Maternal and Paternal Influences on Left Ventricular Mass of Offspring

Tatiana Kuznetsova, Jan A. Staessen, Agnieszka Olszanecka, Andrew Ryabikov, Katarzyna Stolarz, Sofia Malyutina, Robert Fagard, Kalina Kawecka-Jaszcz, Yuri Nikitin, on behalf of the European Project On Genes in Hypertension (EPOGH) Investigators

Abstract—Significant intrafamilial correlations of left ventricular mass exist in first-degree relatives. However, the specific maternal and paternal influences on left ventricular mass of offspring remain unknown. We therefore evaluated familial aggregation of left ventricular mass by type of familial relation in two European populations. A random sample of 159 nuclear families (250 parents and 321 offspring) was investigated in Cracow, Poland, and Novosibirsk, Russia. The mean age of parents and offspring was 51.4 years and 25.1 years, respectively. Two-dimensionally guided M-mode echocardiography was performed, and left ventricular mass was calculated. As a measure of concordance, we computed correlation coefficients for left ventricular mass between first-degree relatives and between spouse pairs. After adjustment for center, gender, age, height, body weight, systolic blood pressure, antihypertensive treatment, smoking, alcohol intake, and physical activity, the intrafamilial correlations for left ventricular mass were 0.06 (P=0.57) in 91 spouse-spouse pairs, 0.14 (P=0.002) in 500 parent-offspring pairs, and 0.32 (P<0.001) in 179 sib-sib pairs. Across the four parent-offspring relations, the intrafamilial correlations of left ventricular mass differed. The mother-son (n=140, r=0.27, P<0.001) and mother-daughter (n=161, r=0.28, P<0.001) correlations were significant, whereas the father-son (n=101, r=0.04, P=0.69) and father-daughter (n=98, r=−0.09, P=0.38) correlations were not different from zero. Overall, the mother-offspring correlation coefficient was significantly higher than the father-offspring correlation (r=0.28 versus r=−0.04; P=0.005). Thus, maternal factors appear to have more impact on left ventricular mass of offspring than do paternal influences. Further studies are required to elucidate the genetic, epigenetic, and ecogenetic mechanisms underlying these divergent parent-offspring correlations. (Hypertension. 2003;41:69-74.)

Key Words: genetics ▪ blood pressure ▪ ventricular function, left ▪ hypertrophy ▪ echocardiography

Left ventricular hypertrophy is a major and independent risk factor for cardiovascular morbidity and mortality,1 even among normotensive subjects.2 Left ventricular mass results from the complex interaction between genetic, environmental, and lifestyle factors. Known and postulated determinants of left ventricular mass include gender, age, body size, systolic blood pressure, physical activity, smoking, alcohol consumption, and various endocrine and paracrine growth factors.3–6 Twin studies in Europe7–8 and the United States9–10 have demonstrated that inherited factors are important determinants of left ventricular mass. The contribution of heredity to the variability of left ventricular mass was also investigated in population-based studies in France11 and in North America,12–14 particularly in Framingham12 and Tecumseh.13 These studies documented significant intraclass correlations of left ventricular mass in first-degree relatives and identified a small but discernible proportion of its variance as being due to heredity. However, the specific maternal and paternal influences on left ventricular mass of offspring remain largely unknown. We therefore evaluated familial aggregation of left ventricular mass by type of familial relation in two Eastern European populations.

Methods

General Outline of the Study

The primary goal of the European Project on Genes in Hypertension (EPOGH) project was to investigate the complex relation between blood pressure analyzed as a continuous or binary phenotype and various candidate genes.15 In addition to blood pressure, several other intermediary or associated phenotypes, such as left ventricular mass, were measured. The epidemiological methods used in EPOGH have been previously validated.16,17 The project was conducted according to the principles outlined in the Helsinki declaration for investigations in human subjects.18 Each local institutional review board approved the study. Participants gave written informed consent.
Study Population

Random samples of nuclear families were recruited in 7 countries (Belgium, Bulgaria, the Czech Republic, Italy, Poland, Romania, and the Russian Federation). To increase the number of hypertensive patients, centers in Czechia, Poland, Romania, and Russia also recruited ~30% of the required number of nuclear families through specialized clinics for hypertensive patients. Nuclear families had to include at least one parent and two siblings. To minimize misclassification of half-sibs and to exclude consanguinity among families, parents were asked to provide a tree-generation pedigree. ABO blood group and rhesus phenotypes were verified for inconsistencies in mendelian segregation. The age range for participation was 18 to 60 years. For the present analysis, the study population was limited to 631 subjects recruited by the two centers that had participated in the optional sub study on echocardiography: Cracow (Poland, center 1) and Novosibirsk (the Russian Federation, center 2). Subjects were not considered for analysis (1) if they had declined the invitation for the echocardiographic examination (n=49), (2) if the echocardiogram was of insufficient quality for the assessment of left ventricular mass (n=7), (3) if the subjects had a history of myocardial infarction with an ejection fraction <40% (n=3), or (4) if they had a valvular disorder (n=1).

