Host Genetics, Steatosis and Insulin Resistance among African Americans and Caucasian Americans with Hepatitis C Virus Genotype-1 Infection

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Key Words

Steatosis • Insulin resistance • Hepatitis C virus • Host genetics

Abstract

Hepatic steatosis is the accumulation of fat in liver cells. Insulin resistance (IR) occurs when normal amounts of insulin do not stimulate insulin activity in cells. Both conditions have been described in hepatitis C virus (HCV) infection and are thought to be biologically related. This study examined the association of genetic variants with steatosis and IR among 167 African Americans and 184 Caucasian Americans with HCV genotype-1. Steatosis was defined as at least 5% of fat in cells on liver biopsy. IR was quantified as a score greater than 2 from the Homeostasis Model Assessment, version 2.2 (HOMA2-IR). Associations were investigated by estimating odds ratios separately by race. Statistically significant associations ($p < 0.05$) were observed for variants in *interleukin-10* (*IL10*), *leptin receptor* (*LEPR*), *interleukin-6* (*IL6*) and *transforming growth factor beta-1* (*TGF-β1*) for both outcomes. Some significant interactions were observed between *IL10*, *LEPR* and *TGF-β1* polymorphisms and HOMA2-IR scores when examining steatosis. The interaction of HOMA2-IR and *IL10* was consistent in both races whereas for *LEPR* and *TGF-β1*

the interactions were statistically significant in only one of the racial groups. These results could imply that some *IL10*, *LEPR* and *TGF-β1* polymorphisms may modify an association between steatosis and IR.

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Introduction

Hepatic steatosis is characterized by the accumulation of fat in the liver and diagnosis is generally made by the histological evaluation of liver biopsies and the quantification of the percentage of fat in liver cells [1]. The prevalence of steatosis has been reported to be as low as 30% and as high as 84% among chronic hepatitis C virus (HCV) patients [2–6]. Steatosis occurs less frequently in the general population (31%) compared to chronic HCV patients [7]. The mechanisms of hepatic steatosis are thought to be multifactorial and the presence of insulin resistance (IR) may be associated with the development of steatosis [8].

African Americans have a lower prevalence of steatosis than Caucasian Americans despite having a higher BMI, which is associated with steatosis, although the mechanisms are not fully understood [7, 9]. Steatosis may

also adversely influence HCV sustained virologic response [6, 10, 11]. One study showed that HCV genotype-1 patients with steatosis achieved sustained virologic response less frequently (40%) compared to those without steatosis (63%) [11].

IR is a condition in which normal amounts of insulin are insufficient to activate insulin function in cells, especially fat, muscle and liver cells, and which results in increased glucose levels [12, 13]. IR may be quantified by the Homeostasis Model Assessment of Insulin Resistance index (HOMA-IR) [14]. Patients with chronic HCV infection were observed in one study to have higher HOMA-IR scores compared to healthy controls [15]. Factors associated with IR include African American race, obesity, older age, fibrosis and cirrhosis [16, 17]. Presence of IR may negatively impact the function of interferon therapy and the ability to achieve sustained virologic response in HCV patients especially those infected with genotype-1 [13, 16].

In this study we hypothesized that genetic variants in *collagen type-1 alpha-1 (COL1A1)*, *cytochrome P450 2E1 (CYP2E1)*, *interleukin-6 (IL6)*, *interleukin-10 (IL10)*, *interleukin-1 receptor type-1 (IL1R1)*, *leptin receptor (LEPR)*, *chemokine (C-C motif) ligand 2 (MCP1/CCL2)*, *chemokine (C-C motif) ligand 8 (MCP2/CCL8)*, *tumor necrosis factor-alpha (TNF- α)* and *transforming growth factor beta-1 (TGF- β 1)* are associated with steatosis or IR in African Americans or Caucasian Americans infected with HCV genotype-1.

