

Genome-wide Linkage Scan for the Metabolic Syndrome: The GENNID Study

Karen L. Edwards^{1,2}, Carolyn M. Hutter^{1,2}, Jia Yin Wan^{1,2}, Helen Kim³ and Stephanie A. Monks^{4,5}

In the United States, the metabolic syndrome (MetS) constitutes a major public health problem with over 47 million persons meeting clinical criteria for MetS. Numerous studies have suggested genetic susceptibility to MetS. The goals of this study were (i) to identify susceptibility loci for MetS in well-characterized families with type 2 diabetes (T2D) in four ethnic groups and (ii) to determine whether evidence for linkage varies across the four groups. The GENNID study (Genetics of NIDDM) is a multicenter study established by the American Diabetes Association in 1993 and comprises a comprehensive, well-characterized resource of T2D families from four ethnic groups (whites, Mexican Americans, African Americans, and Japanese Americans). Principal component factor analysis (PCFA) was used to define quantitative phenotypes of the MetS. Variance components linkage analysis was conducted using microsatellite markers from a 10-cM genome-wide linkage scan, separately in each of the four ethnic groups. Three quantitative MetS factors were identified by PCFA and used as phenotypes for MetS: (i) a weight/waist factor, (ii) a blood pressure factor, and (iii) a lipid factor. Evidence for linkage to each of these factors was observed. For each ethnic group, our results suggest that several regions harbor susceptibility genes for the MetS. The strongest evidence for linkage for MetS phenotypes was observed on chromosome 2 (2q12.1–2q13) in the white sample and on chromosome 3 (3q26.1–3q29) in the Mexican-American sample. In conclusion, the results suggest that several regions harbor MetS susceptibility genes and that heterogeneity may exist across groups.

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The metabolic syndrome (MetS) constitutes a major public health problem with over 47 million Americans meeting clinical criteria for MetS (1). MetS is characterized by the clustering of interrelated cardiovascular disease (CVD) and type 2 diabetes (T2D) risk factors, including dyslipidemia, hypertension, glucose intolerance, insulin resistance, obesity, and a predominance of upper body fat (2).

Principal component factor analysis (PCFA) has been used to define quantitative MetS phenotypes in a variety of populations (3–6). Several groups have used these multivariate phenotypes in genome-wide linkage scans to identify susceptibility loci for MetS and have identified regions showing suggestive linkage for MetS phenotypes (7–16). While some of the regions have been replicated across studies, the majority have not. Genetic heterogeneity is often cited as a potential reason for lack of replication (17). However, variation in statistical methods and phenotypic definition of quantitative MetS factors may contribute to differences in linkage signals across studies.

The goals of this study are (i) to identify susceptibility loci for quantitative MetS phenotypes in well-characterized families

with T2D in four ethnic groups and (ii) to determine whether evidence for linkage varies across the four groups when PCFA is conducted using the same set of MetS risk factors.

METHODS AND PROCEDURES

Study subjects

The GENNID study (Genetics of NIDDM) is a multicenter study established by the American Diabetes Association in 1993 and comprises a comprehensive, well-characterized resource of T2D families from four ethnic groups (whites, Mexican Americans, African Americans, and Japanese Americans). The study protocol and ascertainment scheme has been described in detail (18,19). Data were collected by the GENNID study group using standardized methods and included a medical history questionnaire, a family history questionnaire, a physical exam, fasting blood samples, laboratory data, and a diabetes history form.

For this analysis, data on age, gender, and self-reported diabetes was obtained from the medical history questionnaire; height, weight, waist circumference, and systolic and diastolic blood pressure were obtained from the physical examination; and glucose, insulin, high-density lipoprotein (HDL), and triglycerides were obtained from the laboratory data. Clinical MetS was defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines (20).

