Brief Genetics Report

Heritability of Multivariate Factors of the Metabolic Syndrome in Nondiabetic Japanese Americans

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A rapidly growing body of evidence demonstrates important associations between the metabolic syndrome, characterized by a cluster of risk factors or phenotypes that include dyslipidemia, central obesity, hypertension, and hyperinsulinemia, and both cardiovascular disease and type 2 diabetes. The purpose of the present study was to characterize the metabolic syndrome in a sample of 432 individuals from 68 Japanese-American families, using factor analysis of quantitative phenotypes, and to estimate the heritability of these independent factors. Using nine characteristic phenotypes that included LDL particle size and C-reactive protein (CRP), factor analysis identified three multivariate factors interpreted as lipids, body fat/insulin/glucose/CRP, and blood pressure, explaining 65% of the variance. Heritability analysis revealed significant genetic effects on all of the factors: lipids ($h^2 = 0.52$, $P < 0.001$), body fat/insulin/glucose/CRP ($h^2 = 0.27$, $P = 0.016$), and blood pressure ($h^2 = 0.25$, $P = 0.026$). This analysis shows that independent, multivariate factors of the metabolic syndrome are heritable, demonstrating genetic influences on the underlying pathophysiological mechanisms of the syndrome. *Diabetes* 53:1166–1169, 2004

A rapidly growing body of evidence demonstrates important associations between the metabolic syndrome, characterized by a cluster of risk factors that include dyslipidemia, central obesity, hypertension, and hyperinsulinemia, and both cardiovascular disease (CVD) and type 2 diabetes (1–4). In addition to these risk factors, recent evidence also indicates that the metabolic syndrome involves inflammatory processes and that markers such as C-reactive protein (CRP) should be considered other components of the syndrome (5,6).

Because the metabolic syndrome is characterized by this constellation of highly intercorrelated quantitative phenotypes, >12 studies have used factor analysis to simplify the syndrome and to potentially provide new insights about the underlying pathophysiological mechanisms that may be involved (1,7–10). These studies have included diabetic (4) and nondiabetic (2) subjects, different ethnic groups (3,11–13), and older individuals (6,12). Importantly, several of these studies have shown that the factors identified predict risk of CVD (2,4), stroke (9), type 2 diabetes (3), and all-cause mortality (1).

Only a few studies have examined whether genetic susceptibility may underlie the metabolic syndrome (13,14). However, it has been suggested that the independent multivariate phenotypes of the syndrome, identified by factor analysis, may be useful in mapping susceptibility genes for the syndrome (15).

The purpose of the present study was to characterize the metabolic syndrome in a sample of Japanese-American families, using factor analysis of the phenotypes, and to estimate the heritability of these factors.

RESEARCH DESIGN AND METHODS

The Japanese-American Family Study is an investigation of risk factors for coronary heart disease, type 2 diabetes, and the metabolic syndrome in Japanese-American families. Probands were Nisei (second generation) participants in the Japanese American Community Diabetes Study who had a spouse of Japanese descent, had children, and were nondiabetic at the time of the first community-wide survey conducted in 1983 (16). Because most Nisei married other Japanese Americans, the Sansei (third generation) is predominately of Japanese descent. Probands were contacted by letter, and those interested were asked to give permission to contact family members.

Eligible family members included the parents, spouses, and offspring of the proband, siblings, spouses of siblings, and nieces and nephews of the proband, age ≥18 years, residing anywhere in the U.S., who were not pregnant and not too ill to participate. Approximately one-quarter of study subjects resided outside of Washington. Thus, the study sample consists primarily of two-generation extended Nisei and Sansei kindreds. Family sizes ranged from 2 relatives to 27 family members, with an average of 8.4 members per family. Each proband and relative was contacted individually by letter and phone and asked to participate in the study, including providing a fasting blood sample. The University of Washington Institutional Review Board approved these methods, and all study participants provided written, informed consent.

A self-administered questionnaire was used to obtain demographic infor-

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CRP, C-reactive protein; CVD, cardiovascular disease.

TABLE 1
Characteristics of Japanese-American study subjects (n = 432)

Characteristic	
Age (years)	54.2 ± 15.8 (18–87)
Sex (% female)	56.0
LDL Size (Å)	264.3 ± 9.1 (239–285)
Triglycerides (mg/dl)	140.8 ± 127.4 (30–1,489)
HDL cholesterol (mg/dl)	54.8 ± 15.5 (14–121)
Systolic blood pressure (mmHg)	120.5 ± 18.2 (76–203)
Diastolic blood pressure (mmHg)	75.2 ± 10.0 (44–101)
Waist (cm)	81.7 ± 10.6 (58–125)
Fasting insulin (μU/ml)	13.2 ± 7.5 (2.0–52.0)
Fasting glucose (mmol/l)	94.8 ± 9.8 (68–126)
CRP (mg/l)	1.3 ± 1.6 (0.1–9.95)

Data are means ± SD (range) unless otherwise noted.

mation and medical history information from all local and nonlocal study participants. Study participants were asked to provide information on all medications, and these were coded into 82 different drug classes (β-blockers, diuretics, hormone replacement for women, diabetes medications, etc.).

