Heritability of Subclinical Atherosclerosis in Latino Families Ascertained Through a Hypertensive Parent


Abstract—Although clinical coronary heart disease and many cardiovascular risk factors are well known to aggregate within families, the heritability of carotid artery intima-media thickness (IMT) is less well documented. We report IMT heritability estimates in Mexican American, Salvadoran American, or Guatemalan American (all referred to as Latino) families ascertained through a hypertensive proband. IMT and cardiovascular risk factors (age, sex, blood pressure, body mass index, lipids, fasting glucose, and insulin sensitivity) were measured in 204 adult offspring of 69 hypertensive probands, along with 82 parents (54 probands and 28 spouses). In the offspring, variance component analysis revealed a heritability for IMT of 64% (P<0.0001) after adjustment for significant cardiovascular risk factors. Genetic factors accounted for 50% of the total variation in IMT, whereas significant cardiovascular risk factors explained 22% (14% were due to age). For offspring and parents combined, adjusted IMT heritability was less, 34% (P=0.0005), with genetic factors accounting for 18% of the total IMT variation, whereas significant cardiovascular risk factors explained 46% (38% were due to age). We conclude that variation in common carotid artery IMT is heritable in Latino families with a hypertensive proband. Heritability is particularly evident in younger family members, suggesting that acquired factors contribute progressively to IMT variability with aging. (Arterioscler Thromb Vasc Biol. 2002;22:843-848.)

Key Words: intima-media thickness • coronary heart disease • heritability • genetic effects

In cross-sectional studies, carotid artery intima-media thickness (IMT) measured by B-mode ultrasonography has been shown to be directly correlated with the same thickness in histological specimens,1 with traditional cardiovascular risk factors (such as age, smoking, lipids, and hypertension),2,3 with the angiographic presence of coronary artery disease,4,5 and with a confirmed family history of coronary artery disease.6,7 Longitudinal studies have shown that the progression of carotid artery IMT is significantly related to the risk of subsequent clinical coronary events8 and to the progression of anatomic coronary artery disease.9 There is a growing number of reports indicating that the absolute magnitude of carotid artery IMT is related to the risk of clinical coronary events.10-14 These data suggest that the association between carotid artery IMT and coronary artery disease depends, in part, on the exposure of both arterial beds to the same genetic and environmental risk factors.

Although coronary heart disease15-18 and many of the cardiovascular risk factors19-22 are known to aggregate within families, the heritability of carotid IMT has been less well documented. Duggirala et al23 reported IMT heritability of 92% in Mexico City by using sibship data (mean age 46 years) after adjusting for the effects of traditional cardiovascular risk factors on IMT. Zannad et al24 reported that genetic factors accounted for 30% of IMT variation in east France by using data for both parents (mean age 43 years) and their offspring (mean age 16 years). The present study was conducted to assess heritability of carotid IMT in Mexican American, Salvadoran American, or Guatemalan American (all referred to as Latino) individuals participating in the Los Angeles Molecular Genetics of Hypertension Specialized Center of Research (SCOR) study, a multicentered, family-based, genetic study to identify genes related to hypertension and insulin resistance in Latino individuals.

Methods

The cohort under study consisted of Latino families (parents and offspring) ascertained via a hypertensive parent. Each hypertensive parent met the following inclusion criteria: (1) essential hypertension, defined as sitting blood pressure ≥140/90 mm Hg off medication, (2) age 18 to 65 years, with at least 2 adult offspring willing to
participate, and (3) sufficient other family members to determine identity-by-descent status in phenotyped offspring. Participating offspring were aged at least 16 years, and spouses of the proband were aged between 18 to 65 years. Hypertensive individuals were studied after discontinuing antihypertensive medications for 2 weeks if permissible. Probands were recruited through the Hypertension Clinic at Los Angeles County, University of Southern California Medical Center or the General Clinical Research Center at the University of California at Los Angeles. All subjects gave written consent for participation in the present study, which was approved by both institutional review boards.

Phenotyping
Phenotypic characteristics were measured on study participants on 4 separate mornings. Systolic and diastolic blood pressures were obtained by using a Dinamap (Critikon, Inc) system according to American Heart Association recommendations. Subjects were comfortably seated, with the midpoint of the upper arm at the level of the heart (approximately the fourth intercostal space). The bladder inside the cuff encircled 80% of the arm. Blood pressure and pulse were taken every 5 minutes for 15 minutes and averaged. Height was measured with a stadiometer, and weight was measured on a standard beam balance. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

Plasma total cholesterol (TC), triglycerides (TGs), and HDL cholesterol levels were determined by enzymatic assays and standardized according to the Centers for Disease Control and Prevention with the use of the Lipid Research Clinic protocol. Fasting serum glucose (FSG) concentrations were measured by using a Beckman analyzer (Beckman Instruments).

