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A Major Susceptibility Locus Influencing Plasma Triglyceride Concentrations Is Located on Chromosome 15q in Mexican Americans

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Although several genetic forms of rare or syndromic hypertriglyceridemia have been reported, little is known about the specific chromosomal regions across the genome harboring susceptibility genes for common forms of hypertriglyceridemia. Therefore, we conducted a genomewide scan for susceptibility genes influencing plasma triglyceride (TG) levels in a Mexican American population. We used both phenotypic and genotypic data from 418 individuals distributed across 27 low-income, extended Mexican American families. For the analyses, TG values were log transformed (ln TG). We used a variance-components technique to conduct multipoint linkage analyses for localizing susceptibility genes that determine variation in TG levels. We used an ~10–15–cM map, which was made on the basis of information from 295 microsatellite markers. After accounting for the effects of sex and sex-specific age terms, we found significant evidence for linkage (LOD = 3.88) of ln TG levels to a genetic location between the markers GABRB3 and D15S165 on chromosome 15q. This putative locus explains 39.7 ± 7% (P = .000012) of total phenotypic variation in ln TG levels. Suggestive evidence was found for linkage of ln TG levels to two different locations on chromosome 7, which are ~85 cM apart from each other. Also, there is some evidence for linkage of high-density lipoprotein cholesterol concentrations to a genetic location near one of the regions on chromosome 7. In conclusion, we found strong evidence for linkage of ln TG levels to a genetic location on chromosome 15q in a Mexican American population, which is prone to disease conditions such as type 2 diabetes and the insulin-resistance syndrome that are associated with hypertriglyceridemia. This putative locus appears to have a major influence on ln TG variation.

Introduction

The role of hypertriglyceridemia as an independent risk factor for coronary heart disease (CHD) has been controversial (Gotto 1998). Recently, however, increasingly strong evidence for its role as a CHD risk factor has emerged (Austin et al. 1998; Havel 1998; Jeppesen et al. 1998). Although fasting plasma triglyceride (TG) levels >200 mg/dl have been considered to increase risk, recent evidence suggests that an even lower threshold (>100 mg/dl) could be deleterious in patients with established coronary artery disease (Miller et al. 1998). Hypertriglyceridemia is commonly found in individuals with type 2 diabetes, and it is an element of the so-called metabolic syndrome (Ginsberg 1996; Howard 1996; Garg 1998; Grundy 1998). People with type 2 diabetes and those who are prediabetic have a greater risk of CHD than do individuals who are unaffected (Haffner et al. 1990; Hsueh and Law 1998).

Since the molecular basis of CHD is incompletely understood, there have been continued efforts to disentangle the genetic architecture of CHD risk factors, including fasting plasma TG levels. Numerous genetic epidemiological studies have demonstrated that the variation in TG levels is affected by both genetic and environmental factors (Iselius 1988; Rice et al. 1991; Mitchell et al. 1996). A few studies have examined major locus effects on TG concentrations by making use of segregation analysis, but the results have been inconclusive (Singh et al. 1988; MacCluer 1989). Several forms of hypertriglyceridemia, such as chylomicronemia, familial hypertriglyceridemia, and familial combined hyperlipidemia, are attributable to genetic abnormalities (Grundy 1998). Recently, a susceptibility locus for familial combined hyperlipidemia has been localized to a genetic location on chromosome 1q21-q23 (Pajukanta et al. 1998). Also, the gene for Tangier disease, which is associated with increased levels of TGs, has been assigned to chromosome 9q31 (Rust et al. 1998). However, little is known about the specific major

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genetic determinants of common forms of hypertriglyceridemia.

In this study, we scanned the genome for susceptibility loci influencing the plasma TG levels by making use of pedigree data from a low-income Mexican American population. In Mexican Americans, the prevalence of type 2 diabetes is three times higher than in the general U.S. population (Stern and Haffner 1990). Furthermore, Mexican Americans without diabetes have been shown to be more insulin resistant than members of the non-Hispanic white population (Haffner et al. 1986, 1990). Our genomewide scan for loci affecting plasma TG levels used a multipoint variance-components linkage approach and an ~10–15–cM map.

