A Quantitative Trait Locus on Chromosome 16q Influences Variation in Plasma HDL-C Levels in Mexican Americans


Objective—We conducted a whole-genome, multipoint linkage screen to localize a previously reported major locus accounting for 56% to 67% of the additive genetic effects on covariate-adjusted plasma HDL cholesterol (HDL-C) levels in Mexican Americans from the San Antonio Family Heart Study (SAFHS).

Methods and Results—After using complex segregation analysis to recover the major locus in 472 SAFHS participants from 10 genotyped families, we incorporated covariates required to detect that major locus, including plasma levels of triglycerides and apolipoprotein A-I, in a maximum-likelihood–based variance-components linkage screen. Only chromosome 16 exhibited convincing evidence for a quantitative trait locus (QTL), with a peak multipoint log of the odds (LOD)=3.73 (P=0.000034). Subsequent penetrance model–based linkage analysis, incorporating genotypes at the marker locus nearest the multipoint peak (D16S518) into the segregation model, detected linkage with the previously detected major locus (LOD=2.73, P=0.000642). Initial estimates place this QTL within a 15-cM region of chromosome 16q near the structural loci for lecithin:cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP).

Conclusions—A QTL influencing plasma levels of HDL-C in Mexican Americans from San Antonio maps to a region of human chromosome 16q near LCAT and CETP. (Arterioscler Thromb Vasc Biol. 2003;23:339-345.)

Key Words: HDL ■ genome screen ■ linkage ■ heritability ■ Mexican Americans

Although subsequent analyses of data from the SAFHS and other studies have mapped quantitative trait loci (QTLs) for HDL-C–related measures to chromosome 1q², chromosome 13q³,⁴ and chromosome 9p⁵, other reports localize HDL-C–related QTLs to some chromosomal regions containing candidate loci excluded by our earlier analyses.¹ These regions include chromosome 11q, near the APOAI/APOC3/APOA4 cluster⁶⁻⁷; chromosome 8p22, near the macrophage scavenger receptor locus, MSR1, and the lipoprotein lipase locus, LPL⁵; and chromosome 15, near the hepatic lipase locus, LIPC⁶.⁸ From these observations, we infer 3 possibilities concerning the previously detected major-locus effect: it is attributable to (1) 1 of these candidate loci, whose effects we failed to detect previously; (2) another QTL, already detected in genome screens for HDL-C in the SAFHS or other studies; or (3) another QTL, as yet undetected by the SAFHS or other studies.

In this article, we report results from a series of analyses with the overall objective of localizing a QTL to account for the major-locus effect detected by our earlier segregation analysis. To do this, we conducted analyses to accomplish 3 specific aims: recover the original major-locus model in the current pedigree sample by means of complex segregation analysis; localize a QTL corresponding to this locus by using
a variance-components linkage model approximating the parameterization of the earlier segregation model; and confirm that the QTL and major locus are 1 and the same by means of combined complex segregation and linkage analysis incorporating genotypes for markers linked to the QTL.

Methods

Sample and Phenotype Data

The SAFHS protocol was reviewed and approved by the Institutional Review Board at the University of Texas Health Science Center at San Antonio. All participants gave informed consent. The SAFHS included 1431 individuals in 42 extended pedigrees constructed around probands, randomly ascertained with respect to disease status and phenotype values, who were Mexican Americans living in San Antonio, Tex, 40 to 60 years of age, with at least 6 offspring and/or siblings, 16 or more years of age, who also resided in the San Antonio area. Additional relatives of the proband and proband’s spouse also were invited to participate. In addition to a physical examination, participants provided blood samples for phenotyping and genotyping and information on demographic and lifestyle variables. Additional details on this study population are provided elsewhere.10

The pedigree sample in which the residual HDL-C major locus was first detected included 526 participants: 313 females and 213 males, 16 to 87 years of age (mean age, 39.5 years), and distributed in 25 extended pedigrees. The current study analyzed data from 472 participants: 266 females and 206 males, 18 to 87 years of age (mean age, 38.7 years), from 10 extended pedigrees whose members had been genotyped at 417 microsatellite markers for linkage analyses (NB, these 10 pedigrees have been the focus of all SAFHS genome screens to date). Ten of these individuals were taking lipid-lowering medications at the time of the study, and 72 were diagnosed with diabetes as measured in a commercial laboratory (Medical Laboratories, Cincinnati, Ohio) by means of nephelometry. Neither variable contributed significantly to the likelihood of polygenic or major-locus models for plasma HDL-C in our earlier analyses.1