¹Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington, USA; ²Institute for Public Health Genetics, School of Public Health and Community Medicine, University of Washington, Seattle, Washington, USA; ³Department of Anesthesiology and Perioperative Care, Institute for Human Genetics, University of California San Francisco, San Francisco, California, USA; ⁴Department of Statistics, Oklahoma State University, Stillwater, Oklahoma, USA; ⁵Department of Biostatistics, University of Washington, Seattle, Washington, USA. Correspondence: Karen L. Edwards (keddy@u.washington.edu)

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Genetic markers and genotyping

A 10-cM genome-wide linkage scan using standard sets of highly informative short-tandem-repeat polymorphisms (screening set 6 for Mexican Americans and screening set 8 for all other groups) were performed at the Marshfield Medical Research Foundation (21) as part of the GENNID study. Additional markers were genotyped by GlaxoWellcome (19), to fill in gaps in the genome for a total of 389–395 markers, averaging 8.2–9.0 cM apart and with an average marker heterozygosity of ~0.75. Genotype and MetS phenotype data are available for $n = 69$ white, $n = 53$ Mexican American, $n = 65$ African American, and $n = 15$ Japanese-American extended kindreds.

Statistical analysis

Mendelian inconsistencies. All genetic markers were checked for Mendelian consistency using PEDCHECK (<http://watson.hgen.pitt.edu/register/docs/pedcheck.html>) (22). A total of 14 white, 22 African-American, 1 Mexican-American, and 3 Japanese-American individuals were identified as Mendelian inconsistent (>100 marker errors) and were deleted from their respective family pedigree. An additional 56 white, 52 African-American, 11 Japanese-American, and 26 Mexican-American family members had errors for <25 markers. For these latter individuals, genotype information for the inconsistent markers was excluded. We also excluded two white individuals with genetic data inconsistent with their reported gender and one individual from each of three monozygotic twin pairs.

Principal component factor analysis. Eight variables were defined as core MetS “features” and included in the PCFA: triglyceride (mg/dl), HDL cholesterol (mg/dl), fasting glucose levels (mg/dl), fasting insulin levels (mg/dl), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), waist circumference (cm) and weight (kg). Values for waist circumference, triglyceride, weight, fasting insulin, and fasting glucose were skewed and therefore log-transformed prior to analysis. Subjects with values >4 s.d. from the mean trait values were excluded to improve normality ($n = 4$ for systolic blood pressure, $n = 2$ for HDL, $n = 1$ for diastolic blood pressure, and $n = 1$ for triglycerides). After these exclusions, all the individual variables were adjusted for age and sex using linear regression, and the residuals were included in PCFA for those individuals with complete MetS data, age, and gender. Briefly, PCFA was performed separately in each ethnic group using Intercooled STATA 8.2 for Windows (StataCorp, College Station, TX) (6). Principal component analysis was used to extract the initial components as linear combinations of the variables included in the analysis. These components were rotated using a varimax orthogonal rotation and interpreted by considering only those variables with a factor loading $\geq |0.40|$ (equivalent to sharing 15% of the variance with the factor). Finally, factor scores for each of the rotated components were calculated as weighted sums of the individual MetS features (23). The factor scores are used as the primary quantitative traits reflecting the MetS in the variance components linkage analysis and will be referred to as MetS factors in the following sections.

Variance components linkage analysis. Heritability, h^2 , was estimated for each MetS factor under a polygenic model adjusted for age, sex, and self-reported diabetes as implemented in SOLAR (<http://www.sfbr.org/solar/>) (24). All marker allele frequencies were estimated with a maximum likelihood method assuming Mendelian inheritance using the software package SOLAR (25). Exact conditional probabilities were computed every 1 cM using the Lander–Green algorithm as implemented in the software program MERLIN (<http://www.sph.umich.edu/csg/abecasis/merlin/index.html>) (26). Variance components linkage analysis was implemented in SOLAR as described in Almasy *et al.* (27). An LOD score of 1.9 is taken as suggestive evidence for linkage and an LOD score of 3.3 as evidence for significant linkage (28). For those regions with suggestive

evidence for linkage to the MetS factors, variance components linkage analysis was also performed for the individual features.

