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Lumbers, R.T.; Shah, S.; Lin, H.H.; Czuba, T.; Henry, A.; Swerdlow, D.I.; ... ; Regeneron Genetics Ctr

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The genomics of heart failure: design and rationale of the HERMES consortium

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Abstract

Aims The HERMES (HEart failure Molecular Epidemiology for Therapeutic targetS) consortium aims to identify the genomic and molecular basis of heart failure.

Methods and results The consortium currently includes 51 studies from 11 countries, including 68 157 heart failure cases and 949 888 controls, with data on heart failure events and prognosis. All studies collected biological samples and performed genome-wide genotyping of common genetic variants. The enrolment of subjects into participating studies ranged from 1948 to the present day, and the median follow-up following heart failure diagnosis ranged from 2 to 116 months. Forty-nine of 51 individual studies enrolled participants of both sexes; in these studies, participants with heart failure were predominantly male (34–90%). The mean age at diagnosis or ascertainment across all studies ranged from 54 to 84 years. Based on the aggregate sample, we estimated 80% power to genetic variant associations with risk of heart failure with an odds ratio of ≥ 1.10 for common variants (allele frequency ≥ 0.05) and ≥ 1.20 for low-frequency variants (allele frequency 0.01–0.05) at $P < 5 \times 10^{-8}$ under an additive genetic model.

Conclusions HERMES is a global collaboration aiming to (i) identify the genetic determinants of heart failure; (ii) generate insights into the causal pathways leading to heart failure and enable genetic approaches to target prioritization; and (iii) develop genomic tools for disease stratification and risk prediction.

Keywords Heart failure; Cardiomyopathy; Genetics; Biomarkers; Association studies

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Introduction

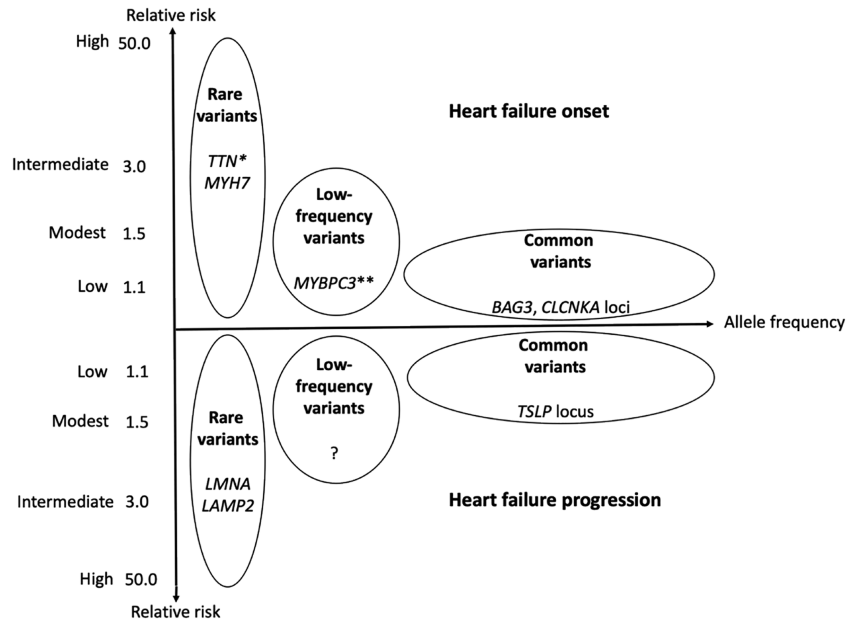
Heart failure (HF) is a complex clinical syndrome that imposes a substantial burden on public health; an estimated 30 million people worldwide are living with HF, and the prevalence is expected to rise with the aging of the global population.¹ HF is associated with substantial morbidity and mortality, underscoring the importance of mitigating the disease burden. Despite the advent of disease-modifying treatments for HF with reduced ejection fraction, considerable unmet need remains.² For HF with preserved ejection fraction, an increasingly prevalent subtype, no treatments are available to improve patient outcomes.³ Decades of research, based on preclinical models of HF, have uncovered numerous potential therapeutic targets; however, few have been successfully validated in phase III outcomes trials, reflecting, in part, the challenge of modelling complex age-associated multi-morbid disease processes.⁴ Human genetics provides a means to study causal biology in the patient: informing target selection and the formulation of a mechanism-based taxonomy of disease subtypes to help identify new therapeutic targets.⁵

