Published in final edited form as:
Stroke. 2004 October ; 35(10): 2243–2247.

Genetic and Environmental Contributions to Carotid Intima-Media Thickness and Obesity Phenotypes in the Northern Manhattan Family Study

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Abstract

Background and Purpose—Both carotid intima-media thickness (IMT) and obesity are independent determinants of stroke and cardiovascular disease. The prevalence of obesity is higher in Hispanics. The genetic basis of IMT and obesity has not been well-characterized in Caribbean Hispanics. The purpose of this study was to examine the genetic and environmental contributions to IMT and obesity in this population.

Methods—The data included 440 subjects from 77 Caribbean Hispanic families. Mean IMT and maximum IMT were measured in the internal carotid artery, common carotid artery, and carotid bifurcation. The total IMT was calculated as the mean value of IMT at all segments. Obesity phenotypes included body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), and skin-fold thickness. Variance component methods were used to estimate age-adjusted and sex-adjusted heritability. Bivariate analyses were conducted to test for genetic and environmental correlations between IMT and obesity.

Results—Heritabilities for IMT ranged from 9% to 40%, with the highest for total maximum IMT and lowest for internal carotid artery maximum IMT. Heritabilities for BMI, waist circumference, WHR, and skin-fold thickness were 44%, 47%, 5%, and 36%, respectively. There were significant genetic, but not environmental, correlations between IMT and BMI, waist circumference, and skin-fold thickness. There were no genetic or environmental correlations between IMT and WHR.

Conclusions—We found a substantial genetic contribution to IMT, BMI, waist circumference, and skin-fold thickness. Obesity and IMT may share common genetic factors. Future gene mapping studies are warranted to identify genes predisposing to IMT and obesity in this population.

Keywords

carotid arteries; genetics; obesity; stroke

Genetic and environmental factors have been linked to the cause of atherosclerosis.[1] Carotid intima-media thickness (IMT) has been demonstrated to correlate well with pathologically and

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clinically defined atherosclerosis and can be used as a surrogate marker of subclinical atherosclerosis.[2–4] IMT has been well-substantiated in large epidemiological studies and has been shown to have a strong association with the risk of myocardial infarction and stroke.[5–7] Recent family studies indicated IMT has substantial heritability.[8–14]

More than half of all adults in the United States are considered overweight or obese.[15] An increasing prevalence of overweight and obesity in children, especially in minority children, contributes to the epidemic of cardiovascular-associated disorders. A study in New York City found that Hispanic children have more than twice the risk of being overweight than other ethnic groups.[16] Body mass index (BMI) is one measurement of overall obesity and correlates strongly with total body fat content. However, BMI may not truly reflect body fat distribution. There is accumulating evidence that excess visceral fat increases the risk of cardiovascular disease and stroke.[17–19] Thus the waist circumference, waist-to-hip ratio (WHR), and skin-fold thickness may provide information in addition to BMI. Significant heritability of these obesity phenotypes has been reported.[20–26]

Stroke continues to have a disproportionate impact on mortality for Hispanics when compared with whites.[27,28] Incidence data from the Northern Manhattan Study (NOMAS) have demonstrated that Hispanics have a 2-fold increased annual stroke incidence compared with whites living in the same community.[29,30] Caribbean Hispanics are 1 of the 2 major groups of Hispanics in the United States and are relatively recent immigrants from the Caribbean Islands including the Dominican Republic and Puerto Rico. Understanding the genetic basis of cardiovascular risk factors in this high-risk population may lead to new prevention and intervention strategies.

Significant associations between obesity and IMT have been previously reported.[31,32] It is likely that shared genetic factors can partially explain the relationship between these 2 traits. In this study, we first estimated heritability of total carotid IMT and IMT at different carotid segments, and heritability of 4 obesity phenotypes (BMI, waist circumference, WHR, and skin-fold thickness) among the high-risk Caribbean Hispanic families participating in the Northern Manhattan Family Study (NOMAFS). We then tested the hypothesis of shared common genes between IMT and obesity phenotypes.

Subjects and Methods

The NOMAFS was derived from the families of the Caribbean Hispanic members of the NOMAS, a prospective community-based cohort.[33] High-risk Caribbean Hispanic probands were identified based on the following criteria: reporting a sibling with a history of myocardial infarction or stroke or having 2 of 3 quantitative risk phenotypes (maximal carotid plaque thickness, left ventricle mass, or homocysteine level) ≥75th percentile in the NOMAS cohort. Families of the eligible probands were considered for enrollment provided that the proband was cognitively able to provide a family history and had at least 3 primary relatives willing to participate. After the proband made the first contact, we followed-up with the relatives to solicit participation. The study was approved by the Columbia University Medical Center Institutional Review Board.

