

These factors were strongly determined by additive genetic influences, as suggested by the family data from SAFADS (23).

In this study, we attempted to identify the susceptibility loci that influence the IRS factor-specific scores, which are composite risk factors, using phenotypic and genotypic data from a subset of nondiabetic individuals from Mexican-American families. We 1) identified the IRS factor structures, 2) determined the genetic basis for these factors, and 3) identified the susceptibility loci for the IRS factors by conducting a multipoint variance components linkage analysis using a 10–15 cM map.

RESEARCH DESIGN AND METHODS

Subjects. Phenotypic and genotypic data were obtained from individuals distributed across 27 Mexican-American families living in San Antonio, Texas, who were participants in the SAFADS. Probands for the SAFADS study were randomly selected, low-income Mexican-Americans with type 2 diabetes identified in a previous epidemiological survey (8,24). All 1st-, 2nd-, and 3rd-degree relatives of the probands, aged ≥ 18 years, were considered eligible for the study. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved all procedures, and all subjects gave written informed consent.

We used phenotypic data from 261 nondiabetic individuals, distributed across the 27 largest pedigrees, for whom genotypic data were also available. Only participants for whom data were available for all the phenotypes were included in the study. We have previously described our genotype data in detail, including the procedures for checking genotypic data for Mendelian discrepancies (25,26). Marker information for discrepant individuals was either corrected or blanked out before conducting the analyses. Although we typed 419 markers for two-point linkage analysis, markers with less than ~80% of the sample typed were not used unless their absence would result in a gap of 20 cM or more (26). Thus, a subset of 301 highly informative microsatellite markers was selected based on their optimal spacing and informativeness.

Physical and biochemical measurements. Blood samples were obtained after a 12-h fast, and various metabolic traits, including glucose, triglyceride (TG), and HDL cholesterol (HDL-C) levels were measured using enzymatic and precipitation procedures, as previously described (8,9). We assessed the extent of measurement error using duplicate measures for a given trait. Accordingly, the technical error of measurement for HDL-C and TG values was 1.1 and 1.2% of the mean, respectively. TG values >800 mg/dl were considered as outliers and were excluded from the analysis. TG values were log transformed (\ln TG) because the raw values exhibited high nonnormality. Fasting specific insulin (FSI) concentrations were measured using a monoclonal antibody-based two-site immunoradiometric assay (27). We used the FSI concentration because, unlike conventional fasting immunoreactive insulin, it does not cross-react with insulin precursors. Serum leptin (LEP) was measured by a radioimmunoassay (28). Blood pressure levels, both systolic (SBP) and diastolic (DBP), were measured to the nearest 2 mmHg with a Random-Zero sphygmomanometer (Gelman-Hawksley, Lancing, Sussex, U.K.). Anthropometric traits, including height and weight, were collected using standardized anthropometric protocols (8,9). BMI was calculated as weight (in kilograms) divided by height (in meters) squared.

Statistical methods. Principal component factor analysis (PCFA) was performed to extract the underlying factors of IRS-related phenotypes. Before conducting PCFA, trait-specific values that fell beyond 4 SDs from the mean of the trait were considered as outliers and were excluded from the PCFA analysis. As stated above, TG values were log transformed to circumvent the problem of high nonnormality. PCFA is a data-reduction technique that reduces a large number of correlated variables into fewer uncorrelated factors, thereby reducing the problem of correcting for multiple comparisons (29,30). PCFA is a three-step process. The first step involves principal component analysis, which is used to reduce highly correlated original variables to fewer uncorrelated components. These components are linear combinations that account for the maximum amount of total variance in the original variables. The first extracted factor accounts for the largest amount of the variability among the measured variables, whereas subsequent factors explain additional variability in decreasing order. The number of significant components is determined based on eigenvalues, which are the sum of the squared factor loadings (29). These eigenvalues represent the amount of variance attributable to each factor. In the second step, the factors with eigenvalues ≥ 1.0 (i.e., factor 1, factor 2, and factor 3, with eigenvalues of 2.8,