Methods

Study Population and Clinical Data

Data were from the Study of Viral Resistance of Antiviral Therapy of Chronic Hepatitis C (Virahep-C). Virahep-C design and primary outcomes have been described elsewhere [3]. Briefly, 401 HCV treatment naïve patients were enrolled in the study, among whom 374 (194 Caucasian Americans and 180 African Americans) agreed to participate in the host genetics ancillary study and had DNA available for genotyping. Twelve individuals identified as Hispanic and 11 individuals using exogenous insulin were removed from analyses, resulting in a final sample size of 351.

Participants had a liver biopsy within 18 months of study enrollment [3, 18]. Liver biopsies were scored by a single pathologist, who was blinded to patient outcome and clinical status [3, 18]. Biopsies were assessed for the severity of hepatitis C by grading inflammation and staging of fibrosis using the modified histologic activity index scoring system [19]. Steatosis was also scored on a scale of 0–4 according to the percentage of cells with fat [4]. For this study, IR was quantified by using the HOMA-IR calculator, version 2.2, released in 2004 and downloaded from www.dtu.ox.ac.uk [20, 21].

Single Nucleotide Polymorphism Selection and Genotyping

The genes examined were chosen from a list of genes already genotyped as part of the Virahep-C host genetics study. Although the original study selected candidate genes for their potential involvement in the response to therapy or liver fibrogenesis, a number of the targeted genes may also be involved with steatosis or IR and were included in the present study.

Two different approaches were utilized in the selection and genotyping of single nucleotide polymorphisms (SNPs) and were based on publically available genetic information and genotyping technology at the time each component was completed. The first method identified SNPs for *IL6*, *IL10*, *TGF- β 1* and *TNF- α* and the subsequent genotyping by allelic discrimination is described elsewhere [18]. Briefly, SNPs were selected and allelic discrimination employing the ABI 7000 Sequence Detection System with TaqMan technology (Applied Biosystems Inc., Foster City, Calif., USA) was used to genotype the SNPs [18]. The second method for SNP selection and genotyping was utilized for *COL1A1*, *CYP2E1*, *IL1R1*, *LEPR*, *MCP1/CCL2* and *MCP2/CCL8*. The SNP selection methods and genotyping using the Illumina BeadArray technology (Illumina, San Diego, Calif., USA) have been described elsewhere [22].

Data Categorization

Steatosis was dichotomized with those having at least 5% fat indicative of the presence of steatosis. For this study, IR was defined as a HOMA2-IR score greater than 2.0 based on a previous study from the Virahep-C cohort [4]. An a priori decision was made that if the less common homozygote genotype had a minor allele frequency of less than 5% it was combined with the heterozygote genotype.

Age, BMI, baseline viral level, weekly alcohol consumption, ALT levels, AST levels, cholesterol levels, triglyceride levels, modified histologic activity index score and Ishak fibrosis score (centered at their mean values), history of diabetes and HCV subtype were examined as potential risk factors for steatosis and IR. Steatosis was included as a predictor for IR, and IR was included as a possible risk factor for steatosis using the continuous natural log of HOMA2-IR scores centered at the mean. Self-reported race was used in this study due to a strong correlation between individual admixture and self-reported race [18].

Genetic Analytical Methods

Genotype and allele frequencies as well as Hardy Weinberg Equilibrium χ^2 tests were calculated by race for each SNP. A genotype call rate, defined as the percentage of individuals where a genotype could be determined compared to the total number of individuals where genotyping was attempted, was calculated for each race group. Minor allele frequencies were examined by race for SNPs with a frequency greater than 5%. The Tagger Program in the Haploview Software Suite version 4.0 was used to calculate the amount of variation accounted for in the gene (r^2) by the tagged SNPs separately by race [23]. This analysis was done to evaluate how well the SNP selection methods utilized for this study captured the common genetic variation compared to the more recently available HapMap Phase II data.

