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Variants in *ZFHX3* are associated with atrial fibrillation in individuals of European ancestry

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Abstract

We conducted meta-analyses of genome-wide association studies (GWAS) for atrial fibrillation (AF) in participants from five community-based cohorts. Meta-analyses of 896 prevalent (15,768 referents) and 2,517 incident (21,337 referents) AF cases identified a novel locus for AF (*ZFHX3*, rs2106261, risk ratio [RR]=1.19; $P=2.3\times10^{-7}$), an association that was replicated in the German AF Network (odds ratio=1.44; $P=1.6\times10^{-11}$). Combining the discovery and replication results, rs2106261 was significantly associated with AF (RR=1.25; $P=1.8\times10^{-15}$).

Keywords

atrial fibrillation; epidemiology; genetics; polymorphism; single nucleotide

With increasing longevity of individuals in developed countries, late-onset chronic cardiovascular diseases such as AF have become important public health problems. AF is an electrical disorder of the heart's upper chambers characterized by an irregular heart rhythm. The overall lifetime risk of AF is almost 25% in the U.S. and Europe1,2. Furthermore, the incidence of AF is increasing over time; in the U.S. it is projected that up to 15.9 million individuals may be affected by 20503. The growing number of individuals with AF is of concern because of its association with significantly increased risks of stroke, heart failure, and death4.

AF is a complex disease with many etiologies, including cardiovascular disease and its risk factors. Families demonstrating Mendelian inheritance of AF have been reported, most frequently in individuals with lone AF (early-onset AF without structural heart disease)5. Recently it was reported that even for typical forms of AF, individuals with an affected relative are at higher risk of AF6. Moreover, a GWAS identified single nucleotide polymorphisms (SNPs) in the chromosome 4q25 region that are associated with increased AF risk7.

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COMPETING INTERESTS STATEMENT

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We hypothesized that additional common genetic variation contributes to the development of AF. We conducted and combined meta-analyses of prevalent AF and incident AF, using existing GWAS data from the *C*ohorts for *H*eart and *A*ging *R*esearch in *G*enomic *E*pidemiology (CHARGE) AF Consortium. CHARGE included the following five community-based cohorts8: Age, Gene/Environment Susceptibility Reykjavik Study (AGES); Atherosclerosis Risk in Communities (ARIC); Cardiovascular Health Study (CHS); Framingham Heart Study (FHS); and Rotterdam Study (RS). Genotyping inclusion criteria were unbiased towards AF as genotyping was performed as a core effort for numerous phenotypes in each cohort. Study design and genotyping features are in Supplementary Tables 1 and 2. Genotypes for more than 2.5 million SNPs were imputed within each study using reference genotype data and linkage disequilibrium patterns from the HapMap CEU population.

Our community-based participants were middle-aged to elderly, with mean ages at DNA collection from 57 (ARIC) to 76 (AGES) years (Supplementary Table 3). To assess potential population stratification, we computed genomic inflation factors (λ) of meta-analyses results: λ was 1.005 for prevalent AF, 1.014 for incident AF, and 1.026 for combined prevalent-incident AF (Supplementary Table 2 provides λ by cohort and analysis). The observed versus expected *P* value distributions (quantile-quantile plots) and Manhattan plots of $\log_{10} P$ values for separate prevalent and incident AF analyses are displayed in Supplementary Figures 1 and 2.

We prespecified genome-wide significance as $P<5\times10^{-8}$, corresponding to significance at 5% adjusting for approximately one million independent tests as estimated in HapMap samples of European ancestry. To prioritize follow-up genotyping, we required SNPs to have $P<4\times10^{-7}$ (corresponding to one expected false positive per GWAS), and that at least six of nine analyses (out of four prevalent and five incident AF analyses) contributed results for the SNP, to reduce possible false-positives due to poor imputation.

The quantile-quantile plot and Manhattan plot of the meta-analysis of combined prevalent and incident AF are depicted in Supplementary Figure 3. We replicated the previously reported chromosome 4 locus7 (rs17042171, $P=6.0\times10^{-27}$; Table 1, Fig. 1a), which was approximately 150 kb telomeric from the transcription factor *PITX2*.