TABLE 1
Characteristics of 261 nondiabetic Mexican-American Individuals

| | |
|-----------------------------------|------------------|
| <i>n</i> (M/F) | 108/153 |
| Age (years) | 38.5 \pm 15.6 |
| Fasting glucose (mg/dl) | 88.6 \pm 10.8 |
| Fasting specific insulin (pmol/l) | 125.5 \pm 80.4 |
| BMI (kg/m ²) | 29.1 \pm 6.3 |
| Systolic blood pressure (mmHg) | 118.4 \pm 16.0 |
| Diastolic blood pressure (mmHg) | 70.9 \pm 10.0 |
| HDL cholesterol (mg/dl) | 37.7 \pm 9.7 |
| <i>ln</i> triglycerides | 4.9 \pm 0.6 |
| Leptin (ng/ml) | 22.1 \pm 17.3 |

Data are *n* or means \pm SD.

1.7, and 1.0, respectively) are extracted using a varimax rotation method to produce interpretable factors (29). The third step involves the interpretation of these factors by examining the factor loadings, which are the correlations between each variable and the factor in question. Factor loadings ≥ 0.40 are generally used to interpret factors and characterize the factor structures (29). All factor analyses were performed using SAS software (31).

Multipoint variance components linkage analyses were performed on the factor scores to identify chromosomal regions containing susceptibility loci for each factor using the variance components approach (32). With this method, the expected genetic covariances between relatives are specified as a function of their identity-by-descent (IBD) relationships at a marker locus that is assumed to be closely linked to a locus influencing the quantitative trait in question. The covariance matrix for a given pedigree is given by the following equation:

$$\Omega = \Pi\sigma_q^2 + 2\Phi\sigma_g^2 + I\sigma_e^2$$

where Ω is the covariance matrix for a pedigree; Π is a matrix with elements (π_{ij}) specifying the expected proportion of alleles that individuals *i* and *j* share IBD at the specific chromosomal location of the quantitative trait locus, which is estimated using genetic marker data; σ_q^2 is the additive genetic variance attributable to the major locus; Φ is the kinship matrix; σ_g^2 is the variance attributable to residual additive genetic effects; I is an identity matrix; and σ_e^2 is the variance attributable to random environmental effects. Location-specific IBD information for pairs of relatives was obtained by the program SOLAR (32). We conducted multipoint variance components linkage analysis according to the procedures outlined in the computer program SOLAR using a 10- to 15-cM map to localize the loci influencing the uncorrelated factors extracted through PCFA analysis. The coefficients of skewness and kurtosis for each factor (i.e., factor scores) after adjusting for the effects of age and sex terms are as follows: factor 1, skewness = 0.9 and kurtosis = 0.8; factor 2, skewness = 0.4 and kurtosis = 0.6; and factor 3, skewness = 0.4 and kurtosis = 0.0. These factor-specific distributional properties suggest that the factor scores used in this study minimally violated the assumption of normality.

To verify our findings on chromosomes 6 and 7, we used simulations to obtain empirical *P* values. In the simulation analysis, a fully informative marker that was not linked to the quantitative trait locus influencing a given factor was simulated. For this simulated marker, IBD information was calculated, and linkage analysis was then conducted. We generated 100,000 replicates to determine the empirical *P* value. This procedure was implemented in the program SOLAR.

RESULTS

The characteristics of the subjects used in the study are presented in Table 1. Correlations among the phenotypes are presented in Table 2. The majority of the correlations among eight phenotypes are significant ($P < 0.001$), although a few correlations are not. BMI and *ln* TG showed significant correlations with all the traits, whereas in men LEP showed significant correlations with BMI, FSI, and *ln* TG, and in women LEP showed significant correlations with all traits except SBP.

