Intrafamilial Aggregation and Heritability of Left Ventricular Geometric Remodeling Is Independent of Cardiac Mass in Families of African Ancestry

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BACKGROUND
Whether left ventricular (LV) geometric remodeling, as indexed by relative wall thickness (RWT), aggregates in families and is inherited independent of LV mass (LVM) and additional confounders is uncertain.

METHODS
We determined whether RWT as assessed from 2D targeted M-mode echocardiography shows intrafamilial aggregation and heritability independent of LVM in 181 nuclear families (73 spouse pairs, 403 parent–child pairs, and 177 sibling–sibling pairs) with 16 families including 3 generations from an urban developing community of black Africans. Intrafamilial aggregation and heritability estimates (S.A.G.E. software) were assessed independent of confounders, including central aortic systolic blood pressure (SBPc) (radial applanation tonometry and SphygmoCor software).

RESULTS
Independent of confounders including SBPc, LV RWT was correlated in parent–child ($r = 0.32, P < 0.0001$) and sibling–sibling ($r = 0.29, P < 0.0001$), but not in spouse ($r = 0.11, P = 0.33$) pairs. The relationships between parent–child ($r = 0.28, P < 0.0001$) and sibling–sibling ($r = 0.24, P < 0.001$) pairs persisted with further adjustments for LVM or LVM indexed to height1–2 (LVMI). Similarly, independent of confounders, LV RWT showed significant heritability ($h^2 \pm SEM = 0.56 \pm 0.09, P < 0.0001$) and this persisted with further adjustments for LVM ($h^2 \pm SEM = 0.48 \pm 0.09, P < 0.0001$) or LVMI ($h^2 \pm SEM = 0.49 \pm 0.09, P < 0.0001$).

CONCLUSIONS
In a group of African ancestry, independent of LVM, LV geometric remodeling shows significant intrafamilial aggregation and heritability. Genetic factors may in-part determine the LV geometric remodeling process independent of the extent of cardiac hypertrophy.

Keywords: blood pressure; hypertension; inheritance; intrafamilial aggregation; left ventricular remodeling.

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As acknowledged by all guidelines, left ventricular hypertrophy (LVH) is a major risk factor for cardiovascular events independent of conventional risk factors and coronary artery disease. In addition, compared to a normal LV geometry, concentric LV remodeling (an increased relative wall thickness (RWT) without an increase in LV mass (LVM)) is associated with a worse prognosis.1–4 Although LVM rather than concentric LV remodeling predicts incident heart failure,5 concentric LV remodeling without LVH is associated with the development of diastolic dysfunction, and concentric rather than eccentric LVH is associated with greater increases in indices of LV filling pressures.5 Thus, the extent of concentric LV remodeling may determine whether progression from LVH to heart failure with a preserved rather than reduced systolic chamber function occurs. The factors that determine LV remodeling are therefore of considerable interest. Although the impact of age, sex, blood pressure, and obesity on LV geometric remodeling has been well described, there is nevertheless uncertainty as to the role of genetic factors independent of LVM, a major determinant of LV wall thickness, and a change that itself is well recognized as being inherited.6–14

Compared to age-, and sex-matched controls, siblings of those with LVH have a greater risk of concentric, but not eccentric LVH.9 However, in that study,9 whether siblings were also at risk for concentric LV remodeling is uncertain and hence LVM may have made a major contribution to the inheritance of concentric LVH. Moreover, in the Framingham Heart Study, the risk for concentric LV remodeling was only modestly increased in related compared to unrelated individuals, whereas the risk for concentric LVH was markedly augmented.15 Hence, again, LVM may have been the major determinant of the inheritance of LV remodeling. Although alternative studies indicate that RWT is indeed inherited,16 none of these studies reported on the inheritance of RWT independent of LVM. To address the

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amongst uncertainty as to the extent to which genetic factors contribute toward concentric LV remodeling beyond LVM, in the present study, we aimed to evaluate the intrafamilial aggregation and heritability of RWT independent of LVM and additional confounders. We hypothesized that RWT would show intrafamilial aggregation and heritability independent of LVM and additional confounders.