After the subjects had rested in the sitting position for 10 minutes or longer, a trained observer obtained 5 consecutive blood pressure readings with a mercury sphygmomanometer, with an interval of 30 to 60 seconds between measurements.19 Body surface area was calculated as body weight (kg)1/3×body height (cm)2/3×71.84.20 Through a standardized interview, the observer also collected information on each participant’s personal and familial medical history, smoking and drinking habits, physical activity, and use of medications. The energy spent in physical activity was calculated from the time devoted to sports and physical labor, with the use of published tables.21

Echocardiographic Methods

In each center, one experienced observer performed all echocardiograms by using a commercially available ultrasonograph equipped with a 3.5-MHz transducer, with the subject in left decubitus position. M-mode echocardiograms of the left ventricle were obtained at end-expiration from the parasternal long-axis view under control of the 2-dimensional image. The ultrasound beam was positioned just below the mitral valve at the level of the posterior chordae tendineae. Left ventricular internal diameter and interventricular septal (IVST) and posterior wall thickness (PWT) were measured at end-diastole according to the recommendations of the American Society of Echocardiography, using the leading edge-to-leading edge convention.22,23 For statistical analysis, the measurements of 3 cardiac cycles were averaged. Studies were recorded on videotape. End-diastolic left ventricular dimensions were used to calculate left ventricular mass by an anatomically validated formula.24 Mean wall thickness was calculated as (IVST+PWT)/2. The intraobserver interseesion reproducibility coefficient for left ventricular mass calculated according to the method of Bland and Altman was 2.5% for center 1 and 2.0% for center 2.

Statistical Analysis

We used the SAS software package version 6.12 (SAS Institute) for database management and statistical analysis. Comparison of means and proportions relied on the standard normal z test and the χ2 statistic, respectively. We calculated for the echocardiographic measurements correlation coefficients between members of the same family as a measure of concordance (positive correlation) or discordance (negative correlation).25 Hence, in the context of this article, the terms correlation and concordance are used interchangeably. To estimate the intrafamilial correlations, we used generalized estimating equations as implemented in the PROC GENMOD procedure26 of the SAS package. In these analyses, we adjusted for confounders, we treated pairs of relatives as clusters, and we defined the working correlation matrix as unstructured. Adjustments were cumulative and performed in 4 steps to check consistency of the parameter estimates while controlling for an increasing number of variables known to influence left ventricular mass.2-6 First, in model 1, we adjusted only for center, gender, and age. Model 2 also included body weight and height. In model 3, we added systolic blood pressure and antihypertensive treatment as explanatory variables. Finally, we considered various lifestyle factors such as smoking, alcohol intake, and physical activity (model 4). We derived the significance of the intrafamilial correlation coefficients from z test statistics. We compared correlation coefficients by using Fisher’s z transformation.27

Results

Demographic and Clinical Characteristics of Parents and Offspring

Our study population (n=571) included 250 parents (101 fathers and 149 mothers), 321 offspring (152 sons and 169 daughters), and 91 two-parent and 68 single-parent families. The number of offspring per family amounted to 1 in 12 families, 2 in 134 families, and 3 in 13 families. We did not detect any case of false paternity and ascertained that each nuclear family belonged to a separate pedigree.

The clinical, demographic, lifestyle, and echocardiographic characteristics are reported by generation in Tables 1 and 2. The mean age of parents and offspring (±SD) was 51.4±5.4 years and 25.1±5.0 years, respectively. As expected, body weight and blood pressure as well as left ventricular mass were higher in parents than in offspring. In both generations, left ventricular mass indexed to body surface area was greater in men than in women. Left ventricular mass indexed to height27 was similar in adult women and men but greater in young men than young women.

