clinical characteristics and testing results in those with and without CHF at the time of their AoD. Those with CHF tended to present in atypical fashion, and whereas CHF at the time of AoD did not appear to lead to inordinate delays in patient presentation, a potential impact of CHF on time to recognition of AoD was noted, and CHF was an independent predictor of surgical delay. In our data set, it is unclear whether these delays were due to clinician preoccupation with CHF or the more subtle presentation of those with CHF and AoD.

Previous case reports have suggested that CHF in the presence of AoD is due to aortic regurgitation from aortic valve disease, incomplete aortic leaflet closure (due to dilation of the sinotubular junction), or aortic valve disruption (1,2,5). An additional mechanism of CHF at the time of AoD includes high-output heart failure (3,4,6). Although we confirm a high percentage of patients with CHF secondary to proximal aortic involvement, we also demonstrated that as many as 20% of patients with CHF at the time of AoD had a distal dissection; consequently, in this considerable minority, the mechanism of CHF must be something other than direct aortic valve involvement by the dissection itself, such as myocardial ischemia/infarction or hypertension. Delays in AoD diagnosis and treatment are notable in our subjects; this may reflect consideration of diagnoses alternative to AoD, given the atypical presentation in our subjects.

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Heritability of Left Ventricular Mass and Other Morphologic Variables in Caribbean Hispanic Subjects: The Northern Manhattan Family Study

To the Editor: Left ventricular (LV) hypertrophy is a risk factor for cardiovascular disease (1–3) and ischemic stroke (4–6). Current data suggest that genetic factors and traditional cardiovascular risk factors contribute to left ventricular mass (LVM) and LV hypertrophy. Several studies demonstrated substantial genetic contribution to LVM in white, black, and American Indian populations (7–12). However, no data exist on heritability of LVM in Hispanic patients.

Echocardiographically derived LVM has been validated by comparison with autopsy data (13). From LVM and relative wall thickness (RWT), three abnormal geometric patterns (i.e., concentric hypertrophy, eccentric hypertrophy, and concentric remodeling) (14) can be derived, and they appear to carry different risks for cardiovascular events (6).

In the current study, we tested for the significance of heritability for several LVM-related phenotypes in the high-risk Caribbean Hispanic families from the ongoing Northern Manhattan Family Study (NOMAFS). The detailed ascertainment scheme has been described elsewhere (15). Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography (16). Left ventricular end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVSD), interventricular septum (IVS), and posterior wall thickness (PWT) at end diastole were measured. To minimize variability, we took measurements in triplicate and averaged them.

Left ventricular mass was calculated from the corrected American Society of Echocardiography method (13): $LVM = 0.8\ (1.04\ [(LVDD + IVS + PWT)^3 - LVDD^3]) + 0.6$. Heritability of LVM also was assessed after correction for the indices of body size most commonly used in published reports: body surface area (LVM/BSA), height (LVM/HT), and height to the 2.7 power ($LVM/HT^{2.7}$). The heritability of LVDD, LVSD, IVS, PWT, and RWT also was assessed. Relative wall thickness was calculated according to two formulas: (IVS + PWT)/LVDD and $2 \cdot PWT/LVDD$ (14). Echocardiographic studies were interpreted by researchers who were blinded to the clinical characteristics. Interobserver variability ranged between 8% and 10%.

All the quantitative phenotypes were expressed as the mean and standard deviation. Log transformations were used for non-normally distributed variables. We used the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package (Southwest Foundation for Biomedical Research, San Antonio, Texas) (17) to

Table 1. Heritability of LVM and Other Cardiac Morphologic Variables (n = 623)

		Heritability			Variance Explained by Covariates		
	Mean ± SD	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LVM (g)	179.6 ± 53.8	0.65	0.51	0.49	17%	38%	39%
LVM/BSA (g/m^2)	99.5 ± 25.0	0.50	0.49	0.48	10%	13%	14%
LVM/HT (g/m)	110.5 ± 31.0	0.57	0.49	0.48	11%	30%	32%
LVM/HT$^{2.7}$	48.8 ± 13.8	0.48	0.48	0.47	9%	31%	32%
RWT (IVS + PWT)/LVDD	0.49 ± 0.09	0.27	0.25	0.23	18%	20%	23%
RWT, 2PWT/LVDD	0.48 ± 0.09	0.26	0.26	0.26	16%	18%	20%
LVDD (cm)	4.5 ± 0.46	0.37	0.23	0.23	16%	28%	28%
LVSD (cm)	2.8 ± 0.46	0.41	0.34	0.35	20%	24%	25%
IVS (cm)	1.1 ± 0.21	0.41	0.34	0.33	18%	28%	30%
PWT (cm)	1.1 ± 0.17	0.45	0.36	0.35	16%	27%	29%

Model 1: adjusted for age and gender; model 2: adjusted for age, gender, weight, and height; model 3: adjusted for age, gender, weight, height, systolic blood pressure, diabetes, and antihypertensive medication.

BSA = body surface area; HT = height; IVS = interventricular septum; LVDD = left ventricular end-diastolic diameter; LVM = left ventricular mass; LVSD = left ventricular end-systolic diameter; PWT = posterior wall thickness; RWT = relative wall thickness.

estimate heritability. Ascertainment correction was performed for families that were enrolled based on probands' LVM/BSA ≥75%.

The current study consisted of 623 subjects from 84 families. The mean family size and age were 11 (range, 3 to 53) subjects and 47 (range, 18 to 95) years, respectively. Men comprised 37% of the total. Mean systolic blood pressure (SBP) was 122.1 ± 19.8 mm Hg. Mean body weight was 76 kg, and average height was 162 cm. The prevalence of diabetes, hypertension, and antihypertensive treatment was 14.2%, 40.6%, and 34.5%, respectively. Means and standard deviations of LV parameters are shown in Table 1. The estimates of heritability for the nine LV phenotypes ranged from 0.49 to 0.23 (all p values ≤0.001, except p = 0.002 for LVDD) after adjusting for demographic and cardiovascular risk factors (Table 1). Left ventricular mass had the highest heritability and LVDD the lowest in model 3.