**METHODS**

**Study participants**

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. Briefly, families of black African descent (Nguni and Sotho chieftdoms) with siblings older than 16 years of age were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa, using the population census figures of 2001. Family members were invited to take part in the study if at least 1 or 2 offspring and one or both parents were available for examination. Eight hundred and twenty-nine participants (91%) consented to an echocardiographic procedure and had no evidence of significant valve abnormalities assessed using 2D and color Doppler imaging. None of the participants had previously had a myocardial infarction (only 3 had a history of ischemic heart disease), and there were no cases of atrial fibrillation. High-quality echocardiograms could be obtained in 694 participants. The high prevalence of obesity limited the quality of echocardiograms obtained in 135 participants of whom 91.5% were female (body mass index = 39.4 ± 5.9 kg/m²). Six hundred and seventy-five participants from 181 nuclear families with 16 families including 3 generations with complete familial pairwise were therefore available for the present analysis.

**Clinical, demographic, anthropometric, and laboratory assessments**

A standardized questionnaire was administered to obtain demographic and clinical data. Regular alcohol consumption was defined as at least 5 glasses of beer per week or 1 bottle of wine per week or half bottle of spirits per week. Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index was ≥25 kg/m² and obese if their body mass index was ≥30 kg/m². Standard laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin were performed. Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or a glycated hemoglobin value greater than 6.1%. Participants’ blood groups (ABO and Rhesus) were evaluated to confirm Mendelian segregation. Mendelian inconsistencies were identified if blood groups of family members were incompatible with relationships between family members representing first, second, or third generations.

**Office blood pressure**

High-quality office BP measurements were obtained by a trained nurse-technician who measured brachial artery systolic and diastolic BP to the nearest 2 mm Hg using a standard mercury sphygmomanometer, according to the recommendations of the European Society of Hypertension and the American Heart Association. The nurse was of the same ethnic origins (black African) as the participants and had previously lived in SOWETO. Korotkov phases I and V were employed to identify systolic and diastolic BP, respectively, and care was taken to avoid auscultatory gaps. Office BP was measured 5 times consecutively using appropriately sized cuffs (a standard sized cuff was used, but if upper arm circumference exceeded 31 cm, then a larger cuff was used) after the subjects had rested for 5–10 minutes in the sitting position in a quiet room away from onlookers. The mean of all 5 office BP measurements was used in the analysis.

**Aortic blood pressure**

To determine central aortic systolic BP (SBPc), pulse wave analysis was conducted using techniques previously described. After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, TX) interfaced with a computer employing SphygmoCor, version 6.21 software (AtCor Medical Pty. Ltd, West Ryde, New South Wales, Australia). Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. All measurements were made by a single experienced trained technician unaware of the clinical history of the participants. To determine SBPc, the pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. From an inbuilt validated generalized transfer function, an aortic waveform was generated from which SBPc was derived.

**Echocardiography**

Two-dimensional targeted M-mode echocardiography was employed to determine short axis dimension measurements as described previously and analyzed according to the American Society of Echocardiography convention. All measurements were recorded and analyzed off line by experienced investigators (C.D.L. and A.J.W.) whom were unaware of the clinical data of the participants. Left ventricular mass (LVM) was determined using a standard formula: (LVM = 0.8 × [1.04 (LV end diastolic diameter + LV end diastolic septal wall thickness + LV end diastolic posterior wall thickness)² – (LV end diastolic diameter)²] + 0.6 g) and indexed (LVMi) to height. The intra- and interobserver variabilities have previously been described. LVH was identified as an LVMi > 51 g/m². LV RWT was calculated as (LV end diastolic septal (anterior) + posterior wall thickness)/LV end diastolic diameter. An RWT of >0.45 was considered as increased.
Results