Because LOD scores may be biased when assumptions of multivariate normality are not met, we also present empirical P values. Empirical P values were calculated at the maximum LOD score for each MetS factor using the “lodadj” and “empp” commands in SOLAR. The empirical P value (empp) is defined as the probability of obtaining the observed LOD score or greater from a simulated distribution of LOD scores. For each of the MetS factors, 100,000 simulations were run under the null hypothesis of no linkage with a fully informative marker (24,29). Multiple testing was accounted for by applying a Bonferroni correction to adjust the empirical P values for the MetS factors (empp $\times 3$) and individual features (empp $\times 8$), referred to as the adjusted empirical P value (adjusted empp).

RESULTS

The characteristics of the GENNID families included in the genome-wide scan are presented in **Table 1**. Average family sizes ranged from 3.9 (African Americans) to 8.2 (Japanese Americans) family members. Japanese-American family members tended to be older and Mexican-American family members younger than the other groups. Prevalence of self-reported T2D and clinical MetS also varied by ethnic group. The highest prevalence of self-reported T2D was among African Americans, and the highest prevalence of clinical MetS was observed among the Mexican-American sample. The prevalence of both conditions was lowest among the Japanese Americans.

Factor analysis

The results of the PCFA are provided in **Table 2** for each ethnic group. Three factors were retained, and exhibited similar factor loading patterns across the four ethnic groups. In all groups, the first factor is interpreted as a weight/waist factor (“wtfactor”) due to the strong positive loadings for weight and waist circumference. Fasting insulin was also shown to load on the wtfactor in all groups. In the Japanese-American sample, HDL also loaded on the wtfactor. The second factor is interpreted as a blood pressure factor (“bpfactor”) due to the strong loadings for systolic and diastolic blood pressure, with very consistent factor loadings across the four ethnic groups. The third factor is interpreted as a lipid factor (“lipidfactor”) due to the strong factor loadings for HDL and triglycerides across all ethnic groups. In addition, fasting glucose and fasting insulin also load on this factor in all groups. Together these factors account for ~70% of the total variance in the data for each group (**Table 2**).

Heritability and standard error estimates for the MetS factors after adjustment for age, gender, and diabetes status are also presented in **Table 2** by ethnic group. In general, the three MetS factors were highly heritable across all ethnic groups. The residual heritabilities were significant for each of the three MetS factors in each ethnic group, except the bpfactor in Japanese Americans (**Table 2**). Covariates accounted for a small proportion of the trait variance: 1–6% of the wtfactor, 2–15% of the lipidfactor, and 1–8% of the bpfactor across ethnic groups (data not shown).

Linkage analysis

The strongest linkage signal for each ethnic group is shown in **Figure 1**. Note that **Figure 1** shows $-\log_{10}$ (adjusted empp)

Table 1 Characteristics of GENNID individuals stratified by ethnic group

Characteristics ^a	White (n = 443)	African American (n = 252)	Mexican American (n = 389)	Japanese American (n = 123)
Age (years)	50.4 (36.7, 63.7)	50.7 (39.6, 62.5)	47 (33.3, 59.6)	61.7 (40.1, 69.2)
Gender (male, %)	44	33	38	52
Genotyped (%)	99	90	92	97
Self-report diabetes (%)	32	50	36	24
MetS ^b (%)	44	42	54	31
HDL cholesterol (mg/dl)	39 (32, 47)	45 (39, 54)	38 (32, 45)	43 (34, 53)
Triglyceride (mg/dl)	106 (65, 165)	78 (55, 120)	124 (82, 191.5)	105 (64, 165)
Waist Circum (cm)	98.7 (89.1, 108.3)	96.5 (86.8, 107.9)	98.7 (90.8, 108)	89.5 (80.2, 95.2)
Weight (kg)	81.9 (70.0, 93.5)	82.5 (71.8, 97.8)	76.7 (66.4, 89.3)	64.6 (54.5, 75.9)
Systolic BP (mm Hg)	123.3 (112, 136)	125.7 (115.5, 139.3)	120.7 (109.3, 134)	119.3 (108.7, 129.3)
Diastolic BP (mm Hg)	78 (70.7, 84)	78.7 (70.7, 86.7)	72.7 (66, 82)	71.3 (63.3, 80)
Fasting glucose (mg/dl)	101 (93, 132)	112.5 (94, 163.8)	107 (96, 176.5)	106 (97, 127)
Fasting insulin (mg/dl)	8.2 (5.0, 13.6)	11.4 (7.0, 18.3)	11.9 (7.2, 18.1)	5.1 (2.9, 9.8)

