Large-scale genome-wide association study of heart failure identifies novel susceptibility loci and provides a platform for drug target validation

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Contributors

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Heart failure (HF) is the most rapidly growing cardiovascular condition worldwide with unmet therapeutic needs[1]. Genetic information can be used to inform drug target identification and validation, but challenge remains due to limited understanding of the genetic basis of HF.

Methods

1. We conducted a meta-analysis of **genome-wide association studies** (GWAS) of HF from 26 studies with European ancestries, comprising 47,309 cases and 930,014 controls.
2. We performed **hierarchical agglomerative clustering** of sentinel variants in each independent loci and compared the genetic association estimates with related **risk factors** and **quantitative cardiovascular imaging traits**.
3. To estimate the extent to which the association signals at each loci are mediated by upstream traits, we performed **multi-trait-based conditional and joint analysis**[2] using GWAS summary statistics of known HF risk factors.
4. We performed **mendelian randomisation** (MR) analyses for **18 plasma protein biomarkers** associated with incident heart failure[3] using *cis*-acting genetic instruments derived from GWAS meta-analysis of plasma proteins from the SCALLOP consortium[4].

Discussion

1. We conducted the largest GWAS meta-analysis of HF to date and identified **12 independent variants at 11 genomic loci**.
2. We identified clusters of HF risk loci relating to **coronary artery disease**, **atrial fibrillation**, and **reduced left ventricular systolic function**, which may indicate different disease subtypes.
3. Eight of the 11 identified risk loci show small attenuation of effect upon conditioning on major risk factors, suggesting **alternative mechanisms** leading to HF.
4. MR analysis reveals possible **reverse causation** and **residual confoundings** in observational studies of plasma proteins. Triangulating this evidence to establish the causal effect could inform drug target identification and validation for HF.

References

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2. Zhu Z, Zheng Z, Zhang F, et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. Nat Commun. 2018 Jan 15;9(1):224.
3. Stenemo M, Nowak C, Byberg L, et al. Circulating proteins as predictors of incident heart failure in the elderly. Eur J Heart Fail. 2018 Jan;20(1):55–62.
4. www.olink.com/scallop/

A **GWAS meta-analysis** of:
47,309 heart failure cases
26 studies with European ancestries
8,246,881 variants (MAF >1%)

12 independent variants identified at
11 genomic loci

Agglomerative clustering
identifies clusters of susceptibility loci related to heart failure subtypes

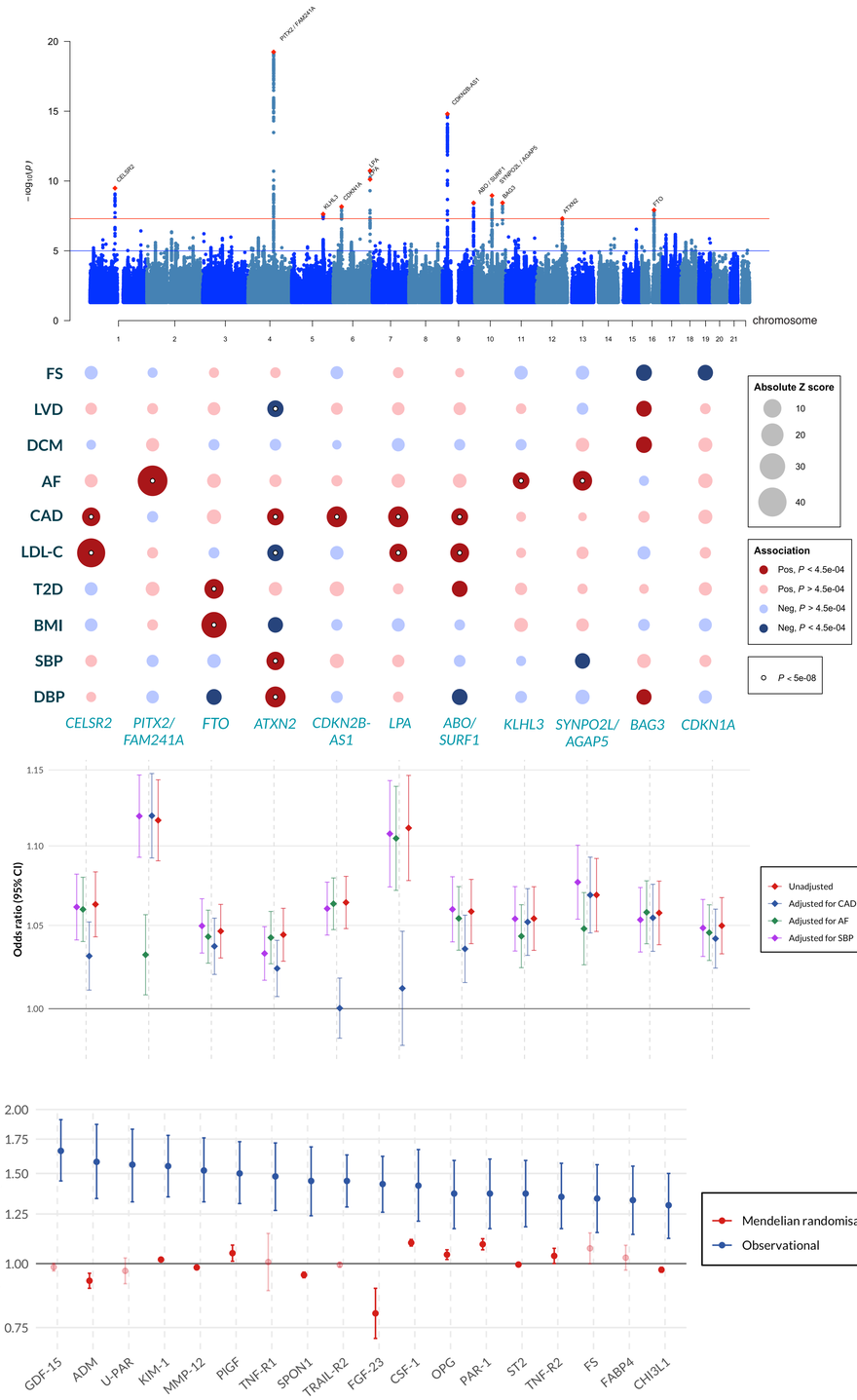
Conditional analysis
reveals pathways not fully mediated by common risk factors

Mendelian randomisation
demonstrates the potential value of these results for drug target identification and validation

GWAS summary statistics
available on the Cardiovascular Disease Knowledge Portal: broadcvdi.org/informational/data

pre-print available on
biorxiv.org/content/10.1101/682013v1

article to be published
on *Nat Comms.*



Abbreviations HF, Heart failure; FS, fractional shortening; LVD, left ventricular dimension; DCM, dilated cardiomyopathy; AF, atrial fibrillation; CAD, coronary artery disease; LDL-C; low density lipoprotein cholesterol; BMI, body mass index; T2D, type 2 diabetes; SBP, systolic blood pressure; DBP, diasolic blood pressure

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HERMES HEART FAILURE MOLECULAR EPIDEMIOLOGY for THERAPEUTIC TARGETS
British Heart Foundation
NHS National Institute for Health Research
HDRUK Health Data Research UK
MRC Medical Research Council
American Heart Association.
SCALLOP
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