Blood pressure was measured in the left arm after the patient had been seated for at least 5 min, and the first- and fifth-phase Korotkoff sounds were recorded (in mmHg), as systolic and diastolic blood pressures, respectively. Waist was self-reported based on a metric tape measure sent with the medical history questionnaire, except for 24 study subjects who had waist and hip measurements performed by a trained technician.

LDL subclasses were characterized by electrophoresis on 2–14% polyacrylamide gels using standard protocols (17). The estimated diameter for the major peak from the gel scan is denoted "LDL peak particle diameter" (LDL size) and was used as a continuous variable in the analyses. Lipid measurements were performed at the Core Laboratory, Northwest Lipid Research Laboratories (18). High-sensitivity CRP was measured using immunonephelometric methods (19). Total immunoreactive insulin was measured using a double-antibody radioimmunoassay. Glucose was measured using the Beckman Synchron LX system by an oxygen rate method.

Pedigrees for all kindreds were initially constructed based on family information reported by probands. Based on DNA samples, the kindred structures were extensively checked using genetic markers from seven different chromosomes, using the PedCheck program (20).

Statistical analyses. Because of skewness, plasma triglycerides and CRP values were natural log transformed before the analysis. Subjects with type 2 diabetes (defined as fasting glucose >125 mg/dl, taking known medication for diabetes, self-reported diabetes, and self-report of taking insulin or oral antidiabetic pills by questionnaire), CRP >10 mg/l, or missing glucose, insulin, blood pressure, or waist measurements were excluded. With these exclusions, a total of 432 study subjects were included in the analysis.

Factor analysis was used to investigate the interrelationships among the phenotypes of the metabolic syndrome, including LDL size, *ln* triglycerides, HDL cholesterol, systolic and diastolic blood pressure, waist circumference, fasting insulin and glucose, and CRP. In addition, the analyses were repeated substituting BMI for waist measurements, as well as using only subjects with self-reported waist measurements, and the results did not differ substantially. We conducted factor analysis using SAS version 8.2 (21). The analyses were adjusted for age and sex by multiple regression analysis, and standardized residuals were used in the factor analysis. Briefly, factor analysis consists of principle components analysis, a varimax rotation, and identification of the variables with factor loadings ≥ 0.4 to facilitate interpretation (7,22). The standardized scoring coefficients were then used to compute factor scores for each study subject, consisting of a weighted sum of the values of the standardized phenotypes for that factor.

The Statistical Analysis for Genetic Epidemiology (SAGE) (23) program was applied to calculate heritability of the factor scores. We conducted variance-components analysis to estimate the heritability of CRP levels using ASSOC program in SAGE. Polygenic effect was specified in the computation of heritability.

RESULTS

The characteristics of the 432 Japanese-American study subjects are presented in Table 1. The average age was 54 years, and slightly more than half of the study subjects were women. As expected in this Asian-American sample, the mean waist measurement was relatively low (82 cm).

Table 2 shows the age- and sex-adjusted Pearson correlations between each pair of phenotypes included in the factor analysis. The highest correlation was between systolic and diastolic blood pressure. Correlations were also high among LDL size, triglycerides, and HDL cholesterol, with LDL size being inversely correlated with *ln* triglycerides and positively correlated with HDL cholesterol. A high correlation was also seen between fasting insulin and glucose levels. CRP was most highly correlated with waist and fasting insulin.

As shown in Table 3, the factor analysis revealed three principle factors that, combined, explained 65% of the overall variance. Factor 1 explained 24% of the variance and had large factor loading for LDL size, triglycerides, and HDL cholesterol and thus can be interpreted as a lipid factor. Factor 2 explained 22% of the variance and had large factor loadings for waist, fasting insulin and glucose, and CRP. Factor 3 was characterized by large factor loadings only for systolic and diastolic blood pressure and explained 19% of the variance.

Using variance components analysis, the heritability analysis demonstrated that all three of the factors have a significant genetic component (Table 3). The highest heritability was seen for the lipid factor (factor 1), with ~50% of the variance attributable to genetic influences ($P <$ 0.001). For factor 2 (body fat/insulin/glucose/CRP) and factor 3 (systolic and diastolic blood pressure), approximately one-quarter of the variance was attributable to genetic influences (P = 0.016 and P = 0.026, respectively).

