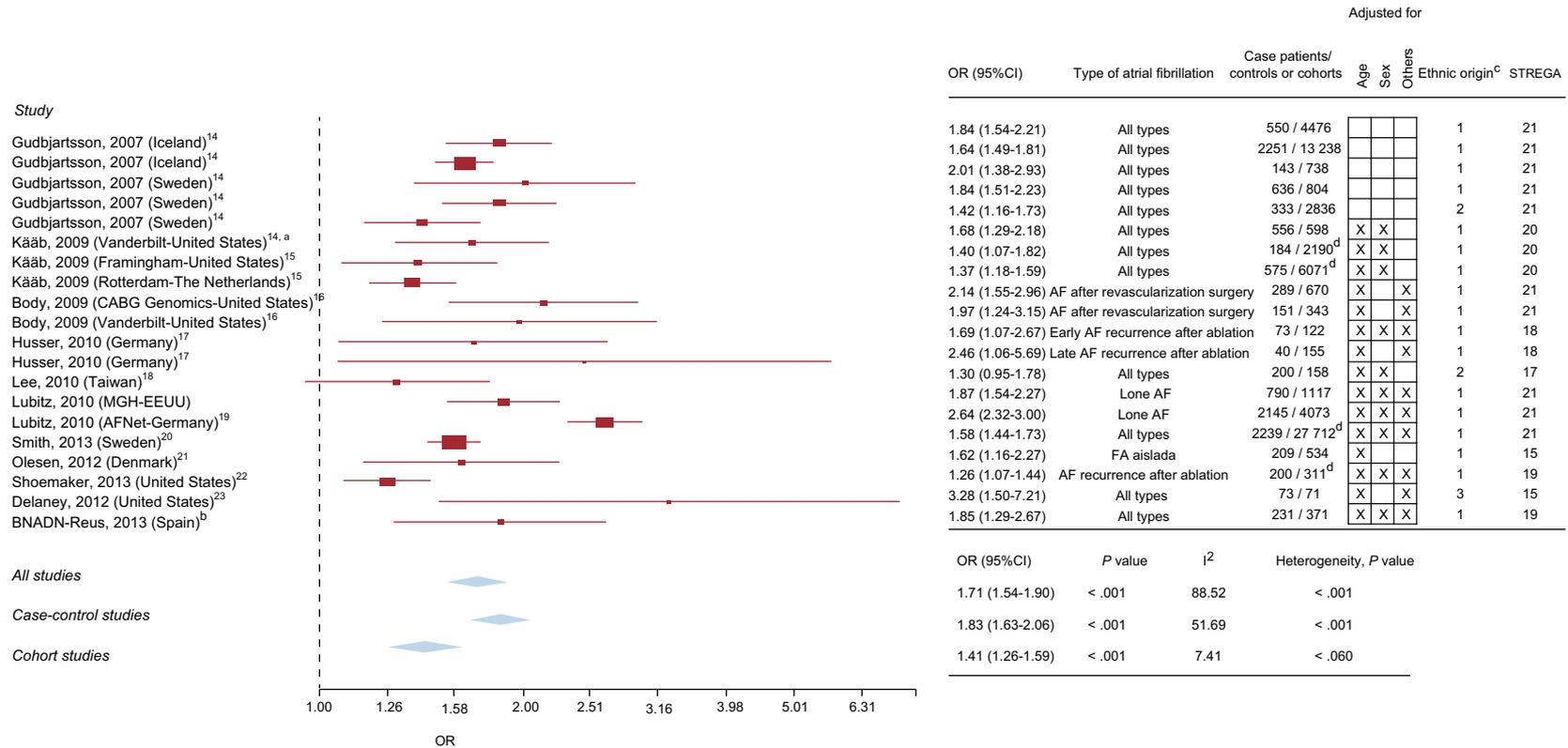


Figure 2. Graphical display of the results of the meta-analysis of studies on the association between rs2200733 and atrial fibrillation (forest plot), including the strength of association observed in individual studies, sample size, adjustment variables utilized, and the results of the evaluation according to the STREGA guidelines. The figure also shows the results of the heterogeneity analysis (I^2), the estimator of the combined association in all the studies, and stratification according to study design (case-control or cohort). 95%CI, 95% confidence interval; AF, atrial fibrillation; BNADN: *Banco Nacional de ADN* (Spanish National DNA Bank); OR, odds ratio.

^aAge < 60 years.

^bResults of the study presented in this article.

^c1, European; 2, Asian.

^dCohort study.

