HOST GENETIC VARIANTS, TREATMENT OUTCOMES AND METABOLIC COMPLICATIONS IN HEPATITIS C VIRUS GENOTYPE-1

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Chronic Hepatitis C Virus (HCV) infection is prevalent in approximately 3.2 million people in the United States. Understanding mechanisms of HCV treatment response and conditions seen in people with HCV such as steatosis and Insulin Resistance (IR) are important to preventing excess morbidity and mortality and improving HCV treatment outcomes. Host genetic factors may be important with respect to these issues.

The purpose of this research was to investigate host genetic relationships with 28 day viral decline after treatment initiation, steatosis and insulin resistance and to examine these associations separately in African Americans and Caucasian Americans infected with HCV genotype-1.

Data from the Study of Viral Resistance of Antiviral Therapy of Chronic Hepatitis C (Virahep-C) were used. Virahep-C was designed to understand the mechanisms of resistance to antiviral therapy for chronic HCV genotype-1 patients. The studies reported in this dissertation included up to 194 Caucasian Americans (CA) and 180 African Americans (AA) who agreed to participate in the Virahep-C genetics ancillary study.

In longitudinal analyses of 28 day treatment induced viral decline, polymorphisms in *Myxovirus resistance 2 (MX2), Oligoadenylate synthetase-like (OASL), Signal transducer and activator of transcription 1 and 2 (STAT1* and *STAT2*) were significantly associated with viral

decline. Additionally, significant *Protein Kinase* (*PKR)* haplotype associations with viral decline were observed among AAs.

In cross-sectional analyses, significant associations between selected genetic variants and either steatosis or IR were observed in *Interleukin-10 (IL10), Leptin Receptor (LEPR), Interleukin-6 (IL6)* and *Transforming Growth Factor Beta 1 (TGF-β1)* for both conditions. Statistically significant interactions were observed between *IL10*, *LEPR* and *TGF-β1* polymorphisms and HOMA2-IR scores when examining steatosis.

Statistically significant associations were observed for *Adiponectin Receptor 1* (*ADIPOR1*) polymorphisms and *3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2* (*HMGCS2*) polymorphisms and steatosis or IR.

Overall, these findings suggest that host genetic factors are associated with treatment induced 28 day viral decline, steatosis and IR. Understanding the biological mechanisms that contribute to these findings has significant public health implications because it could help establish new therapies and interventions to prevent HCV related morbidity and mortality. Results may also contribute to understanding the mechanisms of treatment response, steatosis and IR.

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PREFACE

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1.0 DISSERTATION OVERVIEW AND OBJECTIVES

The Hepatitis C Virus (HCV) is involved in the development of liver disease, liver damage and chronic HCV infection.(Choo, 1989) Hepatitis C virus is a major public health concern and the leading cause of chronic liver disease in the United States (US).(Strader, 2002)

Viral factors, host genetic factors and environmental factors are thought to influence the progression of HCV, development of virus related complications and treatment response.(Seeff, 2002) Viral and host factors have been carefully examined in the literature, but studies that examine host genetic associations with treatment outcomes and complications of HCV infection are still being studied and verified.

Viral dynamics are the examination of viral level change during the early course of treatment and have been used to study the efficacy of various treatment regimens.(Herrmann, 2003; Neumann, 2000; Neumann, 1998; Perelson, 2005; Zeuzem, 2001) Rapid virologic response or very early virologic response, which can be examined using viral dynamics models in the first 28 days of therapy, can be used as a prognostic factor for long-term treatment outcomes.(Neumann, 2000; Neumann, 1998) No studies have been found that examined the association between the polymorphisms of interferon stimulated genes (ISGs) examined in this dissertation and differences in viral level in the first 28 days of treatment. ISGs are important in immune response because they induce antiviral actions and activate mechanisms to enhance

immune response and understanding their mechanisms of action in HCV treatment could lead to the development of more effective therapy.

Steatosis and Insulin Resistance (IR) are two metabolic complications that can occur in people with or without HCV infection. The presence of steatosis or IR are thought to negatively impact the ability to achieve sustained virologic response (SVR).(Guidi, 2005; Jian Wu, 2006; Patton, 2004; Romero-Gomez, 2006; Romero-Gomez, 2005; Soresi, 2006; Westin, 2007) No studies were identified that tested the association between the genetic variants utilized in this dissertation and the pathogenesis of steatosis or IR in HCV infection.

Racial differences exist in the occurrence of chronic HCV infection, in treatment outcomes and development of conditions associated with infection. In the US, the prevalence of chronic HCV is higher among African Americans compared to Caucasian Americans.(Armstrong, 2006) HCV genotype-1, -2 and -3 are commonly identified in US HCV patients and genotype-1 infection is more common in African Americans.(Alter, 1999; Strader, 2004) Individuals with HCV genotype-1 infection are less likely to have long-term treatment response compared to those with other than genotype-1 infection.(Conjeevaram, 2006; MW Fried, 2002; Manns, 2001) Studies also suggest that African Americans with HCV genotype-1 have lower response rates to therapy compared to Caucasian Americans with the same genotype.(Conjeevaram, 2006; Hepburn, 2004; Jeffers, 2004; Kinzie, 2001; Muir, 2004; Strader, 2004) Further, racial differences also exist in the development of complications from HCV infection. African Americans have a lower prevalence of steatosis and higher occurrence of IR compared to Caucasian Americans who have higher prevalence of steatosis and are less likely to have IR.(Browning, 2004; Conjeevaram, 2007; Heathcote, 2002; Petit, 2001; Romero-Gomez,

2005) HCV research has attempted to explain racial differences and testing genetic associations may provide an additional link to understanding these differences.

An initial objective of this dissertation was to examine the host genetic relationships with differences in 28 day treatment induced viral decline and the occurrence of both steatosis and insulin resistance. Further objectives were to determine if associations were present in both Caucasian Americans and African Americans and if the associations remained after adjustment for potential confounding factors. Specifically, the following research questions were addressed in a series of three research articles:

1. Are selected interferon stimulated genes associated with differences in viral levels over the first 28 days of treatment?
    a. Do viral levels significantly differ by genotypes of interferon stimulated gene polymorphisms?
    b. Are the same genetic variants associated with 28 day viral decline in both African Americans and Caucasian Americans?
2. Are selected genes associated with steatosis or insulin resistance in African Americans and Caucasian Americans?
    a. Are polymorphisms for the selected genes associated with steatosis and IR?
    b. Are these associations present in both African Americans and Caucasian Americans?
3. Are *adiponectin receptor 1* (*ADIPOR1)* and *3-hydroxy-3-methylglutaryl-CoA Synthase 2 (HMGCS2)* polymorphisms associated with steatosis and insulin resistance among African Americans and Caucasian Americans with HCV genotype-1?

a. Are tag selected genetic variants in *ADIPOR1* and *HMGCS2* associated with steatosis and IR?
b. Are these associations present in both African Americans and Caucasian Americans?

These research questions were investigated in The Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C), a multi-center treatment study that recruited African Americans and Caucasian Americans with chronic HCV genotype-1 with no prior history of treatment between July 2002 and December 2003.(Conjeevaram, 2006)

2.0 BACKGROUND

2.1 HEPATITIS C VIRUS

The Hepatitis C Virus (HCV) was identified in 1989 and is a causative agent for liver disease, liver damage or chronic HCV infection.(Choo, 1989) HCV infection occurs primarily through contact with blood, blood-derived products, organ donation, perinatal transmission, or body fluids such as vaginal fluids or semen.(Major, 1997; Van Leeuwen, 1996, 2005) HCV is a member of the *Flaviviridae* virus family and has the ability to change and mutate.(Bartenschlager, 2000; Major, 1997; Reed, 2000; Van Leeuwen, 1996, 2005) HCV exhibits genotypes and within each genotype there are multiple subtypes.(Major, 1997; Robertson, 1998)

2.1.1 Epidemiology of the Hepatitis C Virus

Hepatitis C virus is a major public health concern. It is the leading cause of chronic liver disease and is the most common chronic, blood-borne infection in the United States (US).(Alter, 1999; Strader, 2002). It is estimated that 4.1 million people in the US have antibodies to HCV (anti-HCV), and of those, 3.2 million have chronic HCV infection identified as the presence of HCV RNA.(Armstrong, 2006) Approximately 3% of the world population is estimated to be infected with chronic HCV.(Alberti, 1999) Risk factors for HCV include exposure to blood or blood

products, blood transfusion before 1992, intravenous drug use, many sexual partners, tattoos, and body piercings.(Alter, 1999; Armstrong, 2006; Van Leeuwen, 1996, 2005) In the US, the prevalence of chronic HCV infection is higher among African Americans (3.0%) compared to Caucasian Americans (1.5%) and higher among men (2.1%) compared to women (1.1%).(Armstrong, 2006) In the US, there are three common genotypes of HCV: genotype-1 is prevalent in 75% of cases, genotype-2 in 15% of cases, and genotype-3 in 7% of cases.(Alter, 1999) Ninety-one percent of chronic HCV infection in African Americans is genotype-1 compared to 67% of infection in Caucasian Americans.(Strader, 2004)

HCV infection during the first six months is referred to as acute infection. Approximately 20-30% of persons infected with HCV clear the virus naturally during the acute phase. Failure of the immune system to naturally clear the virus results in chronic HCV and occurs in 54-86% of those exposed.(Seeff, 2002) HCV genotypes and subtypes may contribute to the transition from the acute phase of infection to chronic illness.(Farci, 2000) Chronic HCV can be mild or asymptomatic, but an estimated 20-40% of infections can cause severe morbidity and mortality from liver diseases or disease progression resulting from viral complications.(Reddy, 1999; Seeff, 2002) A systematic review of histological activity studies with follow-up ranging from 4-12 years found that cirrhosis developed in 27% of cases and of those 5% died of liver disease.(Pagliaro, 1999) Without treatment, 20-30% of those exposed to HCV may progress to cirrhosis on average in 20 years after infection.("National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10-12, 2002)," 2002)

2.2 DIAGNOSIS OF CHRONIC HEPATITIS C VIRUS

Diagnosis of HCV for an individual may be initiated with the identification of elevated liver enzymes in routine blood tests, blood donor tests or through accidental screening such as medical examinations for health insurance or employment. Assays to detect and quantify the virus can be used to monitor disease progression, liver damage and patient health.(Pawlotsky, 1998, 2002)

2.2.1 Detection of Antibodies for Hepatitis C Virus

Antibodies for HCV (Anti-HCV) are markers of HCV exposure and infection. However, the presence of anti-HCV is not a sign of active infection, but that an individual was exposed to the virus and either resolved the infection naturally or developed chronic infection.(Pawlotsky, 2003) Anti-HCV is identified using enzyme immunoassays (EIA), with specificity greater than 99%, where serum or plasma antibodies or viral antigens are captured on microtiter plate wells using antigen or specific antibodies.(Pawlotsky, 2002)

2.2.2 Detection of Hepatitis C Virus RNA

HCV RNA is considered to be a direct marker of HCV replication and chronic infection.(Pawlotsky, 2003) Chronic infection is characterized by a gradual decline in HCV RNA levels that eventually stabilize and remain in a steady state between virus production and elimination.(Pawlotsky, 2002) HCV RNA concentration can be measured by amplifying viral genome copies enabling quantification of the amount of viral genomes in the sample.(Pawlotsky, 2002) The international unit (IU), a universal standard unit of measurement for HCV RNA, was

established by the World Health Organization (WHO) to adjust for variability among assays.(Pawlotsky, 2000; Saldanha, 1999) Quantitative assays using polymerase chain reaction (PCR) to quantify HCV RNA viral levels have a specificity of 98-99% with a lower limit of detection of approximately 600 IU/mL.(Pawlotsky, 2002) Qualitative HCV RNA assays based on target amplification using PCR extract, amplify and read viral levels and have a lower HCV RNA detection limit of 50 IU/mL.(Pawlotsky, 2002) Qualitative tests are generally used to evaluate sustained virologic response to antiviral therapy.

2.2.3 Identification of HCV Genotype and Subtype

HCV genotype and subtype can also be assessed in infected patients. HCV has 6 genotypes numbered 1-6 which are further subdivided into subtypes denoted with lower case letters.(Simmonds, 1999) Phylogenetic analysis, testing for type-specific antibodies or direct sequencing of the NS5B or E1 region of the virus are used to determine HCV genotype and subtype.(Pawlotsky, 2002; Simmonds, 1999)

2.3 TREATING CHRONIC HEPATITIS C

Treatment for patients with chronic HCV has evolved since the discovery of the virus. Treatment is recommended for all chronic HCV patients.(Fontaine, 2001) The ultimate goal of therapy is to achieve a sustained virologic response (SVR) defined as undetectable levels of HCV RNA in the blood 24 weeks after therapy ends.(Lindsay, 2002)

The first treatment for HCV, interferon (IFN) alpha-2b monotherapy, was developed before the virus was identified and named.(Hoofnagle, 1986) SVR rates were about 10-20% with a high rate of relapse.(Carithers, 1997) Adding the nucleoside analog ribavirin to IFN monotherapy doubled the SVR rates in treatment naïve patients.(McHutchison, 1998; Poynard, 1998) To improve outcomes, pegylated interferon was examined in patient therapy. Pegylated interferon is a chemically inactive polyethylene glycol (PEG) molecule that attaches to IFN-α2a or IFN-α2b to slow the absorption rate of the interferons allowing them to remain in the body longer.(Shiffman, 2001)

The currently recommended treatment for chronic HCV infection is the combination of pegylated IFN-α2a or IFN-α2b weekly and weight-based dosing of ribavirin daily (pegINFα/RBV) for 24 to 48 weeks.(Lindsay, 2002) Interferon treatment is thought to work by stimulating the host's immune system and activating interferon stimulating genes (ISGs).(Zeuzem, 1996) Ribavirin is believed to inhibit viral infection of susceptible cells.(Lau, 2002)

2.4 OUTCOMES OF HEPATITIS C TREATMENT

2.4.1 Factors Associated with Sustained Virologic Response

SVR occurs in 54-56% of individuals treated for HCV infection.(MW Fried, 2002; Manns, 2001) Host and viral factors that have been associated with treatment response include viral levels at the onset of treatment, HCV genotype, race, gender, age, obesity, steatosis and fibrosis.(Gao, 2004; Lau, 1993; McHutchison, 1998; Zeuzem, 2004; Zeuzem, 2000) Higher baseline viral

levels were associated with lower risk of achieving SVR in HCV-genotype-1 patients.(Conjeevaram, 2006) In two studies, fewer patients (42-46%) with HCV genotype-1 infection achieved SVR compared to 76-82% of patients with HCV genotype-2 or -3.(MW Fried, 2002; Manns, 2001)

Several studies have shown that African Americans have lower response rates to therapy compared to Caucasian Americans.(Conjeevaram, 2006; Hepburn, 2004; Jeffers, 2004; Kinzie, 2001; McHutchison, 2000; Muir, 2004; Strader, 2004) Two studies have shown that men have a significantly lower risk of achieving SVR compared to women with the same genotype.(Conjeevaram, 2006; Hayashi, 1998) Younger age was associated with better response to HCV treatment in several studies.(Bruno, 2004; Hayashi, 1998; Martinot-Peignoux, 1995; McHutchison, 2000; Muir, 2004)

Fat mass and hepatic steatosis were associated with poor response to pegIFNα treatment in three studies.(Bressler, 2003; Charlton, 2006; Poynard, 2003) Studies suggested that high fat mass and hepatic steatosis decreased pegIFNα bioavailability, impaired immune response to HCV and increased fibrosis progression reducing treatment response.(Bressler, 2003; Charlton, 2006; Conjeevaram, 2006) The presence of fibrosis was also associated with treatment non-response.(Myers, 2003)

2.4.2 Rapid Virologic Response in the Prediction of Sustained Virologic Response

Assessing virologic response very early during the course of treatment to predict SVR could be useful in HCV treatment research. The ability to accurately detect SVR at four weeks of treatment could identify SVR non-responders. Rapid virologic response (RVR) has been defined as at least a 2 $\log_{10}$ IU/mL drop in viral level in the first four weeks of treatment.(Moucari, 2007)

One study of patients treated with standard IFN three times weekly found that 30% of individuals who achieved a SVR had at least a 3 $\log_{10}$ decrease in viral level from baseline to week 4 of treatment.(Zeuzem, 1998) Another study that compared different treatment regimens in HCV genotype-1 through -6 patients found that all patients, regardless of regimen or genotype, with an HCV RNA level greater than 450,000 IU/mL (5.65 $\log_{10}$ IU/mL) at week 4 were non-responders at the end of treatment.(Berg, 2003) However, using a four week cutoff of 450,000 IU/mL (5.65 $\log_{10}$ IU/mL) only identified 15% of treatment responders.(Berg, 2003) Another study among mostly HCV genotype-1 patients receiving pegIFNα2b plus ribavirin found that 27 of 45 patients achieved at least a RVR.(Moucari, 2007) Of those, 14 patients achieved a SVR resulting in a positive predictive value of 52%.(Moucari, 2007) Of the 18 patients who did not achieve a RVR, 17 did not achieve a SVR resulting in a negative predictive value of 94%.(Moucari, 2007) Due to the relationship of very early viral response to ultimate SVR, identifying factors, including genetic variants, associated with viral decline in the first 28 days may help to understand the mechanisms of treatment response and contribute to improvements in treatment options and ultimately treatment response.

2.5 HEPATITIS C VIRAL DYNAMICS

Viral dynamics are the time course of treatment induced changes in HCV viral levels. HCV viral levels remain stable in chronic HCV infection with only minor changes in untreated patients representing a dynamic equilibrium between viral production and viral clearance.(Nguyen, 1996) Treatment with interferon changes the balance leading to a multi-phasic decline of HCV RNA.(Neumann, 2000; Neumann, 1998)

Viral dynamics models were developed to describe the decay of HCV RNA induced by interferon therapy.(Bekkering, 1997; Neumann, 2000; Neumann, 1998; Nowak, 1996; Perelson, 1996; Powers, 2003; Ribeiro, 2003; Zeuzem, 1996) Obtaining these models requires collecting frequent viral level measurements after the initiation of therapy.(Herrmann, 2003; Neumann, 2000; Neumann, 1998; Powers, 2003; Ribeiro, 2003; Zeuzem, 2001; Zeuzem, 1996) Dynamics models are thought to be useful in evaluating the antiviral effectiveness of therapy, estimating the rate of virion clearance, and approximating the rate of the clearance of HCV infected cells.(Perelson, 2005)

Early viral dynamics research by Neumann et al. described a bi-phasic decline in viral level with interferon monotherapy.(Neumann, 1998) The first phase of decline was rapid, dose dependent, and occurred within the first 24-48 hours of therapy.(Neumann, 1998) The first phase of viral decline reflected clearance of free virions through the effect of IFN on the innate immune response and the blockage of viral production by IFN causing the rapid decline in viral level.(Layden-Almer, 2003; Neumann, 2000; Neumann, 1998; Zeuzem, 2001) The second phase 24-48 hours after initiation of treatment through day 14 was observed to be slower, highly variable and dependent on the effectiveness of IFNα in blocking viral production and causing the loss of infected cells.(Layden-Almer, 2003; Neumann, 2000; Neumann, 1998; Zeuzem, 2001) Early viral dynamics models provided information about the virus and how IFN therapy works.