SNP rs2106261 on chromosome 16q22, located in an intronic region of transcription factor *ZFHX*3 (previously known as *ATBF1*), showed suggestive evidence of association (Table 1, combined prevalent-incident $P=2.3\times10^{-7}$, Fig. 1b). Results were consistent in the separate prevalent ($P=9.0\times10^{-6}$) and incident ($P=7.9\times10^{-4}$) AF analyses (Supplementary Table 4 provides cohort-specific estimates). We replicated the association between SNP rs2106261 and AF in a large independent cohort, the German AFNET consisting of 2,145 cases and 4,073 controls (odds ratio=1.44, $P=1.6\times10^{-11}$; Table 1). In a meta-analysis of the results from the discovery (CHARGE community AF) and replication (German AFNET) studies, rs2106261 was significantly associated with AF (RR 1.25, $P= 1.8\times10^{-15}$; Table 1). *ZFHX3* appears to regulate myogenic9 and neuronal differentiation10. *ZFHX3* has been reported to be a tumor suppressor gene in multiple cancers11, and recently SNPs in *ZFHX3* have been

associated with susceptibility to Kawasaki Disease12. Although the function of *ZFHX3* in cardiac tissue is unknown, it is expressed in mouse13 hearts.

Another significant association signal was on chromosome 1p36 within *MTHFR* (rs17375901, $P=4.6\times10^{-8}$), which encodes 5,10-methylenetetrahydrofolate reductase. The association with the *MTHFR* locus was not confirmed in independent subjects from the AFNET cohort (Table 1). The initial *MTHFR* finding may be a false positive result. However, the region may merit further investigation because *MTHFR* is in linkage disequilibrium with the atrial natriuretic peptide gene (Fig. 1c); a *NPPA* frameshift mutation has been described in a family with AF14.

We acknowledge several study limitations. Although our findings were generally consistent, we observed some between-analysis heterogeneity in effect sizes ($P=0.01$), possibly arising from variation in cohort participant characteristics, duration and etiology of AF, low study-specific precision, subtle locus-specific population stratification, and population differences in underlying haplotype structure. Population stratification at a larger scale did not appear to have a substantial impact on our findings as we did not observe inflation of the genomic control factors in the study-specific analyses or the meta-analyses. We note that for the previously validated *PITX2* locus we observed between-study heterogeneity. Thus, heterogeneity appears to be a general feature of even the strongest genome-wide findings for AF, and remains to be addressed in follow up studies. In addition, our findings may not be generalizable to other races/ethnicities. It also was not possible to perform a pooled analysis using participant specific data given the restrictions imposed by the Institutional Review Boards at some study sites. Furthermore, there is a potential for survival bias in the prevalent AF analysis if the variant is associated with both AF onset and lethality; in this situation individuals who died shortly after AF onset might not survive until DNA collection. Nonetheless, a moderate association was present in prevalent, incident, and combined AF meta-analyses for both the validated chromosome 4q25 and the novel chromosome 16q22 loci. Another limitation is that beyond single SNPs, our study did not analyze patterns of haplotypes, and thus complex haplotype associations may not have been captured in this study. However, our use of imputation to the HapMap does leverage available linkage disequilibrium information. Finally, we recognize that we likely have identified variants in linkage disequilibrium with causal variants rather than the specific functional variants; the pathophysiology by which locus variation contributes to AF risk remains unknown.

Our study has multiple strengths. We included five community-based cohorts, with large numbers of cases, whose participants were not selected for phenotypic characteristics, thereby enhancing the generalizability of our findings. The robustness of the chromosome 16q22 result is strengthened by its documentation in samples ascertained with different study designs including case-control and cohort studies.

In summary, by examining GWAS data for AF in five community-based cohorts we replicated the previously reported association with chromosome 4q25 variants and we identified a novel locus on chromosome 16 in a gene encoding the transcription factor *ZFHX*3. We provided confirmatory support for the novel *ZFHX3* finding by replicating our

findings in a large independent study of AF. Further studies are needed to elucidate functional variants and mechanisms by which the novel 16q22 locus predisposes to AF.