Glucose clamps were performed on individuals with FSG concentrations <140 mg/dL. Subjects rested in the supine position, and intravenous lines were placed in an antecubital vein for infusions and in the ipsilateral dorsal hand for sampling arterialized (60°C) venous blood. A primed infusion (60 mU/m² surface area per minute) of human insulin (Novolin R, Novo Nordisk) was administered for 120 minutes to raise plasma insulin concentrations to ~140 μU/mL. Blood was sampled at 5-minute intervals, and dextrose was infused to maintain plasma glucose concentrations, measured by glucose oxidase (Beckman Glucose Analyzer), at ~100 mg/dL. Potassium chloride was infused at 5 mEq/h to prevent hypokalemia. Blood samples drawn at ~30, ~20, ~10, 160, 170, and 180 minutes were centrifuged within 20 minutes, and plasma was stored at ~8°C until measurement of insulin by radioimmunoassay (Linco Research). Insulin sensitivity (S) was assessed as the mean glucose infusion rate during the final 30 minutes of the 2-hour insulin infusion, expressed relatively to body surface area.

B-mode carotid artery images were obtained with a Toshiba SSH-140A ultrasound system with a 7.5-MHz probe at the University of Southern California Atherosclerosis Research Unit. Longitudinal views of the far wall of the right distal common carotid artery were recorded with the minimum gain necessary for clear visualization of structures. A standardized videotape was used to calibrate the gray scale of the ultrasound monitor, and the same intensity algorithm was used in all families. The distance between the blood-intima and the gray scale of the ultrasound monitor, and the same intensity algorithm. The distance between the blood-intima and the gray scale of the ultrasound monitor, and the same intensity algorithm.

Statistical Analysis
Planned covariates for IMT were age, sex, BMI, systolic and diastolic blood pressures, TC, HDL, TGs, FSG, and S. Average values of these variables were compared across probands, spouses of probands, and their offspring by using repeated-measures ANOVA to account for the dependence of subjects within families. For these analyses, IMT, BMI, TGs, FSG, and S were logarithmically transformed. If statistical significance was obtained for any parameter, pairwise comparisons were performed by using a Bonferroni adjustment.

Univariate and multivariate relationship between IMT and all covariates and the heritability of IMT were estimated by using a classic variance component approach. Data were analyzed in 2 ways: (1) offspring only (offspring) and (2) parents and offspring combined (parents + offspring). In the latter analysis, correction for potential ascertainment bias was performed by conditioning on the proband’s IMT. The analyses were also repeated without ascertainment correction to assess the impact of this correction.

The variance component approach assumed a polygenic model in which IMT was determined by the additive effects of multiple unmeasured genes of small effect (polygenes), unmeasured individual specific environmental effects, and the effects of measured covariates. Covariate effects on IMT were modeled as linear fixed effects through the mean function of IMT, and the variance of IMT was partitioned into an additive genetic variance component (\( \sigma_g^2 \)) and an individual specific environmental variance component (\( \sigma_e^2 \)). Heritability (h²) was estimated in the narrow sense, ie, \( h^2 = \sigma_r^2 / (\sigma_r^2 + \sigma_e^2) \). When there was any adjustment for covariates, the proportion of total IMT variance due to covariates was estimated by comparing the variance with and without covariates included. Heritability was the proportion of the remaining variance, conditional on the covariates. The total IMT variation explained by additive genetic effect was calculated as \( h^2 \times (100 - \text{percent IMT variation explained by covariates}) \). A maximum likelihood approach was used to estimate the parameters of interest, and a likelihood ratio test was used to test for the significance of the covariate effect on IMT and heritability. Because the distribution of IMT was skewed to the right, variance component analyses of IMT were performed on the original and logarithmically transformed scales. Because the 2 sets of results were consistent, only results using logarithmic transformation are reported. The Sequential Oligogenic Linkage Analysis Routine (SOLAR) program was used to conduct the analyses.