ATP III, Adult Treatment Panel III; BP, blood pressure; Circum, circumference; GENNID, genetics of NIDDM; HDL, high-density lipoprotein; MetS, metabolic syndrome.
^aMedian (25th-percentile, 75th-percentile); ^bMetS defined using the ATP III criteria.

Table 2 Factors and factor loadings^a from principal components factor analysis, by GENNID ethnic groups

Factor variable	White (N = 444)		African Americans (N = 253)			Mexican Americans (N = 389)			Japanese Americans (N = 123)			
	WT	BPF	LIPID	WT	BPF	LIPID	WT	BPF	LIPID	WT	BPF	LIPID
HDL cholesterol	-0.08	0.028	0.85	-0.08	0.13	0.77	-0.11	0.14	0.76	-0.39	0.06	0.717
Triglyceride ^b	0.22	0.25	-0.75	0.16	0.24	-0.76	0.10	0.13	0.82	0.13	0.21	-0.851
Waist Circum ^b	0.93	0.10	-0.16	0.94	0.08	-0.14	0.93	0.07	-0.11	0.90	0.08	-0.22
Weight	0.94	0.11	-0.06	0.94	0.02	0.00	0.94	0.06	-0.05	0.93	0.08	-0.10
Systolic BP ^b	0.15	0.89	-0.05	0.06	0.89	-0.05	0.11	0.85	-0.03	0.14	0.91	-0.03
Diastolic BP ^b	0.09	0.89	-0.11	0.05	0.89	-0.07	0.06	0.85	-0.04	0.02	0.90	-0.15
Fasting Glucose ^b	0.30	0.21	-0.45	0.10	0.32	-0.54	0.17	0.20	-0.57	0.29	0.25	-0.46
Fasting Insulin ^b	0.59	0.19	-0.48	0.60	0.07	-0.38	0.57	0.15	-0.42	0.62	0.15	-0.48
% Total variance	28.3	22	22.1	27.2	22.1	20.4	27.0	19.4	22.3	29.1	22.3	22.0
% Cumulative variance	28.3	50.3	72.4	27.2	49.3	69.7	27.0	46.4	68.7	29.1	51.4	73.4
Heritability (s.e.)	0.48 (0.10)	0.42 (0.10)	0.47 (0.09)	0.59 (0.17)	0.39 (0.15)	0.34 (0.19)	0.50 (0.11)	0.47 (0.12)	0.27 (0.09)	0.61 (0.18)	0.15 (0.15) ^c	0.71 (0.15)

BP = blood pressure; BPF, blood pressure factor; Circum, circumference; GENNID, genetics of NIDDM; LIPID, lipid factor; HDL, high-density lipoprotein, WT, weight factor.

^aFactor loadings represent the correlation between the individual variable and each factor; boldface indicates magnitude of factor loadings ≥ 0.40 ; ^bLog transformed;

^cHeritability is not significantly different from 0; *P* value = 0.12.

rather than LOD scores on the γ -axis. On this scale, a “suggestive” linkage signal is represented by a $-\log_{10}$ (adjusted empp) value of 2.77, which is equivalent to a *P* value of 0.0017 or an LOD score = 1.9 (28). **Supplementary Table S1** online provides detailed results from the genome-wide linkage scan by ethnic group, including LOD scores, adjusted empp and chromosomal location for regions with an LOD score >1.90 , along with the LOD scores and adjusted empp for the individual features that comprise each feature. The adjusted empp allows for a more direct comparison of the strength of the linkage signal between the factors and the individual features.