URLS

AGES, http://www.hjarta.is/english/ages

ARIC, http://www.cscc.unc.edu/aric/

CHS, http://www.chs-nhlbi.org/

FHS, http://www.framinghamheartstudy.org/about/index.html

RS, http://www.epib.nl/ergo.htm

BIMBAM, http://stephenslab.uchicago.edu/software.html

EIGENSTRAT, http://genepath.med.harvard.edu/~reich/Software.htm

GenABLE and ProbABEL (http://mga.bionet.nsc.ru/~yurii/ABEL/)

HapMap, http://hapmap.org

MACH v1.0.15/16 (all others; http://www.sph.umich.edu/csg/abecasis/MaCH/index.html)

PLINK http://pngu.mgh.harvard.edu/purcell/PLINK/

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
λ	genomic inflation factor
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
AGES	Age, Gene/Environment Susceptibility Reykjavik Study
ARIC	Atherosclerosis Risk in Communities
CHS	Cardiovascular Health Study
FHS	Framingham Heart Study
RS	Rotterdam Study
GWAS	genome-wide association study
RR	risk ratio
SNP	single nucleotide polymorphism

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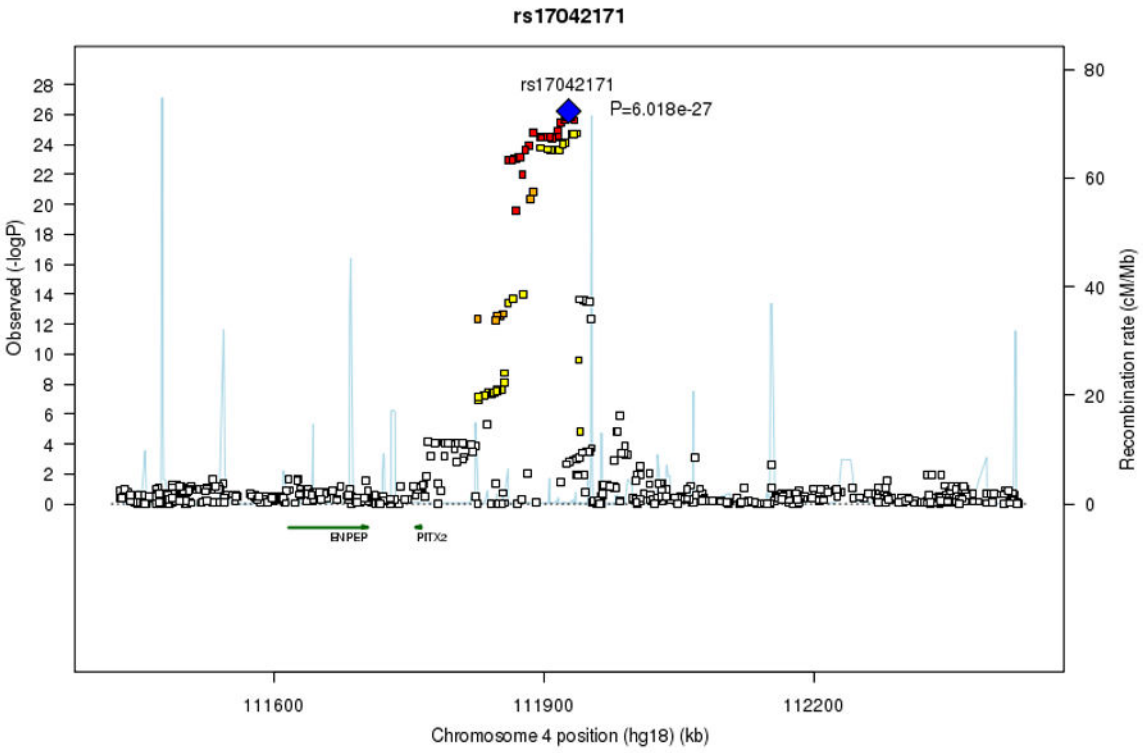