Characteristics of Proband, Spouses, and Offspring
Table 1 shows characteristics of the study participants. Mean ages were 30 years for offspring and 56 years for each of the proband and spouse groups. Only HDL cholesterol did not differ across these 3 groups. IMT, TC, total TGs, and fasting glucose were similar between probands and spouses and were greater in both groups than in the offspring. BMI, systolic and diastolic blood pressures, and insulin resistance were greatest in probands, intermediate in spouses, and lowest in offspring.
TABLE 1. Characteristics of Probands, Spouses and Offspring

<table>
<thead>
<tr>
<th></th>
<th>Probands (n=54)</th>
<th>Spouses of Probands (n=28)</th>
<th>Offspring (n=204)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, mm</td>
<td>0.719 (0.154)†</td>
<td>0.808 (0.242)‡</td>
<td>0.563 (0.082)†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.5 (8.0)†</td>
<td>56.0 (9.0)†‡</td>
<td>30.4 (8.8)†‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.9 (7.7)†‡</td>
<td>29.3 (3.9)†‡</td>
<td>28.4 (5.8)‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>150.2 (23.5)†‡</td>
<td>133.9 (31.0)†§</td>
<td>118.5 (15.0)‡§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.1 (13.7)†‡</td>
<td>76.6 (11.0)†‡</td>
<td>72.0 (9.1)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.44 (1.09)†</td>
<td>5.26 (0.87)‡†</td>
<td>4.66 (0.90)‡†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>4.62 (2.80)†</td>
<td>4.17 (2.64)‡†</td>
<td>3.04 (2.34)‡†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.04 (0.28)</td>
<td>1.05 (0.30)</td>
<td>1.08 (0.30)</td>
<td>0.78</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>6.75 (3.64)†</td>
<td>6.69 (2.67)‡†</td>
<td>5.16 (0.57)‡†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin sensitivity, mmol · min⁻¹ · m⁻²</td>
<td>0.87 (0.39)†‡</td>
<td>1.08 (0.42)‡†</td>
<td>1.29 (0.57)‡†</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean (SD).
*Repeated measures ANOVA. IMT, BMI, triglycerides, fasting glucose, and insulin sensitivity were log-transformed.
†‡§Values that share the same symbols are significantly different after Bonferroni adjustment for multiple comparisons.
|Sample sizes for insulin sensitivity were 39 for probands, 20 for spouses, and 204 for offspring.

Univariate Relationships

Univariate relationships between IMT and each of the covariates tended to be weaker in the offspring alone than in the parents+offspring combined (Table 2). This fact was especially true for variables that are known to change with aging, such as fasting glucose, blood pressure, and lipids. As expected, age was the strongest covariate for IMT, explaining 13.9% and 37.5% of the total IMT variation (P<0.0001) among offspring and parents+offspring, respectively. Fasting glucose, systolic and diastolic blood pressures, and BMI were also significantly correlated with IMT. Individually, they explained 3% to 5% of total IMT variation among offspring and 3% to 19% of total IMT variation among parents+offspring. The sex difference in IMT did not reach statistical significance in offspring but was significant (P=0.003, with males having higher IMT than females) in parents+offspring. Lipids and S_i were not correlated with IMT in the offspring. The 3 lipid measurements were weakly but significantly correlated with IMT when parents were included, explaining 2% to 4% of total IMT variation.

Variance Component Analysis

Variance component analysis is shown in Table 3 and the Figure. Without adjustment for any covariates, heritability was 72% in offspring and 1% in parents+offspring. When age was considered as the sole covariate, it explained 13.9% of IMT variability among offspring and 37.5% among parents+offspring. Of the remaining variability, 64% in offspring and 42% in parents+offspring was attributed to a genetic component (ie, heritability). Adjusting for the genetic and nongenetic effects of covariates in addition to age had only a small additional impact on the results. When all covariates were considered, they accounted for 24.3% of IMT variability among offspring and 47.6% of variability among parents+offspring. In offspring, 64% of the remaining variability was attributed to a genetic effect (heritability). In parents+offspring, heritability was 32%. S_i was excluded from this parents+offsprings analysis because it was not measured in 28% of parents. When only covariates with P<0.10 on multivariate analysis were considered (see listing in footnote of Table 3), they accounted for 21.8% of total IMT variability among offspring and 46.4% among parents+offspring. Corresponding heritabilities were 64% and 34%. Analysis in parents+offspring without correcting for ascertainment by the proband yielded a similar, slightly higher heritability (37%).