We calculated heritabilities for LVM and LV morphologic parameters while adjusting for different combinations of covariates. The results showed substantial heritabilities for all the phenotypes, with LVM having the strongest heritability. Age, gender, weight, and height accounted for the majority of interindividual variation for LV phenotypes. Additional adjustment for SBP, diabetes, and antihypertensive medication almost yielded the same results. Similar to previous reports (12,18), our data showed weight as the most important single predictor of LVM (explained ~20% of LVM variance). Relative wall thickness showed weaker heritability than LVM, suggesting that LV geometry may be more strongly affected by acquired conditions, such as blood pressure variability and other unknown exposures. The age- and sex-adjusted heritability comprises common genes with pleiotropic effects on risk factors for LV phenotypes, as well as unique genes for LV phenotypes. Further adjustment for other covariates helps remove the genetic factors exerting pleiotropic effects on these known risk factors. The persistently significant heritabilities suggested a substantial genetic influence on LV phenotypes. To our knowledge, no heritability information was available in Hispanic patients, especially those of Caribbean origin. The present study suggests that genetic factors contributing to LVM and its related phenotypes may have similar and, possibly stronger, heritability in Caribbean Hispanic patients as in other race-ethnic subgroups.

The Strong Heart Study (SHS) analyzed heritability in mostly sibling data collected from 13 American Indian tribes in different geographic locations (7). They reported significant but smaller estimates of adjusted heritability than ours (Table 2). Dividing their participants into three SHS centers, Bella et al. (7) found no significant heritability in relative pairs from Arizona. The SHS investigators suspected that the Arizona Indians are a more homogenous population, which may segregate fewer genetic polymorphisms influencing LV parameters. Using white twin pairs recruited from the general population, Swan et al. (8) reported substantial unadjusted heritabilities of LVM and LV geometric data (Table 2). Adjustment for age, gender, blood pressure, and weight reduced the estimate of heritability from 0.69 to 0.53 for LVM (no adjusted heritabilities for other parameters were reported). Mayosi et al. (9) showed lower heritabilities in white families ascertained through hypertensive probands (Table 2). Garner et al. (10) presented adjusted heritability of 0.28 for LVM in white European nuclear families. Using the correlation between relative pairs, Post et al. (12) estimated adjusted heritability of

Table 2. Heritability Estimates in the Recent Studies

	Bella et al. (7)*	Garner et al. (10)†	Mayosi et al. (9)‡	Swan et al. (8)§	Post et al. (12)‖
Ethnicity	American Indian	White	White	White	White
Data type	Families	Nuclear families	Families	Twins	Relative pairs
LVM	0.17	0.28	0.23	0.69	0.24–0.32
RWT	0.17	—	—	—	—
LVDD	0.33	—	0.19	0.61	—
LVSD	—	—	—	0.27	—
IVS	0.12	—	0.17	0.34	—
PWT	0.09	—	0.06	0.61	—

*Adjusting for age, gender, research center, weight, height, systolic blood pressure, heart rate, medications, and diabetes. †Adjusting for weight. ‡Adjusting for age, gender, systolic blood pressure, weight, waist-hip ratio, and diabetes. §No adjustment for all parameters. ‖Adjusting for gender, age, height, weight, and systolic blood pressure: heritability was 0.32 from sibling pairs, 0.30 from parent-child pairs, and 0.24 from second-degree relative pairs.

Abbreviations as in Table 1.

approximately 0.30 for LVM in the Framingham Heart Study. Analyzing data among hypertensive siblings, the HyperGEN study found that African American subjects had higher sibling correlation in LVM compared with white subjects (11) but that white subjects had a higher correlation in RWT than did African American subjects. However, no heritability was presented in their study.

Unlike most previous studies, we assessed the heritability of LVM after correction by the three most commonly used indices of body size. The estimates of heritability of LVM were not significantly affected by the type of indexing chosen, especially for model 3, with the greatest number of covariates (Table 1). This observation suggests that no single body size index appears preferable in studies on adult populations similar to ours. Adjustment for covariates other than body size, age, and gender had almost no influence on estimates of heritability in models 2 and 3.

More than 40% of our subjects were hypertensive, and 34.5% were taking antihypertensive medication. In our models, adjusting for SBP and antihypertensive medication did not appreciably influence the estimates of heritability after accounting for age, gender, weight, and height. Furthermore, excluding all participants taking antihypertensive medications had little effect on heritability estimations, although it yielded less significant p values (data not shown). Therefore, the effect of hypertension and antihypertensive medication may not be substantial in our study.

In summary, our study indicated that significant genetic factors influence the familial resemblance of LVM in the Caribbean Hispanic population. The considerable estimates of heritability provide the basis for our long-term goal of NOMAFS to map and detect genetic variants contributing to LVM and its related phenotypes.

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Letters to the Editor

Patent Foramen Ovale/Atrial Septal Defect Closure and Migraine: Searching the Rationale for the Procedure

Azarbal et al. (1) studied closing patent foramen ovale (PFO) or atrial septal defect (ASD) for prophylaxis of migraine. The accompanying editorial highlights areas of caution (2). Additional concerns are: 1) Both right-to-left shunt (PFO) and left-to-right shunt (ASD) appear associated with migraine (3). 2) Closure of ASD improves left ventricular stroke volume; this physiological variable (3) might be involved in precipitating daily migraines. 3)