Intrafamilial Correlation Coefficients for Left Ventricular Mass

Correlation coefficients obtained for adjusted left ventricular mass are shown in Figure 1 for sib-sib, parent-offspring, and spouse-spouse pairs. The intraclass correlations for left ventricular mass adjusted for center, gender, and age (model 1) were highest in siblings (r=0.35; 95% CI, 0.21 to 0.47; P<0.001), intermediate in parent-offspring pairs (r=0.23; 95% CI, 0.15 to 0.31; P<0.001), and lowest between spouses (r=0.11; 95% CI, −0.10 to 0.31; P=0.30). Subsequently, three other models were generated, controlling for an increasing number of variables known to influence left ventricular mass (Figure 1). After further adjustment for anthropometric characteristics, systolic blood pressure, antihypertensive treatment, smoking, alcohol intake, and physical activity (model 4), the intrafamilial correlation coefficients were 0.32 (95% CI, 0.18 to 0.45; P=0.001) in 179 sib-sib pairs, 0.14 (95% CI, 0.05 to 0.22; P=0.002) in 500 parent-offspring pairs, and 0.06 (95% CI, −0.15 to 0.26; P=0.57) in 91 spouse-spouse pairs.

Among siblings (Figure 2), the correlation coefficients tended to be stronger in sister-sister (r=0.49; 95% CI, 0.25 to 0.67; P<0.001) and brother-brother pairs (r=0.32; 95% CI, 0.03 to 0.56; P=0.02) than in opposite-gender pairs (r=0.22; 95% CI, 0.003 to 0.42; P=0.04). Among the four types of parent-offspring pairs, we noticed a divergent pattern of the intrafamilial correlations of left ventricular mass (Figure 3). After full adjustment for all covariables (model 4), the mother-son (r=0.27; 95% CI, 0.11 to 0.42) and mother-
daughter \((r=0.28; 95\% \text{ CI}, 0.13 \text{ to } 0.42)\) correlations were significant \((P<0.001)\), whereas the father-son \((r=0.04; 95\% \text{ CI}, -0.16 \text{ to } 0.23; P=0.69)\) and father-daughter \((r=-0.09; 95\% \text{ CI}, -0.28 \text{ to } 0.11; P=0.38)\) correlations were not different from zero. Overall the mother-offspring correlation coefficient was significantly higher than the father-offspring correlation \((r=0.28 \text{ versus } r=-0.04, P=0.005)\). The pattern of intrafamilial correlations for left ventricular end-diastolic diameter and mean wall thickness was similar to that of left ventricular mass (Table 3).

Because correlation coefficients only express the degree of concordance between relatives, we also evaluated regression coefficients between left ventricular mass of parents and offspring with similar adjustments applied as in model 4. The regression coefficient \((\pm \text{SE})\) was \(0.17 \pm 0.05 \text{ (}P>0.001\) for mother-offspring pairs and \(0.06 \pm 0.05 \text{ (}P=0.26\) for father-offspring pairs.

To exclude that the difference between the mother-offspring and father-offspring correlation coefficients was due to a type I error, we randomly created fictive “parent-offspring” pairs using the RANBIN function provided by SAS software. In this analysis of unrelated subjects, the fictive “mother-offspring” correlation coefficient was 0.09 (95% CI, -0.02 to 0.20; \(P=0.12\)) and the “father-offspring” correlation coefficient was -0.02 (95% CI, -0.16 to 0.12; \(P=0.78\)).

**Intrafamilial Correlation Coefficients for Anthropometric Characteristics**

The intrafamilial correlation coefficients for height, body weight, and body mass index are summarized in Table 4. After adjustment for gender (only if different) and age, correlation coefficients for height ranged from 0.45 in mother-daughter pairs to 0.59 in father-son pairs. For body weight, the adjusted parent-offspring correlation varied from 0.20 to 0.30. The correlation coefficient for body weight in spouse-spouse pairs tended to be weaker than those in sib-sib pairs \((r=0.07 \text{ versus } r=0.30, P=0.06)\).

**Discussion**

We calculated the intrafamilial correlation coefficients as a measure of the degree of similarity between subjects. We
adjusted our analysis first for center, gender, and age (model 1) and subsequently for anthropometric characteristics, systolic blood pressure, use of antihypertensive medications, and lifestyle factors that possibly influence left ventricular structure (models 2 to 4). We found that left ventricular mass is significantly concordant among siblings and in mother-offspring pairs but not in father-offspring pairs or between spouses. Siblings belong to the same generation and have more genetic material in common than their parents. Accordingly, after accounting for the aforementioned confounders, the intraclass correlation between siblings for left ventricular mass was 0.32. After similar adjustments, no significant correlation was found among spouse pairs. These results are comparable with those observed for left ventricular mass in North American populations.12,14 For instance, in the Framingham study,12 the adjusted correlation coefficients for sib-sib and spouse-spouse pairs were 0.16 and 0.05, respectively. The higher intraclass correlation between siblings, which we observed in our study (0.32 versus 0.16 in Framingham;12 P=0.03), may be due to differences in the sampling frame or age range and/or selective inclusion of hypertensive families in the study sample. Furthermore, we noticed that the sib-sib correlations for adjusted left ventricular mass were 0.22 in opposite-gender pairs, 0.32 in brother-brother pairs, and 0.49 in sister-sister pairs. These results are consistent with the findings of Arnett et al,14 who reported a greater adjusted left ventricular mass intraclass correlation in same-gender compared with opposite-gender white hypertensive siblings (0.22 versus 0.05).