In the white sample, two suggestive linkage peaks for the wtfactor were identified. The strongest overall finding in our study was observed on chromosome 2 at 122 cM (1-LOD support interval of 117–127 cM) with an LOD score of 2.88 (adjusted empp = 0.00048) (**Figure 1a**). The second signal was identified on chromosome 1 at 157 cM with an LOD score of 2.43 (1-LOD support interval of 151–164 cM, adjusted empp = 0.00162). Interestingly, log-weight and log-waist also showed suggestive linkage to the same location on chromosome 2 (adjusted empp <0.0017), while only log-weight showed suggestive linkage to the wtfactor peak on chromosome 1 (See **Supplementary Table S1** online).

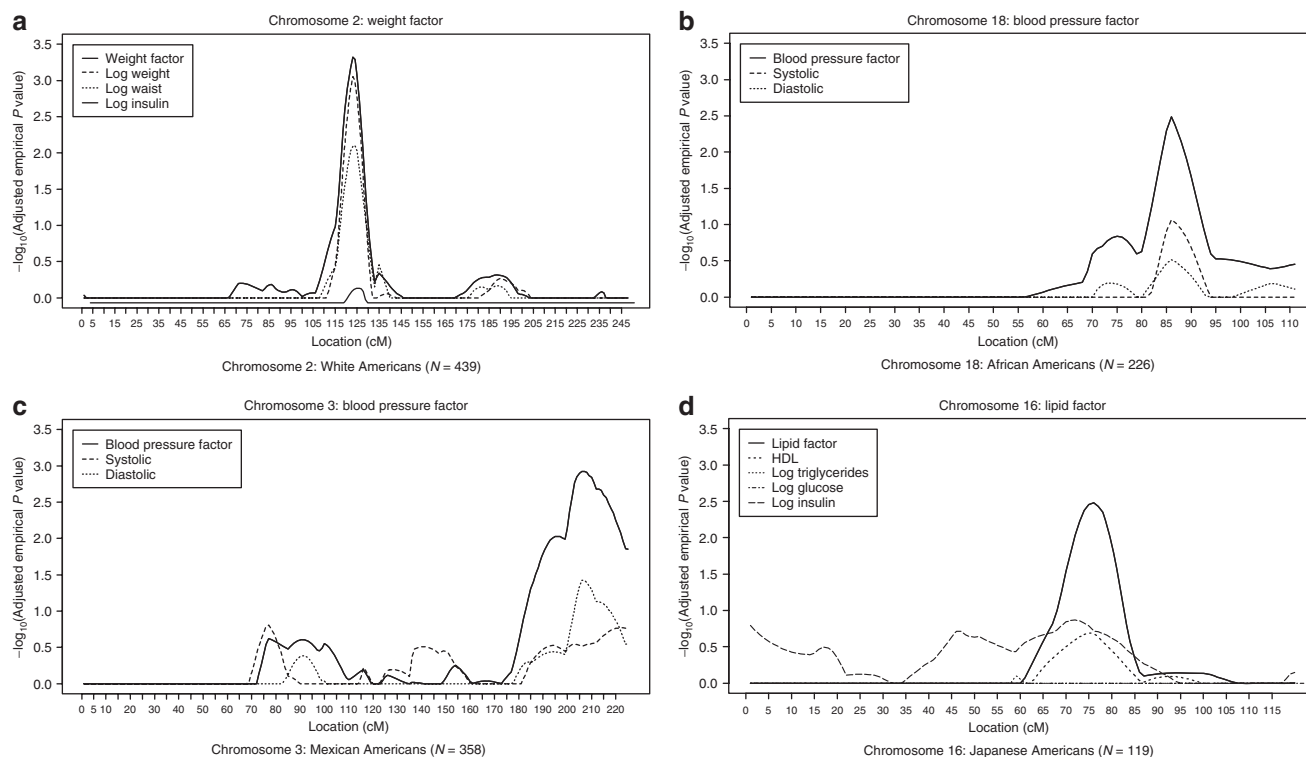


Figure 1 Selected linkage results by ethnic group. Panels (a–d) show linkage results of chromosomes with the maximum genome-wide LOD score within each ethnic group: white, African Americans, Mexican Americans, and Japanese Americans, respectively. On the x-axis the centiMorgan (cM) location is plotted for a given chromosome, and on the y-axis, the $-\log_{10}$ (empirical P value adjusted for multiple traits) is shown; the maximum $-\log_{10}$ (adjusted empirical P value) corresponds to the maximum LOD score. Each trait is specified by a line type noted in each subplot legend box.