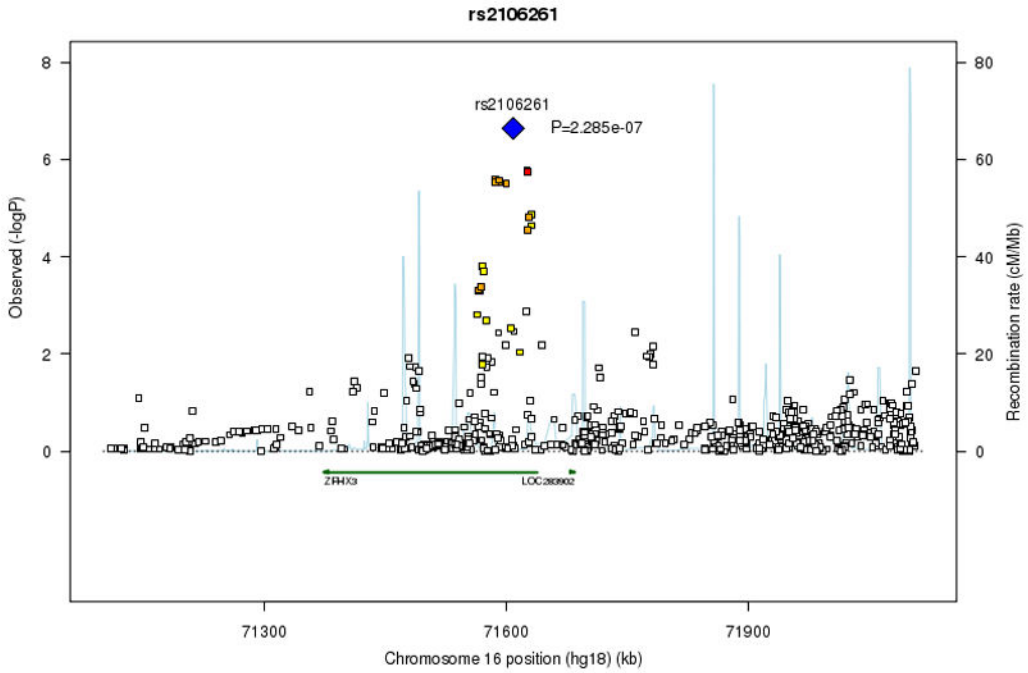

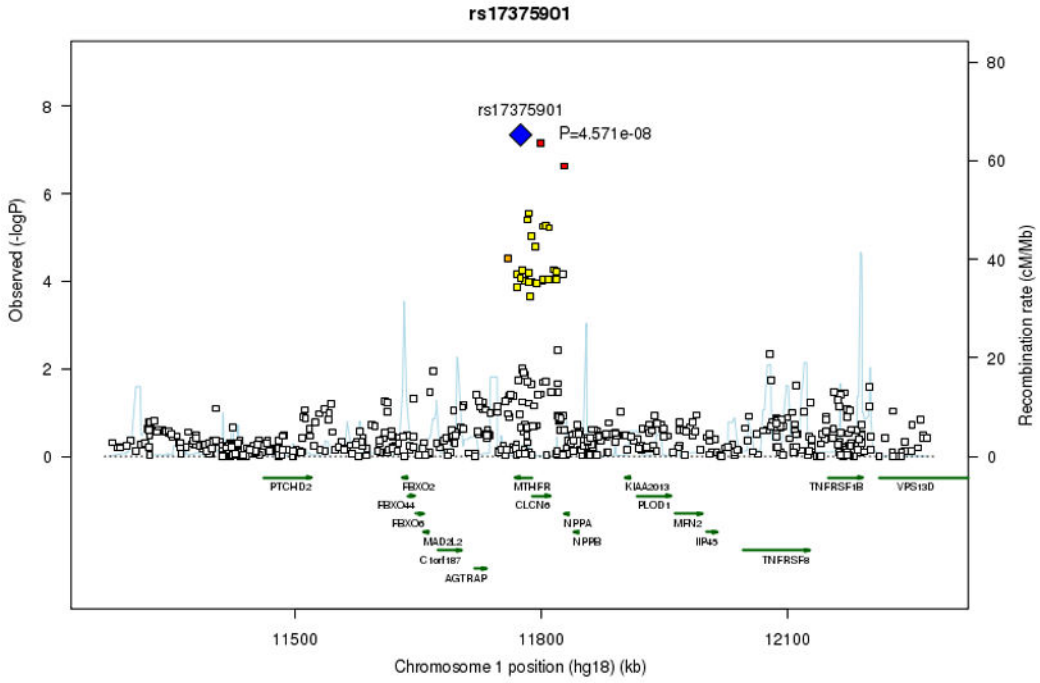

Figure 1. Regional association plots for signal loci on chromosomes 4, 16 and 1

At each SNP location (genomic position, NCBI Build 36) we plot the $\log_{10}$ *P* value from combined analysis of incident and prevalent AF. Symbol colors indicate the strength of linkage disequilibrium derived from CEU HapMap build 22: strong (red, $r^2 \geq 0.8$) moderate (orange, $0.5 \leq r^2 < 0.8$) weak (yellow, $0.20 \leq r^2 < 0.5$) and low (white, $r^2 < 0.2$). Estimated recombination rates are represented by pale blue lines and gene annotations by dark green arrows.

Table 1

Summary of CHARGE atrial fibrillation genome-wide association meta-analysis signals with $P \leq 4\times10^{-7}$ and German AFNET replication analysis

Locus				Prevalent AF analysis		Incident AF analysis		Combined analysis of prevalent and incident AF 896 prevalent 15,768 non-cases 2,517 incident cases and 21,337 non cases					German AFNET 2,145 cases, 4,073 controls			Meta-analysis CHARGE Community-AF and German AFNET results		
SNP nearby gene	**Chromosome position**	**Minor/ major allele**	**Minor allele frequency CHARGE/ German AFNET**	**Odds ratio**	***P* value**	**Hazard ratio**	***P* value**	**Range of Observed/ expected variance ratios**	**Overall *Beta* ± *s.e.***	**Relative risk[a]**	**Meta *P* value**	**Heterogeneity *P* value[b]**	**Supporting signals[c]**	**Overall *B*±*s.e.***	**Odds ratio**	***P* value**	**Overall Beta ± *s.e.***	**Relative risk**	***P* value**