The Figure summarizes partitioning of total IMT variability into its 3 additive component parts by using only covariates associated with IMT with P<0.10 on multivariate analysis. In offspring, 21.8% of total IMT variability was accounted for by measured covariates, 50.0% of total variability (64% of variability after covariate adjustment) was accounted for by genetic factors independent of the covariates, and 28.2% of the total variability was accounted for by unspecified environmental factors. In parents+offspring, 46.4% of IMT variation was accounted for by covariates,
residual IMT variance when parents were added. After 64% of the residual IMT variance in offspring and 42% of the total IMT variance in parents were included (mean age 56 years). After the variance due to age was partitioned out, genetic factors explained essentially no genetic effect could be detected when parents were included. Age alone explained 13.9% of the IMT variation in offspring, and 35.4% was accounted for by unspecified environmental factors.

### Discussion

The results of the present study demonstrate that interindividual variation of common carotid artery IMT is highly heritable. Age plays an important role in the estimation. Without adjusting for age, genetic factors explained 72% of the total IMT variation in offspring, and essentially no genetic effect could be detected when parents were included. Age alone explained 13.9% of the IMT variation in offspring (mean age 30 years), and this was increased to 37.5% when parents were included (mean age 56 years). After the variance due to age was partitioned out, genetic factors explained 64% of the residual IMT variance in offspring and 42% of the residual IMT variance when parents were added. After adjustment for all significant or marginally significant covariates (accounting for 21.8% of the IMT variance in offspring and 46.4% of the IMT variance when parents were included), the heritability estimate remained at 64% in offspring and decreased to 34% in parents+offspring, with genetic factors (independent of the covariates) explaining 50.0% of the total IMT variation in offspring and 18.2% in parents+offspring. Similar results were seen without ascertainment correction. These findings suggest that the traditional cardiovascular risk factors beyond age that are known to affect carotid artery wall thickness are not the genetic factors that account for the majority of the observed heritability of IMT. Thus, as-yet-unidentified genes appear to significantly influence IMT.

Our data were analyzed in offspring alone and in parents and offspring combined. The offspring were ascertained via a hypertensive parent and, therefore, are ideal for studying the genetic basis of hypertension and related diseases. However, without direct measurements on shared environment, heritability estimates based on siblings alone do not differentiate between shared genes and closely shared environment. Parents have an environmental history different from that of their offspring and, therefore, offer a second estimate of genetic influences. Our results showed that when parents were included, the heritability estimate remained statistically significant, although the point estimate was approximately half that from the offspring alone. There are 4 possible explanations for this fall in heritability. First, the majority of parents (58%) but a small minority (9%) of offspring were hypertensive. It is well known that high blood pressure can alter IMT. Similar results were seen without ascertainment correction. These findings suggest that the traditional cardiovascular risk factors beyond age that are known to affect carotid artery wall thickness are not the genetic factors that account for the majority of the observed heritability of IMT. Thus, as-yet-unidentified genes appear to significantly influence IMT.

## Table 3. Explained Variances and Heritability ($h^2$) of Carotid IMT

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Offspring</th>
<th>Parents+Offspring</th>
<th>Offspring</th>
<th>Parents+Offspring*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.72 (0.16)</td>
<td>0.01 (0.08)</td>
<td>0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age</td>
<td>0.64 (0.16)</td>
<td>0.42 (0.12)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All covariates§</td>
<td>0.64 (0.18)</td>
<td>0.32 (0.12)</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Multivariate significant or marginally significant covariates‡</td>
<td>0.64 (0.17)</td>
<td>0.34 (0.12)</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*With ascertainment correction.
†Heritability ($h^2$) is defined as the proportion of IMT variance that is due to an additive genetic effect after adjusting for covariates in first column.
‡Likelihood ratio test for testing the significance of an additive genetic effect.
§For parents to offspring, insulin sensitivity was not included due to missing data on parents. When insulin sensitivity was considered, 23 parents were excluded, all covariates explained 43.0% of total IMT variation, and $h^2$ after adjusting for all covariates was 0.50 (0.14) with $P<0.0001$.
¶The multivariate significant or marginally significant covariates were a) in offspring: age, fasting glucose, and insulin sensitivity ($P<0.05$) and systolic blood pressure ($P<0.05$); b) in parents to offspring: age, systolic blood pressure, total cholesterol ($P<0.05$), and sex ($P=0.055$).