Data Collection

Baseline data were collected through interviews of the subjects by trained bilingual research assistants using standardized data collection instruments. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Blood pressure was measured and fasting blood specimens were drawn.

IMT Measurement

Carotid IMT was assessed by high-resolution B-mode carotid ultrasound (Diasonics 2D-Gateway, 7.5-MHz probe) according to the standardized scanning and reading protocols as previously described.[33] The carotid IMT scanning protocol consisted of near and far wall of 3 segments, defined as follows: (1) 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery (CCA); (2) the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) the proximal 10 mm of the internal carotid artery (ICA). Measurements of IMT were performed offline with the use of the M'Ath automatic computerized edge tracking system (Canevas).[34] The M'Ath program searches for the true wall boundaries using an intensity gradient detection algorithm. Reproducibility studies have been previously reported.[33,34] In our laboratory, the intrareader mean absolute IMT difference was 0.07±0.04 mm, variation coefficient of 5.4%, correlation coefficient of 0.94, and percent error of 5.6%.[33] In each carotid segment, both maximal distance between intima and media (M-IMT) and mean distance between intima and media (m-IMT) were measured out of the proportion of plaques. The total carotid IMT was calculated as a composite measure (mean of the 12 carotid sites) that combined the near and the far wall of the CCA IMT, the bifurcation IMT, and the ICA IMT of both sides of the neck. Total IMT was expressed in 2 ways: as a mean of the means of the 12 carotid sites (total m-IMT) and as a mean of the maximums of the 12 carotid sites (total M-IMT).

Anthropometrical Measurements

Height and weight were determined by the use of calibrated scales. Hip and waist measurements were also performed using standard protocols.[35] BMI was calculated as weight in kilograms divided by height squared in meters. WHR was defined as waist divided by hip circumference. Skin-fold thickness was measured in right triceps and abdominal with Lange calipers. Skin-fold thickness was measured twice. If values differed by >2 mm, then a third measure was taken. The mean of the 2 closest measurements was calculated.[36] The heritability was calculated for the mean of triceps and abdominal skin-fold.

Statistics

The mean and standard deviations of the quantitative phenotypes were evaluated. Log transformations were used for non-normally distributed variables. We used the SOLAR package (Southwest Foundation for Biomedical Research)[37] to fit a variance components model for estimating heritability. Maximum likelihood estimation is applied to a mixed-effects model that incorporates fixed covariate effects, additive genetic effects, and residual error. The additive genetic effects and residual error are assumed to be normally distributed and to be mutually independent. Heritability is calculated as the proportion of phenotypic variance explained by additive genetic effects while accounting for covariates. The bivariate models implemented in SOLAR were used to test for genetic correlation between IMT and obesity phenotypes. The observed phenotypic correlation (ρ_p) between 2 quantitative traits can be partitioned into genetic (ρ_G) and environmental correlations (ρ_E) where h_1^2 and h_2^2 are the heritability of carotid IMT and the obesity phenotype.

$$\rho_P = \rho_G * \sqrt{h_1^2 * h_2^2} + \rho_E \sqrt{(1 - h_1^2) * (1 - h_2^2)}$$

Results

At the time of analysis, we had screened a total of 479 families. Seventy-seven families were included in this analysis, 131 were in the enrollment process, 9 probands were unable to be contacted, 61 probands refused, 79 probands were dead, and 122 families were not eligible.

The cohort consisted of 440 subjects from 77 families who had IMT and obesity data. Table 1 shows characteristics of the study participants. Men accounted for 46% of the study subjects. The mean family size was 10, and ranged from 3 to 50. The mean age was 49 years. The M-IMT at each segment ranged from 0.79 to 0.86 mm, and m-IMT ranged from 0.59 to 0.65 mm. The mean BMI was 29.5 kg/m^2, mean waist circumference was 37 cm, mean skin-fold thickness was 33.9 mm, and mean WHR was 0.90.

The BMI, total m-IMT, and CCA m-IMT and M-IMT data were log-transformed for analysis because of skewness. The estimates of heritability are shown in Table 2. All heritability estimates were adjusted for age and sex. Generally speaking, m-IMT and M-IMT had similar heritability. Heritabilities were highest for the total IMT (36% to 40%), followed by CCA IMT (35% to 39%), bifurcation IMT (25% to 26%), and ICA IMT (9% to 12%). Except for ICA IMT, the heritability estimates for other segments were statistically significant. For the obesity phenotypes, waist circumference had the highest heritability of 47%, followed by BMI (44%), skin-fold thickness (36%), and WHR (5%).

