Familial Combined Hyperlipidemia in Mexicans
Association With Upstream Transcription Factor 1 and Linkage on Chromosome 16q24.1

Adriana Huertas-Vazquez, Carlos Aguilar-Salinas, Aldons J. Lusis, Rita M. Cantor, Samuel Canizales-Quinteros, Jenny C. Lee, Lizzette Mariana-Nuñez, Roopa-Metha, Laura Riba-Ramirez, Anne Jokiaho, Teresa Tusie-Luna, and Päivi Pajukanta

Objective—To investigate the largely unknown genetic component of the common lipid disorder, familial combined hyperlipidemia (FCHL) in Mexicans, we analyzed the upstream transcription factor 1 (USF1) gene that was recently associated with FCHL and high triglycerides (TG) in Finns. We also analyzed the Mexican FCHL families for 26 microsatellite markers residing in the seven chromosomal regions on 2p25.1, 9p23, 10q11.23, 11q13, 16q24.1, 19q13, and 21q21, previously linked to FCHL in Whites.

Methods and Results—We genotyped 314 individuals in 24 Mexican families for 13 SNPs spanning an 88-kb region, including USF1. The FCHL and TG traits showed significant evidence for association with 3 SNPs, hCV1459766, rs3737787, and rs2073658, and haplotype analyses further supported these findings (probability values of 0.05 to 0.0009 for SNPs and their haplotypes). Of these SNPs, hCV1459766 is located in the F11 receptor (F11R) gene, located next to USF1, making it difficult to exclude. Importantly, the association was restricted to a considerably smaller region than in the Finns (14 kb versus 46 kb), possibly because of a different underlying linkage disequilibrium structure. In addition, 1 of the 7 regions, 16q24.1, showed suggestive evidence for linkage (a lod score of 2.6) for total cholesterol in Mexicans.

Conclusions—This study, the first to extensively investigate the genetic component of the common FCHL disorder in Mexicans, provides independent evidence for the role of USF1 in FCHL in an outbred population and links the 16q24.1 region to an FCHL-component trait in Mexicans. (Arterioscler Thromb Vasc Biol. 2005;25:0-0.)

Key Words: familial combined hyperlipidemia ■ USF1 gene ■ complex traits ■ Mexican population ■ coronary heart disease

Familial combined hyperlipidemia (FCHL) is a common heterogeneous disorder, characterized by the presence of multiple lipoprotein phenotypes that increase the risk of premature coronary heart disease (CHD).1 Families with this condition typically exhibit a mixed pattern of lipid abnormalities, with one or more family members affected by high levels of serum total cholesterol (TC) and/or triglycerides (TG). FCHL profiles are often associated with elevated apolipoprotein B (apoB) levels and with an unfavorable decrease in serum high-density lipoprotein cholesterol (HDL-C) levels.2–4 Although it has been evident for 30 years that FCHL has a strong genetic component,2 DNA sequence variants contributing to FCHL and its component traits are largely unknown, especially regarding the prevalence of variants with major effects.

Several genetic studies have been conducted in various ethnic groups to identify susceptibility genes for FCHL and its component traits.4–11 Evidence for a major FCHL locus was first found on chromosome 1q21-q23 in Finns,5 and subsequent replications were observed in US, German, Chinese, and Dutch populations.9–11 Linkage to the 1q21–23 region has also been replicated in 7 extended Mexican families.12 These 7 families comprise a portion of the samples investigated in this present study. Recently, Pajukanta et al (2004)13 reported that FCHL is linked and associated with the gene encoding the upstream transcription factor 1 (USF1) on chromosome 1q21. USF1 is the first major gene implicated in FCHL.

The ubiquitously expressed USF proteins are members of the basic helix-loop-helix leucine zipper (bHLH-zip)
family of transcription factors, and USF1 is known to control expression of several genes involved in glucose and lipid metabolism. Variation in USF1 has been shown to influence features of glucose and lipid homeostasis in the EARS II offspring study. Recently USF1 was shown to stimulate apolipoprotein A-V (APOA5) promoter activity in an insulin-dependent manner, demonstrated by the reduced binding of USF1 to the promoter in the presence of insulin. This connection between APOA5 and USF1 is especially noteworthy because variants of APOA5 have been linked to high TGs in both the general population and in FCHL. However, additional studies are warranted to replicate the role of USF1 in FCHL families originating from other populations.