Viral dynamics models have also examined patients treated with pegIFNα2a monotherapy and showed a bi-phasic decline consisting of a rapid first phase decline within the first 48 hours followed by a second slower phase decline observed through day 28 of treatment.(Zeuzem, 2001) Viral dynamics models in patients treated with pegIFNα2a and ribavirin showed three phases of viral decline.(Herrmann, 2003) In the tri-phasic model, phase

one occurred within the first 24-48 hours after treatment initiation and was characterized by the clearance of free virus.(Herrmann, 2003) The second phase from treatment day 2 to day 6 was distinguished by the exponential decay of productively infected cells.(Herrmann, 2003) The third phase from day 7 to day 28 of treatment was a more rapid viral decay from delayed treatment induced infected cell loss.(Dahari, 2007; Herrmann, 2003)

Viral dynamics are believed to be a prognostic factor in the early course of treatment to identify response to therapy at the end of treatment.(Neumann, 2000; Neumann, 1998) In the tri-phasic model, a more rapid third phase decay was strongly associated with SVR.(Herrmann, 2003) Viral dynamics may also be an important factor in determining why some individuals respond to treatment and others do not.(Layden-Almer, 2003) For example, very early viral decline may vary by race.(Layden-Almer, 2003) Provided that viral clearance is occurring, a small initial decrease in HCV RNA level over the first 24 hours may indicate that peg-IFNα is not effective in blocking viral production and a slow or absent second phase might indicate the inability of the host to clear infected cells.(Layden-Almer, 2003) Caucasian Americans have a higher phase one viral decline and a higher rate of infected cells loss (98%) compared to African Americans (89%).(Layden-Almer, 2003) Fewer African Americans experience a phase two viral decline compared to Caucasian Americans.(Layden-Almer, 2003) These results suggest that the first phase viral decline has a significant influence on the second phase viral decline and ultimately treatment response.(Jessner, 2001; Layden, 2002)

Viral dynamics models could be used to optimize therapy for patients with reduced response rates such as African Americans or HCV genotype-1 patients. Models can be used to monitor individual response early during treatment and to adjust regimens as necessary. These models may also be important in evaluating the antiviral efficacy of new therapies.

Understanding how host immune response, host genetic factors or combination therapy influence viral dynamics may guide the development of novel HCV treatments and provide insight into more effective treatment regimens or drug dosage.

2.6 INTERFERON STIMULATED GENES AND HCV TREATMENT RESPONSE

Clinical implications are not always immediately recognized with one genetic association study, but genetic epidemiology is useful in translational medicine. An underlying assumption of genetic epidemiology is that understanding human disease through basic science will ultimately help lead to clinical improvements by recognizing risk groups that should be treated differently, by identifying novel molecular treatment targets and by generating hypotheses about why and how therapies work differently in different populations.

The interferon system is a vital component of the innate immune response to infectious agents. Interferon stimulated genes (ISGs) induce proteins with antiviral actions and activate mechanisms that enhance immune response. HCV is thought to have developed mechanisms to circumvent the host immune response by inhibiting the functions of several ISGs. Viral proteins may block the production or reduce the effectiveness of ISG proteins which normally have antiviral actions to enhance immune response to infection.(MacQuillan, 2003) Since ISGs are important in immune response, studies have examined the role of host genetics in the response to interferon therapy, although most studies have focused on SVR as the primary outcome.(Hijikata, 2001; Hijikata, 2000; Knapp, 2003; H Saito, 2002; T Saito, 2004; Suzuki, 2004; Tena-Tomas, 2007; Thursz, 1997; Wietzke-Braun, 2006)

2.6.1 Myxovirus Resistance Genes

The myxovirus resistance 1 (MX1 or MXA) protein was observed to influence IFN-induced antiviral activities of host cells against infectious viruses.(Jakschies, 1994; Pavlovic, 1990; Roers, 1994; Zhao, 1996) In a study of Western Australian patients, MX1 mRNA expression has been found to be up-regulated in chronic HCV infection, but intrahepatic MX1 expression did not correlate with baseline HCV viral levels though strong baseline MX1 expression in hepatocytes were associated with HCV treatment non-response.(MacQuillan, 2003) In HCV patients treated with interferon monotherapy, MX1 mRNA levels increased after initiation of therapy and declined after completion of treatment.(Fernandez, 1999) For HCV treatment naïve patients treated with pegIFNα2b/RBV, MX1 expression was lower in people who had SVR than in those who did not respond.(Giannelli, 2004) In spite of these conflicting results, the MX1 protein may be involved in HCV treatment response. Further, *MX1* could be examined at a genetic level because the gene may affect antiviral actions of host cells in response to viral infection.

Studies have examined associations between *MX1* single nucleotide polymorphisms (SNPs) and HCV treatment outcomes. Statistically significant associations between the *MX1* SNP at position -88G/T with respect to the transcription initiation site and HCV treatment response have been reported.(Hijikata, 2001; Hijikata, 2000; Knapp, 2003; Suzuki, 2004) In two studies of interferon monotherapy, the *MX1* -88 GT and TT genotypes were significantly associated with SVR such that carriage of the T allele was associated with SVR.(Knapp, 2003; Suzuki, 2004) Two separate studies in Japanese populations confirmed the association between the *MX1* -88 GT and TT genotypes and SVR.(Hijikata, 2001; Hijikata, 2000) These studies indicate that *MX1* variants may be important to understanding HCV treatment response. A

different study examined the *MX1* -88G/T polymorphism, but found no statistically significant association with initial treatment response defined undetectable HCV RNA at four months into treatment.(Wietzke-Braun, 2006) Though results of these studies are conflicting, they use different methodologies making the association between *MX1* polymorphisms and HCV treatment response uncertain. Thus, further research could contribute to a greater understanding of the importance of this gene in HCV treatment response.

Myxovirus resistance 2 (*MX2*) functions by encoding a protein that has nuclear and cytoplasmic forms.(Rebhan, 2007) The *MX2* gene function with respect to HCV treatment response is unknown. Testing genetic variant associations with *MX1* and *MX2* may contribute to understanding the association of these genes with HCV treatment response.

2.6.2 2'-5' Oligoadenylate Synthetase (OAS) Gene System

The *2'-5' oligoadenylate synthetase (OAS) gene system* contains ISGs that function by degrading cellular and viral RNA thereby inhibiting viral replication.(Hovanessian, 1977; Zhou, 1993) The HCV core protein disrupts normal immune response and studies have suggested that 2'-5' OAS levels before and during IFN treatment are influenced by the virus core protein.(Murashima, 2000; Naganuma, 2000) Increased 2'-5' OAS expression was associated with the effectiveness of pegIFNα2b/RBV in HCV RNA clearance.(Kim, 2006)

2'-5' oligoadenylate synthetase 1 (*OAS1*), an interferon stimulated gene, may influence immune response by breaking down viral and cellular RNA.(Castelli, 1998; Pestka, 1987) Knapp et al. observed a statistically significant association between *OAS1* rs2660 and spontaneous clearance of HCV, but not with response to interferon therapy.(Knapp, 2003) Despite the lack of a significant association with SVR, since *OAS1* covers a 12.97 kilobase (kb)

region on the chromosome with several polymorphisms, additional variants along this gene could be examined to identify associations with HCV treatment response.

2'-5' oligoadenylate synthetase 2 (OAS2) and *2'-5' oligoadenylate synthetase 3 (OAS3)* are thought to function by encoding an enzyme that activates the degradation of viral and cellular RNA.(Hovanessian, 1991) *2'-5' oligoadenylate synthetase like (OASL)* has the ability to bind to double stranded RNA and DNA.(Hovanessian, 1991) The genes in the *OAS* gene system may be important to understanding immune response and genetic variant associations in these genes may contribute to understanding the mechanisms of HCV treatment response.

2.6.3 Protein Kinase

Studies testing the association between Protein Kinase (PKR) expression and HCV treatment response have been conducted. The HCV core protein is thought to inhibit innate *PKR* function and allowing virus transmission to uninfected cells.(Pflugheber, 2002) In one study, PKR expression was found to be enhanced within a few hours of pegIFNα treatment and facilitated the clearance of HCV infected cells.(Clemens, 1997) Other studies have suggested that PKR protein expression was not predictive of SVR.(Giannelli, 2004; MacQuillan, 2002) Although these results are conflicting, *PKR* appears to be implicated in HCV treatment response. Further, *PKR* could be examined at a genetic level because it may be involved in reducing transmission of HCV to uninfected cells. (Clemens, 1997; Pawlotsky, 1998)

Studies have also tested *PKR* polymorphism associations with HCV treatment response. Two different studies were unable to identify a statistically significant association between *PKR* polymorphisms -168 and -180 and HCV treatment response (SVR).(Clemens, 1997; Knapp, 2003) Although these studies did not identify a significant association with treatment response,

PKR is thought to function by shutting down protein synthesis following viral infection of a cell and limiting the transmission of the virus to uninfected cells.(Clemens, 1997; Pawlotsky, 1998) Further, *PKR* is a large gene that contains many polymorphisms and examining associations between additional genetic variants may be important to understanding if this gene is associated with HCV treatment response.

2.6.4 Interferon Regulatory Factor Family

Interferon regulatory factor 1 (*IRF1*) is an activator of interferon alpha and beta transcription and may be involved in immune response.(Rebhan, 2007) The activation of *IRF1* through a *PKR* dependent pathway was observed to impact virus replication directly or through stimulation of the adaptive immune response which may be blocked by the HCV core protein.(Pflugheber, 2002; T Taniguchi, 1997) One study examined the relationship between *IRF1 rs2549009* and initial virologic response in 147 Caucasian HCV patients and did not find a statistically significant association.(Wietzke-Braun, 2006) Although this study did not find a statistically significant association with one genetic variant, IRF1 spans about 7.7 kb and additional variants in this gene may be associated with HCV treatment response. *Interferon regulatory factor 7* (*IRF7)* may also play a role in transcriptional activation of virus-inducible cellular genes and response to viral infection, but its genetic association with HCV treatment response is unknown.(Rebhan, 2007)

2.6.5 Interferon Alpha Receptor Genes

Interferon alpha receptor subunit 1 (*IFNAR1)* and *interferon alpha receptor subunit* 2 (*IFNAR2)* genes were observed to initiate antiviral activity and higher levels of both proteins were observed in HCV treatment responders compared to HCV treatment non-responders.(Gao, 2004) Two polymorphisms in *IFNAR1* were examined in relation to SVR among 103 Brazilian HCV patients treated with conventional IFNα administered three times weekly or pegIFNα administered once weekly with ribavirin.(Tena-Tomas, 2007) This study did not identify a statistically significant association between genotypes of *IFNAR1 L168V* (rs2257167) or *G17470C* and SVR.(Tena-Tomas, 2007) In spite of these non-significant associations with SVR, these genes were observed to initiate antiviral response (Gao, 2004) and examining additional genetic variants may explain their relationship to HCV treatment response. Further, the association between 28 day viral decline and *IFNAR1* or *IFNAR2* is not known.

2.6.6 Signal Transducer and Activator of Transcription Genes

Expression of HCV core proteins is thought to inhibit the interferon induced signal transduction of the Jak-STAT pathway.(Blindenbacher, 2003; Heim, 1999) Over expression of Signal Transducer and Activator of Transcription 1 (STAT1) is able to control HCV viral production.(Lin, 2005) However, since the HCV core protein can block STAT1 protein production, STAT1 may not be able to enhance immune response.(Larrea, 2006; Lin, 2005) In response to interferons, the Signal Transducer and Activator of Transcription 2 (STAT2) protein is thought to act with the STAT1 protein and the IFN regulatory factor family to initiate the immune response to infectious agents.(Rebhan, 2007) An unpublished study in HCV genotype-1

infected patients observed a statistically significant association between *STAT2* rs2066811 and SVR.(Su, 2008) These studies indicate the importance of *STAT1* and *STAT2* in immune and HCV treatment response, but the association between these genes and 28 day viral decline is unknown.

2.6.7 Ubiquitin-Like Modifier Genes

ISG15 ubiquitin-like modifier (*ISG15/G1P2)* functions by encoding a protein that targets interferon stimulation.(Rebhan, 2007) *ISG15/G1P2* has displayed antiviral activity in response to viral infections.(Rebhan, 2007) *G1P3/IFI6* was one of the first interferon induced genes identified and expression was up-regulated in HCV infection and may stimulate interferon activity.(Bieche, 2005) Another ISG, interferon induced protein 35 (IFI35) was found to be up-regulated by the presence of IFNα in human liver cells.(Yan, 2004) These genes have functions related to immune response and may be important in understanding mechanisms of HCV treatment response.

2.6.8 Importance of Genetic Associations with HCV Treatment Response

The studies describing associations between ISGs and HCV treatment SVR indicate that ISGs are important to understanding the mechanisms of SVR, but do not tell us if ISG polymorphisms are important to 28 day viral decline or if ISG polymorphisms are similarly associated with SVR in African Americans and Caucasian Americans. Identifying genetic variant associations with 28 day viral decline in HCV treatment may contribute to understanding factors associated with SVR or biological reasons for treatment non-response. Also, identifying associations in African

Americans, an under-represented population in HCV treatment literature, could contribute to understanding racial differences in treatment response. Identifying genetic variant associations with 28 day viral decline may help to understand the early mechanisms of immune response and treatment effectiveness. These findings could be utilized in the development of new therapies that target those ISGs that stimulate immune response in the early course of treatment to ultimately improve long-term outcomes.

Previous research describing the relationship between ISGs and HCV treatment response has focused on the expression of the ISGs or examined genetic variant associations with SVR.(Clemens, 1997; Fernandez, 1999; Giannelli, 2004; Hijikata, 2001; Hijikata, 2000; Knapp, 2003; MacQuillan, 2002; Murashima, 2000; Naganuma, 2000; Su, 2008; Suzuki, 2004; Tena-Tomas, 2007) No studies were found that examined associations between the ISG polymorphisms described in this dissertation and viral decline in the first 28 days of treatment.

Examining 28 day viral decline is beneficial because it may be possible to draw long-term conclusions in the short time frame where outside influences such as side effects or dose reductions may not occur as often as in the full time course of treatment. Understanding host genetic factors that influence viral decline in the first 28 days of therapy may identify the underlying biological mechanisms responsible for differences in treatment response.

Examining racial differences in the first 28 days of HCV treatment may be useful in achieving better long-term outcomes in African Americans who do not typically respond. Identifying ISG polymorphisms that are associated with greater viral decline in different race groups may be useful in understanding if different factors influence treatment response in the race groups. If different host genetic variants are associated with treatment response in different race groups, then future treatments could even be customized based on host genetics.

Finally, this improved understanding of biological mechanisms may be an important factor not only in improving the HCV treatment outcomes, but also in reducing co-morbidities related to HCV infection. For example, HCV viral clearance has been associated with restoring insulin function and ultimately reducing the occurrence of type 2 diabetes.(Kawaguchi, 2007; Konrad, 2000; Tanaka, 1997)

2.7 CHRONIC HEPATITIS C DISEASE PROGRESSION

Some individuals have rapidly progressing disease which may lead to severe morbidity and mortality due to liver damage while other individuals infected with HCV do not have rapid disease progression and may not experience symptoms. It is not fully understood why some individuals with chronic HCV experience non-progressive disease versus progressive disease. Inflammation and fibrosis are common conditions used to assess disease progression. HCV infection can lead to fibrosis, cirrhosis, steatosis or liver cancer. Liver inflammation is characterized the presence of inflammatory cells in the liver resulting from damage to hepatocytes.(Markiewski, 2006; Nathan, 2002) Inflammation can result in changes in liver structure, slowed blood circulation, death of liver cells or scar tissue formation.(Nathan, 2002) Fibrosis is tissue scarring caused by the healing process from liver injury. Cirrhosis occurs when normal, healthy tissue is replaced with scar tissue, blocking the flow of blood through the liver and preventing proper function. Steatosis is the accumulation of fat in liver cells.

2.7.1 Factors Associated with HCV Disease Progression

The relationship between viral factors and disease progression is still being examined. Most of the literature does not support an association between viral level or genotype and disease progression (Fanning, 1999; Lau, 1993; Poynard, 2001) although one study has suggested that progression was faster in genotype-1b infection compared to genotype-2.(Kobayashi, 1996) Host related factors associated with disease progression include age, race, obesity, sex and alcohol consumption.(Alter, 1999; Benhamou, 1999; Deuffic, 1999; Hickman, 2002; Lesens, 1999; Poynard, 2001; Ragni, 2001; Reddy, 1999; Wiley, 2002) Younger age at infection and female gender were associated with slower disease progression compared to older age at infection and male gender, respectively.(Deuffic, 1999; Poynard, 2001) African Americans have slower progression to cirrhosis compared to Caucasian Americans even though African Americans also have higher rates of chronic HCV infection and lower rates of treatment response.(Reddy, 1999; Wiley, 2002) Further, alcohol consumption was observed to increase the rate of HCV disease progression in several studies.(Corrao, 1998; Frieden, 1999; Noda, 1996; Ostapowicz, 1998; Pessione, 1998; Peters, 2002; Wiley, 1998) Studying host genetic factors associated with HCV related conditions could contribute to better understanding of the differences in progression and may lead to methods of prevention.

2.8 MEASURING DISEASE PROGRESSION

2.8.1 Liver Enzyme Measures

Liver enzyme measures can be used to measure HCV disease progression and the extent of damage to the liver. Liver enzyme tests including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may initially identify a problem because elevated levels could indicate liver damage.

2.8.2 Liver Biopsy and Scoring Systems for Histological Activity

Liver damage or disease progression can be measured by examining liver biopsies. Biopsies are read by a pathologist to determine the extent of liver inflammation, fat cells in the liver and fibrosis. Inflammation and fibrosis can be measured using scoring techniques that were developed to clinically classify the grade and stage of the hepatic process from liver histology.

2.8.2.1 Liver Biopsy Scoring Systems

The first scoring system for liver damage examined in liver biopsies was the Histological Activity Index (HAI).(Knodell, 1981) The HAI grades the amount of inflammation in the liver with scores ranging from 0-18 and fibrosis scores from 0-4.(Desmet, 1994; Di Bisceglie, 1995; Knodell, 1981) The original Knodell HAI scoring system was criticized because it was based on a small number of samples and did not validate the reproducibility of the scoring system.(Desmet, 2003; Hubscher, 1998) The Knodell's HAI scoring system has some additional limitations including the use of a non-continuous scale, combined inflammatory activity and

fibrosis scores, and piecemeal necrosis included with bridging necrosis.(Desmet, 2003; Hubscher, 1998)

The Scheuer System was developed to address some of the concerns with the original HAI score. It scores necroinflammatory activity in chronic hepatitis by classifying grade, lobular activity and stage of chronic HCV.(Scheuer, 1991) The Scheuer System has advantages over the HAI system because it uses a continuous scale of measurement, inflammatory activity is considered separately from fibrosis and bridging necrosis is measured with lobular activity instead of piecemeal necrosis.(Scheuer, 2002) A disadvantage to this system is the narrow range of scores with limited applicability to clinical practice.(Hubscher, 1998)

The Modified HAI Scoring System was developed to further address concerns with the HAI score.(Ishak, 1995) The maximum inflammation score is 18 and fibrosis is measured with a 6 point scale.(Ishak, 1995) The modified HAI scoring system has good inter- and intra-observer reliability and necroinflammatory changes are assessed separately from assessment of fibrosis stage.(Hubscher, 1998; Rozario, 2003)

Another system to quantify histologic activity is the Metavir Scoring System. This system examines necrosis and lobular necrosis to score histological activity and scores fibrosis in 5 levels.(Bedossa, 1994; Bedossa, 1996) The Metavir Scoring System has good inter- and intra-observer reliability.(Bedossa, 1994)

2.9 STEATOSIS AND HEPATITIS C VIRUS INFECTION

Nonalcoholic fatty liver disease (NAFLD) may range from steatosis, or the occurrence of fat cells in the liver, to nonalcoholic steatohepatitis (NASH), a liver disease characterized by both

inflammation and the accumulation of fat in the liver.(Ruhl, 2004; Teli, 1995) Steatosis is prevalent in as few as 30% to as many as 84% of chronic HCV patients.(Adinolfi, 2001; Asselah, 2006; Castera, 2003; Conjeevaram, 2006; Conjeevaram, 2007; Czaja, 1998; Hourigan, 1999; Hui, 2002; Monto, 2002; Patton, 2004; Poynard, 2003; Rubbia-Brandt, 2004; Rubbia-Brandt, 2001; Serfaty, 2001; Westin, 2002)

2.9.1 Diagnosis of Steatosis

Steatosis is most commonly diagnosed by reading a liver biopsy and calculating the percentage of fat in the liver cells.(Brunt, 1999) Liver biopsy is the gold standard for diagnosing and quantifying steatosis, but is an invasive procedure associated with health complications, sampling error and inter-observer variability.(Regev, 2002) Other methods to measure steatosis among HCV patients have been developed that are less invasive such as transabdominal ultrasound or Doppler technology which examines the right hepatic vein.(Celle, 1988; Dietrich, 2002; Dietrich, 1998; Oguzkurt, 2005) Focal hypoechoic areas (FHA) within the liver hilum and hepatic vein flow (HVF) pattern were correlated with liver biopsy findings for steatosis.(Hirche, 2007)

2.9.2 Epidemiology of Steatosis among HCV Patients

Steatosis is thought to occur more frequently in patients with chronic HCV compared to the general population.(Asselah, 2006; Browning, 2004) Studies have suggested that African Americans have a lower prevalence of steatosis compared to Caucasian Americans with chronic

HCV infection.(Browning, 2004; Conjeevaram, 2007) Understanding host genetic associations with steatosis may help to explain the observed racial differences.