18.2% was accounted for by genetic factors independent of the covariates (corresponding to heritability of 34%), and 35.4% was accounted for by unspecified environmental factors.

Percentage of total IMT variance explained by multivariate significant or marginally significant covariates, genetic factors, and random environment in offspring and parents+offspring. For multivariate significant or marginally significant covariates, see Table 3 legend. Ascertainment correction was applied in parents+offspring.
factors that are closely shared among offspring but not between parents and offspring cannot be excluded. Although there are no data to support the last 2 possibilities, we speculate that environmental influences have a progressively larger impact on IMT as our patients age. Such an effect would favor a focus on young family members in studies searching for genetic determinants of IMT as a means to reduce environmental confounders.

Previous studies have shown that about half of coronary heart disease risk is explained by the traditional risk factors, such as sex, elevated blood cholesterol, hypertension, smoking, and glucose intolerance. The importance of heredity in coronary heart disease risk is clear, inasmuch as familial aggregation of coronary artery disease has been well documented. Many traditional risk factors themselves are inherited, as demonstrated by reports of familial aggregation of plasma lipids and lipoproteins, blood pressure, BMI, fasting blood glucose, and insulin. Similar to the findings of previous studies, traditional risk factors were found to account for 48% of total carotid IMT variance in this family cohort in which age ranged from 18 to 65 years. When only offspring were considered (mean age 30 years), traditional risk factors accounted for only 24% of the variance of carotid IMT. Inheritance of these risk factors alone does not account for the heritability of IMT, and as our results indicate, there is a genetic influence on carotid IMT that is independent of traditional atherosclerotic risk factors.

Surprisingly, we observed almost no association between any of the individual lipid components and carotid artery IMT in the offspring. Only when parents were considered did we observe a significant association between IMT and lipids and a much stronger association between IMT and blood pressure and fasting glucose. In addition, the sex of the individual became significant. This observation suggests that chronic exposure is required to bring out acquired variability in IMT based on differences in lipids, blood pressure, and glucose. Whether genetic differences underlie some of the resulting differences is not known.

Two assumptions made during data analyses are worth noting. First, we modeled IMT as the summed effects of multiple unmeasured polygenes, unmeasured individual specific environmental effects, and measured effects of covariates. Failure to account for nonadditive genetic variance (dominance and/or epistasis) could have resulted in different additive genetic variance estimates. Also, failure to account for unrecognized and tightly shared environmental effects could have resulted in an overestimation of the genetic contribution to IMT variability. Second, families included in the present study were not randomly sampled from the Latino population. Rather, they were ascertained through a hypertensive parent. Thus, our results may not apply to other Latino populations or to other populations. However, the highly significant result does suggest that IMT is heritable in Latino families at increased risk for cardiovascular events by virtue of hypertension.

The present study confirms 2 previous reports examining the genetic basis of variation in carotid artery IMT. reported a heritability of 92% for common carotid IMT in 46 adult sibships (mean age 46 years) after adjustment for cardiovascular risk factors. They estimated that genes accounted for 66% of total variation in IMT and that 28% of the variation was attributable to covariates. reported that genetic factors accounted for 30% of IMT variation based on 76 families with both parents (mean age 43 years) and their offspring (mean age 16 years). We offer 2 possible explanations for differences in heritability estimates among the 3 studies. First, the populations from which the cohorts were sampled differed. The cohort in the study of Duggirala et al was from low-income “colonias” in Mexico City, in which ancestry is estimated to be 59% Native American, 34.8% European, and 6.2% African. The cohort in the study of Zannad et al was from eastern France, with European ancestry. Our cohort consists of Latino adult sibships with at least 1 hypertensive parent and an ethnic distribution clearly closer to the cohort studied by Duggirala et al. Second, ages of the cohorts were different. Although age has been adjusted in a linear way in the variance component analysis, environmental factors may obscure the relationship between genetic influences and phenotypic expression of the trait over time. Statistical adjustment of age cannot eliminate those influences. Of importance, carotid IMT has been shown to be significantly heritable in all 3 studies, regardless of these differences.

In summary, our results indicate that genetic factors independent of traditional cardiovascular risk factors strongly influence carotid IMT. Although our data do not identify the exact mode of inheritance of carotid IMT, they support family-based studies focused on direct quantitative assessment of atherosclerosis related traits, such as carotid IMT measurements. Genome-wide scans and candidate gene approaches to locate the specific genes influencing IMT (and thus the atherosclerotic process) are under way.

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References


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