### Methods

#### Subjects and Clinical Features

A total of 24 extended Mexican FCHL families with a history of premature CHD were included in this study, comprising 314 family members (Table 1a and 1b). These families were recruited in the Lipid Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) in Mexico City. The ethnicity and race of these subjects reflect the general population of Mexico. Thus, the race of all of these subjects are Mestizos who are a mixture of American Indian and white. Inclusion criteria for the probands were as follows: Elevated levels of serum TGs (≥90th age/sex-specific Mexican population percentile) and/or elevated levels of serum TC (≥90th percentile) and elevated levels of serum apoB (≥90th percentile). The positive family history of premature CHD before the age of 60 was defined as the manifestation of myocardial infarction either in the proband or a first-degree relative of the proband. The age/sex-specific population percentiles for lipids were based on a 90th age/sex-specific Mexican population percentile.

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tion, as well as smoking and drinking habits. Body mass index (BMI) was determined for all subjects. Each subject provided a written informed consent. The protocol for this study was approved by the Institutional Committee of Biomedical Research in Humans of the INCMNSZ.

**Laboratory Analytical Methods**

All lipid levels for affected individuals were measured before treatment. The measurements were performed with commercially available standardized methods. Glucose was measured using the glucose oxidase method; serum TC and TGs were measured using an enzymatic method (SERA-PAK®); HDL-C levels were assessed using phosphotungstic acid and Mg2+; LDL-C concentrations were estimated by the Friedewald formula, and plasma apoB concentrations were obtained using a commercially available assay (Beckman).

**Genotyping**

We genotyped 314 individuals from the 24 families for 13 SNPs, spanning USF1 and the 2 genes flanking USF1, F11 receptor (F11R), and a hypothetical gene LOC257106. Eight of these SNPs were reported previously. Five additional SNPs (rs1023115, rs1240334, rs2481084, rs2774279, and rs3813610) were selected from the dbSNP database. The SNPs were genotyped using the pyrosequencing technique on the automated PSQ HS96A platform. We genotyped 26 peak microsatellite markers for the previously linked regions on 2p25.1, 9p23, 10q11.23, 11q13, 16q24.1, 19q13, and 21q21.5–8.26 using the ABI Prism 3700 DNA Analyzer and the Genotyper 3.7 software.

**Statistical Analysis**

Because of the acknowledged difficulties to replicate results obtained in genetic analyses of complex traits, we used the same diagnostic criteria, the same methods, and the same markers as described previously with the USF1 gene and Dutch and Finnish genome scans. According to the PedCheck program was used to assess the genotype data for pedigree inconsistencies. Allele frequencies were estimated from all individuals using the DOWNFREQ program. The PedCheck program was used to assess the genotype data for pedigree inconsistencies. The multipoint analyses for 16q24.1 and 10q11.23 were performed using the GENEHUNTER program.

**Statistical Significance**

We performed 2 classes of analyses. In the study of USF1, two traits were tested for association with 13 SNPs. The Bonferroni correction for the probability values obtained in these analyses can be considered overly conservative, because we investigate highly correlated SNPs and traits. We are conducting the same analyses seen in the previous study with the MLINK program of the LINKAGE package, as implemented in the ANALYZE package. We assumed a disease allele frequency of 0.006 under the dominant mode of inheritance and 0.1095 under the recessive mode of inheritance. Allele frequencies were estimated from all individuals using the DOWNFREQ program. The PedCheck program was used to assess the genotype data for pedigree inconsistencies. The multipoint analyses for 16q24.1 and 10q11.23 were performed using the GENEHUNTER program.

