PLOS | GENETICS

RESEARCH ARTICLE

# Whole Exome Sequencing in Atrial Fibrillation

**Steven A. Lubitz[1,2]*, Jennifer A. Brody[3], Nathan A. Bihlmeyer[4], Carolina Roselli[2], Lu-Chen Weng[2,5], Ingrid E. Christophersen[2,5,6], Alvaro Alonso[7], Eric Boerwinkle[8,9], Richard A. Gibbs[9], Joshua C. Bis[3], NHLBI GO Exome Sequencing Project[¶], L. Adrienne Cupples[10,11], Peter J. Mohler[12], Deborah A. Nickerson[13], Donna Muzny[9], Marco V. Perez[14], Bruce M. Psaty[15,16], Elsayed Z. Soliman[17], Nona Sotoodehnia[3,18], Kathryn L. Lunetta[11], Emelia J. Benjamin[11,19,20,21], Susan R. Heckbert[3,22], Dan E. Arking[4], Patrick T. Ellinor[1,2], Honghuang Lin[11,23]***

**1** Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **2** Program in Medical and Population Genetics, The Broad Insitute of Harvard and MIT, Cambridge, Massachusetts, United States of America, **3** Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington, United States of America, **4** McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, **5** Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **6** Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Bærum, Norway, **7** Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, United States of America, **8** Human Genetics Center, UTHealth, Houston, Texas, United States of America, **9** Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas, United States of America, **10** Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States of America, **11** Boston University and National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, United States of America, **12** Dorothy M. Davis Heart & Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States of America, **13** Department of Genome Sciences, University of Washington, Seattle, Washington, United States of America, **14** Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, United States of America, **15** Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington, United States of America, **16** Group Health Research Institute, Group Health Cooperative, Seattle, Washington, United States of America, **17** Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, **18** Division of Cardiology, University of Washington, Seattle, Washington, United States of America, **19** Section of Cardiovascular Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America, **20** Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, United States of America, **21** Preventive Medicine Section, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America, **22** Department of Epidemiology, University of Washington, Seattle, Washington, United States of America, **23** Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America

¶ Membership of the NHLBI GO Exome Sequencing Project is listed in S7 Table.
* slubitz@mgh.harvard.edu (SAL); hhlin@bu.edu (HL)

CrossMark
click for updates

OPEN ACCESS

**Citation:** Lubitz SA, Brody JA, Bihlmeyer NA, Roselli C, Weng L-C, Christophersen IE, et al. (2016) Whole Exome Sequencing in Atrial Fibrillation. PLoS Genet 12(9): e1006284. doi:10.1371/journal.pgen.1006284

**Editor:** Ruth J F Loos, Mount Sinai School of Medicine, UNITED STATES

**Received:** May 26, 2016

**Accepted:** August 9, 2016

**Published:** September 2, 2016

**Copyright:** © 2016 Lubitz et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Individual level sequencing data are available on the NCBI dbGaP portal (https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login). Data are accessible to investigators in accordance with study-specific and dbGaP policies to protect subject privacy using the following study accession numbers: phs000401, phs000651, phs000400, phs000667, phs000398, phs000668, and phs000281.

**Funding:** This work was supported by NIH grants K23HL114724 (SAL) and a Doris Duke Charitable Foundation Clinical Scientist Development Award 2014105 (SAL). NS was supported by HL111089, HL116747, and the Laughlin Family Endowment.

## Abstract

Atrial fibrillation (AF) is a morbid and heritable arrhythmia. Over 35 genes have been reported to underlie AF, most of which were described in small candidate gene association studies. Replication remains lacking for most, and therefore the contribution of coding variation to AF susceptibility remains poorly understood. We examined whole exome sequencing data in a large community-based sample of 1,734 individuals with and 9,423 without AF from the Framingham Heart Study, Cardiovascular Health Study, Atherosclerosis Risk in Communities Study, and NHLBI-GO Exome Sequencing Project and meta-analyzed the