TABLE 2
Adjusted* Pearson product moment correlation coefficients for risk factors of the metabolic syndrome (n = 432)

	LDL size	Triglycerides	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure	Waist	Fasting insulin	Fasting glucose	CRP
LDL size	1.00	−0.63†	0.54†	−0.11‡	−0.13†	−0.25†	−0.23†	−0.10‡	−0.12‡
Triglycerides (ln)	−0.63†	1.00	−0.48†	0.18†	0.23†	0.32†	0.37†	0.10‡	0.20†
HDL cholesterol	0.54†	−0.48†	1.00	−0.13†	−0.12‡	−0.34†	−0.36†	−0.11‡	−0.19†
Systolic blood pressure	−0.11‡	0.18†	−0.13†	1.00	0.67†	0.18†	0.19†	0.19†	0.10‡
Diastolic blood pressure	−0.13†	0.23†	−0.12‡	0.67†	1.00	0.18†	0.19†	0.15†	0.13†
Waist	−0.25†	0.32†	−0.34†	0.18†	0.18†	1.00	0.52†	0.24†	0.37†
Fasting insulin	−0.23†	0.37†	−0.36†	0.19†	0.19†	0.52†	1.00	0.33†	0.29†
Fasting glucose	−0.10‡	0.10‡	−0.11‡	0.19†	0.15†	0.24†	0.33†	1.00	0.12‡
CRP (ln)	−0.12‡	0.20†	−0.19†	0.10‡	0.13†	0.37†	0.29†	0.12‡	1.00

*Adjusted for age and sex; †$P < 0.01$; ‡$P < 0.05$.

TABLE 3
Results of adjusted* factor analysis, variance components, and heritability analysis (n = 432)

	Factor loadings†		
	Factor 1: lipids	Factor 2: body fat/insulin/glucose/CRP	Factor 3: blood pressure
LDL Size (Å)	0.87	−0.03	−0.06
Triglycerides (ln, mg/dl)	−0.82	0.16	0.15
HDL cholesterol (mg/dl)	0.75	−0.24	−0.01
Systolic blood pressure (mmHg)	−0.07	0.12	0.90
Diastolic blood pressure (mmHg)	−0.10	0.11	0.89
Waist (cm)	−0.27	0.74	0.07
Fasting insulin (μU/ml)	−0.29	0.73	0.09
Fasting glucose (mg/dl)	0.07	0.59	0.18
CRP (ln, mg/dl)	−0.09	0.63	−0.01
Percent total variance	24.3	21.6	18.7
Percent cumulative variance	24.3	45.9	64.6
Variance component (SE)			
Polygenic	0.52 ± 0.13	0.27 ± 0.11	0.24 ± 0.11
Environmental	0.48 ± 0.10	0.73 ± 0.11	0.75 ± 0.11
Heritability	0.52, $P < 0.001$	0.27, $P = 0.016$	0.25, $P = 0.026$

*Adjusted for age and sex by regression analysis; †factor loadings represent the correlations between the individual variable and each factor.

DISCUSSION

Using nine phenotypic characteristics of the metabolic syndrome (LDL particle size, triglycerides, HDL cholesterol, systolic and diastolic blood pressure, waist circumference, fasting insulin and glucose, and CRP), factor analysis in this Japanese-American sample identified three independent factors that together explained nearly 65% of the variance in the data. These factors were interpreted as lipids, body fat/insulin/glucose/CRP, and blood pressure. Based on the family data, heritability analyses revealed significant genetic influences on all of the multivariate factors.

The only other study of Asian Americans using factor analysis was performed based on older men in the Honolulu Heart Program (12). Similar results were found among subjects with and without diabetes, resulting in four factors: weight/waist, blood pressure, lipids, and insulin/glucose. Studies of African Americans and Hispanics have found only two factors (11,24), while three or four factors were found among Pima Indians and Canadian Aboriginal groups (3,25). In both the Framingham and Rancho Bernardo studies of European-American men and women (8,10), three independent factors were also observed. Thus, although direct comparisons of the factors are difficult due to the use of different phenotypes, all studies have found at least two, and often three or four, independent factors characterizing the metabolic syndrome, indicating that several pathophysiological pathways are likely to underlie the metabolic syndrome.

Due to the recent recognition that inflammatory factors are also important components of the metabolic syndrome, two studies have included CRP in factor analyses of the metabolic syndrome. The addition of procoagulation, inflammation, and fibrinolysis variables to a factor analysis among the nondiabetic elderly men and women in the Cardiovascular Health Study (6) led to the emergence of a separate "inflammation" factor that included CRP and fibrinogen. In an analysis of middle-aged Finnish men, fibrinogen also loaded on a separate factor (1). Thus, there is growing evidence that inflammatory phenotypes are an independent component of the metabolic syndrome.

Two previous studies have reported heritability values for multivariate factors of the metabolic syndrome, one based on the Kaiser Permanente Womens' Twin Study (14) and the other based on the San Antonio Family Diabetes Study (13); both found significant genetic influences on all of the factors. In the latter study, three factors were identified, similar to those reported here for Japanese-American families, and the heritability of the lipid factor was nearly identical to the value of 0.52. Among the Mexican-American families, heritabilities of the adiposity/insulin (0.51) and blood pressure (0.58) factors were higher than in this study. Taken together, these results demonstrate important underlying genetic susceptibility to the metabolic syndrome.

In summary, this factor analysis of phenotypes of the metabolic syndrome in Japanese Americans confirms previous studies showing that the syndrome consists of three to four independent factors, reflecting different underlying mechanisms for disease risk. Furthermore, each of these factors is genetically influenced, with 25–50% of the variance attributable to polygenic influences. Therefore, genetic mapping studies are needed to identify the specific genes that influence each of the multivariate factors of the syndrome in order to better understand genetic susceptibility to CVD and diabetes.

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