The factors and patterns of factor loadings obtained in this study are shown in Table 3. In the factor analysis, three factors were extracted by PCFA. Factor 1 exhibited high and positive correlations with BMI, LEP, and FSI,

TABLE 2
Pearson product moment correlation coefficients of IRS-related phenotypes

| | BMI | DBP | SBP | FG | FSI | HDL | <i>ln</i> TG |
|---------------------------------|-------|--------|--------|-------|-------|--------|--------------|
| BMI | — | — | — | — | — | — | — |
| DBP | 0.21 | — | — | — | — | — | — |
| SBP | 0.12 | 0.52 | — | — | — | — | — |
| FG | 0.26 | 0.10* | 0.25 | — | — | — | — |
| FSI | 0.63 | 0.15 | 0.05* | 0.25 | — | — | — |
| HDL | -0.37 | -0.17 | -0.07* | -0.13 | -0.26 | — | — |
| <i>ln</i> TG | 0.32 | 0.29 | 0.34 | 0.28 | 0.28 | -0.40 | — |
| Leptin | | | | | | | |
| Men (<i>n</i> = 108) | 0.64 | -0.05* | 0.01* | 0.09* | 0.52 | -0.17* | 0.23 |
| Women (<i>n</i> = 153) | 0.76 | 0.30 | 0.13* | 0.29 | 0.66 | -0.21 | 0.26 |
| Men and women (<i>n</i> = 261) | 0.62 | -0.01* | -0.14 | 0.08* | 0.52 | -0.05* | 0.04* |

*Not significant.

explaining 35% of the total variance. Factor 2 showed high loadings for only DBP and SBP, and factor 3 showed a high positive association with HDL-C values and a negative association with *ln* TG values, thus reflecting the inverse relationship between HDL-C and *ln* TG values. In all, ~68% of the total variance was cumulatively explained by these three factors (Table 3). Because factor 1 is dominated by large positive correlations for BMI, FSI, and LEP, this factor can be interpreted as an adiposity-insulin factor. Because it is dominated by DBP and SBP, factor 2 is interpreted as a blood pressure factor. In contrast, large positive correlation with HDL-C and large negative correlation with *ln* TG dominated factor 3; therefore, this factor can be interpreted as a lipid profile factor.

Heritabilities were estimated for all three factors using variance components analysis. After accounting for covariates (i.e., age and sex terms), heritabilities for the three factors ranged from 49 to 58% (Table 4). Heritabilities of all the factors were moderate to high and statistically significant ($P < 0.0001$) (Table 4). The results of our multipoint linkage analysis for IRS factor susceptibility loci with multipoint peak logarithm of odds (LOD) score ≥ 1.9 are reported in Table 5.

As shown in Fig. 1, we found significant evidence for linkage of the adiposity-insulin factor (factor 1; LOD score = 4.9, empirical P value = 0.00002) to a genetic location at 208 cM from p-ter on chromosome 6q (near marker D6S264). Marker D6S403 region on chromosome 6q was also found to be strongly linked (LOD = 4.2,

TABLE 3
Factor loadings of the IRS-related phenotypes

| Phenotype | Factor loadings | | |
|-------------------------|-----------------|----------|----------|
| | Factor 1 | Factor 2 | Factor 3 |
| BMI | 0.83 | 0.17 | -0.30 |
| DBP | 0.07 | 0.79 | -0.08 |
| SBP | -0.08 | 0.88 | -0.06 |
| FG | 0.26 | 0.38 | -0.22 |
| FSI | 0.80 | 0.11 | -0.22 |
| HDL | -0.12 | 0.02 | 0.89 |
| <i>ln</i> TG | 0.12 | 0.39 | -0.69 |
| Leptin | 0.88 | -0.11 | 0.13 |
| Eigenvalue | 2.8 | 1.7 | 1.0 |
| Total variance (%) | 35 | 21 | 12 |
| Cumulative variance (%) | 35 | 56 | 68 |

empirical P value = 0.00013) with factor 1. We also observed strong evidence for linkage of factor 3, the lipid profile factor, to a genetic location on chromosome 7 between markers D7S479 and D7S471 (LOD = 3.2, empirical P value = 0.00016) (Fig. 2). The blood pressure factor (factor 2) showed suggestive evidence for linkage on chromosome 15 (LOD = 2.0, empirical P value = 0.00181) (Table 5).

