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

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**We conducted meta-analyses of genome-wide association studies 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 new locus for AF (*ZFHX3*, rs2106261, risk ratio RR = 1.19; $P = 2.3 \times 10^{-7}$). We replicated this association in an independent cohort from the German AF Network (odds ratio = 1.44; $P = 1.6 \times 10^{-11}$; combined RR = 1.25; combined $P = 1.8 \times 10^{-15}$).**

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 US and Europe[1,2]. Furthermore, the incidence of AF is increasing over time; in the US it is projected that up to 15.9 million individuals may be affected by 2050 (ref. 3). The growing number of individuals with AF is of concern because of its association with significantly increased risks of stroke, heart failure and death[4].

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 AF[6]. Moreover,

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**Table 1 Summary of CHARGE AF GWAS meta-analysis signals with $P \leq 4 \times 10^{-7}$ and German AFNET replication analysis**

| Locus | | | | Combined analysis of prevalent and incident AF 896 prevalent cases, 15,768 referents 2,517 incident cases, 21,337 referents | | | | 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 frequencies: CHARGE AFNET | Overall *B* ± s.e.m. | Relative risk[a] | Meta *P* value | Heterogeneity *P* value[b] | Overall *B* ± s.e.m. | Odds ratio | *P* value | Overall *B* ± s.e.m. | Relative risk | *P* value |
| rs17042171[c] *PITX2* | 4 111927736 | A/C | 0.122 0.156 | 0.37 ± 0.03 | 1.45 | $6.0 \times 10^{-27}$ | 0.01 | 0.90 ± 0.06 | 2.46 | $6.9 \times 10^{-51}$ | 0.50 ± 0.03 | 1.65 | $3.9 \times 10^{-63}$ |
| rs2106261 *ZFHX3* | 16 71609121 | T/C | 0.174 0.192 | 0.17 ± 0.03 | 1.19 | $2.3 \times 10^{-7}$ | 0.01 | 0.36 ± 0.05 | 1.44 | $1.6 \times 10^{-11}$ | 0.23 ± 0.03 | 1.25 | $1.8 \times 10^{-15}$ |
| rs17375901 *MTHFR* | 1 11775103 | T/C | 0.053 0.058 | 0.29 ± 0.05 | 1.34 | $4.6 \times 10^{-8}$ | 0.45 | 0.04 ± 0.09 | 1.04 | 0.68 | 0.23 ± 0.05 | 1.26 | $5.9 \times 10^{-7}$ |

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. *B*, regression estimate (log odds ratio for prevalent, log hazard ratio for incident). [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]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 had risk ratio = 1.44, $P = 9.3 \times 10^{-27}$; for prevalent AF, odds ratio = 1.59; $P = 3.3 \times 10^{-11}$; for incident AF, hazard ratio = 1.40, $P = 1.2 \times 10^{-17}$.

a genome-wide association study (GWAS) identified SNPs in the chromosome 4q25 region that are associated with increased AF risk[7].

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 Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF Consortium. CHARGE included the following five community-based cohorts[8]: Age, Gene/Environment Susceptibility Reykjavik Study (AGES); Atherosclerosis Risk in Communities (ARIC); Cardiovascular Health Study; Framingham Heart Study; and Rotterdam Study. Genotyping inclusion criteria were unbiased toward AF, as genotyping was performed as a core effort for many 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 (**Supplementary Methods**).

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 ($\lambda$) of meta-analysis results: $\lambda$ was 1.005 for prevalent AF, 1.014 for incident AF and 1.026 for combined prevalent-incident AF (**Supplementary Table 2** provides $\lambda$ 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 $P < 5 \times 10^{-8}$, 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 that SNPs have $P < 4 \times 10^{-7}$ (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) contribute 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 association with a previously reported chromosome 4 locus[7] (rs17042171, $P = 6.0 \times 10^{-27}$; **Table 1** and **Supplementary Fig. 4**), which was approximately 150 kb telomeric to the transcription factor gene *PITX2*.