Statistical Analyses

Distribution of demographic characteristics and risk factors for steatosis and IR were compared between African Americans

Table 1. Demographic characteristics by race

	African American (n = 167)	Caucasian American (n = 184)	p value
<i>Demographic and lifestyle characteristics</i>			
Gender			
Male	107 (64.1)	118 (64.1)	0.99 ^b
Female	60 (35.9)	66 (35.9)	
Age, years	48.7 (6.9)	47.3 (8.4)	0.13 ^a
BMI	30.8 (6.4)	28.2 (5.2)	<0.0001 ^a
Alcohol consumption units/week	3.6 (10.8)	2.3 (6.2)	0.99 ^a
<i>Laboratory measures</i>			
Triglycerides, mg/dl	132.4 (100.0)	114.9 (68.4)	0.14 ^a
Cholesterol, mg/dl	177.7 (36.7)	179.2 (35.5)	0.67 ^a
<i>Measures of disease</i>			
Baseline viral level, log ₁₀ IU/ml	6.2 (0.6)	6.3 (0.8)	0.08 ^a
ALT, U/l	70.6 (45.8)	108.0 (91.5)	<0.0001 ^a
AST, U/l	60.0 (43.2)	73.0 (58.7)	
Modified Histological Activity Index	10.0 (3.2)	10.4 (3.5)	0.21 ^a
Ishak fibrosis score	2.1 (1.4)	2.3 (1.5)	0.33 ^a
<i>Disease complications</i>			
Steatosis			
No steatosis	64 (38.3)	63 (34.2)	0.43 ^b
Steatosis present	103 (61.7)	121 (65.8)	
Insulin resistance			
HOMA2 <2	83 (58.5)	104 (66.7)	0.14 ^b
HOMA2 ≥2	59 (41.6)	52 (33.3)	
ln HOMA2-IR score	0.6 (0.7)	0.4 (0.7)	0.006

For categorical variables the frequency and percent are reported and for continuous variables the mean and standard deviation are reported. ^a χ^2 test. ^b Wilcoxon 2-sample test.

and Caucasian Americans using appropriate association tests. Logistic regression was used and the log odds of the outcome (e.g. steatosis) were modeled as a linear function of the predictors. Models were adjusted for potential confounding variables and backward elimination was used to remove those that did not significantly contribute to the prediction of the outcome. Steatosis was retained in the model predicting IR because steatosis and IR are biologically related [24] and it is unclear if steatosis contributes to the occurrence of IR or vice versa.

Interactions between HOMA2-IR scores (when predicting steatosis) or steatosis (when predicting IR) and the genetic variant were tested, and the log likelihood ratio test was used to assess interactions. Nonsignificant ($p \leq 0.05$) interactions were not included in the model. Statistical significance was set at $\alpha = 0.05$. The SAS®/STAT software system version 9.1.3 was used to complete analyses (SAS Institute Inc., Cary, N.C., USA).

Results

Population Characteristics

Comparisons of demographic characteristics by race are shown in table 1. There were 53 individuals who had missing data for HOMA2-IR because their insulin and glucose levels were not fasting or were not available because glucose or insulin levels were too high for the calculator.

Genotype frequencies, call rate and p values from Hardy Weinberg equilibrium tests are provided in online supplementary table S1 (for all online supplementary material see www.karger.com/doi/10.1159/000214380). The selected SNPs for *IL6*, *IL10*, *TGF- β 1* and *TNF- α* accounted for 38% (11–85%) of the common genetic variation in African Americans and 47% (7–81%) in Caucasian Americans. The selected SNPs for *COL1A1*, *CYP2E1*, *IL1R1*, *LEPR*, *MCP1* and *MCP2* accounted for 19% (0–40%) of the common genetic variation in African Americans and 39% (16–83%) in Caucasian Americans.

Associations with Steatosis

The final model for steatosis included BMI, weekly alcohol consumption, baseline viral level, Ishak fibrosis score and natural log transformed HOMA2-IR scores along with the genetic variant, and results for *IL6*, *IL10*, *LEPR* and *TGF- β 1* polymorphisms are reported in table 2. *CYP2E1*, *IL1R1*, *MCP2/CCL8* and *TNF- α* SNPs were not statistically significantly associated with steatosis. Haplotype analyses for the associations with steatosis yielded similar results to individual SNP analyses and are therefore not reported.