DISCUSSION

Because the IRS consists of several correlated phenotypes, it is important to understand the major component/phenotype or common factors underlying the correlations between these related phenotypes. There is substantial evidence that not only insulin levels and IRS-related phenotypes but also IRS-related factors are under strong genetic influences (10,20,23,32–35). It should be noted that environmental determinants influence these factor structures as well. Results from some studies involving the Mexican-American population have indicated either directly or indirectly that the IRS-related phenotypes are influenced by a common set of genes (i.e., pleiotropy) (9,10,35). Recently, Duggirala et al. (23) found evidence for genetic influences on factor structures underlying the IRS in nondiabetic Mexican-American family members. We therefore conducted variance component linkage analyses to identify the specific chromosomal regions across the genome that harbor susceptibility loci for these IRS factor structures in Mexican-Americans.

In this study, we performed PCFA to extract factors on IRS-related phenotypes, including fasting glucose, FSI, BMI, SBP, DBP, HDL, *ln* TG, and LEP. We obtained three factors that represented an adiposity-insulin factor (BMI, FSI, and LEP), a blood pressure factor (DBP and SBP), and a lipid profile factor (HDL and *ln* TG). These findings were consistent with previous studies that have used factor

TABLE 4
Constructs and heritabilities of factors of IRS-related phenotypes

| Factor | Constructs | Heritability* |
|--------|--------------------------|-----------------|
| 1 | Adiposity-insulin factor | 0.51 \pm 0.13 |
| 2 | Blood pressure factor | 0.58 \pm 0.16 |
| 3 | Lipid profile factor | 0.49 \pm 0.13 |

Data are heritability \pm SE. All heritabilities are significant at $P < 0.0001$.

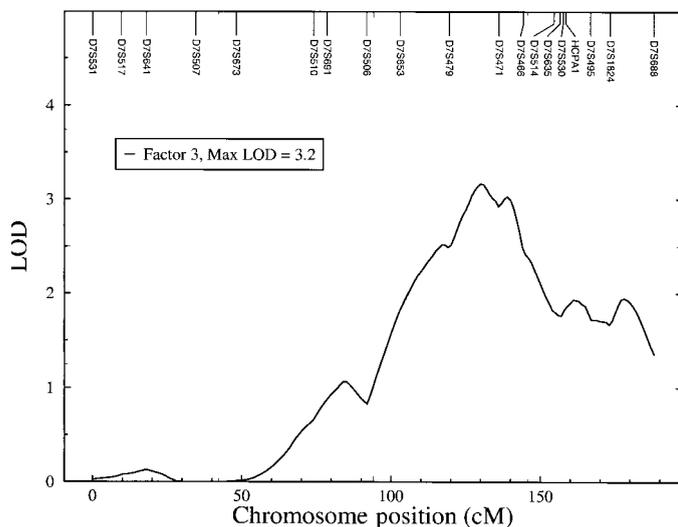


FIG. 2. Multipoint linkage profile of factor 3 on chromosome 7.

information related to three constituents of the IRS: FSI, BMI, and LEP.