Steatosis among people with HCV genotype-1 infection has been associated with host factors such as BMI, alcohol consumption, age, gender, race, hepatic inflammation, hyperlipidaemia, triglyceride levels, cholesterol, ALT levels, AST levels, fibrosis scores and insulin resistance (Adinolfi, 2001; Asselah, 2006; Castera, 2003; Conjeevaram, 2007; Czaja, 1998; Fabris, 2004; Hourigan, 1999; Leandro, 2006; Monto, 2002; Poynard, 2003; Rubbia-Brandt, 2001; Rubbia-Brandt, 2000; Ruhl, 2004; Serfaty, 2001; Serfaty, 2002; Solis-Herruzo, 2005; Younossi, 2004) Moderate alcohol consumption was observed to increase the amount of steatosis.(Hezode, 2003) Evidence from a few studies suggests that higher body mass index (BMI) is associated with steatosis in HCV genotype-1 infection.(Asselah, 2006; Hwang, 2001; Matos, 2006; Ruhl, 2004; Solis-Herruzo, 2005; Younossi, 2004) In general African Americans have a lower prevalence of steatosis, but have higher BMI, compared to Caucasian Americans.(Browning, 2004) Men are more likely to develop steatosis compared to women and the sex difference may be associated with greater alcohol intake in men or hormonal differences.(Browning, 2004) Higher age was also associated with development and progression of steatosis.(Fabris, 2004) Host genetic associations may contribute to a greater understanding of the differences in the occurrence of steatosis.

Steatosis can also affect HCV treatment outcomes and can have an impact on disease progression and fibrosis.(Adinolfi, 2001; Castera, 2003; Hourigan, 1999; Serfaty, 2002; Westin, 2002) HCV genotype-1 patients with steatosis achieved SVR less frequently (29-46%) compared to those without steatosis (62-65%).(Jian Wu, 2006; Soresi, 2006; Westin, 2007) Steatosis and the steatosis grade were found to be predictive of the severity and progression of

fibrosis which could lead to cirrhosis.(Adinolfi, 2001; Castera, 2003; Fartoux, 2005; Hourigan, 1999; Leandro, 2006; Serfaty, 2002; Westin, 2002)

2.10 INSULIN RESISTANCE AND HEPATITIS C VIRUS INFECTION

Insulin Resistance (IR) is a condition in which typical amounts of insulin are insufficient to use blood glucose for energy and metabolism, particularly in fat, muscle and liver cells.(Rao, 2001; Romero-Gomez, 2006) Insulin resistance may be a common pathogenic event linking obesity, type 2 diabetes mellitus, hypertension, and lower high density lipoprotein levels with fatty liver disease.(Meigs, 2000) Studies have suggested that IR is common and can occur early in the course of HCV infection.(Fartoux, 2005; Puri, 2006) Patients with chronic HCV infection were observed to have higher HOMA-IR index scores, a measure of IR, compared to healthy controls.(Hui, 2003) Studies have also suggested that HCV RNA clearance with antiviral therapy may result in the restoration of insulin sensitivity and insulin action.(Konrad, 2000; Tanaka, 1997)

2.10.1 Diagnosis of Insulin Resistance

Insulin resistance can be quantified and measured using fasting insulin and glucose levels.(Pacini, 2003) Several validated methods exist to measure and quantify IR including the Homeostasis Model Assessment Insulin Resistance Index (HOMA-IR) which is calculated as HOMA-IR = [fasting glucose (millimoles per liter) x fasting insulin (milliunits per liter)]/22.5.(Matthews, 1985) However, the HOMA-IR underestimates insulin sensitivity and

overestimates β-cell function (insulin secretion).(Wallace, 2004) More recently, a model to obtain more accurate measures of insulin resistance, the Homeostasis Model Assessment Insulin Resistance Index Version 2.2 (HOMA2-IR) was released and the computer based model was made available in 2004.(Levy, 1998; Wallace, 2004) The HOMA-IR and HOMA2-IR scores have been validated against the hyperinsulinemic euglycemic clamp, the gold standard.(Wallace, 2004) HOMA-IR has been used in studies with various values used to indicate insulin resistance (e.g. 1.5 or 2.0).(Bonora, 1998; Conjeevaram, 2007; Hedblad, 2000; Matsumoto, 1997; Nakai, 2002; A Taniguchi, 2000)

2.10.2 Epidemiology of Insulin Resistance in Hepatitis C Virus Infection

Risk factors associated with IR among HCV patients include African American race, obesity, cirrhosis, age, fibrosis, and gender.(Heathcote, 2002; Petit, 2001; Romero-Gomez, 2005) African Americans had higher odds of IR than Caucasian Americans in one study.(Shaheen, 2007) Obese individuals had higher HOMA-IR scores compared to non-obese controls.(Puri, 2006) Viral genotype appeared to influence the occurrence of IR such that genotype-3 infected patients had lower HOMA-IR scores compared to people with other genotypes after adjusting for BMI and other confounders.(Hui, 2002) Studying host genetics may also contribute to explaining differences in the occurrence of IR.

Other factors related to higher HOMA-IR scores in HCV patients include fibrosis, steatosis, portal inflammation and diabetes.(D'souza, 2005; Fartoux, 2005; Hui, 2003; Knobler, 2000; Lonardo, 2004; Mason, 1999; Petit, 2001; Puri, 2006; Shintani, 2004; Sud, 2004) The prevalence of type 2 diabetes was higher in HCV infected patients (14.5%) compared to the general population (7.8%).(Zein, 2005) Given the high prevalence and the worldwide

distribution of HCV infection, the association between HCV infection and the occurrence of type 2 diabetes may have an important impact on public health and understanding the mechanisms may be important to reducing additional complications from type 2 diabetes in chronic HCV patients.(Knobler, 2000)

The presence of IR before therapy was found to negatively impact the ability to achieve an SVR in HCV genotype-1 infection.(Romero-Gomez, 2006; Romero-Gomez, 2005) Maintaining viral clearance for six months after treatment was associated with improved HOMA-IR scores and insulin function.(Kawaguchi, 2007; Konrad, 2000; Tanaka, 1997) Improvement in HOMA-IR scores among HCV genotype-1 and genotype-2 patients was only observed among individuals achieving SVR.(Kawaguchi, 2007) Understanding factors associated with IR in HCV infection may reduce the occurrence of related conditions such as type 2 diabetes and improving SVR.(Romero-Gomez, 2005)

2.11 GENETIC ASSOCIATIONS WITH STEATOSIS AND INSULIN RESISTANCE

Understanding the biological mechanisms of steatosis and IR in HCV infection may be useful in developing prevention and treatment methods that reduce the occurrence of these conditions, decrease the likelihood of other HCV co-morbidities (such as cirrhosis or type 2 diabetes) and ultimately improve treatment outcomes. Expression or polymorphism associations for genes with functions related to fat metabolism, lipid metabolism, diabetes and obesity have been studied with steatosis and insulin resistance. (Cardellini, 2005; Kubaszek, 2003; Kubaszek, 2003; Qi, 2006; Sartipy, 2003; Scarpelli, 2006; Simeoni, 2004; Testa, 2006; Y Yang, 2003) For the genes examined in this dissertation, only one published study was found that examined genetic

associations with steatosis or IR in HCV infection.(Sanchez-Munoz, 2004) Only one study was found to examine genetic variants with steatosis and IR among African American children.(Crimmins, 2007)

2.11.1 Adiponectin Receptor

The adipocyte, an endocrine cell that releases free-fatty acids and secreting factors called adipokines such as TNF-α, interleukins, leptin, resistin and adiponectin, is considered to be important in the occurrence of steatosis and insulin resistance in obese patients.(Whitehead, 2006) Plasma adiponectin levels were decreased in one study of obese participants (Arita, 1999) and subsequent studies found that low adiponectin levels were associated with IR and steatosis.(Chandran, 2003; Jonsson, 2005; Stefan, 2002)

Adiponectin Receptor 1 (*ADIPOR1*) is a gene that encodes adiponectin which is mainly expressed in skeletal muscle.(Rebhan, 2007) Statistically significant associations were identified in studies between *ADIPOR1* polymorphisms and IR or steatosis.(Collins, 2007; Crimmins, 2007; Siitonen, 2006; Stefan, 2005) Among European decent participants, the *rs6666089*-A allele and the -C allele of the *-1927* polymorphism were associated with insulin resistance and high liver fat.(Stefan, 2005) A study of British participants confirmed the association between *ADIPOR1 rs6666089*-A allele and IR.(Collins, 2007) In a study of healthy African American children aged 10-19, the *rs1342387*-A allele was associated with decreased HOMA-IR scores in a non-obese subset, but no association was observed for *rs6666089*.(Crimmins, 2007) A study examining *ADIPOR1* polymorphisms among a population of Old Order Amish confirmed the association between the *rs1342387*-A allele and lower HOMA-IR scores.(Damcott, 2005) These

studies indicate that *ADIPOR1* is associated with steatosis and IR, but these associations have not been studied in HCV infection.

2.11.2 Tumor Necrosis Factor System

Chronic HCV is thought to activate and up-regulate the tumor necrosis factor (TNF) system.(Itoh, 1999; Nelson, 1997) TNF-α is a pro-inflammatory cytokine secreted by endothelial, smooth muscle cells, macrophages and adipose cells that play a critical role in viral induced liver damage and may participate in the pathobiology of IR.(Hotamisligil, 1999; Puri, 2006) TNF-α was observed to block the action of insulin by inhibiting the insulin receptor tyrosine kinase activity.(Feinstein, 1993) Increased TNF-α levels in the liver were observed in people infected with HCV.(Gershon, 2000; Kallinowski, 1998; Nelson, 1997; Petit, 2001; Valenti, 2005) Other studies also found that increased TNF-α levels were associated with the occurrence of IR (Halse, 2001; Maeno, 2003; Mishima, 2001; Moller, 2000; Valenti, 2005) or the degree of steatosis.(Gochee, 2003; Sougleri, 2001; Valenti, 2005) These studies indicate that TNF-α expression is associated with the occurrence of steatosis and IR.

One study examined *TNF-α* polymorphism associations with steatosis in HCV infection. This study found no statistically significant association between *TNF-α* -238 or -308 in 133 chronic HCV patients with no history of treatment.(Sanchez-Munoz, 2004) Despite these negative results, *TNF-α* is involved in inflammatory response and TNF-α protein expression may be related to steatosis or IR. Examining genetic associations may identify functional *TNF-α* polymorphisms that could contribute to understanding the occurrence of steatosis and IR in HCV infection.

2.11.3 Interleukin Genes

Interleukin 6 (IL6) is a proinflammatory cytokine secreted by immune cells, adipose tissue and muscles that accelerates the inflammatory process.(Fried, 1998; Mohamed-Ali, 1997) Studies have suggested that increased IL6 levels were associated with insulin resistance and type 2 diabetes.(Cardellini, 2005; Danielsson, 2005; Deepa, 2006; Hamid, 2005; Hermann, 2005; Illig, 2004; Kubaszek, 2003; Mohlig, 2004; Qi, 2006; Testa, 2006; Tsiavou, 2004; Vozarova, 2003; X Yang, 2005) These results indicate that the IL6 protein may be important in the development of IR.

IL6 genetic studies have examined the association between the promoter polymorphism (-174 G>C) and IR or type 2 diabetes.(Cardellini, 2005; Fernandez-Real, 2000; Hamid, 2005; Kubaszek, 2003; Qi, 2006; Testa, 2006; X Yang, 2005) Five of these studies identified a statistically significant association between the *IL6* -174 GG genotype and IR in European, healthy or diabetic patients.(Cardellini, 2005; Fernandez-Real, 2000; Hamid, 2005; Testa, 2006; X Yang, 2005) Other studies were unable to identify a statistically significant association between the *IL6* -174 variant and type 2 diabetes.(Kubaszek, 2003; Qi, 2006) Although some of these results are negative, IL6 is thought to accelerate inflammatory response which may be important in the occurrence of both steatosis and IR. This gene spans approximately 5 kb and studying additional variants may contribute to understanding these conditions in HCV infection.

Interleukin 10 (IL10) is an anti-inflammatory cytokine produced by T cells, B cells, monocytes and macrophages and contributes to immune response.(Fiorentino, 1991; O'garra, 1990) Low IL10 levels were associated with the metabolic syndrome, which is also related to IR and steatosis.(Esposito, 2003) In two studies, a positive correlation between IL10 levels and higher insulin sensitivity was observed.(Bluher, 2005; Straczkowski, 2005) *IL10* promoter

polymorphisms (-1082G/A, -819C/T and -592C/A) were also examined with IR in Caucasian Italian diabetic and non-diabetic patients.(Scarpelli, 2006) The A allele of the -592C/A *IL10* polymorphism was associated with higher HOMA-IR scores compared to the C allele in non-diabetic patients.(Scarpelli, 2006) These results indicate that this *IL10* polymorphism is associated with IR in non-diabetic patients. Examining associations between steatosis or IR and the -592 polymorphism and other IL10 polymorphisms among individuals with chronic HCV may contribute to the understanding of these conditions in HCV infection.

2.11.4 Monocyte Chemoattractant Protein Genes

Monocyte chemoattractant protein-1 (*MCP1/CCL2*) is a member of the chemokine family produced by macrophages and endothelial cells and contributes to inflammatory action.(Rebhan, 2007; Rollins, 1996) Subjects with steatosis or IR had increased MCP1/CCL2 levels compared to healthy controls.(Deepa, 2006; Haukeland, 2006) In German subjects, there was a statistically significant association between G allele carriers of *MCP1/CCL2* -2518A>G and decreased prevalence of IR and type 2 diabetes.(Simeoni, 2004) *MCP1/CCL2* -2518 G allele carriers also had lower plasma MCP1/CCL2 levels.(Simeoni, 2004) These studies indicate that this gene may be important to understanding the biological mechanisms of IR. *Monocyte chemoattractant protein-2* (*MCP1/CCL8*) may play a role in host inflammatory response, but its relationship to steatosis and IR is unknown.(Rebhan, 2007)

2.11.5 3-hydroxy-3-methylglutaryl-CoA Synthase 2

3-hydroxy-3-methylglutaryl-CoA Synthase 2 (*HMGCS2*) encodes an enzyme that condenses acetyl-CoA in the HMG-CoA pathway of fatty acid metabolism or ketogenesis.(Rebhan, 2007) The up-regulation of *HMGCS2* is thought to be involved in the pathogenesis of steatosis.(Sanyal, 2001) People with steatosis and with insulin resistance were observed to have higher HMGCS2 expression compared to people with steatosis and without IR.(Chitturi, 2004; Sanyal, 2001; Younossi, 2005; Younossi, 2004) These results indicate that HMGCS2 expression may be important in understanding steatosis and IR, but genetic associations between these conditions and *HMGCS2* has not been examined.

2.11.6 Transforming Growth Factor Beta

Another gene thought to influence steatosis and insulin resistance is *Transforming growth factor-β-1* (*TGF-β1*).(Kharbanda, 2004; Park, 2005) TGF-β1 is a cytokine over-expressed with liver injury.(Kharbanda, 2004) One study of *TGF-β1* polymorphisms in Swedish non-diabetic patients found that those with the Leu10 polymorphism heterozygote genotype had significantly higher HOMA-IR scores compared to homozygote carriers.(Rosmond, 2003) Although this study was completed in a healthy population, a statistically significant association was observed between a *TGF-β1* polymorphism and IR and this could be studied in other populations that experience IR. Infection with HCV could contribute to the occurrence of IR and examining genetic associations with IR in this gene may explain the mechanism of occurrence of IR in HCV infection.

2.11.7 Leptin Receptor

The *leptin receptor (LEPR)* is a member of the cytokine receptor family and is involved in fat metabolism. Leptin, a protein secreted by *LEPR* and produced by inflammatory regulatory cells, may participate in the inflammatory process.(Sanna, 2003) Under normal circumstances, leptin reduces fat accumulation in the liver, but with the presence of IR, leptin does not reduce liver fat and steatosis develops.(Medina, 2004) High leptin levels inhibited actions of insulin and increased insulin resistance in one study.(Marchesini, 2005) One study examined *LEPR* genetic variant associations with IR in healthy Caucasian subjects and found a statistically significant association between the R allele of -223Q>R and the occurrence of insulin resistance.(Chiu, 2004) Although these studies were completed in healthy or diabetic patients, significant associations between *LEPR* and steatosis or IR were observed. *LEPR* may be involved in inflammatory response which also may be important to the occurrence of these conditions in HCV infection. Thus, examining genetic associations between *LEPR* polymorphisms and steatosis or IR may be important to understanding these conditions in HCV infection.

2.11.8 Cytochrome P-450 2E1

Cytochrome P-450 2E1 (*CYP2E1*) is a source of oxidative stress and possibly involved in the pathogenesis of steatosis.(Weltman, 1998) CYP2E1 is up-regulated in patients with steatohepatitis specifically in obese and diabetic patients.(Chalasani, 2003; Dong, 1988; Favreau, 1987; Weltman, 1998) A strong correlation between HOMA-IR levels and hepatic CYP2E1 activity was found in one study.(Chalasani, 2003) *CYP2E1* polymorphism associations with steatosis or IR have not been published.

2.11.9 Importance of Genetic Associations with Steatosis and Insulin Resistance

Most of the previous research on host genetic relationships with steatosis and insulin resistance focused on gene expression or function.(Bluher, 2005; Chandran, 2003; Gochee, 2003; Halse, 2001; Itoh, 1999; Maeno, 2003; Moller, 2000; Nelson, 1997; Younossi, 2005) Some candidate gene associations with steatosis or insulin resistance were observed in obese or diabetic patients.(Cardellini, 2005; Collins, 2007; Crimmins, 2007; Qi, 2006; Scarpelli, 2006; Simeoni, 2004; Stefan, 2005; Testa, 2006; X Yang, 2005) None of these studies examined host genetic associations between the genetic variants in this dissertation and these conditions in HCV infection. HCV may influence the activity of these genes and may be associated with the development of insulin resistance and steatosis. African American adults were not examined in studies of host genetic variants with steatosis or IR that were selected for this dissertation.(Cardellini, 2005; Collins, 2007; Crimmins, 2007; Qi, 2006; Scarpelli, 2006; Simeoni, 2004; Stefan, 2005; Testa, 2006; X Yang, 2005) Examination of steatosis and IR in African Americans may help to understand racial differences in the occurrence of these conditions in HCV infection. Moreover, understanding the mechanisms of steatosis and IR by examining host genetic factors among HCV infected patients may reduce the occurrence of other co-morbidities that may develop such as type 2 diabetes or cirrhosis.