Material and Methods

The San Antonio Family Diabetes Study (SAFADS) aims to identify susceptibility genes for type 2 diabetes and related phenotypes by use of data from extended pedigrees (Stern et al. 1996; Duggirala et al. 1996, 1999). A total of 579 individuals (140 with diabetes) in 32 families ascertained on a type 2 diabetic proband were examined, involving first-, second-, and third-degree relatives aged 18–98 years. Metabolic, anthropometric, demographic, and medical history information were obtained on all the examined individuals. A subset of 440 individuals (116 with diabetes) from the 27 largest pedigrees were selected for genotyping. All procedures were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all subjects gave informed consent.

Blood samples were obtained after a 12-h fast. The blood was assessed for various metabolic traits, including glucose, TG, and high-density lipoprotein cholesterol (HDL-C) concentrations, by methods described elsewhere (Stern et al. 1984). Duplicate measures for a given trait were used to assess the extent of measurement error. The technical error of measurement for HDL-C was 1.1% of the mean; for TG, it was 1.2%. Of the 440 SAFADS subjects, TG values were available for 422 individuals. TG values >800 mg/dl were excluded from the analysis because they were distinct outliers (i.e., only four individuals). For the present analysis, which is based on phenotypic information from 418 individuals, the TG values were log transformed (ln TG). These 418 individuals generated 3,379 relative pairs that were distributed across 17 categories of relative pairs (e.g., sibs, first cousins, second cousins, etc.), as shown in table 1. Glucose levels were also measured 2 h after a standardized oral glucose load. Diabetes was diagnosed according to criteria of the World Health Organization (1985).

Table 1

Distribution of Relative Pairs by Category in a Subset of 27 SAFADS Families Containing 418 Individuals

Relative Pair	Relationship Coefficient[a]	No. of Pairs
Parent-offspring	.5000	396
Sibs	.5000	491
Grandparent-grandchild	.2500	100
Avuncular	.2500	633
Half-sibs	.2500	65
Great-grandparent–grandchild	.1250	12
Grand avuncular	.1250	124
Half-avuncular	.1250	66
First cousins	.1250	656
Great-grandavuncular	.0625	3
Half-grandavuncular	.0625	11
First cousins, once removed	.0625	479
Half–first cousins	.0625	75
First cousins, twice removed	.0312	9
Half–first cousins, once removed	.0312	32
Second cousins	.0312	212
Second cousins, once removed	.0156	15
Total		3,379

[a] The relationship coefficient is 2 × coefficient of kinship of two individuals.

Genotyping

A set of 295 markers was used for the multipoint linkage analysis, which provided coverage at intervals of ~10–15 cM on chromosomes 1–22 (Duggirala et al. 1999). Primers were purchased from Research Genetics. Further details concerning oligonucleotide primer sequences and polymorphisms can be obtained from the Genome Data Base at Johns Hopkins University (Fasman et al. 1996). PCR conditions were optimized by testing a range of annealing temperatures with varying concentrations of $MgCl_2$ so that the PCR amplification produced a specific product that could be visualized by ethidium bromide staining (0.5 μg/ml).

Genotypes were collected primarily by PCR assays with radiolabeled oligonucleotide primers. The antisense primer was 5′-radiolabeled in a standard polynucleotide kinase reaction by 3,000 Ci/mmol [γ^{32}P]-adenosine triphosphate (ATP; from NEN) at a molar ratio of 18 [γ^{32}P]-ATP:1 primer, as described elsewhere (O'Connell et al. 1994; Duggirala et al. 1996). Thirty cycles of PCR (denaturing at 94°C for 30 s, annealing at 55°C for 1 min, and extension at 72°C for 1 min) were done in a 15-μl assay containing 50 ng of DNA template, 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 1–4 mM $MgCl_2$, 0.1 M spermidine (Sigma), 0.1 μM of each PCR primer, 0.1 μM dNTPs (Gibco BRL), and 0.5 U of *Taq* polymerase (PE Biosystems). Amplified DNA was diluted 1:1 with stop solution (97% formamide, 1% EDTA, 0.1% bromophenol blue, and 0.1% xylene cyanol) and denatured at 85°C for 2 min. Three microliters of denatured DNA