Heart failure generally occurs when changes in cardiac structure or function result in impairment of ventricular filling and/or contraction and in impaired cardiac output and/or increased cardiac filling pressures.² Coronary artery disease and diseases causing abnormal cardiac loading (such as hypertension, valvular heart disease, and congenital heart disease) are established and common causes of HF. Many other factors can increase the risk of HF through direct effects on

myocardial structure and function (cardiomyopathy), including, for a small proportion of cases, monogenic cardiomyopathy syndromes.⁶ Familial aggregation and adoption studies suggest a heritable component to HF risk and disease progression with estimates for heritability up to 26%.^{7–9} Linkage studies of familial cardiomyopathies and genome-wide association studies (GWASs) have identified a number of rare and common variants associated with increased HF risk (Figure 1); however, the genetic architecture remains largely unknown.^{10–13}

It is a feature of many complex traits and diseases that common genetic variants account for a proportion of the population genetic variance.¹⁴ The genetic background of individual patients with respect to HF risk may modify the effects of HF risk factors, including influencing the penetrance and expression of Mendelian gene disorders, as has been observed for other common complex diseases.¹⁵ Furthermore, the identification of common disease-associated variants implicates regions of the genome that harbour causal genes and enables the appraisal of the causal role of risk factors and pharmacological targets by Mendelian randomization (MR) analysis.¹⁶ GWASs offer a robust and reproducible approach for the discovery of common disease-associated variants. Large samples, typically achieved by combining multiple studies through meta-analysis, are required to achieve sufficient statistical power to discern genotype–disease associations with modest effects.¹⁷ These approaches help inform a mechanism-based taxonomy of HF to support the development of effective targeted therapeutics.¹⁸

Figure 1 Genetic architecture of heart failure (HF) onset and progression. Examples of genes in which common (allele frequency 5% and greater), low-frequency (1–5%), or rare variants (<1%) have been shown to influence risk for HF onset or progression. Effect sizes are expressed in odds ratios for HF risk and hazard ratios for HF progression. Common variants can be identified in genome-wide association studies as exemplified by *BAG3*, *CLCNKA*, and *TSLP* loci, whereas variations with low population allele frequencies such as familial variants in the *MYH7*, *LMNA*, and *LAMP2* genes associated with cardiomyopathy will typically require sequencing-based approaches (based on a recent review article).²⁷ Familial variants in *LMNA* and *LAMP2* have been associated poor prognosis and particular cardiac phenotypes, manifesting with cardiomyopathy and Danon disease, respectively. *Although individually rare, protein-truncating variants in the large gene encoding Titin (*TTN*) collectively have a reported prevalence of 1% in the population, confer increased risk of HF, and have evidence of interaction with environmental factors such as alcohol, chemotherapy, and pregnancy. **A 25-basepair deletion of the gene encoding cardiac myosin-binding protein C (*MYBPC3*) conferring risk for HF has been reported to have an allele frequency of 4% in Southern Asian populations, highlighting how low-frequency variants of large effect may be population specific.