Among the African-American families five linkage peaks with LOD >1.9 were observed, all showing suggestive evidence for linkage to the bpfactor. These peaks were observed on chromosomes 1, 11, 14, 16, and 18 (**Supplementary Table S1** online). The strongest evidence for linkage (LOD = 2.43; adjusted empp = 0.0032) was observed on chromosome 18 (85 cM; 1-LOD support interval of 81–91 cM) (**Figure 1b**), followed by a signal on chromosome 16 (32 cM, 1-LOD support interval of 14–41 cM) with an LOD score of 2.25 (adjusted empp = 0.0054). The LOD scores for the composite bpfactor were greater than the maximum LOD scores under this linkage peak for either systolic or diastolic blood pressure for chromosomes 1, 11, 16, and 18. In contrast, the LOD score on chromosome 14 was larger for systolic blood pressure (LOD >2.2) than for the composite bpfactor.

Results for the Mexican-American families indicate evidence for linkage on chromosomes 3, 14, and 15 (**Supplementary Table S1** online). The strongest evidence for linkage (LOD = 2.67; adjusted empp = 0.0012) was observed on chromosome 3 (206 cM; 1-LOD support interval of 190–223 cM) for the bpfactor (**Figure 1c**), followed by a signal (LOD = 2.41; adjusted empp = 0.0026) on chromosome 15 (25 cM; 1-LOD support interval of 17–33 cM) for the bpfactor. A suggestive signal (LOD = 1.90, adjusted empp = 0.0016) for the lipidfactor was observed on chromosome 14 (65 cM; 1-LOD support interval of 45–79 cM).

Finally, results for the Japanese-American families indicate evidence for linkage on chromosomes 5 and 16 with the

wtfactor and the lipidfactor, respectively (**Supplementary Table S1** online). The strongest evidence (LOD = 2.33; adjusted empp = 0.0033) for linkage was observed on chromosome 16 (75 cM; 1-LOD support interval of 68–81 cM) with the lipidfactor (**Figure 1d**). A more modest signal (LOD = 1.94, adjusted empp = 0.0032) on chromosome 5 (166 cM; 1-LOD support interval of 152–185 cM) was identified for the wtfactor. Suggestive signals for waist and HDL (LOD >1.90) were observed for these locations on chromosomes 5 and 16, respectively. The generally modest adjusted empirical P values reflect the smaller sample size of this group.

DISCUSSION

In this study, three quantitative MetS factors were identified: (i) a weight/waist factor, (ii) a blood pressure factor, and (iii) a lipid factor. Results from this analysis indicate that the factors and factor loadings identified by PCFA are consistent across the four ethnic groups when the same set of risk factors is included in the PCFA. Evidence for linkage to each of these factors was observed, although the linkage signals varied across the four ethnic groups. These results suggest heterogeneity in MetS susceptibility.

Overall, the strongest evidence for linkage in this study was observed on chromosome 2 for the wtfactor phenotype among the white sample and on chromosome 3 for the bpfactor in the Mexican-American sample. The region identified on chromosome 2 (2q12.1–2q13) includes a candidate gene (*INSIG2*)

previously identified by the Framingham group as influencing adult and childhood obesity on chromosome 2q14 (30). Although, the *INSIG2* obesity association has not been consistently replicated (31–35), the correspondence of this candidate gene for obesity and our linkage finding is intriguing. The region on chromosome 3 corresponds to a region (3q27) that has been identified as harboring a MetS susceptibility locus (36). There are several interesting candidate genes in this region, including adiponectin (*ADIPOQ*), which over the past 10 years has been established as a key player in the processes that affect the clustering of MetS phenotypes (37,38). Additional work is needed to fine-map the regions identified in this study and to further evaluate *INSIG2*, *ADIPOQ*, and other genes in these regions as potential MetS susceptibility genes.