After adjustment for the main confounders, the intrafamilial correlation for left ventricular mass between parents and offspring was 0.14 in our study. Furthermore, we noticed that the parent-offspring correlations were significantly higher in mother-offspring pairs than in father-offspring pairs. The intrafamilial correlation coefficient for adjusted left ventricular mass among father-offspring pairs was not statistically different from zero. Garner et al11 reported no statistically significant differences in father-offspring, mother-offspring, and sib-sib correlations for left ventricular mass. However, in line with the present findings, Garner’s point estimates of the intrafamilial correlation coefficients were 0.12 and 0.05 in father-son and father-daughter pairs and 0.23 and 0.19 in mother-son and mother-daughter pairs.

We excluded false paternity, consanguinity among families, and a type I error as possible explanations for the divergent parent-offspring correlations for left ventricular mass. These findings might be related to specific maternal genetic, epigenetic, or ecogenetic influences. Left ventricular structural adaptation is highly dependent on oxidation of glucose and fatty acids by mitochondria.28 Maximal aerobic power has also been demonstrated to be under predominant
maternal influence. A plausible working hypothesis is that the close concordance between mothers and offspring might be explained by mitochondrial DNA that sons and daughters inherit from their mother. In line with this hypothesis, some genetic mutations of mitochondrial DNA are known to lead to severe cardiomyopathies with matrilineral transmission patterns.

Mitochondrial DNA constitutes only a minor fraction of the genome. The mendelian hypothesis that offspring derived their genetic makeup in equal proportions from their mothers and fathers is known to be incorrect. Genomic imprinting is the differential modification of the maternal and paternal contributions to the zygote. Thus, offspring are under influences of distinct maternal and paternal “imprints” that result in divergent expression of parental alleles during development and growth into adulthood. Furthermore, a recent study found that maternal and paternal chromosomes show many differences in location of recombination maxima and found evidence to suggest that both genetic and environmental factors may affect recombination rates. The intrauterine environment plays a pivotal role in the development of the fetus and is predominantly determined by genetic and environmental factors linked to the mother.

The current study should be interpreted within the context of its limitations. It does not allow differentiating inherited genetic factors from environmental influences later in life. Sons and daughters share the same home as well as nutritional habits. The home environment is usually also shared by the mother and to lesser extent by the father, who is more commonly involved in work outside the home. Thus, environmental factors may also explain why we failed to detect any significant association in left ventricular mass between fathers and offspring. We accounted in our analysis for physical activity, but we cannot exclude that adaptation of left ventricular mass to manual labor remained a confounding factor, especially in the fathers.

Anthropometric characteristics such as body weight and height are strong correlates of left ventricular mass. In the present analysis we did not examine the cross-trait intrainfamilial relations between left ventricular mass and anthropometric characteristics. However, in keeping with the high heritability of anthropometric characteristics in twin studies, we found sib-sib correlation coefficients of 0.52 for height and 0.30 for weight. We also noticed a significant concordance of height between spouses, which is likely to be due to assortive mating. In agreement with previous studies in middle-aged subjects, the spouse-spouse correlations for body weight and body mass index were weak and statistically nonsignificant. These confirmatory findings for body weight and height, in our view, constitute a validation of the present study.

### Perspectives

Maternal factors seem to affect left ventricular mass of offspring more than paternal influences. If confirmed, our findings may be relevant for the interpretation of published studies on the possible effects of candidate genes on left ventricular mass. Further studies are required to elucidate the genetic, epigenetic, and ecogenetic mechanisms underlying the divergent parent-offspring correlations for left ventricular mass.