2.12 SPECIFIC AIMS

This dissertation examined host genetic relationships between interferon stimulated genetic variants and 28 day viral decline among a sample of African American and Caucasian American

HCV genotype-1 infected patients. Further, this dissertation examined associations between host genetic variants and steatosis and insulin resistance among African American and Caucasian American HCV genotype 1 patients.

The aims of *Research Article 1* were to identify associations between interferon stimulated gene (ISG) polymorphisms and 28 day viral decline from treatment.

The aims of *Research Article 2* were to test for an association between selected genes and both steatosis and insulin resistance in a sample of African Americans and Caucasian Americans infected with HCV genotype-1.

The aims of *Research Article 3* were to test the association between *adiponectin receptor 1* (*ADIPOR1)* and *3-hydroxy-3-methylglutaryl-CoA Synthase 2 (HMGCS2)* polymorphisms and the occurrences of steatosis and insulin resistance in African Americans and Caucasian Americans infected with HCV genotype-1. Grant funding from the Epidemiology Department in the Graduate School of Public Health, Epidemiology Small Grants Program was used to partially pay for tag selection and genotyping polymorphisms in the *ADIPOR1* and *HMGCS2* genes reported in Research Article 3.

2.13 THE STUDY OF VIRAL RESISTANCE TO ANTIVIRAL THERAPY OF CHRONIC HEPATITIS C (VIRAHEP-C)

Data were obtained from the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C). "The Virahep-C Study was designed to assess the rates of response to peginterferon combination therapy for chronic HCV genotype-1 among African Americans and Caucasian Americans and to evaluate clinical, immunologic, virologic and host genetic reasons

for treatment non-response."(Conjeevaram, 2006) The Virahep-C Study recruited HCV genotype-1 patients 18-70 years of age who were not previously treated.(Conjeevaram, 2006) Patients were recruited from 8 US clinical centers between 2002 and 2003.(Conjeevaram, 2006) Study inclusion criteria included the presence of HCV RNA, compensated liver disease, histologic evidence of chronic HCV infection on a liver biopsy and self designation of African American or Caucasian American race.(Conjeevaram, 2006) Study patients provided written informed consent before participation.

There were 401 patients (205 CA and 196 AA) enrolled in the study.(Conjeevaram, 2006) Patients were treated for up to 48 weeks with peginterferon α-2a with a dosage of 180μg weekly and ribavirin with a dosage of 1000 or 1200 mg per day based on body weight.(Conjeevaram, 2006) Virologic response to treatment was assessed using the Roche HCV Amplicor version 2 assay (Roche Diagnostic Systems, Somerville, N.J.) at week 24 of treatment and those with positive HCV RNA were considered non-responders and HCV therapy was stopped.(Conjeevaram, 2006) Responders continued treatment for another 24 weeks and SVR was assessed at 24 weeks after treatment completion.(Conjeevaram, 2006)

Results from the Virahep-C study provided information about SVR and factors associated with achieving SVR. SVR was achieved in 28% of African Americans compared to 52% of Caucasian Americans.(Conjeevaram, 2006) Factors associated with achieving an SVR include Caucasian American race, female sex, lower baseline HCV RNA levels, lower Ishak fibrosis scores, and greater amounts of maximum peginterferon taken.(Conjeevaram, 2006)

Viral decline in the first 28 days of treatment was also examined in the Virahep-C study and two phases of HCV RNA decline were observed.(Hoofnagle, 2008) The first phase occurred from treatment initiation to day 7 and the second phase began at day 7 and lasted through day 28.

The median decline in HCV RNA during the first 28 days was 1.81 $\log_{10}$ IU/mL.(Hoofnagle, 2008) The median decline was higher in Caucasian Americans (2.07 $\log_{10}$ IU/mL) compared to African Americans (1.72 $\log_{10}$ IU/mL).(Hoofnagle, 2008) Factors associated with a greater 28 day viral decline included age, body weight, HOMA-IR score, HCV RNA levels and pre-treatment fibrosis score.(Hoofnagle, 2008) Viral decline was examined in association with SVR. Patients with less than a 1 $\log_{10}$ IU/mL decline in HCV RNA at 28 days had only a 5% chance of achieving an SVR.(Hoofnagle, 2008) Ninety-three percent of patients with more than a 4 $\log_{10}$ IU/mL drop in HCV RNA levels in the first 28 days became HCV RNA negative by the end of treatment and 85% achieved SVR.(Hoofnagle, 2008) Virahep-C results indicate that viral decline in the first 28 days was predictive of SVR therefore understanding what factors are associated with very early viral decline may be important in predicting and achieving SVR.

3.0 RESEARCH ARTICLE 1:

INTERFERON STIMULATED GENETIC POLYMORPHISMS AND THE EARLY VIRAL DECLINE DURING TREATMENT OF CHRONIC HEPATITIS C

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3.1 ABSTRACT

Early and rapid viral decline during the first 28 days of treatment for chronic hepatitis C virus (HCV) with pegylated interferon and ribavirin therapy may be an important predictor of achieving a sustained virologic response (SVR). Interferon stimulated genes (ISGs) play an important role in the antiviral response to HCV. This study examines whether genetic variants in ISGs are associated with the 28 day viral decline.

The association between genotypes of ISG polymorphisms and the dynamics of viral decline among 180 African American (AA) and 194 Caucasian American (CA) patients with genotype-1 HCV infection treated with pegylated interferon alpha-2a and ribavirin during the first 28 days of treatment was tested using linear mixed models. Viral levels were obtained prior to treatment and at days 1, 2, 7, 14 and 28. Analyses were conducted separately for CAs and AAs.

Sixteen ISGs were examined in this study and statistically significant ($p<0.05$) associations with viral decline were observed for polymorphisms in *MX2*, *OASL, STAT1* and *STAT2*. Similar viral decline patterns by the same ISG polymorphism genotype were observed in both race groups for *IFNAR1, IRF1, MX1, OAS3* and *PKR*, but were not statistically significant.

Genetic variants in some ISGs were associated with 28 day viral decline, but many of the associations differed by race. These results indicate that some ISG polymorphisms may be important in understanding 28 day viral decline and improving long-term treatment outcomes.

Further studies should be conducted to confirm these results and examine additional polymorphisms in these genes to determine the importance of the gene on 28 day viral decline.

3.2 INTRODUCTION

Infection with the hepatitis C virus (HCV) may lead to adverse outcomes such as cirrhosis of the liver or hepatocellular carcinoma.(Seeff, 2002) Treating patients who have chronic HCV infection with pegylated interferon alpha-2a (pegIFNα) plus ribavirin results in sustained virologic response (SVR), defined as the absence of detectable HCV RNA in the serum at 24 weeks after the end of treatment,(Lindsay, 2002) in only 54-56% of those treated overall.(Conjeevaram, 2006; Fried, 2002; Manns, 2001; Marcellin, 1997; McHutchison, 1999; Poynard, 1996) Among patients infected with genotype-1 virus, lower rates of response (42-46%) have been reported compared to patients with non genotype-1 virus (76-82%).(Fried, 2002; Lindsay, 2002; Manns, 2001; Martinot-Peignoux, 1995; McHutchison, 1998; Poynard, 1998; Zeuzem, 2000) Racial differences have also been observed with African American patients experiencing lower SVR when treated with combination therapy compared to Caucasian American patients infected with the same viral genotype.(Conjeevaram, 2006; Fried, 2002; Kinzie, 2001; Layden-Almer, 2003; Manns, 2001; J. G. McHutchison, 2000; Reddy, 1999; Zeuzem, 2004; Zeuzem, 2000) In particular, African American genotype-1 patients had lower SVR (19%-32%) compared to Caucasian American genotype-1 patients (50-52%).(Conjeevaram, 2006; Jeffers, 2004; Muir, 2004)

Viral dynamics are the time course of treatment induced changes in serum HCV RNA levels. Mathematical modeling of early viral decline during the first 28 days of treatment

suggest that viral levels decline in a bi- or tri-phasic pattern(Bergmann, 2001; Herrmann, 2003; Neumann, 2000; Neumann, 1998) and that the dynamics of the decline may predict SVR.(Conjeevaram, 2006; Neumann, 2000; Neumann, 1998)

Interferon stimulated genes (ISGs) play an important role in the innate immune response against HCV.(Itsui, 2006; Macquillan, 2003) Given the importance of ISGs in immune response, studies have examined the potential role of host genetic diversity in the response to interferon, although most studies have focused on SVR as the primary outcome.(Hijikata, 2001; Hijikata, 2000; Knapp, 2003; H Saito, 2002; T Saito, 2004; Suzuki, 2004; Tena-Tomas, 2007; Thursz, 1997; Wietzke-Braun, 2006) This study utilizes frequent viral level measurements obtained in the initial 28 days of therapy for HCV in a single treatment cohort and examines the association of single nucleotide polymorphisms (SNPs) in selected ISGs including *ISG15 ubiquitin-like modifier (G1P2), Interferon alpha-inducible protein 6 (G1P3), Interferon-induced protein 35 (IFI35), Interferon-alpha receptor 1 (IFNAR1), Interferon-alpha receptor 2 (IFNAR2), Interferon-regulatory factor 1 (IRF1), Interferon-regulatory factor 7 (IRF7), Myxovirus resistance 1 (MX1), Myxovirus resistance 2 (MX2), Oligoadenylate synthetase 1* (*OAS1), Oligoadenylate synthetase 2 (OAS2), Oligoadenylate synthetase 3 (OAS3), Oligoadenylate synthetase-like (OASL), Protein Kinase (PKR), Signal transducer and activator of transcription 1 (STAT1),* and *Signal transducer and activator of transcription 2 (STAT2*) with the dynamics of the 28 day early viral decline.

3.3 MATERIALS AND METHODS

3.3.1 Study Population

Data were from the Study of Viral Resistance of Antiviral Therapy of Chronic Hepatitis C (Virahep-C) which was designed to assess treatment response to combination therapy among African- and Caucasian-Americans.(Conjeevaram, 2006) Further, Virahep-C aimed to examine host genetic reasons for treatment non-response in previously untreated HCV genotype-1 patients.(Conjeevaram, 2006) Briefly, 401 HCV patients consented and were treated with pegylated interferon α-2a and ribavirin.(Conjeevaram, 2006) Of those, 374 (194 CA and 180 AA) provided additional consent for the genetics studies.(Yee, 2007)

3.3.2 Single Nucleotide Polymorphism (SNP) Selection and Genotyping

Interferon stimulated genes were genotyped as part of the genetics component of the Virahep-C study. Two different approaches were utilized for selecting SNPs and genotyping for the polymorphisms targeted in this study. These approaches were based on publically available genetic information and genotyping technology at the time that each component was completed.

The first method for selection was used to identify SNPs for the candidate genes *MX1, IRF1* and *PKR* and details of this process have been described elsewhere.(Yee, 2007) Briefly, SNPs were selected by examining the haplotype blocks for each race and selecting polymorphisms from the International HapMap Project (Phase I) and National Center for Biotechnology Information (NCBI) databases.(Yee, 2007) SNPs with a minor allele frequency of at least 10% in a reference population were selected to cover the entire gene at 2-3 kb intervals

for small genes and 5-9 kb intervals for larger genes.(Yee, 2007) An allelic discrimination assay was used to genotype haplotype-tagging genetic variants in *MX1, IRF1* and *PKR* and was performed using the ABI 7000 Sequence Detection System with TaqMan technology (Applied Biosystems Inc., Foster City, CA).(Yee, 2007)

SNPs for *G1P2, G1P3, IFI35, IFNAR1, IFNAR2, IRF7, MX2, OAS1, OAS2, OAS3, OASL, STAT1, and STAT2* were selected using a two stage approach. For each of these genes, SNPs with a minor allele frequency of at least 5% in a reference population were selected from the International HapMap Project (Phase I) approximately every 3-5 kb to cover the entire gene.(Su, 2008) The Illumina BeadArray System (Illumina, San Diego, CA) was used for genotyping the selected SNPs in stage 1.(Su, 2008) The SNPs selected in the first stage were tested for an association with SVR. If a significant association was observed, additional SNPs were selected for that gene during the second stage of SNP selection.(Su, 2008) The second stage included a comprehensive database scan for possible functional SNPs in potential transcription factor binding sites, intron regions, exon regions, intron-exon borders or potential splice sites.(Su, 2008) Additional SNPs selected in stage 2 were genotyped using ABI TaqMan® technology (Applied Biosystems, Foster City, CA). Further details of the two stage SNP selection method and laboratory methods have been reported elsewhere.(Su, 2008)

3.3.3 Analysis of Genetic Data

Statistical procedures to examine the genetic data used the SAS® 9.1.3 Genetics Component (SAS Institute Inc., Cary, NC, 2002-2003). Genotype frequencies and Hardy Weinberg Equilibrium (HWE) chi square tests were calculated by race for each SNP studied. Minor allele

frequencies (MAF) were examined by race and SNPs with a MAF less than 5% in the study sample were not analyzed.

Haplotypes were estimated for ISGs separately by race using the EM algorithm.(Excoffier, 1995) SNPs were excluded from haplotype analyses if they violated assumptions of HWE (Kirk, 2002; Yang, 2003) *(rs455055, rs1476415, rs2248420, rs17000900, rs2660, rs2285934, rs6489865, rs1981557, rs6489879* and *rs2107418*), were monomorphic *(rs1141746, rs1316896, rs12298890, rs12315068, rs28360476, rs3861793, rs7969180, rs2066816* and *rs2228259*) or had minor allele frequencies less than 5% (*rs2831495* and *rs2307478*). Following these exclusions, 84 of 107 SNPs initially identified were used in haplotype estimation. The probability of being a true haplotype had to be at least 0.7 to be retained and used in further analyses. Haploview software 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.(Barrett, 2005) The variation accounted for by selected SNPs refers to a measure of the percent of variation captured and reflecting SNPs cataloged in the International HapMap Project, Phase II. 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.

3.3.4 Evaluation of Population Structure

Based on previous evaluation of population structure in the Virahep-C cohort, a strong association was observed between self-reported race and estimated individual admixture.(Yee, 2007) For this reason, this study utilized self-reported race to stratify the analyses.

3.3.5 Viral Level Measures in the First 28 Days of Treatment

The primary goal was to determine if viral levels differed over the first 28 days of treatment by the genotypes of ISG polymorphisms. Data were stratified by race to examine differences in viral level by ISG polymorphism genotypes. Viral levels were obtained prior to treatment at baseline and at days 1, 2, 7, 14 and 28 after initiation of treatment using the Roche HCV Amplicor version 2 assay (Roche Diagnostic Systems, Somerville, N.J.). Since the assay had a lower limit of detection of 600 International Units (IU)/mL, viral level measures after baseline that were below the detectable level were imputed using a uniform distribution. The time on treatment variable was expressed in days and treated as a discrete variable.

3.3.6 Potential Confounders and Model Building

Risk factors considered to be associated with 28 day viral decline included age, gender, weight, Ishak fibrosis score, alanine aminotransferase (ALT), aspartate aminotransferase (AST), amount of medication taken, source of infection, number of years since HCV infection, viral subtype and time on treatment, and were used to build models to determine if viral levels differed over the first 28 days of treatment by genotypes of the ISG polymorphisms. Age was centered by subtracting the mean age for the population (47.8) from each patient's age. Backwards elimination was used to remove variables that did not contribute, as defined below, to the model. The first elimination removed variables with a p-value greater than 0.25, the second elimination excluded variables with a p-value greater than 0.15 and the final elimination removed variables with a p-value greater than 0.05. The final models included each individual genetic variant, time on treatment, age and the interaction between time on treatment and the genetic variant.

3.3.7 Data Categorization

For each SNP, indicator variables were created for the genotypes to test for genotype associations with viral decline in the first 28 days of therapy. 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 to test for a difference. Haplotypes were categorized as carrier (at least one copy) or non-carriers (no copies). For regression analyses, haplotypes with a frequency less than 5% in one race group were not analyzed in that race group.

3.3.8 Statistical Methods

Linear mixed models were used to determine if viral levels differed significantly over the first 28 days of treatment for each ISG polymorphism. A random intercept model was used to account for inter-patient variability by allowing the intercept to vary for all study patients. The variables age (centered), SNP genotype, time on treatment, and SNP genotype by time on treatment interaction were included in the final model as fixed effects. Statistical significance was set at α=0.05. Pictorial depictions of viral level over the first 28 days of treatment were completed by graphing the predicted mean viral level at each time point for a representative individual for each ISG polymorphism genotype or ISG haplotype separately by race. Statistically significant associations were retested excluding 12 individuals of Hispanic ancestry to determine if these individuals influenced the association with the outcome. SAS® version 9.1.3 (SAS Institute Inc., Cary, NC, 2002-2003) was used to analyze the data.

Several methods were initially utilized to examine 28 day viral decline in the early stages of this project. One method examined a three level categorical variable based on the absolute

difference in viral decline from baseline to day 28.(Taylor, 2007) Poor responders (N=149) were defined by a 0 to 1.4 log drop in viral level, intermediate responders (N=108) were defined by a 1.4 to 3.5 log drop in viral level, and marked responders (N=103) were defined by a > 3.5 log drop in viral level.(Taylor, 2007) In the categorical analyses, the relative risk of achieving a marked response was examined for genotypes of each ISG SNP. The categorical outcome only allowed comparisons between baseline and day 28 viral levels and the viral level measurements in between were not considered. Also, in the categorical analyses the intermediate group was removed excluding 108 participants and reducing the ability to detect associations. A second method examined viral decline in each of two phases (Phase I: Day 0 – Day 7 and Phase II: Day 7- Day 28) with the ISG polymorphisms using linear mixed models. When the Phase I and Phase II overall F tests from the linear mixed models were compared to the results from the full 28 day viral decline models, the results were similar. These results are not included in this manuscript because the pattern of decline over the first 28 days may be more useful in understanding the association between ISG polymorphisms and early viral dynamics. Thus, the full 28 day viral decline models are presented to represent the whole picture of viral decline including the multiple viral level measurements at time points between baseline and day 28.

3.4 RESULTS

3.4.1 Sample Characteristics

Table 3-1 describes the baseline characteristics. The average viral levels at baseline, day 1, 2, 7, 14 and 28 are also presented in Table 3-1. African Americans and Caucasian Americans did not

differ significantly with respect to gender, source of infection, duration of infection or Ishak fibrosis score. African Americans were significantly older, weighed more and had higher ALT and AST levels than Caucasian Americans. Baseline viral levels did not differ significantly by race, but starting on treatment day 2 through day 28 Caucasian Americans had significantly lower viral levels compared to African Americans.

3.4.2 Interferon Stimulated Genetic Polymorphisms

Table 3-2 presents the genotype frequencies for the SNPs examined in this study. The average 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 99% in Caucasian Americans and 98% in African Americans. Overall, the SNP selection method for *MX1, IRF1* and *PKR* accounted for 39% (20-94%) of the variation in African Americans and 56% (33-88%) of the variation in Caucasian Americans and the two stage SNP selection method accounted for 29% (11-100%) of the variation in African Americans and 54% (23-100%) of the variation in Caucasian Americans.