Characteristics of participants

The number of offspring (second and third generations) per family (n = 181) amounted to 1 in 63 families, 2 in 84 families (7 of these families included grandchildren), 3 in 20 families, and more than 3 in 14 families (which included 4 families with 4 offspring, 1 family with 5 offspring, and 9 families with grandchildren and half-siblings). Pairs were defined based on relationships within families. Consequently, an individual can be part of more than 1 pair. There were 73 father–mother pairs, 403 parent–child pairs (46 father–son, 70 father–daughter, 104 mother–son, and 183 mother–daughter pairs), and 177 sibling–sibling pairs (24 son–son, 84 daughter–daughter, and 69 daughter–son pairs). No cases of Mendelian inconsistency were noted. More women than men participated in the study. The characteristics of the parents and siblings are given in Table 1. Importantly, 43% of participants were hypertensive, 25% of participants were receiving antihypertensive medication, and 35% of participants had uncontrolled hypertension (those that were not receiving antihypertensive medication plus those that were receiving antihypertensive therapy but whose blood pressure was not controlled). Sixty-seven percent of participants had a normal LVMI and RWT, 11% had a normal LVMI, but an increased RWT (concentric LV remodeling), 6% had an increased LVMI and RWT (concentric hypertrophy), and 16% had an increased LVMI, but a normal RWT (eccentric hypertrophy). The prevalence of concentric or eccentric LVH in siblings was low (Table 1). The general characteristics of participants not included in the study were similar to the characteristics of the participants evaluated (data not shown).

LVM and LVMI are associated with RWT

Both LVM (r = 0.30, P < 0.0001) and LVMI (r = 0.33, P < 0.0001) were correlated with RWT.

Heritability of LVM and LVMI

With adjustments for confounders, LVM and LVMI were inherited (Table 2).

Intrafamilial aggregation of RWT

With adjustments for confounders, the correlation coefficients of parent–sibling and sibling–sibling pairs were significant for RWT and these relationships persisted with further adjustments for either LVM or LVMI (Figure 1). With adjustments for confounders, no significant correlations were noted for RWT between spouse pairs (Figure 1).

Heritability estimates of RWT

With adjustments for confounders, as well as with further adjustments for either LVM or LVMI, RWT showed heritability (Table 3).
Table 1. Characteristics of parents and offspring of the study sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parents (n = 320)</th>
<th>Offspring (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% females)</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>30 ± 11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33 ± 7</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>% Regular smoking</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>% Regular alcohol intake</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>% With DM or HbA1c &gt; 6.1%</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>% With hypertension</td>
<td>71</td>
<td>19</td>
</tr>
<tr>
<td>% Treated for hypertension</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Office SBP/DBP (mm Hg)</td>
<td>140 ± 23/88 ± 13</td>
<td>119 ± 16/80 ± 12</td>
</tr>
<tr>
<td>Central aortic SBP (mm Hg)</td>
<td>132 ± 23</td>
<td>110 ± 18</td>
</tr>
<tr>
<td>Left ventricular mass (LVM) (g)</td>
<td>172 ± 57</td>
<td>139 ± 40</td>
</tr>
<tr>
<td>LVM index (g/m²²)</td>
<td>48 ± 16</td>
<td>38 ± 10</td>
</tr>
<tr>
<td>LV relative wall thickness</td>
<td>0.43 ± 0.09</td>
<td>0.37 ± 0.07</td>
</tr>
<tr>
<td>LV mean wall thickness (cm)</td>
<td>0.96 ± 0.21</td>
<td>0.83 ± 0.17</td>
</tr>
<tr>
<td>LV end diastolic diameter (cm)</td>
<td>4.80 ± 0.59</td>
<td>4.70 ± 0.52</td>
</tr>
<tr>
<td>% Concentric LVH</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>% Eccentric LVH</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>% Concentric LV remodeling</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic BP; DM, participants receiving medication for diabetes mellitus; HbA1c, glycated hemoglobin; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

*Fourteen participants are included as both offspring and parents as they are parents of third-generation offspring.