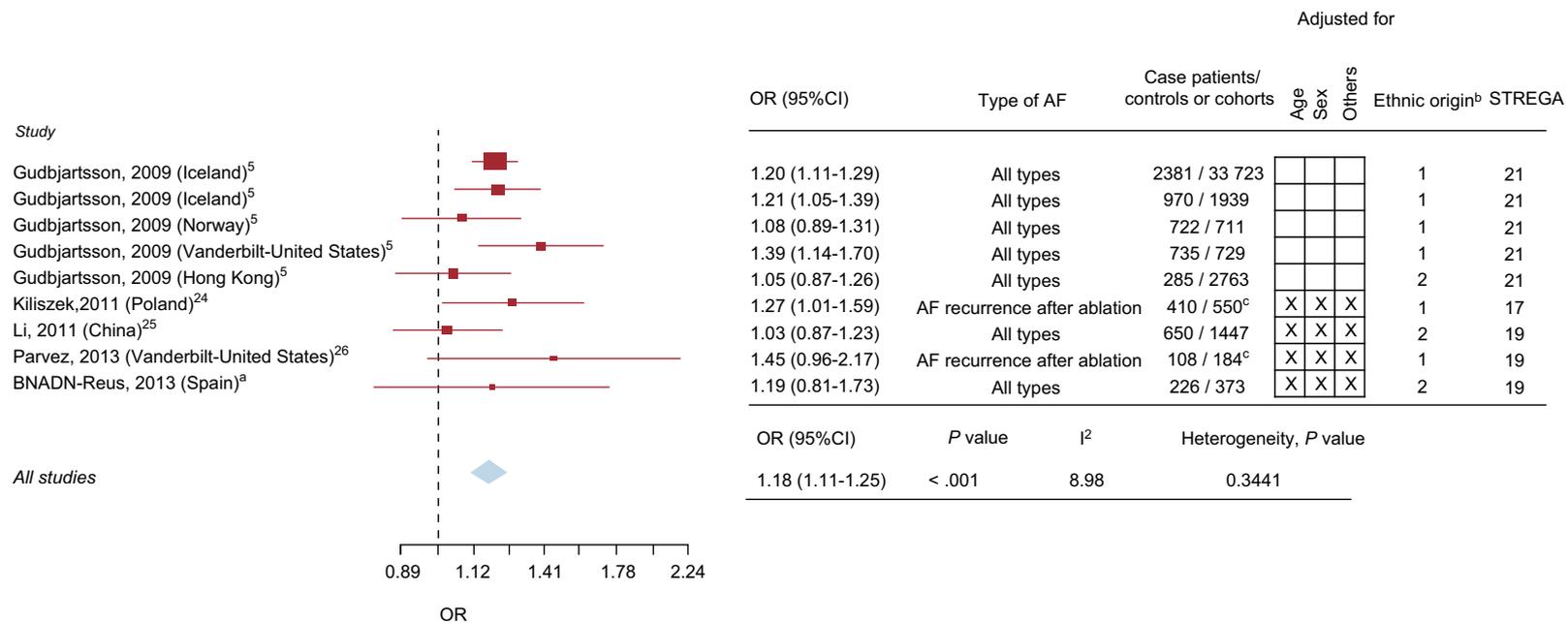


Figure 3. Graphical display of the results of the meta-analysis of studies on the association between rs7193343 and atrial fibrillation (forest plot), including the strength of the association observed in individual studies, sample size, adjustment variables utilized, and the results of the evaluation according to the STREGA guidelines. The figure also shows the results of the heterogeneity analysis (I^2) and the estimator of the combined association in all the studies. 95%CI, 95% confidence interval; AF, atrial fibrillation; BNADN: *Banco Nacional de ADN* (Spanish National DNA Bank); OR, odds ratio

^aResults of the study presented in this article.

^b1, European; 2, Asian.

^cCohort study.

We detected heterogeneity in the meta-analysis of the single nucleotide polymorphism rs220733 (total AF, $I^2 = 88.52$; lone AF, $I^2 = 13.59$). Meta-regression analysis indicated that one of the variables that partially explained this heterogeneity was the type of study design: case-control or cohort. When the meta-analysis was stratified for study design, we observed that there continued to be heterogeneity across the case-control studies ($I^2 = 51.69$), that the strength of the association was greater than that of the cohort studies (OR = 1.83; 95%CI, 1.63-2.06 vs OR = 1.41; 95%CI, 1.26-1.59), and, moreover, that there was no heterogeneity among the latter (Figure 2).

There was a statistically significant association between rs7193343 and total AF (OR = 1.18; 95%CI, 1.11-1.25) (Figure 3). When studies were eliminated one by one in the sensitivity analysis, the OR ranged between 1.17 and 1.20. We observed no heterogeneity among studies ($I^2 = 8.98$; $P = .34$). When we analyzed lone AF, only 2 studies were included and the strength of association was similar (OR = 1.11; 95%CI, 0.89-1.39).