3.4.3 Interferon Stimulated Gene Haplotypes

There was at least a 0.7 probability of being a true haplotype for 371 of 374 patients for *G1P2, IFI35, IFNAR1, IRF7, OAS1* and *STAT2*. Haplotypes were estimated in 340, 363, 334, 345, 360, 365, 356 and 347 individuals for *IFNAR2, IRF1, MX1, OAS2, OAS3, OASL, PKR and STAT1*, respectively. Haplotypes were not estimated for *G1P3* because there was only one polymorphic SNP or *MX2* because there was not enough correlation between the selected SNPs. Table 3-3

presents the common haplotypes for the ISGs that were present in at least 5% of African Americans or Caucasian Americans. Individual haplotypes were tested for 14 ISGs to see if there was a difference in viral levels over the first 28 days of treatment by presence or absence of the haplotype using the linear mixed models. For most of the ISGs, the haplotype results did not provide further information about differences in viral level for ISG polymorphisms in the gene in addition to what was observed in the individual SNP association tests.

3.4.4 Interferon Stimulated Gene Associations with 28 Day Viral Decline in Virahep-C

Analyses were completed for all ISGs, however only the associations with a p-value less than 0.10 are reported in this manuscript. Results of all tests are included in the supplement to this manuscript (Appendix A). The exclusion of the 12 self-identified Hispanics did not result in any differences and these individuals were retained in the analyses. The direction of the predicted mean viral levels at different time points during the first 28 days differed by race for several of the SNPs and haplotypes examined. Estimates for the difference in viral level over the first 28 days are shown in Table 3-4 for SNPs and in Table 3-5 for haplotypes.

Three *MX2* SNPs were significantly associated with differences in viral decline over the first 28 days of treatment. Associations with genotypes in *Mx2 rs443099* were observed in both African Americans and Caucasian Americans (Figures 1A and 1B). Different genotypes for *Mx2 rs443099* were associated with viral decline over the first 28 days in the two race groups. African Americans with the TT genotype demonstrated lower HCV RNA levels throughout the 28 days, but in Caucasian Americans it was not always clear which genotype showed the greater decline. Statistically significant differences in viral decline were also observed for *MX2 rs369908* genotypes in Caucasian Americans and *MX2 rs464090* genotypes in African

Americans. The pattern of decline and the genotype associated with greater 28 day viral decline differed in the two race groups. Although individual *MX2* haplotypes could not be estimated for study participants, haplotype frequencies for different outcome groups categorized in previous Virahep-C studies (Taylor, 2007) showed no additional statistically significant associations that were not identified through the SNP association tests.

Greater viral decline was observed among Caucasian Americans with *OASL rs1169279-GG* genotype compared to those with either the AA or AG genotypes (Table 4). Among African Americans, the pattern of viral decline for *OASL rs1169279* was not statistically significant and showed that those with the AA or AG genotype had a greater decline compared to those with the GG genotype. Statistically significant differences in viral level over the first 28 days of treatment were observed in *STAT1* and *STAT2* SNPs (Table 4). For each of the SNPs, the genotypes that were associated with greater viral decline over 28 days differed by race.

Although not statistically significant, there was a similar pattern of viral decline for both race groups with the CC or CG genotype of *OAS3 rs1981557* showing a more rapid decline compared to those with the GG genotype (Figures 2A and 2B). A similar, but not statistically significant pattern of viral decline was observed among Caucasian Americans and African Americans and *IFNAR1 rs1041868* ($p=0.47$, $p= 0.07$, respectively). Individuals with the AA or AG genotype for *IFNAR1 rs1041868* had a greater viral decline over the first 28 days compared to those with the GG genotype (Figures 3A and 3B).

A similar pattern of decline was observed with the absence of the *IRF1 ATCCATCC* haplotype among both race groups, but the difference in the viral decline was not statistically significant. Individuals with no copies of the *IRF1 ATCCATCC* haplotype had a greater viral decline compared to those with one or more copies of the haplotype (Figures 4A and 4B). Two

PKR haplotypes had statistically significant differences in viral levels over the first 28 days. The presence of either haplotype (AAT or CAC) was associated with greater decline among African Americans (Table 5).

3.5 DISCUSSION

This study investigated differences in viral level over the first 28 days of treatment by polymorphisms of ISGs among Caucasian Americans and African Americans. Statistically significant differences in viral decline were observed for *MX2, OASL, STAT1 and STAT2* SNPs and *PKR* haplotypes.

This study found statistically significant differences in 28 day viral decline with ISG polymorphism genotypes, but the pattern of viral decline differed by race. One explanation may be that the associated SNPs were not directly affecting viral decline, but rather were in linkage disequilibrium or correlated with functional polymorphisms. If this were the case, the different patterns of results may be explained by different linkage disequilibrium patterns in the populations and 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 even present in the other population. Alternatively, if the functional genetic variants are newer or more recent in the population history and the associated genetic variants are old, the associations may differ in race groups because of differences in migration out of Africa. This study also identified some differences in 28 day viral decline that were not statistically significant, but showed a similar pattern of decline by the ISG polymorphism genotypes in both race groups. Since the viral decline pattern was similar in both race groups

and people with the same polymorphism genotype showed the faster decline, it seems plausible that these genetic variants may be associated with early viral decline. Below is a summary of results for *MX2* and *OASL*.

Statistically significant differences in 28 day viral decline induced by treatment were found for *MX2 rs443099* genotypes for both Caucasian Americans and African Americans. Differences in viral decline were also observed for *MX2 rs369908* genotypes in Caucasian Americans and *MX2 rs464090* genotypes in African Americans. These findings may indicate a true causal relationship with 28 day viral decline or may be the result of linkage disequilibrium with one or more nearby causal polymorphisms. *MX2 rs443099* has no known function, *rs369908* is predicted to be an intronic enhancer and *rs464090* has no known function reported from the Fast SNP website.(Yuan, 2006) An intronic enhancer could change the way the protein is produced (Yuan, 2006) and may influence that association between the polymorphism and viral decline.

Individual haplotypes for *MX2* could not be estimated in this study because there was not enough correlation between the selected genetic variants. The *MX2* selected SNPs accounted for 15% of the genetic variation in African Americans and 34% in Caucasian Americans. Thus, further exploration of this gene by selecting more SNPs may be useful in understanding the importance of *MX2* in 28 day viral decline and identifying other genetic variants that could be associated with viral decline.

Statistically significant differences in 28 day viral decline were observed for genotypes of two *OASL* SNPs, but these differences were not consistent across race. Caucasian Americans possessing the *OASL rs1169279*-GG genotype or *OASL rs3213545*-CT or -TT genotype had greater viral decline in the first 28 days compared to the other genotypes for these variants. No

statistically significant differences were observed in African Americans. Since the observed SNPs were associated with different decline patterns by race, it is possible that the true causal polymorphism is nearby the associated polymorphisms on the gene. *OASL rs1169279* is located in the 5' upstream region of the gene and is predicted to be a promoter polymorphism, which may regulate gene expression.(Yuan, 2006) *OASL rs3213545* is located in the coding region of the gene and predicted to be involved in splicing regulation.(Yuan, 2006) Alternative splicing allows a gene to express different combination of exons which encode gene products such as proteins with diverse functions.(Mercatante, 2000) Additional studies to determine the proteins encoded by these polymorphisms and understanding the function of the polymorphism may help to determine how these polymorphisms influence viral decline. Due to the percentage of genetic variation accounted for by the selected *OASL* SNPs in African Americans (40%) and Caucasian Americans (52%), haplotypes were examined. No statistically significant *OASL* haplotype associations with 28 day viral decline were observed. Since there was unaccounted variation in *OASL,* it was not possible to provide a whole picture of the gene association. As a result, it is possible that the true causal variant was not captured by the selected polymorphisms or may be close to associated polymorphisms.

Previous work on ISGs in the Virahep-C cohort identified an association between three alleles in different *OASL* SNPs and SVR.(Su, 2008) The study by Su et al. identified positive and similar associations by race in *OASL* genetic variants (*rs1169279*-A allele, *rs3213545*-T allele and *rs2859398*-C allele) with SVR. The current study found statistically significant differences in 28 day viral decline for individuals with the *rs1169279*-GG and *rs3213545*-CT or –TT genotypes implying greater viral decline in Caucasian Americans compared to the other genotypes. However, these differences were neither significant nor consistent with the findings

in African Americans. Results of the two studies were likely different because the outcomes in the two studies were different. The Su et al. study examined the association between selected ISGs and SVR and the current study examined associations between ISG polymorphisms and 28 day viral decline. The different results might indicate that some ISGs may take more than 28 days to be effective in enhancing immune response. Thus over the full course of treatment (24-48 weeks), some ISGs may be more important in activating immune response and achieving SVR as well as important to 28 day viral decline.

Although the Virahep-C study allowed for the examination of viral dynamics in the first 28 days with a reasonable sample size, the study was not adequately powered to test genetic associations. Despite the relatively small sample size, statistically significant associations were observed between ISG polymorphisms and 28 day viral decline. On the other hand, this study did not adjust for multiple comparisons since it was an exploratory examination of the association between ISG polymorphisms and 28 day viral decline. Thus, the results of this study should be validated with an additional sample of HCV infected patients to confirm the findings. Another limitation of this study was the selection of SNPs for these genes. 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 race groups. The second phase of HapMap has the ability to better capture the common variation in the genes. Since much of the variation was not accounted for using the selected SNPs, it is difficult to understand the overall association of many of the genes examined in this study.

In conclusion, this study identified some differences in 28 day viral decline in ISG polymorphisms. Several of the associations showed varying patterns of decline by the SNP

genotype when comparing the race groups. Reasons for HCV treatment response may be complex and influenced by host genetic, environmental and viral factors. Treatment response is likely to be associated with several genes and the association may vary over the time course of treatment. Additional studies could be completed to confirm the results of the current study in other HCV populations, examine additional genes related to immune response, or select more polymorphisms in the ISGs with observed associations with 28 day viral decline. Based on these results, it is difficult to positively conclude whether or not ISGs are important to early viral dynamics for HCV.

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Table 3-1: Baseline Demographic and Viral Characteristics for Study Participants by Race (N = 374)

Characteristic	African Americans (N=180)	Caucasian American (N=194)	P-Value
Gender, n (%)			
Men	118 (65.6)	126 (65.9)	
Women	62 (34.4)	68 (35.1)	0.90*
Age (years), mean (SD)	48.7 (7.1)	47.0 (8.6)	0.03†
Weight (kg), mean (SD)	91.0 (19.2)	83.9 (17.3)	0.001†
Duration of HCV Infection (yrs)‡, mean (SD)	24.4 (9.4)	25.5 (10.0)	0.27†
Baseline ALT Levels†, mean (SD)	71.3 (45.8)	107.9 (91.9)	<0.0001†
Baseline AST Levels†, mean (SD)	60.4 (42.1)	73.7 (60.5)	0.06†
Ishak Fibrosis Score†, mean (SD)	2.2 (1.4)	2.3 (1.6)	0.56†
HCV RNA Level, (log_{10}IU/ml), mean (SD)			
Baseline	6.2 (0.7)	6.3 (0.8)	0.13†
Day 1	5.8 (0.8)	5.6 (1.2)	0.07†
Day 2	5.6 (1.0)	5.3 (1.2)	0.02†
Day 7	5.7 (1.1)	5.2 (1.4)	<0.0001†
Day 14	5.3 (1.3)	4.6 (1.7)	<0.0001†
Day 28	4.6 (1.6)	3.5 (2.0)	<0.0001†

† Wilcoxon Two Sample Test

* Chi-square test

‡ Estimated duration of HCV infection was obtained for 148 Caucasian Americans and 134 African Americans

Table 3-2: Genotype Frequencies for Single Nucleotide Polymorphisms in African Americans and Caucasian Americans

Single Nucleotide Polymorphisms		African Americans N = 180	Genotype Call Rate	HWE*	Caucasian Americans N = 194	Genotype Call Rate	HWE*
IFNAR1 rs1041868							
	AA	8 (0.05)			4 (0.02)		
	AG	65 (0.36)			55 (0.29)		
	GG	106 (0.59)	0.99	0.62	134 (0.69)	0.99	0.55
IRF1 rs839							
	AA	48 (0.27)			24 (0.12)		
	AG	81 (0.45)			92 (0.48)		
	GG	50 (0.28)	0.99	0.20	77 (0.40)	0.99	0.67
IRF1 rs2070726							
	GG	50 (0.28)			79 (0.41)		
	GT	82 (0.46)			86 (0.45)		
	TT	48 (0.27)	1.0	0.23	28 (0.15)	0.99	0.56
Mx1 rs462903							
	AA	131 (0.73)			65 (0.34)		
	AG	46 (0.26)			92 (0.47)		
	GG	53 (0.29)	1.0	0.65	37 (0.19)	1.0	0.66
Mx2 rs443099							
	GG	116 (0.64)			28 (0.15)		
	GT	57 (0.32)			94 (0.49)		
	TT	7 (0.04)	1.0	0.99	71 (0.37)	0.99	0.73
Mx2 rs369908							
	AA	9 (0.05)			128 (0.66)		
	AG	68 (0.38)			55 (0.29)		
	GG	102 (0.57)	0.99	0.59	10 (0.05)	0.99	0.21
Mx2 rs464090							
	CC	57 (0.32)			130 (0.67)		
	CT	89 (0.49)			54 (0.28)		
	TT	34 (0.19)	1.0	0.94	9 (0.05)	0.99	0.55
Oas1 rs3741981							
	CC	92 (0.51)			29 (0.15)		
	CT	81 (0.45)			98 (0.51)		
	TT	7 (0.04)	1.0	0.03	65 (0.34)	0.99	0.42
Oas3 rs1981557							
	CC	4 (0.02)			15 (0.08)		
	CG	17 (0.10)			98 (0.51)		
	GG	157 (0.88)	0.99	0.73	80 (0.42)	0.99	0.04
Oas3 rs6489879							
	AA	161 (0.89)			80 (0.42)		
	AG	19 (0.11)			99 (0.51)		
	GG	0 (0)	1.00	1.0	14 (0.07)	0.99	0.03
Oas3 rs2107418							
	GG	39 (0.22)			33 (0.17)		
	GT	71 (0.39)			106 (0.55)		
	TT	70 (0.39)	1.0	0.01	54 (0.28)	0.99	0.12
OASL rs1169279							
	AA	20 (0.11)			29 (0.15)		
	AG	80 (0.44)			82 (0.43)		
	GG	80 (0.44)	1.0	1.0	82 (0.83)	0.99	0.26

Table 3-2 (Continued)							
OASL rs3213545							
	CC	125 (0.69)			95 (0.50)		
	CT	52 (0.29)			74 (0.39)		
	TT	3 (0.02)	1.0	0.56	23 (0.12)	0.99	0.15
PKR rs2307479							
	AA	142 (0.79)			185 (0.95)		
	AC	33 (0.18)			9 (0.05)		
	CC	4 (0.02)	0.99	0.26	0 (0)	1.0	1.0
STAT1 rs2066797							
	AA	123 (0.68)			168 (0.88)		
	AG	51 (0.28)			23 (0.12)		
	GG	6 (0.03)	1.0	0.78	1 (0.01)	0.99	0.83
STAT1 rs1467199							
	CC	84 (0.47)			124 (0.64)		
	CG	78 (0.43)			61 (0.32)		
	GG	18 (0.10)	1.0	0.99	8 (0.04)	0.99	0.89
STAT2 rs2066811							
	AA	125 (0.69)			192 (0.99)		
	AG	49 (0.27)			1 (0.01)		
	GG	6 (0.03)	1.0	0.66	0 (0)	0.99	1.0

* P-value from test of Hardy Weinberg Equilibrium

Table 3-3: Haplotype Frequencies for Interferon Stimulated Genes (ISGs) in African Americans and Caucasian Americans

Haplotype	SNPs*	African Americans N = 180	Caucasian Americans N = 194
IFNAR2	*rs9636866, rs2300370, rs4986956, rs2252650, rs2834165, rs2834166, rs2250226, rs2834167*		
TGTTGAAA		0.17	0.25
IRF1	*rs839, rs2070726, rs2070723, rs2070721, rs2549009, rs2549006, rs2549003, rs736801*		
ATCCATCC		0.38	0.35
OAS2	*rs2010604, rs2072138, rs1293762, rs1293739*		
GGAA		0.03	0.07
OASL	*rs1169279, rs7134141, rs2259697, rs12819210, rs7969180, rs2260399, rs10849829, rs3213546, rs3213545, rs10849832, rs10849833, rs2859394, rs2589398, rs7134069*		
AGTCGTAGTTGTCA		0.13	0.27
PKR	*rs2307479, rs2287350, rs2254958*		
AAT		0.05	0.04
CAC		0.09	0.02
STAT1	*rs2066797, rs3088307, rs1400657, rs1914408, rs2280234, rs12693950, rs2066802, rs1467199*		
ACAGCATC		0.11	0.44
STAT2	*rs2066808, rs2068807, rs2066811, rs2228259, rs2066816, rs2066819*		
CGGGAC		0.16	0.01
TGAGGT		0.42	0.91

* SNPs are listed in order that they appear in the haplotype and along the chromosome

Table 3-4: Multivariable Model Estimating Change in Viral Level by Interferon Stimulated Gene Single Nucleotide Polymorphisms During the First 28 Days of Treatment by Race*

	African Americans (N = 180) Estimated Change in Viral Level by Treatment Day*								Caucasian Americans (N = 194) Estimated Change in Viral Level by Treatment Day*							
Genetic Marker	N	0**	1	2	7	14	28	p-value	N	0**	1	2	7	14	28	p-value
IFNAR1 rs1041868																
AA/AG	73	6.20							59	6.37						
GG	106	6.23	0.01	0.09	0.06	0.31	0.18	0.07	134	6.18	0.03	0.17	0.17	0.06	-0.14	0.47
IRF1 rs839																
AA	48	5.31							25	6.45						
AG	81	5.19	0.004	-0.18	-0.12	-0.27	-0.21		92	6.39	-0.01	-0.13	-0.19	-0.33	0.03	
GG	50	6.15	0.003	-0.13	0.10	-0.03	0.01	0.55	77	6.19	-0.19	-0.26	-0.20	-0.46	0.14	0.09
IRF1 rs2070726																
GG	50	6.15							79	6.20						
GT	82	6.24	0.003	-0.05	-0.21	-0.23	-0.21		86	6.39	0.19	0.13	0.03	0.14	-0.07	
TT	48	6.24	-0.01	0.13	-0.14	0.002	-0.03	0.55	28	6.45	0.12	0.18	0.14	0.36	-0.25	0.08
Mx1 rs462903																
AA	131	6.25							65	6.26						
AG/GG	49	6.13	-0.01	-0.06	0.05	-0.12	-0.21	0.42	129	6.35	0.19	0.25	0.45	0.41	0.13	0.07
Mx2 rs443099																
GG	116	6.24							28	6.33						
GT	57	6.18	0.10	-0.01	-0.04	-0.07	0.04		94	6.35	0.30	0.45	-0.03	-0.10	-0.29	
TT	7	6.02	-0.76	-0.83	-0.62	-0.91	-0.99	0.04	71	6.27	0.17	0.38	-0.10	-0.10	0.04	0.03
Mx2 rs369908																
AA	9	6.18							128	6.35						
AG	68	6.19	0.77	0.88	0.64	0.61	0.55		55	6.25	-0.30	-0.44	-0.50	-0.61	-0.97	
GG	102	6.23	0.69	0.83	0.56	0.54	0.36	0.06	10	6.32	0.18	0.10	-0.11	-0.40	0.10	0.003
Mx2 rs464090																
CC	57	6.25							130	6.38						
CT/TT	123	6.20	0.16	0.23	0.03	0.17	0.29	0.045	63	6.18	-0.20	-0.31	-0.43	-0.59	-0.63	0.14
OAS1 rs3741981																
CC	92	6.20							29	6.52						
CT	81	6.26	0.06	0.05	0.01	0.20	0.03		98	6.17	0.03	0.16	0.12	0.20	0.39	
TT	7	5.90	-0.36	-0.66	-0.32	-0.003	0.12	0.08	65	6.43	0.24	0.26	0.48	0.62	0.67	0.35
OAS3 rs1981557																
CC/CG	21	6.20							113	6.25						
GG	157	6.22	-0.04	-0.001	0.11	-0.01	0.17	0.67	80	6.41	0.22	0.16	0.39	0.51	0.46	0.09