Table 2. Unadjusted and multivariate-adjusted heritability estimates (\(h^2\)) of left ventricular mass (LVM) and left ventricular mass index (LVMI)

<table>
<thead>
<tr>
<th>Adjustments*</th>
<th>(h^2 ± SEM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.52 ± 0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjustors including aortic SBP</td>
<td>0.49 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjustors including brachial SBP</td>
<td>0.48 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.47 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjustors including aortic SBP</td>
<td>0.46 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjustors including brachial SBP</td>
<td>0.48 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjustments are for age, age², sex, aortic systolic blood pressure (SBP) or brachial SBP, body weight, body height (except for LVMI), regular smoking, regular alcohol intake, treatment for hypertension, treatment for diabetes mellitus or a glycated hemoglobin >6.1%, and pulse rate.

DISCUSSION

In a relatively large family-based study, we show that RWT, an index of the extent of concentric LV geometric remodeling, demonstrated intrafamilial aggregation and heritability (\(h^2 ± SEM: 0.56 ± 0.09\)). Importantly, the intrafamilial aggregation and heritability of RWT were independent of LVM and LVMI as well as other confounders (\(h^2 ± SEM: 0.48 ± 0.09\)).

Although a number of prior studies have reported heritability or intrafamilial aggregation of LVM or LVMI, few studies have assessed the intrafamilial aggregation or heritability of LV RWT\(^9,10,12,14,16\). Only 2 of these 5 prior studies reported heritability values (\(h^2 ± SEM: 0.17 ± 0.08\); 0.25\(^{16}\)) and in another prior study, heritability could be estimated from twice the sibling correlations (ranged from 0.08 to 0.24\(^{16}\)). In none of these studies\(^10,12,16\), was the heritability of RWT identified to be independent of LVM or LVMI. In our study without adjustments for LVMI, we obtained heritability estimates for RWT of 0.56 ± 0.09. The higher heritability values obtained in our study compared to 2 of these previous studies\(^10,12\) could be due to the characteristics of the populations assessed. Indeed, the mean RWT in the current study was considerably greater (0.49 in the parents and 0.37 in the offspring) than in 2 of the prior studies (0.35 in both).\(^10,12\) In one of these previous studies,\(^10\) the majority of the participants were hypertensives receiving antihypertensive medication, which would have influenced LV structural values.

Although 3 prior studies\(^10,12,16\) have demonstrated that RWT is inherited (\(h^2 ± SEM: 0.17 ± 0.08\); 0.25\(^{16}\); 2 × sibling correlation ranged from 0.08 to 0.24\(^{16}\)) and aggregates in families\(^10,12\) in these studies, no adjustments for LVM or LVMI were made and hence these effects can be attributed to the well-known influence of hypertrophy on concentric...
LV geometric remodeling. Indeed, in the present study, both LVM and LVMI were strongly associated with RWT. One prior study has reported on familial aggregation of concentric, but not eccentric LVH. In contrast, however, familial aggregation was noted for both concentric and eccentric LVH in the Framingham study. Nevertheless, in the Framingham study, concentric LV remodeling (with or without LVH) also showed intrafamilial aggregation, an effect that suggests that concentric LV geometric remodeling may be inherited independent of LVM. However, in that study, no adjustments for LVM or alternative structural determinants of RWT were reported on. The present study extends the findings of this prior study and shows that RWT indeed aggregates in related individuals in families and shows heritability independent of LVM ($h^2 \pm \text{SEM: } 0.48 \pm 0.09$) and LVMI ($h^2 \pm \text{SEM: } 0.49 \pm 0.09$). The present and this prior study together therefore provide a degree of confidence that concentric LV remodeling shows heritability independent of hypertrophy or alternative LV structural parameters.