Here, we describe the HERMES (HEart failure Molecular Epidemiology for Therapeutic targetS) consortium: a global scientific collaboration of genetic studies linked to HF and related phenotypes. The consortium will develop tools and methods to enable the definition of HF subtypes and related traits across multi-modal datasets, including derivation of validated phenotypes from genomic biobanks linked to electronic health records.¹⁹ HERMES aims to unlock the potential for human genetics to inform the identification and validation of novel therapeutic approaches in HF by creating an open collaborative resource for the scientific community.^{20,21}

Study design

Aims

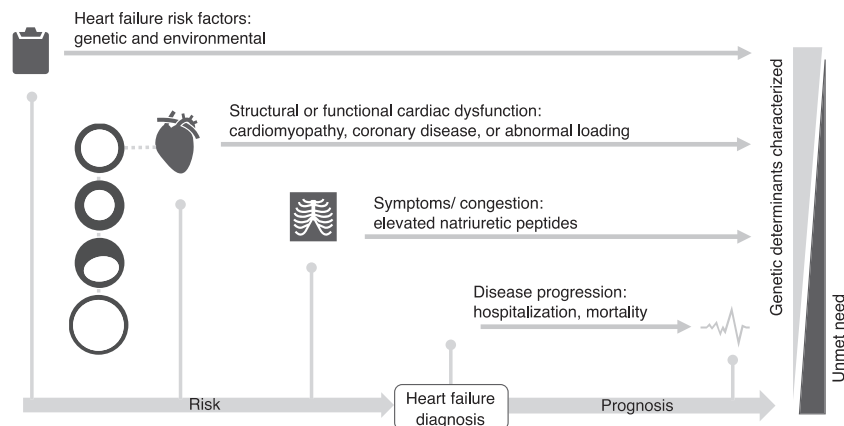
The core objective of the HERMES consortium is to conduct large-scale genetic association studies of HF and related phenotypes in order to identify common and low-frequency

genetic variants associated with HF risk and prognosis (Figure 2). In subsequent stages, we will extend these analyses to include rare variant association studies, based on sequence data available in a subset of studies. GWASs will be complemented by a range of follow-up analyses, including MR and rare variant burden tests, in order to identify novel disease mechanisms and to test existing therapeutic hypotheses.

Addressing syndromic heterogeneity

A stepwise approach to the genetic study of HF phenotypes and sub-phenotypes will be employed. The first completed analysis addressed the undifferentiated HF syndrome, without subtyping according to conventional classifiers of aetiology or phenotypes of left ventricular ejection fraction (LVEF).²² This study maximizes statistical power for the discovery of genetic factors influencing common pathophysiological mechanisms, such as left ventricular fibrotic remodeling, increased filling pressures, neurohormonal activation, and extracellular fluid retention (systemic and pulmonary

Figure 2 Component phenotypes of heart failure (HF). Schematic representation of HF phenotypes across the life course that will be studied in HERMES. HF diagnosis is typically preceded by cardiometabolic risk factors and genetic susceptibility factors for endophenotypes of structural and functional cardiac dysfunction. Circles on the left represent common structural endophenotypes, from top to bottom: normal ventricle, ventricle with symmetric hypertrophy, ventricle with asymmetric (septal) hypertrophy, and dilated ventricle. The natural history of HF extends from the initial time point of diagnosis (Dx) through a gradual decline with increasing episodes of worsening typically necessitating in-hospital care (decompensations) towards terminal pump failure. Sudden death from arrhythmia may occur at any point. Heritable contributions have been described for both risk factors, endophenotypes, HF onset, and HF progression.



vascular congestion) that may modify risk associated with upstream HF risk factors. Subsequent studies will address HF subtypes, including established and novel aetiological and cardiac morpho-functional phenotypes.

HERMES collaborating studies

At present, HERMES is a collection of 51 studies that have derived genome-wide genotyping data from community-based participants or hospitalized patients with clinical HF, including longitudinal population-based cohort studies, hospital-based electronic health record cohorts, case-control studies, and clinical trials. Detailed case ascertainment for HF and related cardiovascular phenotypes has been done for most studies; in others, phenotyping is based on routinely collected data from clinical care, national quality registers, or public data repositories. In addition to studies based in academic institutions, the collaboration includes many clinical trial datasets, providing a unique opportunity to study the genetic determinants of disease progression in HF. Due to the provenance of data currently available in contributing cohorts, currently ongoing initial analyses are limited to individuals of European ancestry; however, a central objective will be to include subjects of non-European ancestry as data from ancestrally diverse populations become available. Each contributing study in HERMES has appropriate ethical approval from the respective institutional review boards, and all participants provided informed consent for the use of their genetic data for research.