The second major region on chromosome 7 between markers D7S479 (7q21.3) and D7S471 (7q31.1) with strongest evidence for linkage of our lipid profile factor (factor 3; LOD = 3.2), has also reported to be linked with type 2 diabetes or its related quantitative traits in Pima Indians (41). In addition, these results correspond well with the findings of Imperatore et al. (42), who reported evidence of linkage for lipid factor in Pima Indians on chromosome 7 at q22.2. In another study (26), based on univariate linkage findings, we found that TG concentrations were suggestively linked (LOD = 2.1) to a genetic location centromeric to marker D7S479, and that HDL concentrations were also linked to a location near marker D7S479 (LOD = 1.7). Although the LOD curves peaked at different locations for these phenotypes, the trait-specific linkage curves overlapped, which may indicate a locus influencing both phenotypes. In fact, the genetic location found to be strongly linked (LOD = 3.2) to the lipid construct (factor 3) overlaps very well with our earlier HDL linkage finding on chromosome 7q.

The genetic regions of interest on chromosome 6q contain several known candidate genes for the IRS. The genetic location near marker D6S403 is very close to the plasma cell membrane glycoprotein PC-1 (6q22-q23), a potential candidate gene for insulin resistance (43). The second linked region near D6S264 also appears to harbor candidate genes for IRS, such as IGF2R (6q26) (44) and ACAT2 (6q25.3-q26) (44). The chromosomal region of interest near D7S479 (7q21.3) contains several potential candidate genes for the IRS, such as paraoxonase and plasminogen activator inhibitor. Another candidate gene for the IRS, which is not far from our chromosomal region of interest on chromosome 7, is the collagen and thrombospondin receptor CD36 (44), which is localized to band 7q11.2 (45).

To our knowledge, only one other study has attempted to identify loci affecting the IRS factors using data from the Pima Indian population (42). In this study, strong evidence was found for a locus near marker D1S2141 on chromosome 1 linked to an insulin-glucose factor, and another

locus on chromosome 7 was found to influence one or more components of the metabolic syndrome, including the lipid factor. We failed to replicate the finding involving the marker region near D1S2141. However, as shown in Table 5, we found evidence for one locus near marker D1S305 (LOD = 2.6) influencing the adiposity-insulin factor and another locus near marker D1S431 (LOD = 1.9) influencing the lipid factor. These markers are about 29 cM apart on our map. The marker D1S305 region strongly overlaps with the chromosomal region (i.e., a genetic location between markers D1S305 and D1S1600) reported to be linked to familial partial lipodystrophy (Dunnigan variety), which is characterized by conditions such as insulin resistance, diabetes, and dyslipidemia (46). Also, our regions near markers D1S305 and D1S431 overlap with the genetic location(s) on chromosome 1q found to be linked with diabetes in the Pima population (47). The marker D1S431 region also overlaps with the chromosomal region reported to be linked with diabetes in a Caucasian population (34).

Several of the chromosomal regions found to be suggestively linked to the IRS factors in this study (Table 5) have been shown to be linked to one or more phenotypes related to the IRS in various populations. For example, suggestive evidence for linkage of diabetes to the marker D9S301 was found using family data from the Botnia region in Finland (48). In Pima Indians, some evidence for linkage of fasting insulin was reported to a genetic location close to the D9S301 marker region (44). The adiposity-insulin factor was found to be linked to a location near marker D2S141, which overlaps with a region on chromosome 2q that shows some evidence of linkage to diabetes-related phenotypes (35,49). Several studies have reported linkage of diabetes- or obesity-related phenotypes to different, but overlapping, genetic regions on chromosome 20q (35,50), which correspond to the genetic region near marker D20S170 found to be suggestively linked to adiposity-insulin factor in this study.

In conclusion, we determined factor structures that underlie the IRS-related phenotypes in a Mexican-American population. We also found that these factors of the IRS are substantially influenced by additive genetic factors. Subsequently, by the use of a multipoint variance components technique, we identified two major loci on chromosome 6q that influence the adiposity-insulin factor, and another locus on chromosome 7q that significantly influences the lipid factor. In addition, several other chromosomal regions, identified earlier as influencing one or more of the constituents of the IRS, have also been found to influence the various factor structures examined in this study. These results provide strong evidence for major locus effects on the phenotypic variance of the factor structures that underlie the IRS in Mexican-Americans.

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