Genetic variation in NCAM1 contributes to left ventricular wall thickness in hypertensive families.

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Abstract

RATIONALE: Left ventricular (LV) mass and related phenotypes are heritable, important predictors of cardiovascular disease, particularly in hypertensive individuals.

OBJECTIVE: Identify genetic predictors of echocardiographic phenotypes in hypertensive families.

METHODS AND RESULTS: A multistage genome-wide association study (GWAS) was conducted in hypertensive-ascertained black families (HyperGEN, stage I; GENOA, stage II); findings were replicated in HyperGEN white families (stage III). Echocardiograms were collected using a common protocol, and participants were genotyped with the Affymetrix Genome-Wide Human SNP 6.0 Array. The following were analyzed using mixed models adjusted for ancestry: in stages I and II, 1258 and 989 blacks, respectively; and in stage III, 1316 whites. Phenotypes included LV mass, LV internal dimension (LVID), wall thicknesses (posterior [PWT] and intraventricular septum [IVST]), and relative wall thickness (RWT). In stage I, 5 single nucleotide polymorphisms (SNPs) had P≤10(-6). In stage II, 1 SNP (rs1436109; NCAM1 intron 1) replicated with the same phenotype (PWT, P=0.025) in addition to RWT (P=0.032). In stage III, rs1436109 was associated with RWT (P=5.47×10(-4)) and LVID (P=1.86×10(-4)).
Fisher combined probability value for all stages was $RWT = 3.80 \times 10^{-9}$, $PWT = 3.12 \times 10^{-7}$, $IVST = 8.69 \times 10^{-7}$, LV mass $= 2.52 \times 10^{-3}$, and $LVID = 4.80 \times 10^{-4}$.

**CONCLUSIONS:** This GWAS conducted in hypertensive families identified a variant in NCAM1 associated with LV wall thickness and RWT. NCAM is upregulated during the remodeling period of hypertrophy to heart failure in Dahl salt-sensitive rats. Our initial screening in hypertensive blacks may have provided the context for this novel locus.

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