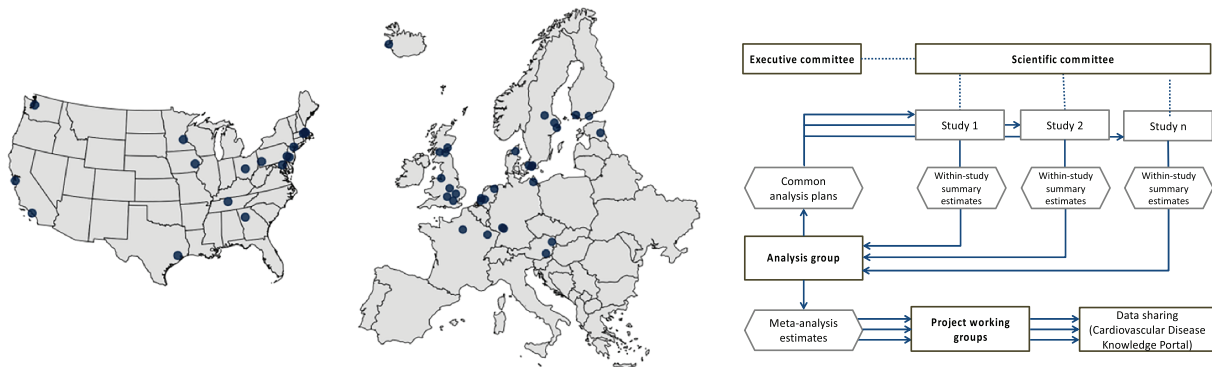
Organization

The collaborative framework of HERMES is similar to that of other collaborative consortia for genetic investigations, as shown in *Figure 3*.²³ All studies participate on an equal basis and operate under mutually agreed policies concerning project management, results sharing, and publication, which are articulated in a Memorandum of Understanding (see Supporting Information).

Data sharing and governance

To obviate the need for sharing of individual participant-level data and attendant data governance considerations, the consortium has adopted a distributed analysis model based on pre-planned meta-analysis of summary-level data contributed by each participating cohort study (*Figure 3*). Common analysis plans, methods and analytical scripts for quality control, phenotype and sub-phenotype derivation, and genetic association analyses are implemented in each study by local analysts. The resulting within-study summary data are then returned to the coordinating centre for quality control and meta-analysis. Meta-analysis is conducted at two independent centres to enable validation of results. Following the publication of results, summary data from HERMES meta-analyses are published in full on the Cardiovascular Disease Knowledge Portal (<http://www.broadcvdi.org/>).

Figure 3 International participation in HERMES and distributed analysis workflow. The HERMES consortium includes investigators from 12 countries from North America and Europe. Activities are overseen by a scientific committee with representatives from each contributing cohort and an executive committee. Common analysis plans are developed by the analysis group and deployed by participating studies. Meta-analysis is conducted by the analysis group and results shared with project working groups. Upon publication, the full genome-wide association summary estimates from meta-analysis are made available publicly through the Cardiovascular Disease Knowledge Portal (<http://www.broadcvdi.org/>).