Several other groups have performed genome-wide linkage analysis on MetS phenotypes defined by PCFA and have reported evidence for genetic influences on these phenotypes. Studies have been conducted in Mexican-American families (7,11), white families (8,10), African-American families (12), Native Americans (14), and multiethnic samples stratified by race/ethnicity (9,15,16). In general, there are very few overlaps in reported signals across these studies, and none of the previous suggestive or significant linkage results for composite MetS phenotypes overlaps with regions identified in our study. However, the results of these studies are difficult to directly compare. In particular, while all previous studies have included features related to obesity, glucose intolerance, lipids, and blood pressure, there has been variation in the individual features included in the PCFA.

While the potential impact of these differences on linkage scans has not been fully evaluated, an interesting example can be seen by contrasting two linkage studies performed by Kraja and colleagues (15,16). In both analyses, Kraja *et al.* used family data from HyperGEN and defined MetS phenotypes using PCFA. Ten individual MetS features were included in the PCFA in one paper, while the second paper included eleven MetS features. In both analyses, four factors were identified and used as composite phenotypes in the linkage analysis (obesity-insulin, lipids-insulin, central obesity, and blood pressure). In some cases, there was direct overlap in the linkage regions identified between the two studies, while in other cases linkage signals were not replicated even though it appears that the same population was used. The lack of replication may be due in part to differences in the composite factors identified by PCFA.

Another potentially important difference with regard to defining composite MetS phenotypes by PCFA relates to whether the retained factors are rotated or not. For example, six studies performed an orthogonal rotation, most often a varimax rotation, whereas three of the previous linkage studies did not use a rotation step (9,10,13). While there is debate about the most appropriate approach, work in this field will benefit from more standard practices in carrying out factor analysis (39).

We performed PCFA with varimax rotation in four ethnic groups, using the same set of MetS features, retaining the same number of factors, and applying the same statistical methods. This standardized approach resulted in very similar composite

phenotypes for MetS in all ethnic groups. However, despite these efforts different patterns of linkage emerged across ethnic groups. First, the specific MetS factors showing suggestive evidence for linkage differed across groups. For example, among the African-American families only the bpfactor showed evidence for linkage, while among the whites, it was only the wtfactor. Second, evidence for linkage for specific MetS factors was observed for different regions across groups. Among the African-American families, five suggestive regions for the bpfactor were identified that did not overlap with the two bpfactor regions identified in the Mexican-American sample.

A strength of the current study was the use of a set of large, well-characterized families from four different ethnic groups, allowing comparisons of linkage signals across these groups. Based on the different linkage patterns observed across the four groups, it is tempting to speculate that specific genomic regions may play a more prominent role in MetS disease susceptibility in different ethnic groups. However, it is not clear whether these differences truly represent evidence for genetic heterogeneity. While it is possible that the slight differences in factor loadings may account for differences in linkage patterns, it is more likely that these signals reflect differences in power among the different groups (due to both sample size and differences in LD patterns between the groups), environmental effects, gene \times environment interactions, or combinations of these hypotheses. Evaluating the impact of each of these potential effects is a focus of our ongoing work.

In summary, several regions with suggestive evidence for linkage to composite MetS phenotypes were identified in each ethnic group. By identifying genetic factors influencing susceptibility to the MetS our understanding of the molecular mechanisms underlying the pathogenesis of MetS will be enhanced. This understanding is a necessary prerequisite for the rational development of preventive and improved therapeutic approaches for MetS. The challenge in years to come will be to understand how risk is influenced by the interaction of susceptibility genes with each other and with pertinent social and environmental factors and to establish how best to apply this understanding to provide individuals with clinically useful preventive, diagnostic, prognostic, and therapeutic information.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/oby>

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DISCLOSURE

The authors declared no conflict of interest.

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