HDL-C, TG, and apo A-I were assayed from frozen plasma aliquots obtained from blood samples drawn in a clinical setting after a 12- to 14-hour fast. Total cholesterol and TG concentrations were assayed enzymatically with a Gilford SBA-300 clinical chemistry analyzer with reagents supplied by Boehringer-Mannheim Diagnostics and Stanbio, respectively. To measure HDL-C, apo B-containing lipoproteins were precipitated from plasma by use of dextran sulfate-Mg2+.11 The interassay coefficients of variation for control samples obtained in medical history interviews conducted during the clinic visit at which blood samples were drawn. Likelihood-ratio test criteria for inclusion of these specific covariates in the original complex segregation analysis model were described in detail previously.1 Individual TG levels were transformed to natural logarithms to reduce skewness. No other transformations were applied to data before statistical genetic analyses. Given their expected effects on plasma HDL-C levels in this population, lipid-lowering medication use and diabetes diagnosis also were screened again in this genotyped subsample.

Genotype Data

DNA was prepared from lymphocytes and used in polymerase chain reactions (PCRs) with fluorescently labeled primers from the MapPairs Human Screening set, versions 6 and 8 (Research Genetics, Huntsville, Ala), containing 417 highly polymorphic short-tandem-repeat (STR) marker loci from 22 autosomes spaced at ~10-cM intervals. PCRs were performed separately, according to the manufacturer’s specifications. Aliquots were pooled into multiplexed panels for typing on an automated DNA sequencer (model 373 with Genescan 672 and Genotyper programs; Applied Biosystems, Foster City, Calif). Distances between markers (Kosambi cM) were estimated using CRI-MAP routines implemented by the MultiMap expert systems software.13 Distances were verified for consistency with genetic maps from Marshfield Medical Research Foundation (Marshfield, Wis; http://www.mfldclin.edu/genetics) and the University of Southampton (Southampton, UK; http://cedar.genetics.soton.ac.uk/public_html/gene.html). The average intermarker interval was 10 cM. We obtained maximum-likelihood allele-frequency estimates using all pedigree information.

Statistical Genetic Methods

Statistical genetic analyses were conducted using maximum-likelihood–based approaches implemented in the computer programs SOLAR14 and PAP.15 Pedigree, phenotype, and genotype data management and preparation were accomplished by PEDSYS.16

We used complex segregation analysis17 in an approach described in detail elsewhere1 to recover a fully maximized segregation model for the HDL-C major locus in the 10 pedigrees to be used in the current whole-genome linkage analysis. Our genetic model in this study included the same 18 parameters as the fully maximized codominant mixture model (hereafter referred to as the “major-locus model”) required to detect the HDL-C major locus earlier: frequency of an allele producing lower plasma HDL-C levels (p1); means of 3 phenotypic distributions (μA1, μA2, and μA0); an additive genetic residual (β2, “heritability”); a common phenotypic standard deviation (σ); 3 transmission probabilities (τ1, τ2, and τ3); plus mean effects of sex (βsex), age-by-sex (βage*sex and βage*sex), age2-by-sex (βage2*sex and βage2*sex), ln TG (βlnTG) levels, apoA-I (βapoA-I) levels, exogenous sex hormone use (βphorhones), and menopause status (βmenopause). Alternative models were parameterized identically to those described earlier.1 These included a sporadic model, in which all residual phenotypic variance was attributable to random environmental effects; a polygenic model, in which this residual was due to additive genetic and random environmental effects; and an environmental mixture model, allowing for a major environmental factor plus additive genetic and random environmental effects.