Caucasian Americans possessing the *IL6* rs2069845-AG or GG genotype had significantly higher odds of steatosis (OR = 2.5, 95% CI = 1.1–6.0) compared to those with the AA genotype (table 2). No significant associations were observed for this polymorphism in African Americans and the direction of the odds ratio was different. The odds of steatosis among African Americans with the *TGF- β 1* rs2278422-GG genotype were 4.4 times the odds of steatosis among African Americans with the CC or CG genotype and a similar, although non-significant, trend was observed among Caucasian Americans (table 2). A statistically significant interaction was observed in the prediction of steatosis between HOMA2-IR scores and *TGF- β 1* rs2241716 indicating that the relationship between steatosis and HOMA2-IR scores differs by genotype. Specifically, higher odds of steatosis were observed for a 1 unit higher HOMA2-IR score for African Americans possessing the *TGF- β 1* rs2241716-GG genotype

Table 2. Adjusted ORs for steatosis for selected SNPs and for the interaction between SNPs and HOMA2-IR among African Americans and Caucasian Americans

	African Americans ^a (n = 167)					Caucasian Americans ^a (n = 184)				
	n	genetic variant		HOMA2-IR ^b		n	genetic variant		HOMA2-IR ^b	
		OR (95% CI)	p	OR (95% CI)	p		OR (95% CI)	p	OR (95% CI)	p
<i>IL6 rs1880242</i>										
GG/GT	52	1.00	0.55	2.11 (1.18–3.79)	0.01	140	1.00	0.61	3.01 (1.44–6.29)	0.003
TT	115	1.28 (0.57–2.89)				43	0.78 (0.29–2.06)			
<i>IL6 rs2069837</i>										
AA	132	1.00	0.65	2.10 (1.17–3.79)	0.01	159	1.00	0.76	3.12 (1.53–6.37)	0.002
AG/GG	34	0.81 (0.32–2.04)				25	0.82 (0.23–2.91)			
<i>IL6 rs2069845</i>										
AA	75	1.00	0.70	2.14 (1.19–3.86)	0.01	60	1.00	0.04	2.98 (1.44–6.16)	0.003
AG/GG	92	0.86 (0.40–1.86)				123	2.52 (1.06–6.00)			
<i>IL10 rs3024496</i>										
CC	28	1.00	0.23	0.27 (0.05–1.31)	0.10	50	1.00	0.04	1.46 (0.52–4.15)	0.47
CT	82	2.02 (0.64–6.36)		3.39 (1.31–8.78) ^c	0.01	86	3.27 (1.06–10.09)		7.66 (2.31–25.42) ^c	0.001
TT	57	3.98 (1.15–13.77)		2.24 (0.80–6.28)	0.13	48	1.69 (0.48–5.92)		9.30 (1.45–59.53) ^c	0.02
<i>IL10 rs1800890</i>										
AA/AT	70	1.00	0.24	2.16 (1.20–3.88)	0.01	116	1.00	0.99	3.19 (1.57–6.47)	0.001
TT	97	1.60 (0.73–3.48)				67	1.00 (0.41–2.43)			
<i>LEPR rs1137100</i>										
AA	112	1.00	0.001	2.25 (1.22–4.15)	0.01	100	1.00	0.81	3.21 (1.58–6.54)	0.001
AG/GG	55	0.25 (0.11–0.58)				83	0.90 (0.40–2.05)			
<i>LEPR rs1805096</i>										
CC	52	1.00	0.10	2.38 (1.30–4.35)	0.01	74	1.00	0.03	2.01 (0.75–5.40)	0.17
CT	83	2.11 (0.87–5.13)				70	4.36 (1.21–15.73)		29.60 (4.27–205.2) ^c	0.001
TT	32	0.63 (0.21–1.90)				38	2.36 (0.76–7.33)		1.01 (0.31–3.32)	0.98
<i>LEPR rs1892534</i>										
AA	33	1.00	0.04	2.35 (1.28–4.30)	0.01	40	1.00	0.41	1.20 (0.37–3.90)	0.76
AG	83	2.98 (1.07–8.33)				69	1.79 (0.45–7.16)		26.22 (3.81–180.4) ^c	0.001
GG	51	1.55 (0.52–4.62)				74	0.44 (0.15–1.34)		1.97 (0.74–5.25)	0.18
<i>TGF-β1 rs2278422</i>										
CC/CG	85	1.00	0.001	3.10 (1.59–6.05)	0.001	130	1.00	0.37	3.25 (1.59–6.63)	0.001
GG	82	4.42 (1.84–10.65)				54	1.50 (0.62–3.60)			
<i>TGF-β rs2241716</i>										
AA/AG	16	1.00	0.50	0.65 (0.22–1.94)	0.44	0	1.00	d	d	
GG	151	1.48 (0.47–4.62)		3.34 (1.61–6.91)	0.001	183	d			