In the present study, independent of confounders, heritability estimates ($h^2 \pm \text{SEM}$) for RWT were $0.56 \pm 0.09$ before adjustments for confounders and LVM or LVMI. These RWT heritability estimates ($h^2 \pm \text{SEM}$) are stronger than those previously reported on in American Indians ($0.17 \pm 0.08$) and in largely treated (70%) hypertensive African Americans ($0.25$) without adjustments for LVM or LVMI. At present, there are no data on RWT heritability estimates in Caucasians. The greater heritability estimates reported on in the present study compared to previous studies are possibly because we studied randomly recruited South African families of black African ancestry with a low prevalence (25%) of treatment for hypertension, and it is well recognized that groups of African descent have a greater RWT than other ethnic groups, a difference that could be attributed to stronger genetic effects on LV geometric remodeling. However, sibling correlations for RWT have been reported to be greater in European compared to African Americans. Nevertheless, in that study, only hypertensive siblings were evaluated and hence intrafamilial correlations for LV structure may have been confounded by the effects of BP or antihypertensive treatment. Importantly, in the Multi-Ethnic Study of Atherosclerosis, compared to non-Hispanic whites, non-Hispanic blacks had an increased risk for concentric remodeling with an odds ratio of $1.4$. An important consideration of the present study is that the intrafamilial aggregation of RWT was independent of LVM or LVMI. Thus, although LVM and LVMI showed heritability, the heritability of LV hypertrophy does not appear to determine the intrafamilial aggregation and heritability of the geometric LV remodeling process. Hence, the genes that determine LV hypertrophy should not be seen as necessarily the same genes that influence the overall LV geometric remodeling process. This has important implications for genetic studies as it is possible that the molecular mechanisms that determine cardiomyocyte cell growth (hypertrophy) are unable to account for a significant portion of the LV remodeling process.

The limitations of the present study require consideration. Due to the young age of the siblings studied, a low prevalence of LVH was noted in sibling pairs. Consequently, few siblings had either concentric or eccentric LVH. Therefore, we could not assess the intrafamilial aggregation and heritability of either concentric or eccentric LVH, considered as discrete traits, independent of LVM or LVMI. Second, we assessed the intrafamilial aggregation and heritability of RWT in 1 ethnic group only. Whether similar effects are noted in alternative ethnic groups requires further study. Third, bearing in mind the high prevalence of cardiovascular risk factors such as obesity, hypertension, diabetes mellitus or abnormal blood glucose control, and LVH in the parents,
it is possible that the heritability of RWT tracks the heritability of these risk factors. However, this is unlikely given that the adjusted intraclass correlation coefficients were similar between parent–child pairs and sibling pairs despite the higher prevalence of cardiovascular risk factors in the parents compared to the children. Moreover, in the present study on multivariate analyses, the heritability of RWT was independent of these cardiovascular risk factors.

In conclusion, in the present study, we demonstrate that RWT, an index of concentric LV geometric remodeling, aggregates in families and shows heritability, independent of LVM and LVMI. Thus, a considerable proportion of the genetic factors that determine LV geometric remodeling occur independent of those genes that influence myocyte hypertrophy. As LV geometric remodeling predicts outcomes independent of LVH and may influence whether LVH progresses to heart failure with a preserved or reduced ejection fraction, discovering the genes associated with RWT independent of LVH may cast further light on the genetic mechanisms responsible for adverse cardiovascular outcomes and the progression to heart failure.

PERSPECTIVES

The findings of this study suggest that the genes determining RWT are independent of those that determine LVM. Understanding the genetic factors that determine RWT independent of LVM may provide new insights into the pathophysiological mechanisms of cardiac remodeling. Improved knowledge of these mechanisms is likely to impact on future intervention, thereby reducing the incidence of adverse cardiovascular outcomes.

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DISCLOSURE

The authors declared no conflict of interest.

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