For linkage analysis of microsatellite markers, we carried out the same parametric and nonparametric 2-point analyses as were used previously. The 90th Mexican age/sex-specific population percentiles of TC and TGs (the FCHL trait) and the 90th age/sex-specific percentiles of TGs (the high TG trait). The extent of pairwise linkage disequilibrium (LD) between the marker genotypes was tested using the JLIN: JAVA LD PLOTTER program available online (http://www.genepl.com.au/project/jlin).

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TABLE 2A. Association Analyses of Individual SNPs in the F11R-USF1 Region for the TG and FCHL Traits

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs Number for the SNP</th>
<th>SNP Type</th>
<th>Distance Between SNPs (bp)</th>
<th>Het/Freq</th>
<th>HRRR</th>
<th>Gamete</th>
<th>FBAT P‡</th>
<th>FCHL P‡</th>
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<tbody>
<tr>
<td>IG</td>
<td>rs1023115</td>
<td>IG</td>
<td>3,145</td>
<td>0.50/0.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IG</td>
<td>rs1240334</td>
<td>IG</td>
<td>30,260</td>
<td>0.40/0.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F11R</td>
<td>rs836 (f11rs1)§</td>
<td>UTR</td>
<td>21,390</td>
<td>0.37/0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F11R</td>
<td>rs2481084</td>
<td>I</td>
<td>7,140</td>
<td>0.41/0.28</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>F11R</td>
<td>hCV1459766 (f11rs4)§</td>
<td>I</td>
<td>10,572</td>
<td>0.34/0.21</td>
<td>0.02</td>
<td>0.002</td>
<td>0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>F11R</td>
<td>rs4339888 (f11rs5)§</td>
<td>UTR</td>
<td>2,197</td>
<td>0.35/0.22</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USF1</td>
<td>rs377787 (usf1s1)§</td>
<td>E</td>
<td>1,239</td>
<td>0.35/0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>USF1</td>
<td>rs2073658 (usf1s2)§</td>
<td>I</td>
<td>593</td>
<td>0.35/0.22</td>
<td>0.04</td>
<td>0.003</td>
<td>0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>USF1</td>
<td>rs2073656</td>
<td>I</td>
<td>1,235</td>
<td>0.38/0.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USF1</td>
<td>rs2073655</td>
<td>I</td>
<td>1,780</td>
<td>0.34/0.22</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>USF1</td>
<td>rs2516838 (usf1s8)§</td>
<td>UTR</td>
<td>3,186</td>
<td>0.22/0.12</td>
<td></td>
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<td></td>
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<tr>
<td>LO257106</td>
<td>rs2774279</td>
<td>C-S</td>
<td>5,083</td>
<td>0.21/0.12</td>
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<tr>
<td>LO257106</td>
<td>rs3813610</td>
<td>I</td>
<td></td>
<td>0.46/0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All results represent P values; *P values for association with the HRRR test; †P values for linkage and association with the gamete competition test; and ‡P values with the FBAT test using the options —o and —e, respectively (for differences in these test statistics, see methods). Analyses for cells left blank resulted in P values >0.05. Het/Freq indicates heterogeneity/allele frequency; E, exonic; C-S, coding-synonymous; I, intronic; IG, intergenic; ITLN2, intelectin 2 gene; F11R, F11R receptor gene; USF1, upstream transcription factor 1 gene; LOC257106, hypothetical protein LOC257106.

§The SNPs associated in Finns and the symbol used for these SNPs previously.13

Results

To investigate the underlying genetic component for FCHL within the USF1 region in the Mexican population, we genotyped a total of 13 SNPs spanning an 88-kb region, including three genes, USF1, F11 receptor (F11R), and hypothetical gene LOC257106 (Table 2a). The F11R and hypothetical gene LOC257106 were investigated besides USF1 in Mexicans, because in Finns the associated region extended to an ~46-kb region that also covered the F11R gene, specifically in TG-affected Finnish males.13