from each sample were loaded onto a 7% denaturing polyacrylamide gel (19:1 acrylamide/bis-acrylamide) containing 32% formamide and 34% urea and fractionated by gel electrophoresis for 2.5 h at 60 W. Gels were transferred to filter paper (Whatman 3MM; from W. R. Balston) covered with plastic wrap, equilibrated with 20% methanol–20% acetic acid solution, and dried. Dried gels were exposed to X-ray film (Fuji Photo Film). As reported elsewhere (Duggirala et al. 1999), data for some of the markers were collected by means of fluorescent-labeled primers, purchased from Research Genetics. These were PCR amplified, as described above, and were loaded onto an Applied Biosystems model 373 sequencer, and the data were analyzed by Applied Biosystems GENOTYPER software.

The genotypic data used for this study were analyzed for discrepancies (i.e., violations of Mendelian inheritance) by the program INFER (Dyke 1996). Before conducting linkage analyses, the SAFADS pedigree structures were verified with information from ~50 polymorphic loci, including red blood cell antigens. The discrepancies were checked for mistyping in the laboratory, and a few instances that could not be resolved were presumed to be due to factors such as sample mix-up, nonparentage, or mutations. These unresolved cases were treated as missing data. Pedigree information was rechecked with family members, and blood samples were redrawn from relevant individuals whenever possible. Checking and rechecking the pedigree resulted in eight discrete pedigree revisions.

The genotypic information for SAFADS participants was routinely verified, and discrepancies were checked in the laboratory for mistyping. Markers for discrepant individuals were either corrected or blanked out prior to analysis. The average percentage of genotypes blanked (i.e., the number of genotypes blanked divided by the total number of genotypes) is ~.06%. Thus far, >400 markers have been typed, and all markers were used for two-point linkage analysis. Since our multipoint linkage approach yields optimum results when similar numbers of individuals are genotyped at all loci, markers with <80% of the sample genotyped were not considered for multipoint analysis unless their absence would result in a map gap of 20 cM (Duggirala et al. 1999). This arbitrary requirement excluded ~25% of the markers. Thus, the multipoint analyses are made on the basis of a total of 295 markers. In addition, ~4% of the total SAFADS marker data set could not be used for the multipoint analyses because of genotyping problems (i.e., markers failed to map to their expected positions or led to map expansion).

Statistical Genetic Analysis

We used a variance-components approach to test for linkage of a genetic location with ln TG levels by means of maximum-likelihood methods (Amos 1994; Blangero and Almasy 1997; Almasy and Blangero 1998). The variance-components method uses information from all possible biological relationships simultaneously in an attempt to disentangle the genetic architecture of a quantitative trait. This method specifies the expected genetic covariances between relatives as a function of their identity-by-descent (IBD) relationships at a marker locus (which is hypothesized to be linked to a locus influencing the quantitative trait [QTL]). It allows for locus-specific effects (h^2_q is heritability attributed to the QTL), residual additive genetic effects (h^2 is heritability attributed to the residual genetic effects), covariate effects (e.g., age and sex), and individual-specific random environmental factors [$e^2 = 1-(h^2_q + h^2)$].

In this study, in addition to the variance components, mean and SD of the phenotype and covariate effects (i.e., sex-specific age, and age^2 and sex terms) were simultaneously estimated by maximum-likelihood techniques. Hypothesis testing was performed by the likelihood ratio tests. The hypothesis of no linkage (i.e., additive genetic variance due to the $QTL = 0$) was tested by comparing the likelihood of this restricted model with that of a model in which the additive genetic variance due to the QTL is estimated. Twice the difference in ln likelihoods of these two models yields a test statistic that is asymptotically distributed as a ½:½ mixture of a χ^2_1 and a point mass at zero (Self and Liang 1987). LOD scores were obtained by converting the ln likelihood values into values of $\log_{10}$. After obtaining locus-specific IBD information for pairs of relatives by the computer program SOLAR (Almasy and Blangero 1998), the multipoint mapping strategy proposed by Fulker et al. (1995) was extended and modified (Almasy and Blangero 1998) to perform multipoint variance-components linkage analysis. These procedures were implemented in the SOLAR program.