rs17042171[d] *PITX2*	4 111927736	A/C	0.122 0.156	1.59	3.1×10^{-11}	1.40	8.3×10^{-18}	0.96–1.0	0.37±0.03	1.45	6.0×10^{-27}	0.01	75	0.90±0.06	2.46	6.9×10^{-51}	0.50±0.03	1.65	3.9×10^{-63}
rs2106261 *ZFHX3*	16 71609121	T/C	0.174 0.192	1.33	9.0×10^{-6}	1.14	7.9×10^{-4}	0.66–1.0	0.17±0.03	1.19	2.3×10^{-7}	0.01	7	0.36±0.05	1.44	1.6×10^{-11}	0.23±0.03	1.25	1.8×10^{-15}
rs17375901 *MTHFR*	1 11775103	T/C	0.053 0.058	1.41	8.5×10^{-4}	1.30	1.2×10^{-5}	0.81–1.0	0.29±0.05	1.33	4.6×10^{-8}	0.45	8	0.04±0.09	1.04	0.68	0.23±0.05	1.26	5.9×10^{-7}

Please see Supplementary Table 3 for cohort specific signals of top findings. For all odds, hazard and risk ratios, the reference group is the major allele homozygote; risk is expressed per each additional copy of the minor allele

[a] Combination of odds and hazard ratios from four prevalent AF and five incident AF analyses

[b] *P* value for Cochran's statistic of heterogeneity of effect across the four prevalent and five incident analyses.

[c] Number of corroborating SNPs within 500kb with $r^2>0.2$ and $P<10^{-5}$; r^2 was computed using HapMap CEU samples.

[d] AFNET results for Chromosome 4 were available for rs2200733, a perfect proxy for rs17042171 ($r^2=1$) in HapMap CEU samples. In CHARGE, the previously reported chromosome 4 SNP, rs2200733, for combined prevalent and incident AF has risk ratio =1.44, $P=9.3\times10^{-27}$; for prevalent AF, OR=1.59; $P=3.3\times10^{-11}$; for incident AF, HR 1.40, $P=1.2\times10^{-17}$.

Beta, regression estimate (log OR for prevalent, log HR for incident); s.e., standard error