After determining that the major locus for the same residual HDL-C phenotype could be detected in these 10 pedigrees, we used a variance decomposition approach implemented in SOLAR14 to test for evidence of linkage between QTLs for plasma HDL-C level and the 417 autosomal STR loci. This method, described in detail elsewhere,14 entails specification of the genetic covariance between arbitrary relatives as a function of the identity-by-descent (IBD) relationships at a given marker locus and models the covariance matrix for a pedigree as the sum of the additive genetic covariance attributable to the QTL, the additive genetic covariance due to the effects loci other than the QTL, and the variance due to unmeasured environmental factors. We approximated the specification of the major-locus model from our segregation analysis in this analysis by including the same covariates. Because the variance-component model does not explicitly specify mendelian segregation, we did not model genotype-specific mean effects of sex and ln TGs.

We tested the hypothesis of linkage by comparing the likelihood of a restricted model in which variance due to the QTL equalized zero (no linkage) to that of a model in which it did not equal zero (ie, is estimated). The log of the odds (LOD) score of classic linkage analysis was obtained as the quotient of the difference between the 2 ln likelihoods divided by ln 10.18 To correct for departures in multivariate normality that might inflate evidence for linkage, a simulation approach was used to estimate a robust LOD score (LOD) as the product of the observed LOD score and the slope from the regression of expected LOD scores on observed (and possibly biased) LOD scores based on 10,000 simulations for an unlinked locus.19

We estimated marker-locus–specific IBD probabilities for the pedigrees by using a pairwise maximum-likelihood–based procedure.14 To permit multipoint analysis for QTL mapping, we employed an extension to the method of Fulker et al20 to estimate IBD
probabilities at 1-cM intervals along each chromosome. An LOD score evaluation was performed every centimorgan along each chromosome.

To determine whether the QTL and the previously detected major locus were the same, we conducted a formal penetrance–segregation analysis and reparameterized the model to include both the genetic model at the values estimated in the prior complex linkage analyses. We fixed penetrance parameters in the general model (\(D^*/P_{11005} = 1.0\)), we maximized the model under a range of conditions from negative-to-positive linkage Disequilibrium (\(D^*/H11005\)) between the marker and the most likely association. Assuming complete linkage disequilibrium (\(D^*=1.0\)), we maximized the model under a range of conditions from complete linkage to no linkage between the detected major locus and the marker (ie, \(\theta=0\) to \(\theta=0.50\)). To facilitate numerical maximization of the penetrance-parameter–based linkage model, we used PEDSYS routine DOWNGCODE\(^{16}\) to reduce the large number of size alleles at the microsatellite locus to a more manageable number. We used this procedure to iteratively combine the rarest alleles in the sample with more common alleles into a single “type,” evaluating the affect of this downcoding on numbers of informative triplets (ie, mother-father-offspring groupings), heterozygotes, and nuclear families. We accepted the combination that reduced the number of alleles from 12 or more to 6, with a minimum decrease of information. This same analysis was repeated with “negative-control” loci selected from areas of the genome in which our linkage screens had not detected evidence for a QTL.

**Results**

As in our earlier analyses,\(^1\) we found no significant contribution of either diabetes diagnosis or lipid-lowering medication use to the likelihoods of either the polygenic or major-locus model for this trait (\(P>0.10\)) in this genotyped subsample of the SAFHS, so they were not included in these analyses. Table 1 displays the maximum-likelihood estimates (MLEs) of parameters for 5 alternative models for this HDL-C trait in the 10 pedigrees and the results of likelihood-ratio tests comparing the 4 restricted models to the general model. All restricted models, except the major-locus model, had significantly worse likelihoods than the unrestricted general model (\(P=0.037\) to \(P<0.000001\)), indicating a major-locus effect on variation in plasma HDL-C levels. Comparison of these MLEs with those obtained in the earlier analysis\(^1\) strongly supports the contention that the same major-locus effect has been recovered. For example, the estimated frequency of the “low” HDL-C allele, \(p(A)\), in the currently maximized model was 0.83 versus 0.81 in the model maximized earlier; the newer residual \(h^2\) estimate is 0.62 versus the earlier estimate of 0.61; and the relative importance of parameters and the genotype-specific effects of sex and ln TG observed in the earlier analyses were retained.