One F11R SNP, hCV1459766, and 2 USF1 SNPs, rs3777877 and rs2073658, within a 14-kb region, showed evidence for association with the FCHL and TG traits (Table 2a and 2b). Specifically, the TG trait produced the most significant signal for association, resulting in probability values of 0.001, 0.005, and 0.001 for SNPs hCV1459766, rs3777787, and rs2073658, respectively, when testing for linkage and association in nuclear families using the FBAT option —o (Table 2a). When testing for association and accounting for linkage using the FBAT option —e, the SNPs hCV1459766 and rs3777787 resulted in probability values of 0.04 and 0.02 (Table 2a). These results are in accordance with the results obtained when testing for linkage and association in the extended families using the gamete competition test (Table 2a). Moreover, haplotype analysis for SNPs hCV1459766-rs3777787 provided evidence of association with both traits, TGs (P=0.0009) and FCHL (P=0.02) using the HBAT option —e (Table 2b). Although these 3 SNPs are in strong LD with one another, their pairwise r2 measurements of 0.86 for SNPs hCV1459766 and rs3777787 in probands compared with 0.64 in spouses appears to allow for the additional evidence of association obtained by haplotype analysis. The pairwise r2 measurement for SNPs rs3777787 and rs2073658 was 1.0 in probands and 0.73 in spouses. Interestingly, LD between the SNPs hCV1459766, rs3777787, and rs2073658 appeared thus to be tighter in probands than in spouses. The Figure shows the locations of the 13 SNPs and the pairwise LD between them separately in spouses and probands. As in the Finns,13 the preferentially transmitted alleles of these SNPs and their haplotypes were the major alleles (Table 2b). The haplotype of the minor alleles in turn was significantly less transmitted to the affected individuals (P=0.001 for TGs and P=0.02 for FCHL) (Table 2b). None of the other SNPs produced significant probability values. The nucleotides for minor alleles in Mexicans are shown in Supplementary Table I (available at the web site, http://www.genetics.ucla.edu/labs/pajukanta/fchlmex/).

TABLE 2B. Haplotype Analysis for the TG and FCHL Traits

<table>
<thead>
<tr>
<th>Haplotype of SNPs</th>
<th>TG</th>
<th>FCHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCV1459766-rs3777787</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3777877-rs2073658</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haplotype 11</td>
<td>0.0009</td>
<td>0.02</td>
</tr>
<tr>
<td>Haplotype 22</td>
<td>0.001</td>
<td>0.02</td>
</tr>
</tbody>
</table>

All results represent P values for association with the HBAT —e option. The segregating susceptibility haplotype was 1-1 (1 indicates the major allele) in all of the analyses above. The haplotype 2-2 (2 indicates the minor allele) was less transmitted, protective haplotype in all of the analysis above.
The pedigree structure and phenotypic characteristics of the Mexican families used in the full pedigree linkage analyses are shown in Tables 1a and 1b. In 2-point linkage analyses of the 7 regions previously linked to FCHL and its component traits, we obtained maximum lod scores of 1.8 for chromosome 10q11.23 with marker D10S1772 for TGs and 2.6 for chromosome 16q24.1 with marker D16S505 for TC (Table 3). We also analyzed these 2 regions in a multipoint analysis using the GENEHUNTER software. For chromosome 16q24.1, an NPL score of 2.2 was obtained, whereas for 10q11.23, an NPL score of 0.6 was observed. Thus, no additional support was obtained for chromosome 10q11.23 in the multipoint analysis. No lod scores over 2.0 were observed for TG, FCHL, or low HDL-C in any of the investigated regions, nor for TC in the 6 remaining regions. Linkage results for all analyzed regions with the FCHL and its component traits are shown in Supplementary Table II (available at the web site, http://www.genetics.ucla.edu/labs/pajukanta/fchlmex/).