The phenotypic correlations between m-IMT at any segment and the 3 obesity phenotypes (BMI, waist circumference, skin-fold thickness) were significant, except for skin-fold thickness and ICA m-IMT (Table 3). The correlations between m-IMT and WHR were not significant except for ICA m-IMT and WHR. The phenotypic correlations between M-IMT and obesity phenotypes were consistent with those between M-IMT and obesity (data not shown). For the bivariate analyses between m-IMT and obesity, BMI had significant genetic correlations with total, CCA, and bifurcation m-IMT. Waist circumference was genetically correlated with total and CCA m-IMT. Skin-fold thickness was genetically correlated with CCA m-IMT (Table 4). There were no genetic correlations between m-IMT and WHR (data not shown). None of the environmental correlations was significant between m-IMT and the 4 obesity phenotypes. The results of bivariate analyses between M-IMT and obesity were generally similar to those between m-IMT and obesity phenotypes, but less significant (data not shown).

Discussion

The heritabilities for total carotid IMT, CCA, and carotid bifurcation IMT were significant, with estimates ranging from 25% to 40%. The total M-IMT had the strongest heritability among all carotid IMT measurements. The heritabilities of IMT measurements of the ICA were smaller and not significant. Three obesity phenotypes, BMI, waist circumference, and skin-fold thickness, had substantial heritabilities, but WHR did not have a significant heritability in our Caribbean Hispanic population. Significant phenotypic correlations (ranging from 0.08 to 0.23) were found between IMT at each segment and the 3 obesity phenotypes (BMI, waist circumference, and skin-fold thickness). Partitioning the phenotypic correlation into genetic and environmental components, we found that in general, the genetic correlations were more significant and stronger than environmental correlations. In particular, BMI and IMT may share substantial common genetic factors. These results highlight the importance of underlying common genetic factors for both types of quantitative traits in the Caribbean Hispanic population. This also suggests that any interventions to alter gene expressions may reduce IMT and obesity simultaneously, both of which are independent cardiovascular and stroke risk factors.

Our study of heritability for the total IMT is generally consistent with previous studies conducted in different ethnic groups. A heritability of 92% for CCA M-IMT and 86% for ICA M-IMT were first reported in an early study.[8] However, that study had several weaknesses. The data only consisted of 88 subjects, and the study population was a mixture of Native American, European, and African descent. Subsequent studies demonstrated heritability of m-

IMT of 30% in healthy French families,[10] 21% in American Indians,[14] 34% in hypertensive Latino families,[9] 32% in type II diabetic individuals of mixed white and black families,[11] and 44% for CCA (45% for CCA M-IMT) and 37% for ICA m-IMT (33% for ICA M-IMT) in the Framingham Offspring cohort.[12] However, the only twin study using the population of the West of Scotland failed to demonstrate significant genetic contribution to M-IMT or m-IMT at any segment.[38] Two studies also separately analyzed heritability of IMT at different segments[8,12] and, like our findings, they reported stronger heritability in CCA than ICA IMT. Furthermore, it was previously reported that traditional cardiovascular risk factors had stronger effects on IMT in the bifurcation and ICA than in the CCA.[13,39] Hemodynamic factors including shear-stress are different in the segments of carotid artery, and thus the pathogenesis and underlying genetic factors contributing to IMT may vary among CCA, bifurcation, and ICA. Accordingly, based on the findings from epidemiological studies of the association between risk factors and IMT,[13,39] and heritability estimates from family studies,[8,12] CCA IMT may be under a stronger genetic influence than bifurcation and ICA IMT.

There are some limitations in this study. The heritability estimates might be influenced by shared environmental factors because the variance component approach did not account for these factors among family members. The SOLAR statistical program cannot count the genetic effects caused by gene–environment interactions. Therefore, the estimation of heritability is conservative.

In our study population, we found that BMI, waist circumference, and skin-fold thickness had heritabilities higher than that for WHR. This finding is in concert with the findings in several previous studies.[20–26,40] Heritability estimates ranged from 36% to 80% for BMI, from 37% to 49% for waist circumference, from 11% to 54% for skin-fold thickness, and from 6% to 42% for WHR. Among the aforementioned studies, only Pausova et al[22] reported that WHR had a higher heritability than BMI. BMI represents total body size, waist circumference reflects central fat, skin-fold thickness is a parameter for subcutaneous fat, and WHR is used for body fat distribution. Therefore, the 4 phenotypes are related but may not be influenced by the same genetic factors. In our data, the ignorable environmental correlations between IMT and obesity phenotypes suggested that the same underlying genes play a major role on both types of traits.