Figure 1 summarizes the results of the multipoint, whole-genome linkage screen with a variance-components model with parameters and initial values approximating the HDL-C major-locus model maximized in the aforementioned complex segregation analysis. In this “string plot” format, multipoint LOD score curves for each of 22 autosomes are

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**Table 1. Maximum-Likelihood Parameter Estimates: Alternate Models From Complex Segregation Analysis of Plasma HDL-C Levels (SI Units) in 472 Mexican Americans**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sporadic</th>
<th>Polygenic</th>
<th>Major Locus</th>
<th>Environmental Major Factor</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p_A)</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.83±0.04</td>
<td>0.85±0.04</td>
<td>0.80±0.04</td>
</tr>
<tr>
<td>(\tau_A)</td>
<td>0.000*</td>
<td>0.000*</td>
<td>1.000*</td>
<td></td>
<td>1.000†</td>
</tr>
<tr>
<td>(\sigma)</td>
<td>0.14±0.01</td>
<td>0.14±0.01</td>
<td>0.13±0.01</td>
<td>0.11±0.01</td>
<td>0.12±0.01</td>
</tr>
<tr>
<td>(h^2)</td>
<td>0.000*</td>
<td>0.42±0.10</td>
<td>0.62±0.14</td>
<td>0.57±0.15</td>
<td>0.60±0.15</td>
</tr>
<tr>
<td>(\beta(sex)_A)</td>
<td>0.03±0.02</td>
<td>0.03±0.02</td>
<td>0.09±0.03</td>
<td>0.08±0.03</td>
<td>0.10±0.03</td>
</tr>
<tr>
<td>(\beta(sex)_A)</td>
<td>0.02±0.001</td>
<td>0.02±0.001</td>
<td>0.02±0.002</td>
<td>0.02±0.002</td>
<td>0.02±0.01</td>
</tr>
<tr>
<td>(\beta(10LnTG)_A)</td>
<td>-0.02±0.003</td>
<td>-0.02±0.003</td>
<td>-0.02±0.003</td>
<td>-0.02±0.003</td>
<td>-0.02±0.01</td>
</tr>
<tr>
<td>(\beta(10LnTG)_A)</td>
<td>-0.03±0.003</td>
<td>-0.03±0.003</td>
<td>-0.02±0.003</td>
<td>-0.02±0.003</td>
<td>-0.02±0.01</td>
</tr>
<tr>
<td>(\beta(hormones))</td>
<td>-0.05±0.02</td>
<td>-0.05±0.02</td>
<td>-0.04±0.02</td>
<td>-0.04±0.02</td>
<td>-0.04±0.02</td>
</tr>
<tr>
<td>(\beta(menopausal))</td>
<td>0.03±0.03</td>
<td>0.03±0.03</td>
<td>0.04±0.02</td>
<td>0.03±0.03</td>
<td>0.039±0.02</td>
</tr>
<tr>
<td>(\beta(apo A-I))</td>
<td>0.39±0.01</td>
<td>0.01±0.001</td>
<td>0.01±0.001</td>
<td>0.01±0.001</td>
<td>0.01±0.001</td>
</tr>
<tr>
<td>(\ln Likelihood)</td>
<td>-1664.01</td>
<td>-1649.44</td>
<td>-1636.93</td>
<td>-1639.70</td>
<td>-1635.45</td>
</tr>
<tr>
<td>(\chi^2) (df)</td>
<td>57.21 (9)</td>
<td>27.98 (8)</td>
<td>2.96 (3)</td>
<td>8.50 (3)</td>
<td></td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.0000001</td>
<td>0.000478</td>
<td>0.397834</td>
<td>0.036734</td>
<td></td>
</tr>
</tbody>
</table>

*Maximum-likelihood of model obtained with parameter constrained at this value. †MLE on boundary of parameter space.
displayed. We observed significant evidence for linkage (i.e., LOD > 3.0) on chromosome 16 only, with suggestive evidence (LOD > 1.96) observed at a single additional site on chromosome 8p. On chromosome 16, the maximum multipoint LOD = 4.33 (P = 0.000008) was obtained ≈92 cM from the pter-most marker locus on that chromosome (Figure 2), between microsatellite markers D16S2624 (16q22 to 16q22) and D16S518 (16q23.1 to 16q24.2). Adjusting the evidence for linkage at this peak for nonnormality in the underlying distribution yields LOD$_a$ = 3.73 (P = 0.000017).

