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Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.

For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Experimental design

1. Sample size

   Describe how sample size was determined.

   The sample size of this study was not predetermined. We included as many study participants as possible to improve power for discovering novel genetic associations.

2. Data exclusions

   Describe any data exclusions.

   Some of the participating studies excluded from the control population individuals with cardiac arrhythmias/conduction disorders other than atrial fibrillation. This was predetermined.

3. Replication

   Describe the measures taken to verify the reproducibility of the experimental findings.

   We replicated 89% of the previously reported atrial fibrillation risk loci and we found that the effect sizes of the index variants that we report were homogeneous across all included studies. This support a high external validity of our findings. Further, for many of the reported index variants, we found an association with one or more ECG traits, reflecting cardiac physiology and anatomy, and hence support that the variants we report are important for cardiac function and might be involved in atrial fibrillation. Finally, we performed a number of down-stream pathway and enrichment analyses analyses, all pointing to relevant biology and hence further support our findings.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   Randomization was not relevant to the human data due to the observational study design. For the rabbit experiment, rabbits were randomly allocated into a control group (n=4) and an intervention group (n=4).

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   Blinding was not relevant to this observational study. Participants were analyzed according to observed disease status (atrial fibrillation yes vs. no).

Note: all in vivo studies must report how sample size was determined and whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ Test values indicating whether an effect is present *Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes noted.*
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars in all relevant figure captions (with explicit mention of central tendency and variation)

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	The softwere most essential to this study were: METAL 2011-03-25, GCTA 1.91.1, Plink 1.9, SAIGE 0.19, BOLT-LMM 2.3.1, EPACTS 3.3, Genome Analysis Toolkit version 3.4.0, DEPICT 2014-07-21, GREGOR 1.4.0, R software pSI package 1.1, Philips TraceMasterVue ECG Management System, R 3.4.3, Python 3.4.5, BAFRegress 0.9.3, Illumina GenomeStudio (module 1.9.4, algorithm GenTrain 2.0), LASER 2.0, Minimac3, SQLite3.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a third party.	No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	No antibodies used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	No eukaryotic cell lines were used.
b. Describe the method of cell line authentication used.	No eukaryotic cell lines were used.
c. Report whether the cell lines were tested for mycoplasma contamination.	No eukaryotic cell lines were used.
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No commonly misidentified cell lines were used.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide all relevant details on animals and/or animal-derived materials used in the study.

We used New Zealand white male rabbits, 1-2kg in size and about 1 year old. A total of 8 rabbits were used, including 4 controls (sham operated) and 4 in which heart failure was induced.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

More that one million participants were recruited via various genetic studies. All participants were older than 18 years of age. Both sexes were included. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.