**Discussion**

Our results taken in aggregate provide evidence that variants in *USF1* are associated with FCHL and TGs in Mexican FCHL families. The SNPs hCV1459766, rs3737787, and rs2073658 showed significant evidence for association with both traits. As in the original study, the most significant association was observed with the high TG trait. Furthermore, haplotype analysis for SNPs hCV1459766-rs3737787 showed significant evidence for association with both traits, TGs (*P* = 0.0009) and FCHL (*P* = 0.02). As in the Finns, the major alleles and haplotypes formed by the major alleles were associated with FCHL and TGs. Similarly, the transmission of the haplotype of minor alleles to the affected individuals was reduced. However, there were differences in these results when compared with the Finns, possibly because of a different underlying LD structure. First, the most significant evidence for association was observed with the haplotypes of the SNPs hCV1459766-rs3737787 (versus the SNPs rs3737787-rs2073658 in Finns). Second, the association was restricted to a 14-kb region in the Mexican families with FCHL when compared with the 46-kb in the TG-affected Finnish males. Third, in contrast to these Finnish results that showed extension of the associated region specifically in TG affected males, no sex-specific effects were observed in the Mexican families. Although we cannot exclude the possibility that the relatively small sample size of this Mexican study contributes to these results, the observed results suggest that the FCHL/TG-associated region can be restricted to 14 kb between intron 7 of *USF1* (rs2073658) and intron 1 of *F11R* (hCV1459766). Thus the association evidence extends to *F11R* with the FCHL and TG traits, and we cannot genetically exclude *F11R* as an underlying gene for FCHL. However, the known functions of *F11R*, mainly associated with T-cell migration and epithelial tight junction formation, make it a substantially less likely candidate for FCHL than *USF1*.

None of the associated SNPs in the Finns or Mexicans result in an amino acid change, and in sequence analyses of the Finnish probands, no missense or nonsense variants were identified in *USF1*. Therefore, restriction of the associated region by 70% in these Mexican families makes the possibility for functional analysis of these variants considerably more feasible because a shorter region with fewer variants is now available for these analyses. This conclusion is also supported by the differences we observed in the LD structure between probands and spouses in the Mexican families.

In spite of the compelling evidence for the replication of the original association in the Mexican population, it is important to emphasize the need to sequence the *USF1* and *F11R* genes in the Mexicans in future studies. We could fail to detect additional, possibly even coding variants that are associated in the Mexican population, as well as important differences in LD structure and allelic heterogeneity. Therefore, a gene-based approach that considers all common variations within a gene jointly is needed to resolve the possible inconsistencies arising from population differences.

Here we also report a region on chromosome 16q24.1 to show suggestive evidence for linkage with TC in the Mexican families. Previous data from a combined analysis of the Dutch and Finnish genome-wide scans for FCHL provided evidence that the 16q24.1 region is linked to low HDL-C, producing a parametric multipoint LOD score of 3.6 for the low HDL-C trait. Importantly, this region on 16q24.1 has also been linked to HDL-C in an independent study of Mexican Americans. In the combined analysis of the Dutch and Finnish FCHL families, the maximum 2-point LOD score of 2.0 was obtained with marker D16S505 for low HDL-C; whereas for TC, the adjacent marker D16S3091 (2.1 cM apart) produced the highest 2-point LOD score of 1.6. Interestingly, the TC trait produced the highest evidence for linkage in the Mexican FCHL families, resulting in a 2-point ASP LOD score of 2.6 with marker D16S505 and a multipoint NPL score of 2.2. Although the maximum LOD scores for this region on 16q24.1 were observed for different traits in the Mexicans than in the Finns and Dutch, we assume that the complexity of the genetic and environmental processes that regulate the expression of the complex FCHL phenotypes in each population contributes to this difference.

Several studies have demonstrated that the Mexican population has a high genetic predisposition to the type 2
diabetes mellitus, metabolic syndrome, and some primary forms of dyslipidemias.22–24 In Mexicans, at age 50, 27.6% of men and 21% of women exhibit mixed dyslipidemia.23 These data suggest that the most common causes of mixed dyslipidemias, such as type 2 diabetes mellitus and FCHL, are common abnormalities in the Mexican population. Therefore, it is critical to identify genetic variants that confer susceptibility to high serum lipid levels in this population. The present study is the first report to extensively investigate the genetic component of the common FCHL disorder in the Mexican population.

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References


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