Results

The characteristics of the subjects used for this study are reported in table 2. All genetic analyses included sex and sex-specific age and age^2 terms as covariates of ln TG values. After accounting for the significant covariate effects, the overall polygenic heritability (h^2) for ln TG values was estimated to be 33.6 ± 9%, with high statistical significance ($P < .0001$). The covariates explained ~14% of total phenotypic variation in ln TG. Following this, the multipoint linkage analysis was conducted, and the results of our genome scan (i.e., peak LOD score by chromosome) are summarized in figure 1. All LOD scores reported below relate to multipoint analysis, and only multipoint LOD scores near 2 or above are discussed.

The highest LOD score that we observed was 3.88,

Table 2

Characteristics of SAFADS Subjects Distributed across 27 Families Included in the Genotyping Set

Variable	Mean ± SD or %
Age at examination (years)	43.3 ± 17.3
Men	41.2%
Women	58.8%
Diabetics	26.4%
Body mass index (kg/m^2)	30.0 ± 6.7[a]
TGs (mg/dl)	173.6 ± 109.2[b]
ln TGs	5.0 ± .6[c]
HDL-C (mg/dl)	38.0 ± 10.2[d]

[a] Subjects with diabetes, 31.9 ± 6.6; subjects without diabetes, 29.4 ± 6.6.
[b] Subjects with diabetes, 212.4 ± 116.4; subjects without diabetes, 160.3 ± 103.5.
[c] Subjects with diabetes, 5.2 ± .5; subjects without diabetes, 4.9 ± .5.
[d] Subjects with diabetes, 37.9 ± 11.0; subjects without diabetes, 38.0 ± 9.9.

which is highly statistically significant and corresponds to a susceptibility locus for ln TG on chromosome 15q between the markers GABRB3 (gamma-aminobutyric acid A receptor, beta-3) and D15S165 (fig. 2). The multipoint LOD scores obtained for ln TG were plotted against map positions on chromosome 15 (fig. 2). As can be seen from this figure, the markers GABRB3 and D15S165 cover a region of ~10 cM, which appears to harbor a major susceptibility locus for hypertriglyceridemia. The heritability attributable to this putative locus (h^2_q) was estimated to be 39.7 ± 7% (P = .000012). Although the QTL heritability (h^2_q) is greater than the overall polygenic heritability (h^2), it is within the estimated SE around the overall polygenic heritability (i.e., h^2 = 33.6 ± 9%). Also, since the polygenic model was rejected in favor of the model including the QTL effect, the latter gives a more unbiased estimate of the heritability.

Two regions on chromosome 7 are suggestively linked (i.e., a multipoint LOD score near 2 or above) to ln TG levels: a genetic location between markers D7S506 and D7S653 (LOD 2.05) and a location between markers D7S1824 and D7S688 (LOD 1.86). This is shown in figure 3. The former peak is relatively broad and covers a region of ~11 cM between the sequential markers D7S506 and D7S653. The two suggestive susceptibility loci on chromosome 7 are ~85 cM apart from each other. No other multipoint LOD scores near 2 or above were observed in our genomewide scan. Given the known correlation between TGs and HDL-C, only one of the three chromosomal regions of interest for ln TGs in this study appears to be also linked with HDL-C levels—namely, the region near marker D7S479 (i.e., between markers D7S653 and D7S479) on chromosome 7 (fig. 3). Although the LOD curves peak at different locations for these phenotypes (ln TGs at 94 cM and HDL-C at 117 cM), the trait-specific linkage curves exhibit appreciable overlapping. The region on chromosome 15q, however, failed to show any evidence for linkage to HDL-C (LOD score = 0).

We conducted two independent analyses after our original findings were concluded to verify whether our results were sensitive to ascertainment bias or to the diabetic status of the subjects. Since the SAFADS families were ascertained on type 2 diabetic probands, we reran the analysis, as a conservative approach, by correcting for the ascertainment by conditioning on likelihood of observing the ln TG of the proband with diabetes. We also reran the analysis after accounting for the effect of type 2 diabetes on ln TG values. However, the differences between the three analyses were trivial.