We also estimated the population risk attributable to these 2 genetic variants using the OR from the meta-analysis and the prevalence of the genotypes of our population by applying the following formula: population attributable risk = prevalence of the risk genotype $\times [(OR - 1) / OR]$. The population risk attributable to polymorphism rs220733 was 13.77% and that of rs7193343, 4.99%.

DISCUSSION

In this study, we observed an association between rs220733 and risk of AF in a Spanish population. However, the association between rs7193343 and the presence of AF did not reach statistical significance. A systematic review and a meta-analysis of previous studies demonstrates an association between the 2 genetic variants analyzed and the risk of AF, but the strength of the association is greater in the case of rs220733. Moreover, we observed heterogeneity among the studies that analyze the association between rs220733 and the risk of AF; this heterogeneity is partially explained by the study design.

Up to 9 genetic variants associated with the risk of AF have recently been identified.⁸ In our study, we analyzed only 2 of these variants (rs220733 and rs7193343) because they are the ones most frequently identified in genome-wide association studies as being associated with AF and those in which this association is strongest.

Variant rs220733 is found in the 4q25 region, where the *PITX2* gene is also located. This gene is a transcription factor that plays a key role in the development of the fetal heart,²⁷ and is also expressed in the adult heart, where it regulates the expression of genes related to ion channels.²⁸ *PITX2* expression in atrial myocardial tissue has been found to be decreased in patients with AF, a circumstance that leads to atrial electrical and structural remodeling that favors arrhythmogenesis.²⁹ Our findings in the Spanish population analyzed here agree closely with the results of the meta-analysis and indicate an association between the presence of the rare variant and greater probability of developing AF.

On the other hand, certain studies in murine models have found that carriers of the risk allele of polymorphism rs220733 undergo atrial remodeling.²⁹ In our study, the group of homozygous carriers of the risk allele of this variant had atrial enlargement, although this association disappeared when it was corrected for body surface area. We should point out that the available echocardiographic measurements of left atrium corresponded to a subgroup of patients and that the methodology utilized for measurement was not designed specifically to assess this association, as this was

not among the objectives defined for this study. Properly designed studies are necessary to confirm the association between rs220733 and atrial remodeling.

Variant rs7193343 is in the 16q22 region, where the *ZFHX3* gene is located. This gene regulates neuronal and muscle differentiation and is a tumor suppressor gene in several types of cancer. Although it is expressed in mouse heart,³⁰ its function in heart tissue is unknown. This variant is associated with AF in the meta-analysis, but not significantly in this Spanish population, probably because of the small size of the sample in our study and to the fact that the association observed is not as strong. With the sample size of our study (257 case patients and 379 controls), we were only able to identify as statistically significant those associations with an OR ≥ 1.63 . There is another variant in the region, rs2106261, which is in linkage disequilibrium with rs7193343 ($R^2 = 0.77$ in a Caucasian population from the HapMap-based study). It has also been analyzed in some studies and in 2 meta-analyses,^{7,8} and has a strength of association similar to that observed in our study (OR = 1.24 and OR = 1.22, respectively). Thus, the data indicate that both variants provide similar information.

Our study differs with respect to 2 characteristics. First, we analyzed the lone AF phenotype independently, observing that, in the case of rs220733, the association is stronger than that observed for all types of AF.

Second, we analyzed the presence of heterogeneity across studies and its causes. We observed that the study design explains part of the heterogeneity observed in the association between rs220733 and AF: the case-control studies have a stronger association than the cohort studies and, moreover, heterogeneity continues to be found between the case patients and controls. The heterogeneity across case-control studies is probably related to the varying quality of those studies,³¹ and the strength of the association observed in the case-control studies, which is probably greater than that of the cohort studies, is also a known phenomenon.³¹

Knowledge of the genetic bases of AF may contribute to the identification of new therapeutic targets. From the clinical point of view, it may also contribute to an improvement in the ability to predict the onset of AF in the future. A recent study performed with data from the Women's Health Study found that the inclusion of genetic information in the prediction model improves the discrimination and reclassification of AF risk.³² Another clinical application that is still pending examination and validation is the ability to identify those patients who will have a recurrence of AF following radiofrequency ablation.

Limitations

Among the limitations of our study, we must point out that the size of the Spanish sample population is small, although the results agree with those of the meta-analysis performed. The distribution of ages and sexes in the control population differed from that of the case patients; this difference could influence the results. In any case, in the adjusted analyses and age- and sex-matched analyses, the results observed were very similar and consistent. The association between the genetic variants of interest and atrial remodeling has the limitations mentioned above, and it is necessary to confirm the findings in studies specifically designed to evaluate this hypothesis.

CONCLUSIONS

Genetic variants rs220733 and rs7193343 are associated with a higher risk of AF. These variants could have a clinical utility in estimating AF risk. On the other hand, case-control studies tend to

overestimate the strength of the association between these genetic variants and the presence of AF.

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CONFLICTS OF INTEREST

None declared.

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