Table 3-4 (Continued)

OAS3 rs6489879																
AA	161	6.20							80	6.41						
AG/GG	19	6.34	0.11	0.07	0.07	0.19	0.07	0.85	113	6.25	-0.22	-0.16	-0.39	-0.51	-0.46	0.09
OAS3 rs2107418																
GG	39	6.27							33	6.37						
GT	71	6.14	-0.05	0.10	-0.08	-0.07	-0.18		106	6.24	0.10	0.28	0.23	0.67	0.77	
TT	70	6.26	-0.09	-0.08	0.05	0.07	-0.02	0.97	54	6.44	0.20	0.32	0.35	0.49	0.36	0.06
OASL rs1169279																
AA/AG	100	6.20							111	6.34						
GG	80	6.23	0.07	0.16	0.12	0.05	0.15	0.58	82	6.28	-0.08	-0.11	-0.26	-0.19	0.24	0.007
OASL rs3213545																
CC	125	6.20							95	6.28						
CT/TT	55	6.24	-0.05	-0.10	-0.12	0.05	0.01	0.63	97	6.35	-0.01	0.08	0.18	0.05	-0.33	0.02
PKR rs2307479																
AA	142	6.20							185	6.30						
AC/CC	37	6.25	-0.22	-0.34	-0.32	-0.57	-0.57	0.045	9	6.64	0.10	0.06	-0.16	-0.20	0.06	0.90
STAT1 rs2066797																
AA	123	6.25							168	6.31						
AG/GG	57	6.14	-0.08	-0.12	-0.10	-0.10	0.02	0.78	24	6.32	0.22	0.20	0.44	0.42	-0.11	0.04
STAT1 rs1467199																
CC	84	6.18							124	6.37						
CG/GG	96	6.24	-0.17	-0.12	0.09	0.03	-0.15	0.02	69	6.21	-0.12	-0.26	-0.17	-0.25	-0.10	0.43
STAT2 rs2066811																
AA	125	6.21							192							
AG/GG	55	6.23	0.21	0.21	0.01	0.01	0.23	0.02	1	†						

* Model adjusted for age, time, genetic variant and interaction between time and genetic variant

** Reflects the mean HCV RNA levels

† Minor allele frequency less than 5% in one race group

Only the results for the genotype variable are presented

Table 3-5: Multivariable Model Estimating Change in Viral Level for Interferon Stimulated Gene Haplotypes During the First 28 Days of Treatment by Race*

	African Americans (N = 180) Estimated Change in Viral Level by Treatment Day*								Caucasian Americans (N = 194) Estimated Change in Viral Level by Treatment Day*							
Genetic Marker	N	0**	1	2	7	14	28	p-value	N	0**	1	2	7	14	28	p-value
IFNAR2																
TGTTGAAA	54	6.25	-0.18	-0.16	-0.06	-0.08	0.13	0.10	72	6.19	-0.02	-0.05	0.03	-0.02	0.24	0.46
IRF1																
ATCCATCC	113	6.24	0.02	0.10	-0.001	0.02	-0.04	0.84	113	6.41	0.16	0.16	0.07	0.22	-0.09	0.07
OAS2																
GGAA	5	†							24	6.50	-0.10	-0.15	0.01	0.06	-0.46	0.09
OASL																
AGTCGTAGTTGTCA	43	6.20	-0.01	-0.11	-0.05	0.13	0.03	0.47	85	6.33	0.01	0.06	0.17	0.12	-0.24	0.057
PKR																
AAT	13	6.29	-0.31	-0.27	-0.20	-0.72	-0.76	0.02	14	6.29	0.03	0.21	0.33	0.28	0.28	0.96
CAC	21	6.15	-0.31	-0.42	-0.41	-0.65	-0.95	0.008	8	†						
STAT1																
AGAGCATC	26	6.22	0.25	0.24	0.29	0.44	0.65	0.15	36	6.35	0.28	0.31	0.08	0.23	0.48	0.08
STAT2																
CGGGAC	52	6.27	0.15	0.17	0.03	0.02	0.24	0.10	1	†						
TGAGGT	122	6.05	-0.17	-0.19	0.05	-0.07	-0.15	0.048	193	‡						

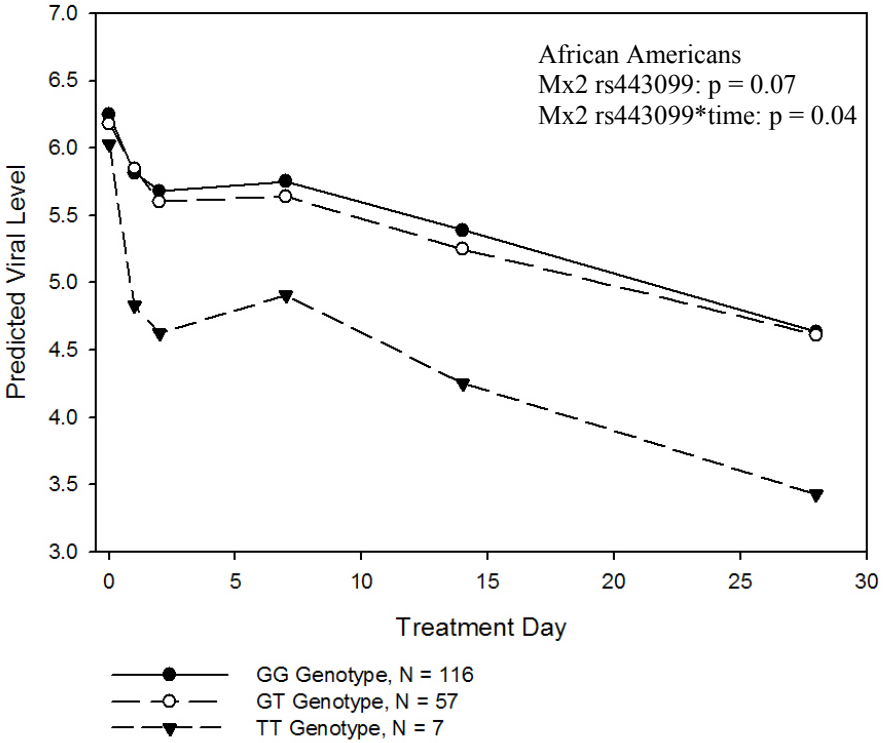
* Model adjusted for age, time, genetic variant and interaction between time and genetic variant

** Reflects the mean HCV RNA levels

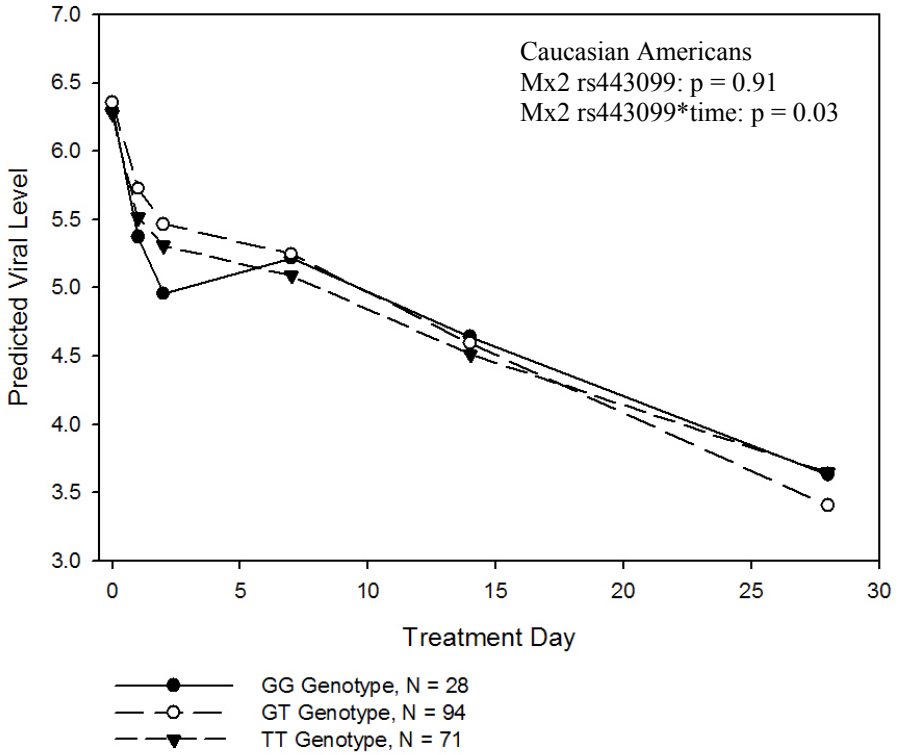
† Haplotype frequency less than 5% in a population

‡ No variation in the haplotype

Only the results for the haplotype variable are presented



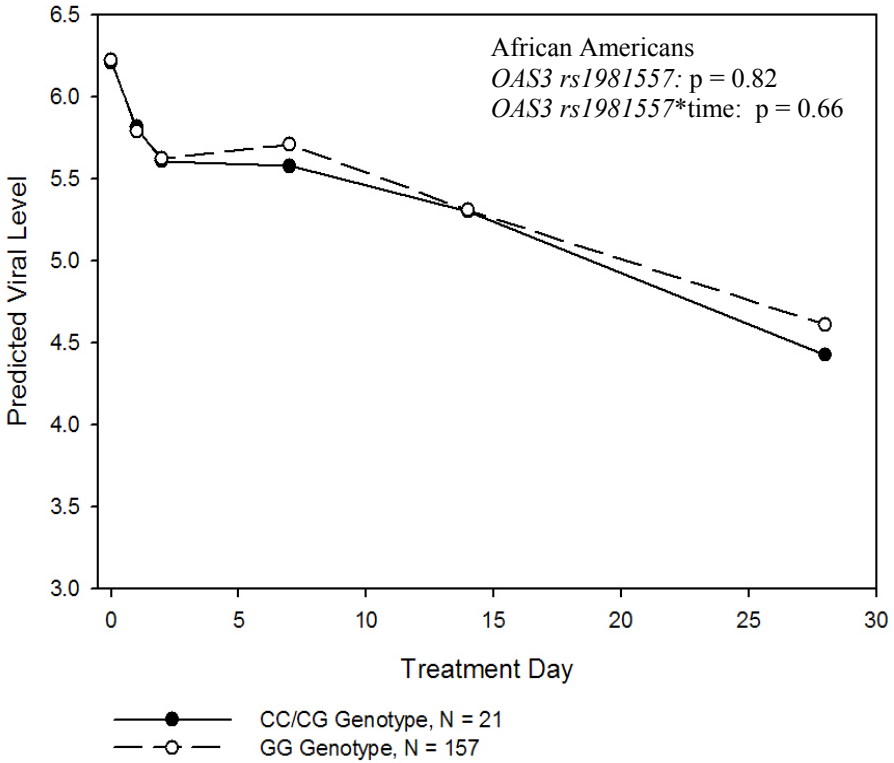
p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GT	-	0.30	0.93	0.77	0.67	0.82
TT	-	0.001	0.01	0.09	0.03	0.03



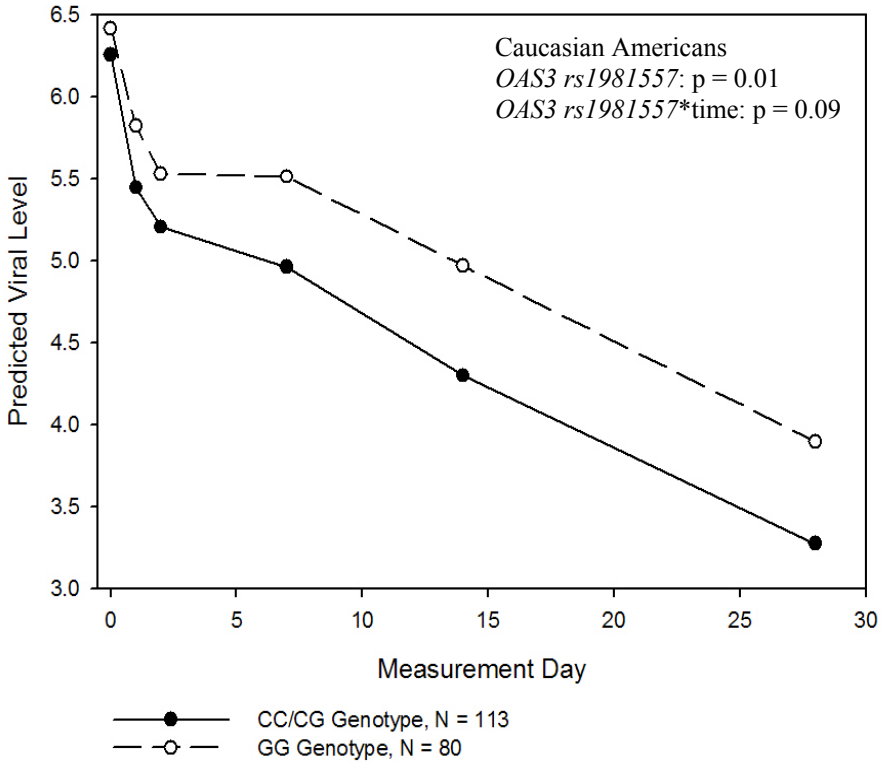
p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GT	-	0.34	0.12	0.72	0.75	0.91
TT	-	0.08	0.05	0.92	0.73	0.38

Figure 3-1a and 3-1b: Predicted Viral Decline for *Mx2 rs443099* During the First 28 Days of HCV Treatment for African Americans (N=180) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



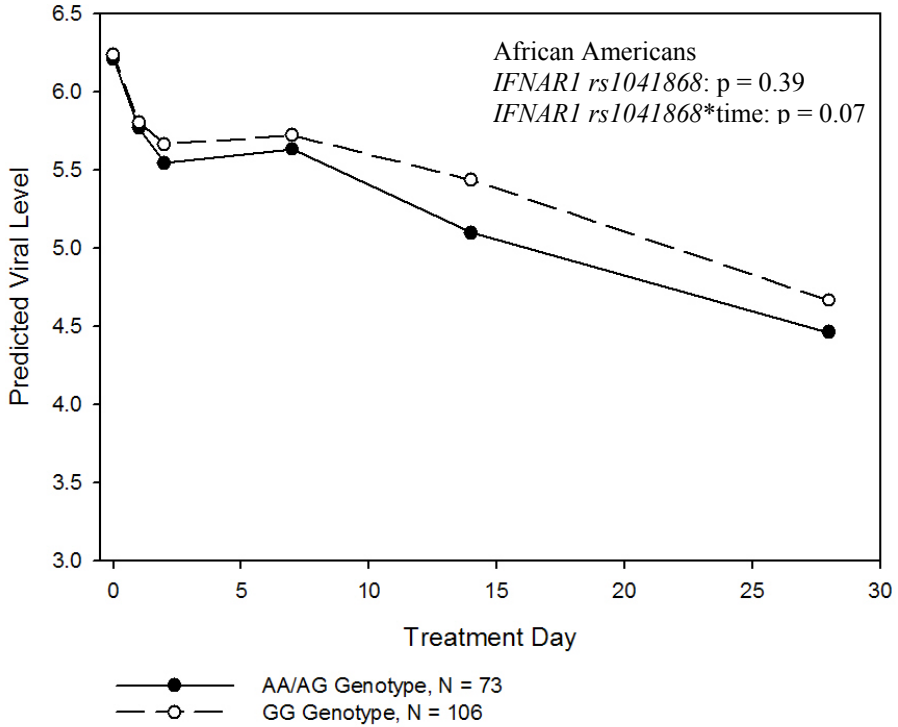
p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GG	-	0.76	0.99	0.61	0.97	0.54

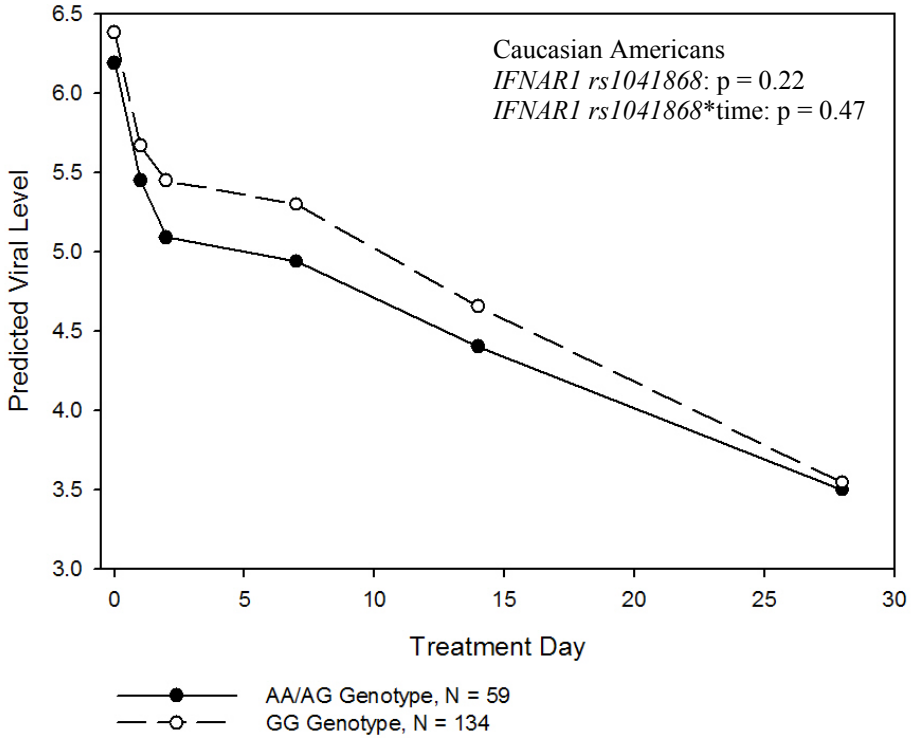


p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GG	-	0.06	0.31	0.03	0.02	0.04

Figures 3-2a and 3-2b: Predicted Viral Decline for *OAS3 rs1981557* During the First 28 Days of HCV Treatment for African Americans (N=178) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