^a Model adjusted for the genetic variant, centered Ishak fibrosis score, centered weekly alcohol consumption, centered ln HOMA2-IR score, centered BMI, centered log₁₀ baseline viral levels and interaction between the genetic variant and ln HOMA2-IR score (where significant).

^b Adjusted OR for HOMA2-IR score when no statistically significant interaction present. If a statistically significant interaction, OR for HOMA2-IR score within a given genetic variant genotype.

^c Statistically significant log likelihood ratio test for the interaction between the genetic variant and ln HOMA2-IR scores.

^d Selected results are presented, results for all SNPs available in supplementary online materials.

(OR = 3.3, 95% CI = 1.6–6.9) compared to the odds for a 1 unit higher HOMA2-IR score among those with the AA or AG genotype (OR = 0.7, 95% CI = 0.2–1.9).

Statistically significant interactions between *IL10* SNPs and HOMA2-IR scores were observed with respect to steatosis and seen in both Caucasian Americans and African Americans. The odds of steatosis for a 1 unit higher HOMA2-IR score for Caucasian Americans pos-

sessing the *IL10 rs3024496*-CT (OR = 7.7, 95% CI = 2.3–25.4) or TT (OR = 9.3, 95% CI = 1.5–59.2) genotype were significantly higher than the odds for a 1 unit higher HOMA2-IR score for those with the CC genotype (OR = 1.5, 95% CI = 0.5–4.2). In African Americans, the odds of steatosis for the *IL10 rs3024496*-CT genotype with a 1 unit higher HOMA2-IR score were higher (OR = 3.4, 95% CI = 1.3–8.8) compared to the odds for HOMA2-IR for

Table 3. Adjusted ORs by selected SNPs and IR in African Americans and Caucasian Americans

SNP	African Americans ^a (n = 142)				Caucasian Americans ^a (n = 156)			
	n	OR	95% CI	p	n	OR	95% CI	p
<i>IL6 rs1880242</i>								
GG/GT	45	1.00			119	1.00		
TT	97	1.06	0.47–2.39	0.89	36	0.29	0.10–0.80	0.02
<i>IL6 rs2069837</i>								
AA/AG	112	1.00			135	1.00		
GG	29	2.07	0.81–5.28	0.13	21	0.24	0.06–0.88	0.03
<i>IL6 rs2069845</i>								
AA	63	1.00			52	1.00		
AG/GG	79	1.59	0.73–3.48	0.24	103	1.70	0.75–3.85	0.20
<i>IL10 rs3024496</i>								
CC	20	1.00			44	1.00		
CT	70	0.26	0.08–0.82	0.03	75	0.52	0.22–1.23	0.14
TT	52	0.41	0.12–1.41	0.16	37	0.47	0.17–1.33	0.16
<i>IL10 rs1800890</i>								
AA/AT	55	1.00			102	1.00		
TT	87	0.39	0.18–0.88	0.02	53	0.65	0.29–1.43	0.28
<i>LEPR rs1137100</i>								
AA	93	1.00			88	1.00		
AG/GG	49	1.77	0.78–4.03	0.17	67	1.44	0.69–2.98	0.33
<i>LEPR rs1805096</i>								
CC	44	1.00			62	1.00		
CT	68	0.65	0.27–1.60	0.35	58	0.54	0.23–1.28	0.16
TT	30	1.88	0.65–5.44	0.24	34	1.05	0.41–2.74	0.91
<i>LEPR rs1892534</i>								
AA	31	1.00			36	1.00		
AG	68	0.38	0.14–1.02	0.06	57	0.57	0.22–1.50	0.25
GG	43	0.62	0.22–1.78	0.38	62	1.00	0.39–2.57	0.99
<i>TGF-β1 rs2278422</i>								
CC/CG	76	1.00			111	1.00		
GG	66	0.38	0.17–0.89	0.03	45	0.35	0.14–0.87	0.02
<i>TGF-β rs2241716</i>								
AA/AG	16	1.00			0	1.00		
GG	126	1.32	0.41–4.29	0.64	155	^b		