Heart failure phenotype definition

While formal, international definitions of HF are in use,² case definitions vary across participating studies, as do methods for ascertainment, reflecting differences in study design and data availability (Supporting Information, *Table S1*). The performance of several HF ascertainment criteria in widespread use has, however, been shown to be similar.²⁴ For the initial GWAS meta-analysis, a broad definition was used based on physician adjudication, electronic health records-based phenotype algorithms, and corroborated self-report. Subsequent studies will follow a stepwise strategy for phenotype definition to address HF subtypes based on aetiology, LVEF, and disease progression (*Figure 2*). Mobilizing HF subtype data from electronic health records, leveraging large genomic biobanks, will be necessary to ensure sufficient statistical power for subtype analysis, and this will be achieved through the deployment of validated multi-modal rule-based phenotyping algorithms.²⁵

Given the mortality associated with HF, inclusion of incident and prevalent cases in analyses may lead to attenuation of effect estimates, due to survivorship or collider bias and increased heterogeneity^{26,27}; however, this bias is partially mitigated by the increased power associated with a larger sample size that can be achieved when prevalent cases are included.

Genotyping and imputation

Participants have been genotyped with a range of genome-wide single nucleotide polymorphism (SNP) arrays (Supporting Information, *Table S1*). All collaborating studies conducted imputation from directly measured genotype using public reference panels (1000 Genomes Project,

Haplotype Reference Consortium) or from local whole-genome sequence-based reference panels; for each meta-analysis project, genotype imputation was performed against a common pre-specified reference panel. Phasing and imputation were conducted using Eagle, MaCH, SHAPEIT, minimac2, or IMPUTE2 software at the discretion of participating cohorts.

Approach to genetic analyses

For GWASs, the analysis plan specifies quality filters to be applied to the data and the regression models for association testing. Once study-specific GWAS results have been uploaded to the central analytic team, these datasets undergo a second round of QC in order to identify and rectify any study-specific issues, align effect alleles across studies, and apply minor allele frequency and imputation quality filters, prior to meta-analysis. Analyses are conducted in parallel at two independent sites and are subsequently reconciled.

In study-specific GWAS analyses, logistic regression or Cox proportional hazards regression analyses are used, assuming additive genetic effects. Models are adjusted for age, sex, and principal components and family structure as appropriate for individual cohorts. Analytical softwares are left to the discretion of individual cohorts and include genetest, ProbABEL, mach2dat, QuickTest, PLINK2, SNPTEST, or R.

Quality controls of study-specific results are conducted according to accepted guidance, as previously reported.²⁸ In brief, variant identifiers and alleles are harmonized using the EasyQC tool and allele frequencies compared with the European reference panel of the 1000 Genomes Project. Distributions of reported *P*-values are plotted against *P*-values derived from *Z*-scores and reviewed, as well as distributions of beta estimates and standard errors, and Manhattan plots.

Variants with low imputation quality (<0.5) and with extreme betas and standard errors (>10) are excluded. Genomic control is applied at the study level where genomic inflation is identified ($\lambda_{GC} > 1.1$). Single-variant tests are limited to common and low-frequency variants (minor allele frequency $\geq 1\%$).

Meta-analyses are conducted using inverse-variance weighting using METAL software (https://genome.sph.umich.edu/wiki/METAL_Documentation). Heterogeneity of effect estimates across studies is evaluated from Cochrane's Q and I^2 statistics. The contribution of cryptic population structure to test statistics is estimated based on the linkage disequilibrium score (LDSC) regression intercept (<https://github.com/bulik/ldsc>). Statistical significance thresholds are based on the Bonferroni adjustment for the number of tests performed.

Power for statistical analyses

Power calculations for HF onset were based on R implementation of the widely used algorithms from the CaTS power calculator for one-stage association studies, with power calculations from the standard normal distribution.²⁹ Power to detect genome-wide significant associations ($P < 5 \times 10^{-8}$), based on the current HERMES sample size for cases with corresponding control subjects, was calculated as a function of effect allele frequency under different effect sizes (odds ratios of 1.05, 1.1, 1.2, 1.3, 1.4, and 1.5 in additive models). Similar power will apply to the reciprocal of the odds ratios < 1.0 for protective alleles. Additive-model odds ratios of identified common variants have typically been in the range of 1.1–1.2, with larger studies further identifying even smaller effects. Power calculations for HF mortality were based on the *survSNP* package in R,³⁰ included all cases, and plotted similarly to HF onset. Power calculations were conducted using the computing environment R Version 3.5.1 (R Core Team, Vienna, Austria), and results were plotted using STATA Version 15 (StataCorp, College Station, Texas, USA).

