Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data.

CONTEXT: Echocardiographic measures of left ventricular (LV) structure and function are heritable phenotypes of cardiovascular disease. OBJECTIVE: To identify common genetic variants associated with cardiac structure and function by conducting a meta-analysis of genome-wide association data in 5 population-based cohort studies (stage 1) with replication (stage 2) in 2 other community-based samples. DESIGN, SETTING, AND PARTICIPANTS: Within each of 5 community-based cohorts comprising the EchoGen consortium (stage 1; n = 12 612 individuals of European
ancestry; 55% women, aged 26-95 years; examinations between 1978-2008), we estimated the
association between approximately 2.5 million single-nucleotide polymorphisms (SNPs; imputed to
the HapMap CEU panel) and echocardiographic traits. In stage 2, SNPs significantly associated with
traits in stage 1 were tested for association in 2 other cohorts (n = 4094 people of European
ancestry). Using a prespecified P value threshold of 5 x 10(-7) to indicate genome-wide significance,
we performed an inverse variance-weighted fixed-effects meta-analysis of genome-wide association
data from each cohort. MAIN OUTCOME MEASURES: Echocardiographic traits: LV mass, internal
dimensions, wall thickness, systolic dysfunction, aortic root, and left atrial size. RESULTS: In stage 1,
16 genetic loci were associated with 5 echocardiographic traits: 1 each with LV internal dimensions
and systolic dysfunction, 3 each with LV mass and wall thickness, and 8 with aortic root size. In stage
2, 5 loci replicated (6q22 locus associated with LV diastolic dimensions, explaining<1% of trait
variance; 5q23, 12p12, 12q14, and 17p13 associated with aortic root size, explaining 1%-3% of trait
variance). CONCLUSIONS: We identified 5 genetic loci harboring common variants that were
associated with variation in LV diastolic dimensions and aortic root size, but such findings explained a
very small proportion of variance. Further studies are required to replicate these findings, identify the
causal variants at or near these loci, characterize their functional significance, and determine whether
they are related to overt cardiovascular disease.

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