Discussion

Hypertriglyceridemia is an important component of the risks associated with CHD, type 2 diabetes, and the metabolic syndrome. Increased concentrations of TG are associated with several types of dyslipidemias. Fasting plasma TG levels are surrogates for TG-rich lipoproteins (e.g., chylomicrons and very-low-density lipoproteins; Grundy 1998). Hypertriglyceridemia often correlates with hyperinsulinemia in the general population (Steiner and Lewis 1996) and is associated with increased concentrations of small, dense, low-density lipoproteins (Mykkänen et al. 1997).

A number of studies have examined population associations between various candidate genes related to lipoprotein metabolism and plasma TG levels. For ex-

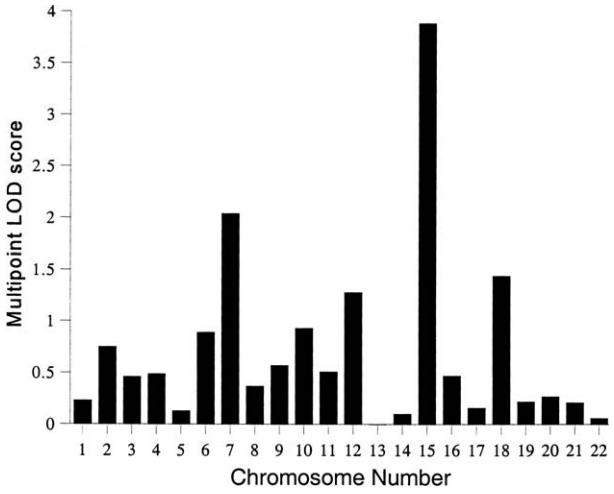

Figure 1 Summary of the multipoint linkage analyses of *ln* TG: peak multipoint LOD score by chromosome.

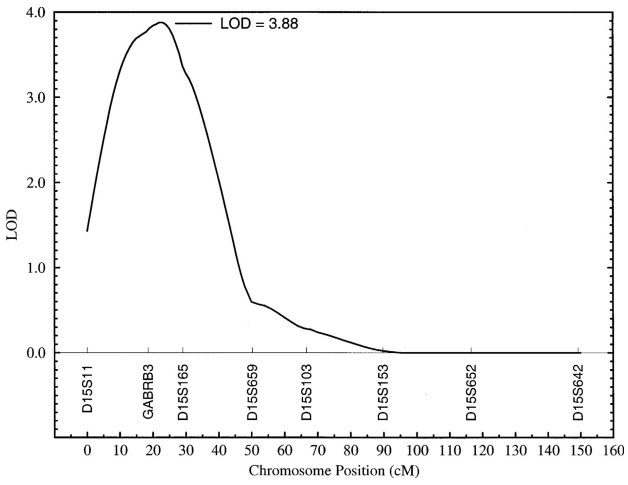

Figure 2 Linkage of ln TG to a quantitative trait locus between markers GABRB3 and D15S165 on chromosome 15.

ample, studies have shown associations between variation in or near the lipoprotein lipase (LPL) gene (chromosome 8p22) and plasma TG levels (Gerdes et al. 1995; Humphries et al. 1998). Also, TG levels have been shown to be correlated with variants in the promotor region of the LPL gene (Ehrenborg et al. 1997; Wittrup et al. 1997; Talmud et al. 1998). Recently, a meta-analysis was conducted to assess the effect of various mutations at the LPL locus (i.e., Gly188Glu, Asp9Asn, Asn291Ser, and Ser447Ter substitutions) in the heterozygous state on lipid metabolism and risk of ischemic heart disease in whites (Wittrup et al. 1999). Individuals who carry the Gly188Glu, Asp9Asn, and Asn291Ser substitutions, compared with individuals who do not carry these substitutions, were shown to have an atherogenic lipoprotein profile, whereas individuals who carry the Ser447Ter substitution were found to have a protective lipoprotein profile. There is evidence for an association between TG levels and variation in the APO CIII (apolipoprotein CIII) gene (chromosome 11q23) or in its promotor (Zeng et al. 1995; Surguchov et al. 1996; Hegele et al. 1997). Our failure to find linkage in genetic regions containing loci such as the LPL and the APO CIII in Mexican Americans may be due to the possible heterogeneity of common forms of hypertriglyceridemia across the populations.