Selected results are presented here, results for all SNPs available in supplementary online materials.

^a Model adjusted for the genetic variant, centered Ishak fibrosis score, centered body mass index, steatosis, centered age and centered triglyceride levels.

^b Model could not be estimated because minor allele frequency <5% for the SNP.

^c Homozygote genotype combined with heterozygote genotype to estimate association.

those with the CC genotype (OR = 0.3, 95% CI = 0.1–1.3). In Caucasian Americans, the *IL10 rs3024496*-CT and TT genotypes have similar increasing log odds of steatosis and the CC genotype has more slowly increasing log odds of steatosis as the HOMA2-IR score increases. Individuals who possess the *IL10 rs3024496*-associated genotypes and have higher HOMA2-IR scores also have higher odds

of steatosis compared to those with lower HOMA2-IR scores.

African Americans with the *LEPR rs1137100*-AG or GG genotype had 0.3 (95% CI = 0.1–0.6) times lower odds of steatosis compared to those with the AA genotype (table 2). A similar, although nonsignificant, trend was observed for Caucasian Americans. African Americans

possessing the *LEPR* rs1892534-AG genotype had triple the odds of having steatosis compared to those with the AA genotype (table 2). For a 1-unit increase in HOMA2-IR score among Caucasian Americans, the odds of steatosis for *LEPR* rs1892534-AG genotype were 29.6 (95% CI = 4.3–205.2) times greater compared to those with the AA genotype (OR = 1.2, 95% CI = 0.4–3.90). The odds of steatosis for a 1-unit higher HOMA2-IR score among Caucasian Americans possessing the *LEPR* rs1805096-CT genotype were significantly higher (OR = 26.2, 95% CI = 3.8–180.4) than the odds for a 1-unit higher HOMA2-IR score among those with the CC genotype (OR = 2.0, 95% CI = 0.8–5.4). Results for SNPs not presented in table 2 are available in online supplementary table S2.

Associations with Insulin Resistance

No statistically significant SNP associations with IR were observed in either race group for *COL1A1*, *CYP2E1*, *IL1R1*, *MCPI/CCL2*, *MCP2/CCL8* or *TNF- α* . Additional SNP results not described in table 3 are presented in the supplementary online tables. Haplotype analysis for the association with IR yielded results similar to those from individual SNP analyses and are not presented. No significant interactions between the genetic variants and steatosis contributed to associations with IR.

African Americans with the *IL10* rs3024496-CT genotype (OR = 0.3, 95% CI = 0.1–0.8) or the rs1800890-TT genotype (OR = 0.4, 95% CI = 0.2–0.9) had lower odds of IR compared to the rs3024496-CC genotype or the rs1800900-AA or AT genotype. A similar trend for these SNPs was observed among Caucasian Americans. Caucasian Americans with the *IL6* rs1880242-TT genotype had 0.3 times lower odds of IR compared to Caucasian Americans with the GG or GT genotype. For *TGF- β 1* rs2278422, African Americans with the GG genotype had 0.2 times lower odds of IR (95% CI = 0.2–0.9) and Caucasian Americans with the GG genotype had 0.4 times lower odds of IR (95% CI = 0.1–0.9) compared to those with either the CC or CG genotype.