Study description

Participating studies

The HERMES consortium currently includes investigators from 12 countries (*Figure 3*) including 7 industry partners, representing 16 population-based cohorts, 1 hospital-based electronic health record cohort, 9 case cohorts of which 6 with control samples, and 25 clinical trials of which 9 with non-HF control samples (Supporting Information, *Table S1*). Ten of the clinical trials of HF were conducted within the NHLBI HF clinical research network. Detailed cohort

descriptions are provided in the Supporting Information. For a continuously updated list of included cohorts, please refer to the consortium webpage (www.hermesconsortium.org).

In aggregate, the 51 HERMES cohorts comprise 68 157 HF cases and 949 888 controls of European ancestry with array-based genotyping (Supporting Information, *Table S1*). Most of the 16 population-based cohorts identified cases based on ICD codes in hospital registers (10 cohorts), while a few had adjudicated events from patient records (4 cohorts) or included re-exams (2 cohorts). Of the nine case collections, seven were primarily focused on HF while two identified HF cases from an at-risk population (COGEN and LURIC). Of the 25 clinical trials, 17 had HF as inclusion criterion, whereas 8 included broader groups of patients with cardiometabolic diseases and identified HF from adjudicated outcomes (three trials) or case report forms (five trials).

Characteristics of participating studies

Baseline characteristics of the contributing studies are presented in Supporting Information, *Table S2*. As expected, clinical trials typically included younger cases (median age < 70 years in most trials) and had a lower burden of co-morbid disease compared with population-based cohorts. Risk factor distributions were largely as expected, with a particularly high burden of hypertension and coronary artery disease in all studies. Information on LVEF was available in a subset of cohorts: 16 151 had LVEF $< 40\%$, 4113 had LVEF 40–50%, and 9676 had LVEF $> 50\%$, corresponding to HF with reduced ejection fraction, HF with mid-range ejection fraction, and HF with preserved ejection fraction.²

Follow-up times and mortality of HF cases are presented in Supporting Information, *Table S1*. Overall, mortality among HF cases was 27%; however, the duration of follow-up was highly variable across studies, with median study follow-up ranging from 1 to 116 months.

Genotypic information

Genotyping was conducted on different high-density SNP platforms (Supporting Information, *Table S1*) and imputed based on European ancestry imputation panels for up to 8 246 881 common or low-frequency variants (minor allele frequency $> 1\%$) in the combined dataset. Detailed sequence data were available in at least 30 000 subjects from eight cohorts with exome-wide coverage and 140 000 subjects from six cohorts with whole-genome coverage (Supporting Information, *Table S1*) and were planned or ongoing in several additional cohorts.

Statistical power

Power calculations were conducted based on all 68 157 cases described earlier for HF progression, with an average mortality of 27%, and all cases with corresponding controls for HF onset (949 888 controls, 44 016 cases). For HF risk, HERMES is powered (>0.8) to detect effects down to odds ratios of 1.10 for common variants (minor allele frequency > 0.05) and 1.20 for low-frequency variants (0.01–0.05) (Figure 4A). For HF mortality, HERMES is powered to detect effects down to hazard ratios of 1.20 for variants with minor allele frequency > 0.08 and 1.40 for low-frequency variants (Figure 4B).

Discussion

With the recent exception of combination angiotensin receptor blockade and neprilysin inhibition and sodium-glucose transport protein 2 inhibitors, successful drug development in HF has, for many years, been limited. Almost all current therapies are repurposed from other indications (e.g. angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists for systemic hypertension and sodium-glucose transport protein 2 inhibitors for T2DM) and may not directly target processes leading to adverse cardiac remodelling. Human genetic and genomic studies provide unique opportunities to explore the causal biology in patients; the HERMES consortium provides a collaborative platform that enables these approaches.