Population association studies have limitations attributable to problems such as misclassification and population stratification, and they are more likely to generate false-positive results (Khoury et al. 1993). Also, it is usually not possible to evaluate the magnitude of the genetic effects exerted by such loci on the basis of association analysis; linkage approaches, on the other hand, that make use of data gathered from members of families can be helpful in determining the magnitude of genetic effects (Cox and Bell 1989). Recently, by making use of linkage analysis, susceptibility genes for familial combined hyperlipidemia (Pajukanta et al. 1998) and Tangier disease (Rust et al. 1998), which are associated with elevated TG levels, have been localized. However, our failure to find evidence for linkage in regions corresponding to familial combined hyperlipidemia and Tangier disease may be related to their distinct etiologies, which could play a minor role in determining variation in TG levels in Mexican Americans.

Knowledge of the major determinants of common forms of hypertriglyceridemia in humans is limited. We conducted a genomewide search for susceptibility genes influencing ln TG levels in a Mexican American population by using pedigree data and a variance-components linkage approach; we found significant evidence for a major susceptibility locus influencing TG concentrations on chromosome 15q between markers GABRB3 (15q11.2) and D15S165 (15q12-q13.1). Several criteria have been proposed to verify a claim of significant linkage at the level of a genomewide scan (Lander and Kruglyak 1995; Elston 1998; Morton 1998). For example, in reference to the allele-sharing methods, such as the one used in this study, Lander and Kruglyak (1995), by making use of simulations, proposed the term "significant linkage" to refer to LOD scores for various types of relative pairs in the range of ~3.3–3.8. Following this suggestion, the observed multipoint LOD of 3.88 at this location on chromosome 15q corresponds to a significant linkage.

Since a multivariate normal distribution is assumed in our linkage approach, there may be some concerns about violations of this assumption (Elston 1998; Al-

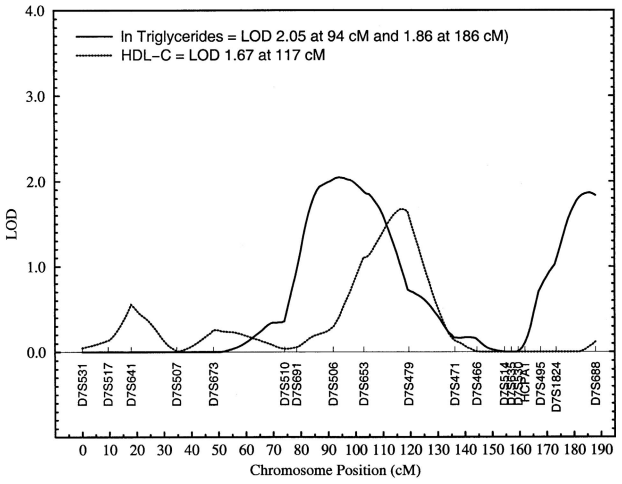

Figure 3 Plot of LOD scores obtained for ln TG and HDL-C concentrations against map positions on chromosome 7.

lison et al. 1999). Although the variance-component approach has been shown to be robust to such violations (Beaty et al. 1985; Amos 1994), recently, sib-pair–based data simulations have shown that some types of nonnormality (e.g., leptokurtosis) can lead to inflated type I error rates and that the degree of such an inflation rate seems to be directly related to the residual sib correlation (Allison et al. 1999). In this connection, the significance of the present finding is less likely to be spuriously inflated for the following reasons. After accounting for the effects of covariates on ln TG levels, the violation of nonnormality of the residuals used in this study appears, on the basis of the coefficients for skewness (.37) and kurtosis (.02), to be minor. Also, the extent of proportion of variance explained by the major QTL in our study implies the low residual sibling correlation.

There are no obvious candidate genes for hypertriglyceridemia in this region of chromosome 15q, although it is worth noting that the Prader-Willi syndrome (MIM 176270) and the Angelman syndrome (MIM 105830) map to the chromosomal region 15q11-13, which is close to the area of interest in our study. The hepatic lipase (HL) gene (MIM 151670), which has a role in TG metabolism, has been localized to chromosomal region 15q21-23 (Sparkes et al. 1987). The HL gene is located ~25–30 cM centromeric to the genetic location (i.e., peak) of interest in the present study. However, given our recent finding, in another set of Mexican American families, of significant linkage between a genetic location near the HL gene and a component of HDL-C—namely, unesterified HDL_{2a}-C (Almasy et al. 1999)—we are planning to screen the HL gene to assess its relation to the present finding.