### Table 3. Adjusted Correlation Coefficients for Left Ventricular Measurements

<table>
<thead>
<tr>
<th>Relation</th>
<th>LVID</th>
<th>P</th>
<th>MWT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouse-spouse, n=91</td>
<td>0.06 (0.15-0.26)</td>
<td>0.57</td>
<td>-0.05 (0.25-0.16)</td>
<td>0.64</td>
</tr>
<tr>
<td>Sib-sib, n=179</td>
<td>0.33 (0.19-0.45)</td>
<td>&gt;0.001</td>
<td>0.27 (0.12-0.39)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Father-son, n=101</td>
<td>0.07 (-0.13-0.26)</td>
<td>0.52</td>
<td>0.13 (-0.07 to 0.32)</td>
<td>0.19</td>
</tr>
<tr>
<td>Father-daughter, n=98</td>
<td>-0.10 (-0.29-0.10)</td>
<td>0.32</td>
<td>-0.08 (-0.27-0.12)</td>
<td>0.43</td>
</tr>
<tr>
<td>Father-offspring, n=199</td>
<td>0.03 (-0.11-0.17)</td>
<td>0.67</td>
<td>0.04 (-0.10-0.18)</td>
<td>0.57</td>
</tr>
<tr>
<td>Mother-son, n=140</td>
<td>0.35 (0.20-0.49)</td>
<td>&gt;0.001</td>
<td>0.21 (0.05-0.36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mother-daughter, n=161</td>
<td>0.18 (0.03-0.33)</td>
<td>0.02</td>
<td>0.14 (-0.01-0.29)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mother-offspring, n=301</td>
<td>0.23 (0.12-0.33)</td>
<td>&gt;0.001</td>
<td>0.17 (0.06-0.28)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Correlation coefficients are fully adjusted (see Model 4 in Figure 1). MWT indicates mean wall thickness; CI, confidence interval.

### Table 4. Adjusted Correlation Coefficients for Anthropometric Characteristics

<table>
<thead>
<tr>
<th>Relation</th>
<th>Height, cm</th>
<th>P</th>
<th>Weight, kg</th>
<th>P</th>
<th>Body Mass Index, kg/m²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spouse-spouse, n=91</td>
<td>0.39 (0.20-0.55)</td>
<td>&gt;0.001</td>
<td>0.07 (-0.14-0.27)</td>
<td>0.51</td>
<td>0.07 (-0.14-0.27)</td>
<td>0.51</td>
</tr>
<tr>
<td>Sib-sib, n=179</td>
<td>0.52 (0.40-0.62)</td>
<td>&gt;0.001</td>
<td>0.30 (0.16-0.43)</td>
<td>&gt;0.001</td>
<td>0.19 (0.04-0.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Father-son, n=101</td>
<td>0.59 (0.45-0.70)</td>
<td>&gt;0.001</td>
<td>0.30 (0.11-0.47)</td>
<td>0.002</td>
<td>0.22 (0.03-0.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Father-daughter, n=98</td>
<td>0.53 (0.37-0.66)</td>
<td>&gt;0.001</td>
<td>0.21 (0.01-0.39)</td>
<td>0.04</td>
<td>0.23 (0.03-0.41)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mother-son, n=140</td>
<td>0.46 (0.32-0.58)</td>
<td>&gt;0.001</td>
<td>0.20 (0.04-0.35)</td>
<td>0.02</td>
<td>0.12 (-0.05-0.28)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mother-daughter, n=161</td>
<td>0.45 (0.32-0.57)</td>
<td>&gt;0.001</td>
<td>0.23 (0.08-0.37)</td>
<td>0.003</td>
<td>0.20 (0.05-0.34)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correlation coefficients were adjusted for gender and age.
Appendix

Coordination and Committees

Project Coordinator: J.A. Staessen; Scientific Coordinator: K. Kawecka-Jaszcz; Steering Committee: S. Babeau (Romania), E. Casiglia (Italy), J. Fillipovsky (Czech Republic), K. Kawecka-Jaszcz (Poland), C. Nachev (Bulgaria), Y. Nikitin (Russian Federation), J. Peleská (Czech Republic), J.A. Staessen (Belgium); Data Management Committee: T. Kuznetsova, J.A. Staessen, K. Stolarz, V. Tikhonoff, J.G. Wang; Publication Committee: E. Casiglia, K. Kawecka-Jaszcz, Y. Nikitin; Advisory Committee on Molecular Biology: G. Bianchi (Milan), E. Brand (Berlin), H.A. Struijker-Boudier (Maastricht); EPOGH-EurNetGen Liaison: A. Dominiczak (Glasgow), J.A. Staessen (Leuven).

EPOGH Centers

A complete list of the EPOGH Investigators has been previously published. 18

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References

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