Figure 2 also shows the multipoint LOD scores obtained when covariate effects from the major-locus model were not included in the variance-component linkage analysis. Without these covariates, there is no interval on chromosome 16 in which LOD > 0.30.

Covariate effects accounted for ≈70% of the total phenotypic variance in this linkage model. The QTL on chromosome 16q was estimated to account for 13.2% of the total phenotypic variance; 44% of the residual phenotypic variance; and 81% of the additive genetic variance. Additive
effects of loci other than this QTL accounted for the remaining 19% of the additive genetic variance and 3% of the total phenotypic variance in plasma HDL-C levels.

We conducted combined segregation and linkage analyses as described previously by reparameterizing the major-locus segregation model to include the relative frequencies of alleles at the microsatellite marker nearest the chromosome 16 multipoint peak (D16S518, locus-specific LOD = 4.01). Downcoding the 13 STR size alleles at D16S518 to 6 resulted in loss of 2 of 147 informative triplets. The strongest evidence for linkage between the detected major locus and marker locus D16S518 occurred at \( \theta = 0.10 \) (LOD = 2.73, \( P = 0.000642 \)). Repetition of this analysis with 2 negative-control marker loci, D4S1652 (7 alleles, downcoded to 6; none of 167 informative triplets lost) and D4S2431 (14 alleles, downcoded to 6; 1 of 172 informative triplets lost), showed no evidence of linkage when \( \theta = 0.45 \) to 0.25 and excluded linkage (ie, LOD < -2) at \( \theta < 0.20 \).

**Discussion**

In a whole-genome linkage screen with data from 10 extended pedigrees in the SAFHS, we have identified a region on chromosome 16q that harbors a QTL that contributes to quantitative variation in plasma concentrations of HDL-C. Evidence for this QTL remains significant when adjusted for departures from multivariate normality in the phenotype data.

As reported previously, simultaneous estimation of the described covariates yields a genetic model for a residual HDL-C phenotype that is independent of the phenotypic effects of plasma concentrations of apo A-I and TG. The detected QTL on chromosome 16 is responsible for the additive genetic effects on quantitative variation in total plasma HDL-C concentrations not attributable to QTLs that also influence plasma concentrations of apo A-I and TG. Given the probable structure of HDL-C particles, it is likely that our models helped us to detect a QTL that influences variation in the amount of cholesterol per HDL particle. This interpretation was first suggested by Amos et al, who noted that including information on apolipoprotein levels in a segregation model could more clearly define a major-locus effect on HDL-C levels in the Bogalusa Heart Study.

Our linkage analyses do not address directly the cardioprotective effects of either this residual HDL-C phenotype or the detected QTL in this population. However, the magnitude of the QTL-specific heritability suggests that this QTL has a moderately important influence on quantitative variation in plasma HDL-C levels in the SAFHS. Accounting for approximately 13% of the total phenotypic variation, we estimate that the QTL accounts for nearly one half of the phenotypic variance remaining after partitioning out covariate effects and up to 81% of the residual additive genetic variance after partitioning out additive genetic effects in common between plasma concentrations of HDL-C, apo A-I, and TG. Because QTL-effect size estimates obtained by all linkage methods can be biased upward, the relative importance of this QTL awaits confirmation by pointwise estimation in an independent data set.

Structural genes for 2 proteins involved in HDL-C metabolism have been localized by others to within 5 to 15 cM of the QTL detected in this study: lecithin:cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP). Both have been associated with reverse cholesterol transport, variation in plasma levels of HDL-C and related apolipoproteins, and, in some cases, cardiovascular disease risk.

LCAT, likely the closer of the 2 to this QTL, maps to 16q22.1 (http://www.ncbi.nlm.nih.gov/gdb-bin/genera/genera/hgd/GenomicSegment?GDB:119359). The enzyme LCAT is synthesized in the liver and circulates in blood plasma complexed with HDLs. It plays an important role in reverse cholesterol transport by facilitating the removal of excess cholesterol from the peripheral tissues. Cholesteryl esters, produced by LCAT-catalyzed esterification of cholesterol with the sn-2 fatty acid of phosphatidylcholine, are incorporated into the core of HDL particles before transportation to the liver. LCAT deficiency is associated with increases in total cholesterol, HDL-C, and TGs, with disproportionate increases in unesterified cholesterol. Mutations at the LCAT locus have been reported in both Norum disease and fish-eye disease, in which plasma levels of HDL-C, apo A-I, and apo A-II are reduced, but with no increased risk of premature atherosclerotic cardiovascular disease in either form of LCAT deficiency.