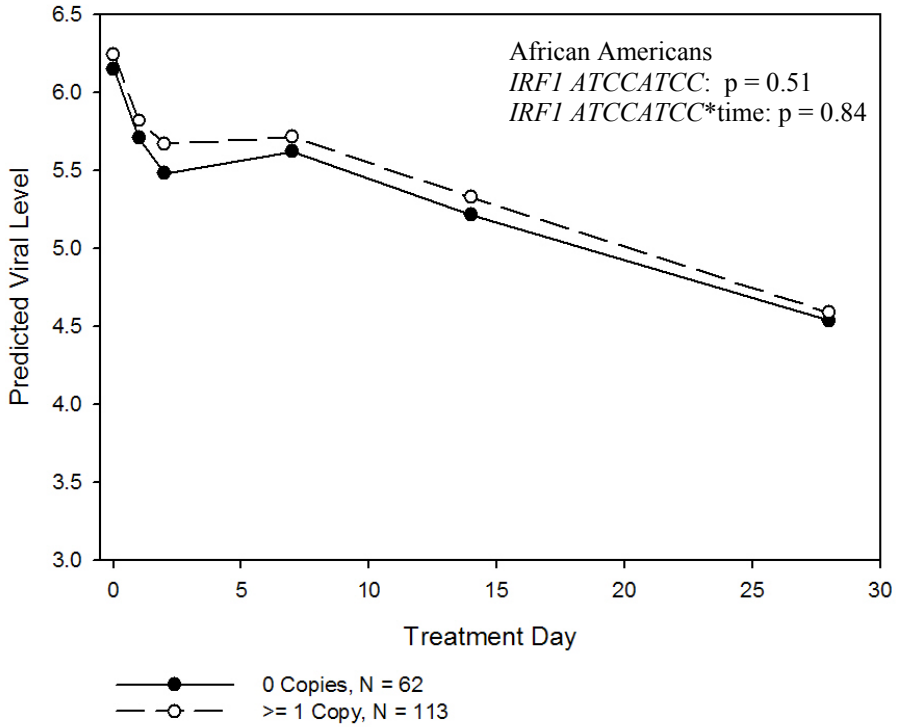


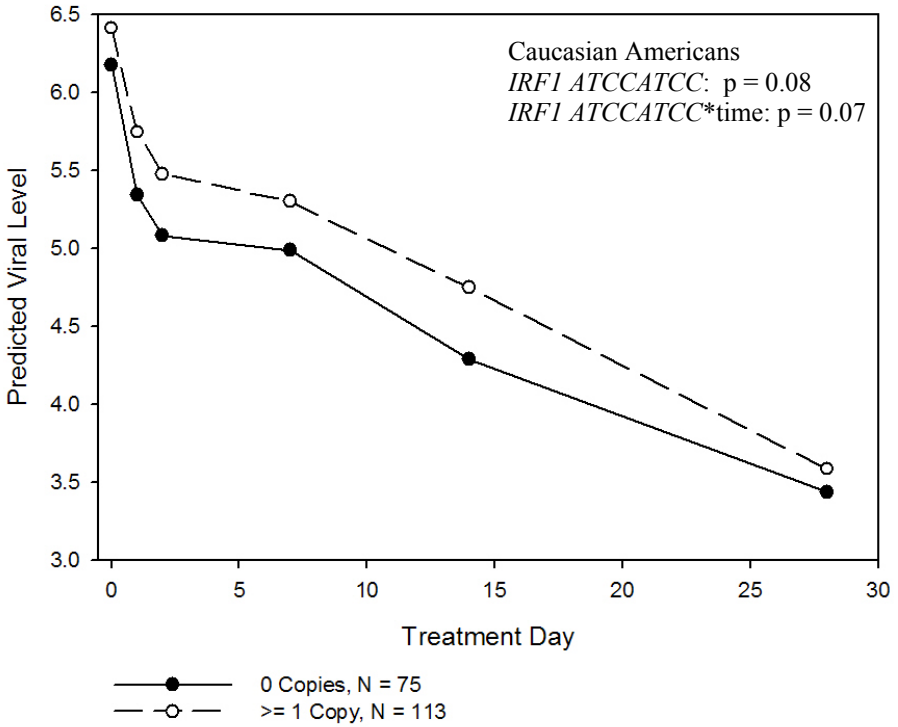
p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GG	-	0.94	0.46	0.67	0.06	0.32

p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
GG	-	0.83	0.33	0.39	0.78	0.55

Figures 3-3a and 3-3b: Predicted Viral Decline for *IFNAR1 rs1041868* During the First 28 Days of HCV Treatment Among African Americans (N=179) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant





p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
≥ 1 Copy	-	0.84	0.46	0.99	0.90	0.81

p-value	Baseline	Day 1	Day 2	Day 7	Day 14	Day 28
≥ 1 Copy	-	0.17	0.33	0.70	0.30	0.69

Figure 3-4a and 3-4b: Predicted Viral Decline for *IRF1 ATCCATCC* During the First 28 Days of HCV Treatment Among African Americans (N=175) and Caucasian Americans (N=188)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant

4.0 RESEARCH ARTICLE 2:

HOST GENETICS, STEATOSIS AND INSULIN RESISTANCE AMONG AFRICAN AMERICANS AND CAUCASIAN AMERICANS WITH HEPATITIS C VIRUS GENOTYPE-1 INFECTION

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4.1 ABSTRACT

Hepatic steatosis is the accumulation of fat in the liver and is prevalent in 30-84% of chronic hepatitis C virus (HCV) patients. Insulin resistance (IR) is the condition for which normal amounts of insulin do not produce a typical response from cells. Both are common in HCV infection and are thought to be biologically related.

This study tested genetic variant associations with steatosis and IR among 167 African Americans (AA) and 184 Caucasian Americans (CA) infected with HCV genotype-1. Steatosis was defined as having at least 5% of fat in cells on liver biopsy. The Homeostasis Model Assessment (HOMA) Version 2.2 was used to quantify IR and the presence of IR was categorized as a score greater than 2. Associations between genetic variants and the occurrence of steatosis or IR were investigated using logistic regression models separately by race.

Statistically significant associations ($p<0.05$) were observed for polymorphisms 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. When examining IR, there were no significant interactions observed between the SNPs and steatosis. Both AAs and CAs possessing the GG genotype for *TGF-β1 rs2278422* had significantly lower odds of IR compared to those with the CC or CG genotypes.

If IR is along the causal pathway for steatosis, these results could imply that some *IL10, LEPR* and *TGF-β1* polymorphisms may modify an association between steatosis and IR. Understanding genetic associations with these conditions and further learning the function of the

associated polymorphisms may help to explain the mechanisms of steatosis and IR in HCV infection.

4.2 INTRODUCTION

Hepatic steatosis is characterized by the accumulation of fat in the liver and diagnosis is generally made by examining a biopsy to calculate the percentage of fat in liver cells.(Teli, 1995) 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.(Adinolfi, 2001; Asselah, 2006; Castera, 2003; Conjeevaram, 2006; Conjeevaram, 2007; Czaja, 1998; Hourigan, 1999; Hui, 2002; Monto, 2002; Patton, 2004; Poynard, 2003; Rubbia-Brandt, 2004; Rubbia-Brandt, 2001; Serfaty, 2001; Westin, 2002) Steatosis occurs less frequently in the general population (31%).(Browning, 2004) The mechanisms of hepatic steatosis are thought to be multifactorial and the presence of insulin resistance may be associated with its development.(Adinolfi, 2001; Castera, 2003; Hourigan, 1999; Rubbia-Brandt, 2000; Serfaty, 2001; Serfaty, 2002)

Factors previously identified to be associated with steatosis in HCV infection were alcohol consumption, higher body mass index (BMI), older age, male gender, Caucasian American race, presence of hepatic inflammation, hyperlipidaemia, increased triglyceride levels, higher cholesterol levels, increased alanine aminotransferase (ALT) levels, increased aspartate aminotransferase (AST) levels, higher fibrosis scores and the presence of insulin resistance.(Asselah, 2006; Browning, 2004; Conjeevaram, 2007; Fabris, 2004; Leandro, 2006; Matos, 2006; Ruhl, 2004; Solis-Herruzo, 2005; Younossi, 2004) African Americans have a lower prevalence of steatosis despite having a higher BMI.(Browning, 2004; Ruhl, 2004) The

presence of steatosis was found to be associated with fibrosis progression in HCV patients.(Adinolfi, 2001; Castera, 2003; Hourigan, 1999; Serfaty, 2002; Westin, 2002) Steatosis may also adversely influence HCV sustained virologic response (SVR).(Fabris, 2005; Guidi, 2005; Jian Wu, 2006; Patton, 2004; Soresi, 2006; Westin, 2007) HCV genotype-1 patients with steatosis achieved SVR less frequently (29-46%) compared to those without steatosis (62-65%).(Jian Wu, 2006; Soresi, 2006; Westin, 2007)

Insulin resistance (IR) is a condition in which normal amounts of insulin are insufficient to produce a typical response from cells, especially fat, muscle and liver cells.(Rao, 2001; Romero-Gomez, 2006) IR is often measured and quantified by the Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR).(Matthews, 1985) IR can occur early in the course of HCV infection.(Petit, 2001) Patients with chronic HCV infection were observed in one study to have higher HOMA-IR scores compared to healthy controls.(Hui, 2003) Risk factors for IR among people with chronic HCV infection include older age, African American race, obesity, cirrhosis, and fibrosis.(Heathcote, 2002; Petit, 2001; Romero-Gomez, 2005) Presence of IR may negatively impact the function of interferon therapy and the ability to achieve SVR in HCV patients, especially those infected with genotype-1.(Romero-Gomez, 2006; Romero-Gomez, 2005)

Genes with functions related to fat metabolism or lipid metabolism were examined for associations with steatosis or IR in primarily diabetic, obese or healthy subjects.(Cardellini, 2005; Kubaszek, 2003; Kubaszek, 2003; Qi, 2006; Sartipy, 2003; Scarpelli, 2006; Simeoni, 2004; Testa, 2006; Y Yang, 2003) In patients with chronic HCV infection, increased expression of *tumor necrosis factor alpha* in the liver was associated with IR (Gershon, 2000; Halse, 2001; Kallinowski, 1998; Maeno, 2003; Mishima, 2001; Moller, 2000; Nelson, 1997; Petit, 2001;

Valenti, 2005) or steatosis.(Gochee, 2003; Sougleri, 2001; Valenti, 2005) Previous observations found that higher *Interleukin 6* and *Monocyte chemoattractant protein-1* expression was associated with IR in HCV infection.(Cardellini, 2005; Danielsson, 2005; Deepa, 2006; Hamid, 2005; Hermann, 2005; Illig, 2004; Kanda, 2006; Kubaszek, 2003; Mohlig, 2004; Qi, 2006; Testa, 2006; Tsiavou, 2004; Vozarova, 2003; X Yang, 2005) In studies of steatosis, *transforming growth factor-β1* was over expressed with fatty liver (Kharbanda, 2004) and increased *Interleukin 10* production was associated with less steatosis.(Den Boer, 2006) *Cytochrome P-450 2E1* activity was found to be positively correlated with HOMA-IR levels.(Chalasani, 2003) These studies indicate the importance of these genes in the occurrence of steatosis or IR, but little is known about the associations with polymorphisms in these genes and these conditions in HCV infection. Understanding these genetic associations with steatosis and IR may help to understand the mechanisms of these conditions in HCV infection and reduce additional morbidity and mortality.

This study 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-β1)* are associated with steatosis or insulin resistance in a sample of African Americans and Caucasian Americans infected with HCV genotype-1.

4.3 MATERIALS AND METHODS

4.3.1 Study Population and Clinical Data

Data were from the Study of Viral Resistance of Antiviral Therapy of Chronic Hepatitis C (Virahep-C), a multicenter study supported by the National Institutes of Health (NIH). Virahep-C study design and primary outcomes have been described elsewhere.(Conjeevaram, 2006) Briefly, there were 401 HCV treatment naïve patients who were enrolled in the study among whom 374 (194 Caucasian and 180 African Americans) agreed to participate in the genetics studies and included in the present analyses.

4.3.2 Measurement of Steatosis and Insulin Resistance

Per protocol, patients without cirrhosis were to obtain a liver biopsy within 18 months of study enrollment.(Conjeevaram, 2007; Yee, 2007) Liver biopsies were scored by a single pathologist, who was masked with respect to patient outcome and clinical status. Biopsies were assessed for the severity of chronic HCV by grading inflammation and staging of fibrosis using the modified histologic activity index (HAI) scoring system.(Ishak, 1995) Steatosis was scored on a scale of 0 to 4 according to the percentage of cells with fat where: 0 = none, 0.5 = <5%, 1 = 5-<25%, 2 = 25-<50%, 3 = 50-<75%, 4 = ≥75%.(Conjeevaram, 2007) For this study, IR was quantified by using the Homeostasis Model Assessment-Insulin Resistance (HOMA2-IR) Calculator Version 2.2 based on the mathematical model released in 2004 and downloaded from http://www.dtu.ox.ac.uk/.(Levy, 1998; Wallace, 2004) The HOMA2-IR model estimates insulin

sensitivity using fasting glucose and insulin levels and is calibrated with current insulin assays.(Levy, 1998; Wallace, 2004)

4.3.3 Single Nucleotide Polymorphism (SNP) Selection and Genotyping

Prior to this study, Virahep-C supported the selection and genotyping of single nucleotide polymorphisms as part of a study of host genetics. The genes examined for this manuscript were chosen from a list of genes already genotyped as part of the previous study. The list included genes that have been associated with steatosis or IR in diabetic, obese or healthy populations in the literature. Two different approaches were utilized in the selection of SNPs and genotyping and were based on publically available genetic information and genotyping technology at the time that each component was completed.

One selection method identified SNPs for the candidate genes *IL6, IL10, TGF-β1* and *TNF-α* and details of this process have been described elsewhere.(Yee, 2007) Briefly, SNPs were selected by examining the haplotype blocks for each race and identifying polymorphisms from the International HapMap Project (Phase I) and National Center for Biotechnology Information (NCBI) databases.(Yee, 2007) SNPs with a minor allele frequency of at least 10% in a reference population were selected to cover the entire gene at 2-3 kb intervals for small genes and 5-9 kb intervals for larger genes.(Yee, 2007) An allelic discrimination assay employing the ABI 7000 Sequence Detection System with TaqMan technology (Applied Biosystems Inc., Foster City, CA) was used to genotype the haplotype-tagging SNPs.(Yee, 2007)

The second method for SNP selection and genotyping was utilized for *COL1A1, CYP2E1, IL1R1, LEPR, MCP1/CCL8* and *MCP2/CCL8*. For each of these genes, SNPs with a minor allele frequency of at least 5% in a reference population were selected from the

International HapMap Project (Phase I) approximately every 3-5 kb to cover the entire gene.(Su, 2008) SNPs identified were genotyped using Illumina BeadArray technology (Illumina, San Diego, CA).(Su, 2008) Further detail of the SNP selection and laboratory methods have been reported elsewhere.(Su, 2008)

4.3.4 Variable Categorization

Steatosis was categorized into a dichotomous variable using data from the liver biopsies with steatosis (steatosis score greater than 0) versus no steatosis. In general, a HOMA-IR score of at least 1.5 is thought to indicate decreased insulin sensitivity.(Conjeevaram, 2007) For this study, IR was defined as HOMA2-IR score of at least 2.0 based on a previous study of the Virahep-C cohort.(Conjeevaram, 2007) For each SNP, indicator variables were created for the genotypes to test for genotype associations with steatosis or IR. 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. Haplotypes were categorized as having at least one copy of the haplotype or having no copies.

4.3.5 Risk Factor Variables and Model Building

Ishak fibrosis score, weekly alcohol consumption, age, BMI, $\log_{10}$ of baseline viral level, inflammation score, ALT levels, AST levels, cholesterol levels and triglyceride level were continuous factors centered at their mean values and examined in the model building for steatosis and IR. Diabetes status and HCV subtype were categorical factors examined in the model building for the outcomes. Self-reported race was used in this study since it was previously

reported that the individual admixture in the Virahep-C study strongly agreed with self-reported race.(Yee, 2007) Steatosis was assessed as a risk factor for IR and IR was assessed as a risk factor using the continuous HOMA2-IR scores when examining steatosis. HOMA2-IR scores were transformed using the natural log and were centered at the mean.

4.3.6 Genetic Analytical Methods

Genotype and allele frequencies as well as Hardy Weinberg Equilibrium (HWE) chi square 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 (MAF) were examined by race and SNPs with a MAF less than 5% were not analyzed. Haplotypes were estimated using the EM algorithm for all genes separately by race.(Excoffier, 1995) SNPs that violated HWE assumptions or were monomorphic or had an allele frequency less than 5% were excluded from haplotype estimation.(Kirk, 2002) Estimated haplotypes for individuals with at least a 0.7 probability of being the true haplotype were retained and used in subsequent analyses. If estimated haplotypes had a probability less than 0.7, no haplotypes were assigned to the study patient. Haplotypes with a frequency of at least 5% in either Caucasian Americans or African Americans were investigated in analyses. SAS® Genetics Version 9.1.3 was used to conduct SNP and haplotype analyses (SAS Institute Inc., Cary, NC, 2002-2003). 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.(Barrett, 2005) 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.

4.3.7 Statistical Analyses

Twelve individuals identified as Hispanics and 11 individuals using exogenous insulin were removed from analyses resulting in a sample size of 351. Demographic characteristics and risk factors for steatosis and insulin resistance were assessed by race using appropriate association tests. SNP association tests were completed with steatosis and insulin resistance separately by race using the genotype case control chi square test (results in Appendix B).(Nielsen, 1999) A haplotype trait chi square test was performed to identify an association between any possible haplotype for a gene and steatosis or IR (results in Appendix B).(Zhao, 2000)

Odds ratios were used to quantify the association between steatosis or IR and the SNPs or haplotypes. Adjusted models were built using backwards elimination that included possible confounding variables and removing those that did not significantly contribute to the prediction of the outcome. The backwards elimination method first removed variables with p-values greater than 0.25. The second elimination removed variables with p-values greater than 0.15 and the final elimination removed those variables with a p-value greater than 0.05. To avoid problems with multicollinearity with significantly correlated variables, only one variable was used in the model building and was chosen because there was more support in the literature for an association. For example, steatosis was significantly correlated with ALT levels and steatosis was used because the literature commonly describes associations between steatosis and IR. Steatosis was retained in the model predicting IR because steatosis and IR are thought to be biologically related and it is unclear if steatosis contributes to the occurrence of IR or vice versa.

All possible interaction terms between the main effects variables remaining in the model after the three elimination steps were tested to determine their contribution to the prediction of the outcome. A significant log likelihood ratio test ($p<0.05$) was used to determine if an interaction term significantly contributed to the prediction of the outcome.

After the final model was determined for each outcome, an interaction between the natural log transformed HOMA2-IR scores (when predicting steatosis) or steatosis (when predicting IR) and the genetic variant was tested separately in African- and Caucasian-Americans. The log likelihood ratio test was used to determine the significance of the interaction. For log likelihood ratio tests with p-values greater than 0.05, the interaction was not included in the model. If the log likelihood was significant, then the model included the interaction to predict the outcome. Odds ratio (OR) estimates and 95% Confidence Intervals (CI) were estimated for each genetic variant in both unadjusted (results in Appendix B) and adjusted models separately by race. An alpha level of 0.05 was used to determine statistical significance. The SAS®/STAT software system version 9.1.3 was used to complete analyses (SAS Institute Inc., Cary, NC, 2002-2003).

4.4 RESULTS

4.4.1 Population Characteristics

Comparisons of demographic characteristics by race are shown in Table 4-1. African Americans and Caucasian Americans did not significantly differ by gender, age, hepatic inflammation score, baseline viral level, Ishak fibrosis score, steatosis, AST levels, cholesterol levels, triglyceride

levels or weekly alcohol consumption. African Americans had significantly higher HOMA2-IR scores, ALT levels and BMI compared to Caucasian Americans. There were 53 individuals who had missing data for HOMA2-IR because their insulin and glucose levels were not fasting or were not available.

4.4.2 SNP Genotyping and Estimation of Haplotypes

Genotype frequencies, call rate and p-values from HWE tests are shown in Table 4-2. Haplotype estimation used 45 of 52 genotyped SNPs because four SNPs violated assumptions of HWE (*rs1880242, rs1805096, rs1892534* and *rs2229094)*, two were monomorphic (*rs3917257* and *rs3917879*) and one had an allele frequency less then 5% in either race group (*rs3917275*). Haplotype estimation with a 0.7 probability of being a true haplotype occurred in four of the genes *(IL10, TNF-α, MCP1/CCL2* and *MCP2/CCL8)* with 350 of a possible 351 haplotypes estimated. Haplotypes were estimated in 344, 339, 336, 325, 313 and 293 individuals for *LEPR, TGF-β1, IL1R1, IL6, CYP2E1* and *COL1A1*, respectively. Results of haplotype estimation are in Appendix B. The selected SNPs for *IL6, IL10,* T*GF-β1* and *TNF-α* accounted for 38% (11-85%) of the common variation of the gene 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. Common genetic variation tables for each gene are found in Appendix B.