Discussion

This study investigated the association of host genetic markers with steatosis and IR for African American and Caucasian American patients with HCV genotype-1 infection. This study stratified all data by race as SNPs may have different effects in different ethnic groups based on their different population histories. Some associations identified in this study were only statistically significant

in one race group or the direction of the association was different by race. One explanation may be that the associated genetic variants were not directly affecting the conditions, but rather were in linkage disequilibrium with functional genetic variants. If this were the case, the different patterns of results may be explained by different linkage disequilibrium patterns or the different population histories of African Americans and Caucasian Americans. For example, an associated SNP could be 'tagging' a causal genetic variant in one population that is not present in another population. Alternatively, different relatively new functional variants could lie on the same ancestral haplotype in different populations.

The findings from this study imply that some genetic variants may moderate or influence the association between steatosis and IR. For example, the association between steatosis and IR may be affected by *IL10* rs3024496. Those with higher HOMA2-IR scores who possess the CT or TT genotype were more likely to also have steatosis compared to those with the CC genotype and higher HOMA2-IR scores. *IL10* rs3024496 is located in the 3' untranslated region of the gene and has no known function [25]. Future work aimed at understanding the biological function of associated genetic variants may provide more information about how this genetic variant influences steatosis or IR.

For the *LEPR* gene, there were main effects associations of SNPs with steatosis or IR. The *LEPR* rs1137100-AG or GG genotype was associated with lower odds of steatosis. Two statistically significant interactions were also observed between *LEPR* SNPs and HOMA2-IR scores with respect to steatosis in Caucasian Americans. *LEPR* rs1137100 is located in the coding region and may contribute to splicing regulation [25]. *LEPR* rs1892534 is located in the 3' downstream untranslated region with no known function [25]. Further understanding of the function of the associated genetic variants may explain the relationship with steatosis or IR in HCV infection.

There were statistically significant associations between *TGF- β 1* SNPs and steatosis or IR indicating that polymorphisms in this gene may be important in understanding these conditions in HCV infection. In particular, possession of the *TGF- β 1* rs2278422-GG genotype indicated lower odds of IR for both race groups compared to the CC or CG genotype. *TGF- β 1* rs2278422 is located in the intron region with no known function [25]. In addition, one significant interaction was observed in African Americans between *TGF- β 1* rs2241716-GG genotype and higher HOMA2-IR scores such that higher odds of steatosis were observed than expected for the main ef-

fects of HOMA2-IR scores and the genotype alone. *TGF- β 1 rs2241716* is located in the intron region and predicted to be an intronic enhancer which could change how the encoded protein is produced [25].

Future studies are needed to replicate our findings; however, a similar sample that included a sufficient number of African Americans was not available. Another limitation was the different methods utilized for selecting genetic variants. At the time the selection of SNPs was completed, HapMap Phase I was the main source of reference population data and was not able to identify SNPs to account for more of the common genetic variation observed in different racial groups. Thus, the amount of common variation characterized by the tag-SNPs selected is not as high as those expected by the second phase of HapMap which has the ability to better capture the common variation in the genes. Additionally, due to the hypothesis-generating nature of this study, adjustment for multiple comparisons was not completed and future studies are needed to confirm these findings. Nevertheless, our SNP results provide useful information about genetic variant associations with the conditions in HCV infection.

In conclusion, this study identified host genetic associations with steatosis or IR in African Americans and Caucasian Americans with HCV genotype-1. Significant associations between *IL6*, *IL10*, *LEPR* or *TGF- β 1* and steatosis or IR were identified and the relationship between IR and steatosis may be moderated by genetic variants such as SNPs in the *IL10* gene.

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