SNP rs2106261 on chromosome 16q22, located in an intronic region of transcription factor *ZFHX3* (previously known as *ATBF1*), showed suggestive evidence of association (**Table 1**, combined prevalent-incident $P = 2.3 \times 10^{-7}$, **Fig. 1**). Results were consistent in the separate prevalent ($P = 9.0 \times 10^{-6}$) and incident ($P = 7.9 \times 10^{-4}$) 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 AF Network (AFNET), consisting of 2,145 cases and 4,073 controls (odds ratio = 1.44, $P = 1.6 \times 10^{-11}$; **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, $P = 1.8 \times 10^{-15}$; **Table 1**). *ZFHX3* appears to regulate myogenic[9] and neuronal differentiation[10]. *ZFHX3* has been reported to be a tumor suppressor gene in several cancers[11], and recently SNPs in *ZFHX3* have been associated with susceptibility to Kawasaki disease[12]. Although the function of *ZFHX3* in cardiac tissue is unknown, it is expressed in mouse hearts[13].

Another significant association signal was on chromosome 1p36 within *MTHFR* (rs17375901, $P = 4.6 \times 10^{-8}$), 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 *NPPA*, the atrial natriuretic peptide gene (**Supplementary Fig. 4**); a *NPPA* frameshift mutation has been described in a family with AF[14].

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 seem 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

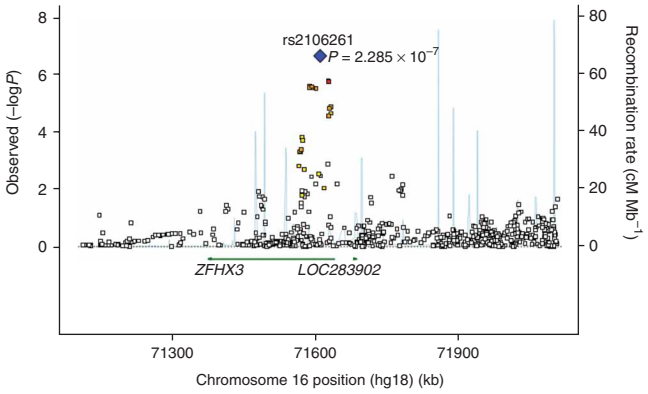


**Figure 1** Regional association plots for signal loci on chromosome 16. At each SNP location (genomic position, NCBI build 36) we plot the $-\log_{10} P$ value from combined analysis of incident and prevalent AF. Symbol colors indicate the strength of linkage disequilibrium derived from CEU HapMap 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.

general feature of even the strongest genome-wide findings for AF, and it remains to be addressed in follow-up studies. In addition, our findings may not be generalizable to other populations. 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 die 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 new chromosome 16q22 loci. Another limitation is that, beyond single SNPs, our study did not analyze patterns of haplotypes, and thus this it may not have captured complex haplotype associations. However, our use of imputation to the HapMap does take advantage of 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.

The strengths of our approach include the use of five large community-based cohorts, 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 new locus on chromosome 16 in a gene encoding the transcription factor *ZFHX3*. We provided confirmatory support for the *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 16q22 locus predisposes to AF.

**URLS.** AGES, http://www.hjarta.is/english/ages; ARIC, http://www.cscc.unc.edu/aric/; Cardiovascular Health Study, http://www.chs-nhlbi.org/; Framingham Heart Study, http://www.framinghamheartstudy.org/about/index.html; Rotterdam Study, 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 (http://www.sph.umich.edu/csg/abecasis/MaCH/index.html); PLINK, http://pngu.mgh.harvard.edu/purcell/plink.

*Note: Supplementary information is available on the Nature Genetics website.*


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## COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.


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

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In the version of this article initially published online, the name of author H.-Erich Wichmann was incorrectly given as Hans-E. Wichmann and this author's affiliation at the Institute of Medical Informatics, Biometry and Epidemiology, Ludwig Maximilians University, Munich, Germany, was missing. The error has been corrected for the print, PDF and HTML versions of this article.