In conclusion, we report substantial heritability for m-IMT and M-IMT in the carotid artery except for the ICA IMT. The analyses for obesity phenotypes show that BMI, waist circumference, and skin-fold thickness have higher heritabilities than WHR. There is a significant genetic pleiotropic effect on obesity and IMT, which suggests that common genetic susceptibility may account for the higher prevalence of stroke and obesity in the Caribbean Hispanic population.

Acknowledgements

This work was supported by grants from the National Institute of Neurological Disorders and Stroke R01 NS NS40807 (S.-H.H.J., T.R., R.L.S., B.B.-A., E.A.S., N.P.), RO1 NS047655 (S.H.H.J., T.R., R.L.S., N.P.), and Irving General Clinical Research Center (2 M01 RR00645). Dr. Rundek was supported by the Goddess Fund for Stroke Research in Women. Hsiu-Fen Lin is supported by the Kaohsiung Medical University fellowship training grant. Min-Yu Lan is supported by the Chang Gung Memorial Hospital fellowship training grant. We thank all the staff and participants in the Northern Manhattan Family Study. There is no conflict of interest for any author.

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TABLE 1

Characteristics of the Study Participants

	Mean (SD)
Family size	10 (7)
Age, y	49.4 (17.9)
Male	46%
Total M-IMT, mm	0.82 (0.08)
Total m-IMT, mm	0.61 (0.06)
CCA M-IMT, mm	0.79 (0.11)
CCA m-IMT, mm	0.60 (0.09)
Bif M-IMT, mm	0.86 (0.09)
Bif m-IMT, mm	0.65 (0.07)
ICA M-IMT, mm	0.79 (0.07)
ICA m-IMT, mm	0.59 (0.06)
BMI, kg/m^2	29.5 (5.73)
Waist circumference, cm	37.0 (5.38)
Skin-fold thickness, mm	33.9 (11.5)
WHR	0.90 (0.10)

Bif indicates bifurcation.

TABLE 2

Estimates of Sex-Adjusted and Age-Adjusted Heritability of IMT and Obesity Phenotypes

	Adjusted Heritability (SE)	*P*
Total M-IMT	0.40 (0.10)	<0.0001
Total m-IMT	0.36 (0.11)	0.0002
CCA M-IMT	0.35 (0.10)	<0.0001
CCA m-IMT	0.39 (0.10)	<0.0001
Bif M-IMT	0.25 (0.11)	0.005
Bif m-IMT	0.26 (0.11)	0.007
ICA M-IMT	0.09 (0.12)	0.19
ICA m-IMT	0.12 (0.12)	0.14
BMI, kg/m^2	0.44 (0.11)	<0.0001
Waist circumference	0.47 (0.12)	<0.0001
Skin-fold thickness	0.36 (0.11)	0.0001
WHR	0.05 (0.11)	0.32

TABLE 3

Phenotypic Correlations Between m-IMT and 4 Obesity Phenotypes With Adjustment for Sex and Age

	BMI		Waist		Skin-fold		WHR	
	β	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Total m-IMT	0.23	<0.0001	0.20	<0.0001	0.15	0.003	0.08	0.117
CCA m-IMT	0.21	<0.0001	0.16	0.001	0.13	0.016	0.06	0.208
Bif m-IMT	0.17	0.001	0.15	0.001	0.14	0.004	0.02	0.699
ICA m-IMT	0.16	0.001	0.15	0.002	0.08	0.115	0.10	0.044

β indicates correlation coefficient.

TABLE 4

Bivariate Analysis for Genetic and Environmental Correlations Between m-IMT and BMI, Waist Circumference and Skin-fold With Adjustment for Sex and Age

	BMI		Waist Circumference		Skin-fold Thickness	
	ρ_G (*P* value)	ρ_E (*P* value)	ρ_G (*P* value)	ρ_E (*P* value)	ρ_G (*P* value)	ρ_E (*P* value)
Total m-IMT	0.47 (0.03)	0.08 (0.51)	0.48 (0.03)	0.03 (0.80)	0.38 (0.11)	0.06 (0.62)
CCA m-IMT	0.42 (0.03)	0.06 (0.64)	0.40 (0.04)	0.02 (0.85)	0.40 (0.03)	−0.05 (0.64)
Bif m-IMT	0.60 (0.02)	−0.04 (0.75)	0.40 (0.12)	0.02 (0.89)	0.52 (0.06)	0.01 (0.90)
ICA m-IMT	0.01 (0.98)	0.22 (0.06)	0.32 (0.35)	0.10 (0.42)	−0.24 (0.55)	0.21 (0.06)

ρ_G indicates genetic correlation; ρ_E, environmental correlation.