Two different locations on chromosome 7 are suggestively linked to susceptibility loci influencing ln TG levels. The first susceptibility locus (LOD 2.05) is between markers D7S506 and D7S653. A candidate gene close to marker D7S653 is the collagen and thrombospondin receptor CD36 (MIM 173510), which maps to 7q11.2 (Fernández-Ruiz et al. 1993). Recently, Aitman et al. (1999) identified CD36 as an insulin-resistance gene that underlies defective fatty acid metabolism and hypertriglyceridemia in the spontaneously hypertensive rat. These authors suggested a possible role for CD36 in the etiology of the insulin-resistance syndrome in humans. Earlier, in a sibship-based analysis, we reported evidence for linkage of insulin precursors (intact and 32,33 split proinsulin) to a genetic location near marker D7S479 on 7q (Duggirala et al. 1996), which is ~16 cM telomeric to the region of interest (i.e., the region between markers D7S506 and D7S653) in the present study. As discussed earlier, there is some evidence for linkage of HDL-C levels to a genetic location near marker D7D479, and the LOD curves for both ln TG and HDL-C exhibit appreciable overlap, suggesting the possibility that a locus is influencing both phenotypes. Other genes of interest in this region of 7q are paraoxonase genes and plasminogen activator inhibitor 1 (Klinger et al. 1987; Mochizuki et al. 1998; Sanghera et al. 1998). Recently, we have found strong evidence for linkage (LOD 3.6) of HDL-C levels to a region on chromosome 9p near markers D9S925 and D9S1121 (Arya et al. 1999), although this region failed to show evidence for linkage to ln TG. These findings are consistent with those of an earlier study involving the Mexican American population—that TG and HDL-C concentrations are influenced by both shared genes and that each of these phenotypes appears to be influenced independently by unshared genes as well (Mahaney et al. 1995).

The second susceptibility locus on chromosome 7q for ln TG is near marker D7S688. In a previous sibship-based analysis, we found evidence for a susceptibility locus for various obesity-related traits, which is linked to a genetic location near marker D7S495 (i.e., between markers D7S495 and D7S688) on chromosome 7q (Duggirala et al. 1996). It is possible that our earlier and present results may be related to the same susceptibility locus. Given the known association between pancreatitis and TG levels, it is interesting to note that the gene for hereditary pancreatitis (MIM 167800) maps to chromosome 7q35 (Whitcomb et al. 1996; Gorry et al. 1997). The chromosomal region between markers D7S495 and D7S688 has been shown to encompass the hereditary pancreatitis locus (Pandya et al. 1996). Our second susceptibility locus on chromosome 7 lies in the same region, and it is 2 cM centromeric to marker D7S688.

In conclusion, on the basis of a genomewide scan, we found evidence for a major susceptibility locus on chromosome 15q influencing ln TG levels in a Mexican American population. This putative locus appears to have substantial influence on the phenotypic variation in ln TG levels. Also, two other susceptibility loci on chromosome 7 appear to have minor influences on variation in ln TG levels. One of these two loci on chromosome 7 may have a common influence on both ln TG and HDL-C. These findings may be unique to the Mexican Americans, a population prone to diseases such as obesity, insulin-resistance syndrome, and type 2 diabetes. However, as noted earlier, the findings appear not to be influenced by the diabetic condition. Given the possibility of heterogeneity across populations, generalization of our observations would require evidence for influence of the same loci on variation in TG levels in other populations. For precise localization of these susceptibility loci, especially the one on chromosome 15q, we plan to conduct fine-structure map-

ping with single nucleotide polymorphisms and linkage disequilibrium mapping techniques.

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Prader-Willi syndrome [MIM 176270], Angelman syndrome [MIM 105830], HL [MIM 151670], CD36 [MIM 173510], and hereditary pancreatitis [MIM 167800]

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