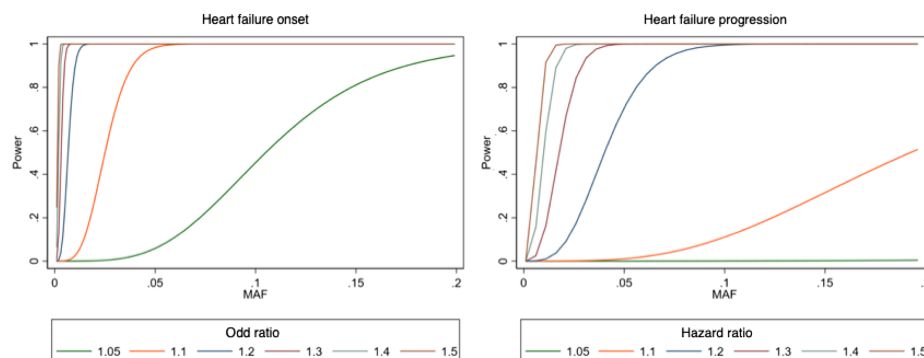
Heart failure is a broadly defined syndromic disorder with diverse causes leading to a range of phenotypes. While this complexity is mirrored in other common cardiovascular diseases, such as coronary artery disease, heterogeneity is

particularly marked for HF. Beyond the scope of conventional GWAS consortia, HERMES has a strong focus on the development and clinical validation of multi-modal definitions for HF in an effort to harmonize across different study designs and healthcare contexts. It is recognized that existing clinical classifiers may not optimally enrich for common disease mechanisms,¹⁸ and HERMES seeks new opportunities to dissect out disease heterogeneity using genomic and data science approaches.¹⁹ We describe a stepwise strategy for phenotype definition, starting with the clinical syndrome of HF and moving towards disease subtypes defined with precision. The approach allows for the definition of HF subtypes based on our emerging understanding, without prior assumptions about disease stratification.¹⁸

A substantial number of individuals with Mendelian disorders causing HF, such as dilated or hypertrophic cardiomyopathies, are included. We aim to develop polygenic scores for HF and component traits that may be useful in anticipating the likely penetrance and expression of rare variants associated with Mendelian cardiomyopathies. Inclusion of large longitudinal studies, including clinical trials and electronic health records-linked datasets, offers an opportunity to explore longitudinal phenotypes of HF onset and progression, which are likely to be essential for clarifying the key underlying causal mechanisms.

In future work, we aim to build on the HERMES collaborative platform through more detailed harmonization of covariates and imaging data across studies, enabling analysis at the individual participant level or under a distributed analysis model. Such a framework will enable the platform to support analysis of emerging data-driven definitions of HF subtypes with complex specifications, including those relating to trajectories of disease. We plan to extend our collaborative efforts to include other genome-scale molecular measurements, including serum proteomics and metabolomics, and to include populations with diverse ancestry.

Figure 4 Power estimates across the allele frequency spectrum for genome-wide association studies of heart failure risk and prognosis in HERMES. Figure illustrating empirical power for detecting different genetic variant effect sizes by varying minor allele frequencies (MAF), for (A) heart failure risk (odds ratio) and (B) heart failure prognosis (hazard ratio). Based on current HERMES sample size, with 949 888 controls compared with 44 016 cases for risk and 68 157 cases for prognosis.



The emergence of large genetic studies linked to information on HF and related traits presents an exciting opportunity to explore the causal biology of this increasingly prevalent disorder. HERMES provides a framework for scientific collaboration in support of this aim, bringing together relevant data resources and leading domain experts to address this challenging phenotype. The collaboration is open; we invite interested patients, providers, and researchers to participate and join in our efforts to inform new approaches to the prevention and treatment of HF.

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Conflict of interest

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Table S1. Summary of participating studies: design, case ascertainment, genotyping and follow-up.

Table S2. Characteristics of participating studies.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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