

Description of Additional Supplementary Files

File Name: Supplementary Data 1

Description: Characteristics of non-HF controls and HF cases including clinical subtypes in the MVP cohort of non-Hispanic European (EUR) and non-Hispanic African Americans (AFR).

File Name: Supplementary Data 2

Description: Characteristics of non-HF controls and HF cases in the UK Biobank cohort of European ancestry.

File Name: Supplementary Data 3

Description: Summary statistics of genome-wide significant SNPs from the meta-analysis of unclassified heart failure. Meta-analysis was performed using inverse-variance weighted fixed-effects model. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 4

Description: Summary of 20 genome-wide significant loci and sentinel variants associated with unclassified heart failure. Meta-analysis was performed using inverse-variance weighted fixed-effects model. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 5

Description: Replication of previous reported variants associated with composite heart failure or dilated cardiomyopathy. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 6

Description: Summary of genome-wide significant loci and sentinel variants associated with HFrEF or HFpEF. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 7

Description: Associations with unclassified HF, HFrEF and HFpEF in autosomal genes related to cardiomyopathy. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 8

Description: Genetic associations between HFrEF- and HFpEF-associated sentinel variants and heart failure risk factors. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 9

Description: Genetic associations with ~2,400 traits tested in the UK Biobank searched in the PheWeb browser (listed as “-” if no associations with $p < 10^{-6}$ identified).

File Name: Supplementary Data 10

Description: Summary of Mendelian Randomization analyses between heart failure risk factors and unclassified heart failure, HFrEF and HFpEF using three methods. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 11

Description: Independent secondary signals within the genome-wide significant loci identified by conditional analysis. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 12

Description: Candidate causal variants from credible set analysis for all genome-wide significant loci. All tests were two-sided without adjustment for multiple testing.

File Name: Supplementary Data 13A

Description: SIFT prediction scores for non-synonymous substitution of amino acid.

File Name: Supplementary Data 13B

Description: PolyPhen prediction scores for non-synonymous substitution of amino acid.

File Name: Supplementary Data 14

Description: Expression quantitative trait loci (eQTLs) for the genetic variants associated with unclassified HF, HFrEF and HFpEF.

File Name: Supplementary Data 15

Description: Protein-quantitative trait loci (pQTLs) for the genetic variants associated with unclassified HF, HFrEF and HFpEF.

File Name: Supplementary Data 16

Description: Genome-wide significant loci overlapping with human enhancers for unclassified HF, HFrEF and HFpEF.

File Name: Supplementary Data 17

Description: Statistically significant ($p < 5E-7$) associations of genetically predicted gene expression with HFrEF in 48 tissues and eQTL colocalization.

File Name: Supplementary Data 18

Description: Gene-set analysis using DEPICT for HFrEF and HFpEF.

File Name: Supplementary Data 19

Description: Pathway enrichment analysis using DEPICT for HFrEF and HFpEF.