CETP is slightly closer to the p-terminus of chromosome 16 than LCAT (http://www.ncbi.nlm.nih.gov/gdb-bin/genera/genera/hgd/GenomicSegment?GDB:119773). Also known as lipid transfer protein 1, CETP facilitates transfer of cholesteryl ester from HDL-C to lower-density \( \beta \)-lipoproteins in exchange for TGs. Patients deficient in CETP exhibit increased circulating levels of plasma HDL-C and decreased levels of VLDL and LDL. Mutations in CETP also have been associated with this pattern. These observations are consistent with CETP’s being a candidate atherosclerosis-susceptibility locus. In support of this hypothesis, several groups have reported associations between mutations at CETP and cardiovascular disease risk itself.

A few previously published linkage studies have provided only nominal or suggestive evidence that variation in HDL-C is influenced either by a QTL in this region of chromosome 16 or by the 2 candidate loci, CETP or LCAT. A sib-pair linkage analysis of HDL-C concentration data for 30 coronary artery disease families yielded suggestive evidence of linkage (LOD = 2.06), with a QTL linked to D16S313, a marker locus that maps to within 6 cM of the marker loci nearest our multipoint peak. A linkage study of data from the Framingham Study families reported nominal evidence for QTls, influencing log TG levels (LOD = 1.5) and log TG/HDLC (LOD = 1.1) within 10 cM of the markers nearest the multipoint peak in our analyses. Penetrance-model–based linkage analyses of data from the Bogalusa Heart Study and a study by Heiba et al yielded nominal evidence for linkage (LOD = 1.7 and \( P < 0.05 \), respectively) between a QTL for HDL-C levels and a haptoglobin locus marker situated within 5 cM of the marker loci nearest our multipoint peak. In contrast, MacPherson et al found no evidence for a QTL for plasma HDL-C levels linked to the CETP locus in their study of data from 104 nuclear families.
Our analyses provide evidence that this QTL and a major locus, previously detected in the SAFHS pedigrees by complex segregation analysis,\(^1\) very likely are 1 and the same. We attribute the differences in the LOD scores obtained by these 2 analyses to 2 factors. The first is our imperfect duplication of the penetrance-model’s specification in the variance-component model; ie, the lack of genotype-specific sex and TG effects in the variance-component model. The second is the fact that our 2-allele, 3-“genotypic classes” penetrance-based linkage model does not utilize the same genetic information at the marker loci as does the variance-component model when we reduce effective allele numbers at the marker locus by downcoding.

The series of analyses described in this article illustrates the importance of specification of the underlying models in statistical genetic analysis. Neither our earlier segregation analysis with data for individuals from 25 SAFHS pedigrees\(^1\) nor the current 1 with data for individuals from 10 SAFHS pedigrees detected this major locus unless we included the effects of specific biological and environmental covariates. Similarly, both our earlier\(^6\) and current linkage screens did not detect the QTL on chromosome 16q in the very same 10-pedigree sample when these covariates were missing from the variance-component models for the phenotype. In simulation studies of complex phenotypes with oligogenic modes of inheritance, we and others have demonstrated the importance of model specification in both segregation analysis\(^2\) and multiple approaches to QTL mapping.\(^3\) The current study, as well as others (eg, an HDL-C study by Peacock et al\(^4\) and an LDL study by Hokanson et al\(^5\)) show that incorporation of covariates accounting for a significant proportion of the phenotypic variance may improve the genetic signal-to-noise ratio and refine the phenotype to a degree such that previously undetected QTLs may be localized. A review of the cardiovascular genetics literature from the past 15 years reveals several major loci detected by segregation analyses for which there have been no obvious, successful, follow-up linkages. Although not necessarily true for all cases, using covariates from earlier, successful major-locus analyses to better specify newer linkage screens may be of utility in searches for individual genes contributing to variance in cardiovascular disease risk.

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