4.4.3 Associations with Steatosis

The final model used to estimate the odds of steatosis was adjusted for Ishak fibrosis score, weekly alcohol consumption, baseline viral level, natural log transformed HOMA2-IR scores and body mass index. Results from the adjusted models for *IL6, IL10, LEPR* and T*GF-β1* polymorphisms are reported in Table 4-3. *CYP2E1, IL1R1*, *MCP2/CCL8* and *TNF-α* SNPs were not statistically significantly associated with steatosis. Haplotype analysis for the association with steatosis yielded similar results to individual SNP analyses and were not reported in this manuscript.

Among Caucasian Americans possessing the *COL1A1 rs2586494*-CC genotype, the odds of steatosis for a one unit increase in HOMA2-IR score (OR=2.3: 95% CI=1.1-5.0) were significantly lower than the odds for a one unit increase in HOMA2-IR score for those with the AA or AC genotype (OR=19.5: 95% CI=2.3-164.5). The odds of steatosis were significantly higher for a one unit higher HOMA2-IR score among African Americans with the *MCP1/CCL2 rs2857657*-CG/GG genotypes (OR=24.8: 95% CI=1.2-500.2) compared to those with the CC genotype and a one unit higher HOMA2-IR score (OR=1.7: 95% CI=0.95-3.16). Results for SNPs not presented in Table 4-3 are available in Appendix B.

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 4-3). 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-β1 rs2278422*-GG genotype were 4.4 times the odds of steatosis among African Americans with the CC or CG genotype. No significant associations were observed in Caucasian Americans for this polymorphism, but the direction of the odds ratio

was the same (Table 4-3). Higher odds of steatosis were observed for a one unit higher HOMA2-IR score for African Americans possessing the *TGF-β1 rs2241716*-GG genotype (OR=3.3: 95% CI=1.6-6.9) compared to the odds for a one 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 in the prediction of steatosis. The odds of steatosis for a one unit higher HOMA2-IR score for Caucasian Americans possessing 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 one 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 one unit higher HOMA2-IR score were higher (OR=3.4: 95% CI=1.3-8.8) compared to those with the CC genotype (OR=0.3: 95% CI=0.1-1.3). Table 4-4 shows the *IL10 rs3024496* genotype frequencies for those with and without steatosis and those with or without IR and may be useful for understanding the observed interaction. There were higher percentages of individuals with the CT (90%) and TT (85%) genotypes with higher HOMA2-IR scores who had steatosis compared to individuals with the CT (60%) and TT (67%) genotypes and lower HOMA2-IR scores. Figures 4-1A and 4-1B graphically depict the interaction between the *IL10 rs3024496* genotypes and HOMA2-IR scores in the prediction of steatosis through different slopes for the log odds of steatosis for the polymorphism genotypes. For African Americans, the graph shows that the *IL10 rs3024496*-CT and TT genotypes have similar increasing log odds of steatosis and the CC genotype has a very different and decreasing slope for the log odds of steatosis as HOMA2-IR score increases. In Caucasian Americans, the *IL10 rs3024496*-CT and TT genotypes have similar increasing log odds of steatosis and the CC genotype has slower 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.

Statistically significant associations were observed between *LEPR* SNPs and steatosis (Table 4-3). 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. The observed association in Caucasian Americans was not statistically significant, but the direction of the odds ratio was the same. African Americans possessing the *LEPR rs1892534*-AG genotype had triple the odds of having steatosis compared to those with the AA genotype (Table 4-3). Statistically significant interactions were observed between HOMA2-IR scores and two *LEPR* polymorphisms in Caucasian Americans. For a one 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 one 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 one unit higher HOMA2-IR score among those with the CC genotype (OR=2.0: 95% CI=0.8-5.4). Table 4-5 shows the *LEPR rs1805096* genotype frequencies for both race groups by steatosis and IR. In Caucasian Americans, There is a higher percentage of steatosis among those with the heterozygote genotype and higher HOMA2-IR scores (100%) compared to those with the same genotype and lower HOMA2-IR scores (56%). Figure 4-2A depicts the log odds of steatosis by HOMA2-IR scores in African Americans. This graph shows similar log odds of steatosis for the *LEPR rs1805096* genotypes and the interaction was not observed to be statistically significant (p=0.13). Figure 4-2B graphically describes the

statistically significant interaction between the *LEPR rs1805096* genotypes and HOMA2-IR scores in the prediction of steatosis in Caucasian Americans by showing three very different log odds of steatosis slopes for the genotypes.

4.4.4 Associations with Insulin Resistance

Models predicting the odds of IR were adjusted for Ishak fibrosis score, BMI, age, steatosis and triglyceride levels. Results of the adjusted main effects models are presented in Table 4-6. No statistically significant SNP associations with IR were observed in either race group for *COL1A1, CYP2E1, IL1R1, MCP1/CCL2, MCP2/CCL8* or *TNF-α*. Additional SNP results not described in Table 4-6 are in presented in Appendix B. Haplotype analysis for the association with insulin resistance yielded similar results as those from individual SNP analyses and were not presented in this manuscript. Haplotype results are available in Appendix B. No significant interactions between the genetic variants and steatosis contributed to the prediction of IR.

Statistically significant associations were observed between *IL6, IL10, LEPR* and *TGF-β1* polymorphisms and insulin resistance in either race group. African Americans with the *IL10 rs3024496*-CT genotype (OR=0.3: 95% CI=0.1-0.8) or the *rs1800900*-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. No statistically significant associations for these SNPs were observed in Caucasian Americans, but the odds ratios were in the same direction. 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-β1 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 time lower odds of IR (95% CI=0.1-0.9) compared to those with either the CC or CG genotype.

4.5 DISCUSSION

This study investigated host genetic associations with steatosis and IR for African American and Caucasian American patients with HCV genotype-1 infection. Statistically significant associations with steatosis or IR were identified in *IL6, IL10, LEPR* or *TGF-β1* in both race groups.

This study stratified all data by race for the purpose of detecting gene associations with steatosis and IR. The decision to complete the analyses separately by race was based on an *a priori* genetic expectation of different effects of SNPs in different ethnic groups. Even if the same gene is affecting the outcome in Caucasian Americans and African Americans, there is an expectation that different SNPs within a gene for each race will show an association because of 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 in the populations and 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 even present in the other population. Alternatively, if the functional genetic variants are newer or more recent in the population history and the associated genetic

variants are old, the associations may differ in race groups because of differences in migration out of Africa.

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 is predicted to have no known function.(Yuan, 2006) Determining the function of associated genetic variant 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 in the prediction of steatosis in Caucasian Americans. Based on findings from the models, it seems plausible that the association between the *LEPR* polymorphisms and steatosis could be moderated by higher HOMA2-IR scores. The interactions between *LEPR rs1805096*-CT and *rs1892534*-AG and HOMA2-IR scores could have been the result of influential points because there were no individuals who carried the heterozygote genotypes in the no steatosis and higher HOMA2-IR score group. *LEPR rs1137100* or *rs1805096* are located in the coding region and contribute to splicing regulation.(Yuan, 2006) *LEPR rs1892534* is located in the 3' downstream untranslated region with no known function.(Yuan, 2006) The genetic variants with predicted functions related to splicing regulation may allow the gene to express different exons which encode gene products such as proteins.(Mercatante, 2000) Further, understanding the

function of the associated genetic variants may explain how these genetic variants are related to the occurrence of steatosis or IR in HCV infection.

There were statistically significant associations between *TGF-β1* SNPs and steatosis or IR. Possession of the *TGF-β1 rs2278422*-GG genotype indicated lower odds of IR for both race groups compared to the CC or CG genotype. One significant interaction was observed in African Americans between *TGF-β1 rs2241716*-GG genotype and higher HOMA2-IR scores such that higher odds of steatosis were observed than expected for the main effects of HOMA2-IR scores and the genotype alone. *TGF-β1 rs2241716* is located in the intron region and predicted to be an intronic enhancer which could change how the encoded protein is produced.(Yuan, 2006) This change in the production of the protein may influence the occurrence of these conditions.

Three previous studies described associations between the *IL6 rs1800795-G* allele and the occurrence of IR in Caucasian European decent, healthy or diabetic populations.(Cardellini, 2005; Testa, 2006; X Yang, 2005) The current study did not identify a statistically significant association between this polymorphism and the occurrence of IR. Furthermore, in the current study the direction of the association contradicted the previous work. The observed differences could be related to different phenotype measures, statistical methods and different populations. The previous studies examined Caucasian individuals who were healthy or diabetic compared to the current student that examined both Caucasian Americans and African Americans infected with HCV genotype-1. HCV infection may contribute to the occurrence of IR and the mechanisms for the development of IR may be different in populations with and without HCV. The three previous studies used HOMA-IR to quantify IR compared to HOMA2-IR used in the current study and HOMA2-IR is a more accurate estimate of IR.(Wallace, 2004)

A different study found an association between the *MCP1/CCL2 rs1024611-A* allele and the occurrence of IR among 2798 Caucasians in a CVD risk cohort.(Simeoni, 2004) In the current study, no statistically significant association was observed in 156 Caucasian Americans. The difference in the findings could be due to different sample sizes, phenotype measures and cohorts. The previous study utilized HOMA-IR and treated IR as a continuous outcome and the current study used HOMA2-IR and created a categorical variable for IR. Another difference is that the previous study examined IR in a cohort of CVD risk patients compared to HCV genotype-1 infected patients and HCV may contribute to the occurrence of IR.

A limitation of this study was that the Virahep-C cohort was small and had limited power to detect host genetic associations. However, even with the small sample size this study was able to detect statistically significant associations between genetic variants and steatosis or IR. The results of this study are also limited by the inability to validate the findings because a similar sample of HCV infected patients with the conditions of interest was not available. It is important to validate these findings because no adjustment for multiple comparisons was made. 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 race 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. Since much of the variation was not accounted for using the selected SNPs in some of the genes, it is difficult to understand the overall gene association with these conditions. However, the single SNP results still provide useful information about genetic variant associations with the conditions in HCV infection.

Nevertheless, the results of this study are an important contribution to the literature by identifying genetic variants associated with steatosis and insulin resistance among Caucasian American and African American patients infected with HCV genotype-1. The findings from this study should be validated by additional studies to confirm the findings. A next step in research could be to examine genetic variants that are in high linkage disequilibrium or close to the associated genetic variants to identify the true causal genetic variant. In addition, further research is needed to understand the functional purpose of the associated genetic variants to better understand how they influence the occurrence of steatosis and IR. In particular, it may be important to complete functional studies for the associated genetic variants that currently have no known function. These studies would further contribute to understanding how these genetic variants affect steatosis and IR.

To make conclusions about gene associations with steatosis and IR, additional SNPs from the examined genes could be selected and genotyped to account for more of the common variation and possibly identify additional associations. The genetic variants examined in this study should be investigated in other studies with a larger cohort of HCV patients or other patient populations with steatosis or IR to possibly identify associations not observed in this study.

In conclusion, this study identified host genetic associations with steatosis or insulin resistance in African Americans and Caucasian Americans with HCV genotype-1. Significant associations between *IL6*, *IL10*, *LEPR* or *TGF-β1* 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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Table 4-1: Demographic Characteristics by Race

Characteristics	African American N = 167	Caucasian American N = 184	p-value
	N (%)	N (%)	
Gender			
Male	107 (64.1)	118 (64.1)	
Female	60 (35.9)	66 (35.9)	0.99‡
Portal Inflammation Score (HAI)			
Mild	27 (16.2)	30 (16.3)	
Moderate	108 (64.7)	101 (54.9)	
Severe	32 (19.2)	53 (28.8)	0.09‡
Steatosis			
No Steatosis	64 (38.3)	63 (34.2)	
Steatosis Present	103 (61.7)	121 (65.8)	0.43‡
Insulin Resistance			
HOMA2 < 2	83 (58.5)	104 (66.7)	
HOMA2 ≥ 2	59 (41.6)	52 (33.3)	0.14‡
	Mean (SD)	Mean (SD)	
Homeostasis Model Assessment 2 (ln HOMA2-IR)	0.6 (0.7)	0.4 (0.7)	0.006†
Alanine Aminotransferase (ALT)	70.6 (45.8)	108.0 (91.5)	<0.0001†
Aspartate Aminotransferase (AST)	60.0 (43.2)	73.0 (58.7)	0.06†
Age (years)	48.7 (6.9)	47.3 (8.4)	0.13†
Body Mass Index (BMI)	30.8 (6.4)	28.2 (5.2)	<0.0001†
Baseline Viral Level (log_{10} IU/mL)	6.2 (0.6)	6.3 (0.8)	0.08†
Total Inflammation (HAI)	10.0 (3.2)	10.4 (3.5)	0.21†
Triglycerides (mg/dL)	132.4 (100.0)	114.9 (68.4)	0.14†
Cholesterol (mg/dL)	177.7 (36.7)	179.2 (35.5)	0.67†
Ishak Fibrosis Score	2.1 (1.4)	2.3 (1.5)	0.33†
Alcohol Consumption (Week)	3.6 (10.8)	2.3 (6.2)	0.99†

† Chi-square test
‡ Wilcoxon Two Sample Test

Table 4-2: Frequencies of Genotypes for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

Single Nucleotide Polymorphism		African Americans N = 167 Genotype Frequency	Call Rate	HWE*	Caucasian Americans N = 184 Genotype Frequency	Call Rate	HWE*
IL6 rs1880242							
	GG	4 (0.02)			34 (0.19)		
	GT	48 (0.29)			106 (0.58)		
	TT	115 (0.69)	1.0	1.0	43 (0.24)	0.99	0.03
IL6 rs2056576							
	CC	54 (0.32)			69 (0.38)		
	CT	79 (0.48)			94 (0.51)		
	TT	33 (0.20)	0.99	0.67	20 (0.11)	0.99	0.15
IL6 rs2069827							
	GG	158 (0.96)			152 (0.83)		
	GT	7 (0.04)			30 (0.16)		
	TT	0 (0)	0.99	1.0	1 (0.01)	0.99	1.0
IL6 rs1800797							
	AA	0 (0)			23 (0.12)		
	AG	22 (0.13)			92 (0.50)		
	GG	144 (0.87)	0.99	1.0	69 (0.38)	1.0	0.37
IL6 rs1800795							
	CC	0 (0)			27 (0.15)		
	CG	23 (0.14)			91 (0.49)		
	GG	143 (0.86)	0.99	1.0	66 (0.36)	1.0	0.63
IL6 rs2069830							
	CC	133 (0.81)			182 (0.99)		
	CT	30 (0.18)			1 (0.01)		
	TT	2 (0.01)	0.99	0.69	0 (0)	0.99	1.0
IL6 rs2069837							
	AA	132 (0.80)			159 (0.86)		
	AG	34 (0.20)			25 (0.14)		
	GG	0 (0)	0.99	0.20	0 (0)	1.0	1.0
IL6 rs1554606							
	GG	79 (0.48)			60 (0.33)		
	GT	71 (0.43)			95 (0.52)		
	TT	16 (0.10)	0.99	0.99	29 (0.15)	1.0	0.40
IL6 rs2069845							
	AA	75 (0.45)			60 (0.33)		
	AG	75 (0.45)			95 (0.52)		
	GG	17 (0.10)	1.0	0.78	28 (0.15)	0.99	0.34
IL10 rs11119474							
	AA	0 (0)			0 (0)		
	AG	2 (0.01)			27 (0.15)		
	GG	175 (0.99)	1.0	1.0	156 (0.85)	0.99	0.61

Table 4-2 (Continued)

IL10 rs3024505							
	CC	148 (0.89)			138 (0.76)		
	CT	19 (0.11)			40 (0.22)		
	TT	0 (0)	1.0	1.0	4 (0.02)	0.99	0.54
IL10 rs3024498							
	AA	128 (0.77)			96 (0.53)		
	AG	39 (0.23)			67 (0.37)		
	GG	0 (0)	1.0	0.13	20 (0.11)	0.99	0.12
IL10 rs3024496							
	CC	28 (0.17)			50 (0.27)		
	CT	82 (0.49)			86 (0.47)		
	TT	57 (0.34)	1.0	0.87	48 (0.26)	1.0	0.38
IL10 rs1554286							
	CC	61 (0.37)			132 (0.72)		
	CT	79 (0.47)			50 (0.27)		
	TT	27 (0.16)	1.0	0.87	3 (0.02)	1.0	0.76
IL10 rs2222202							
	CC	84 (0.50)			48 (0.26)		
	CT	68 (0.41)			86 (0.47)		
	TT	15 (0.09)	1.0	0.82	50 (0.27)	1.0	0.38
IL10 rs1800890							
	AA	10 (0.06)			29 (0.16)		
	AT	60 (0.36)			87 (0.47)		
	TT	97 (0.59)	1.0	0.86	67 (0.37)	0.99	0.93
LEPR rs6673324							
	AA	42 (0.25)			51 (0.28)		
	AG	87 (0.52)			90 (0.50)		
	GG	37 (0.22)	0.99	0.53	41 (0.22)	0.99	0.91
LEPR rs1137100							
	AA	112 (0.67)			100 (0.55)		
	AG	49 (0.29)			69 (0.68)		
	GG	6 (0.04)	1.0	0.82	14 (0.08)	0.99	0.66
LEPR rs1343982							
	AA	16 (0.10)			16 (0.09)		
	AG	75 (0.45)			69 (0.38)		
	GG	76 (0.45)	1.0	0.69	99 (0.54)	0.99	0.45
LEPR rs1137101							
	AA	42 (0.25)			53 (0.29)		
	AG	73 (0.44)			91 (0.50)		
	GG	52 (0.31)	1.0	0.11	39 (0.21)	0.99	0.99
LEPR rs2376018							
	AA	115 (0.69)			124 (0.68)		
	AG	49 (0.29)			54 (0.29)		
	GG	3 (0.02)	1.0	0.58	5 (0.03)	0.99	0.76
LEPR rs1805096							
	CC	52 (0.31)			74 (0.41)		
	CT	83 (0.50)			70 (0.38)		
	TT	32 (0.19)	1.0	0.91	38 (0.21)	0.99	0.01

Table 4-2 (Continued)							
LEPR rs1892534							
	AA	33 (0.20)			40 (0.22)		
	AG	83 (0.50)			69 (0.38)		
	GG	51 (0.31)	1.0	0.94	74 (0.40)	0.99	0.003
TGF-B1 rs2278422							
	CC	14 (0.08)			29 (0.16)		
	CG	71 (0.43)			101 (0.55)		
	GG	82 (0.49)	1.0	0.80	54 (0.29)	1.0	0.11
TGF-B1 rs2241716							
	AA	0 (0)			0 (0)		
	AG	16 (0.10)			0 (0)		
	GG	151 (0.90)	1.0	1.0	183 (1.0)	0.99	-
TGF-B1 rs1800471							
	CC	0 (0)			1 (0.01)		
	CG	23 (0.14)			17 (0.09)		
	GG	144 (0.86)	1.0	1.0	165 (0.90)	0.99	0.38

* P-value from test of Hardy Weinberg Equilibrium

Table 4-3: Adjusted Odds Ratios for Steatosis for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

	African Americans* N = 167					Caucasian Americans* N = 184				
		SNP Main Effects		HOMA2-IR			SNP Main Effects		HOMA2-IR	
Single Nucleotide Polymorphism	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**
IL6 rs1880242										
GG/GT	52	1.00				140	1.00			
TT	115	1.28 (0.57-2.89)	0.55	‡		43	0.76 (0.29-2.06)	0.61	‡	
IL6 rs2056576										
CC	54	1.00				69	1.00			
CT	79	1.08 (0.47-2.52)	0.85	‡		94	0.57 (0.23-1.42)	0.23	‡	
TT	33	1.10 (0.38-1.34)	0.86	‡		20	0.91 (0.23-3.65)	0.90	‡	
IL6 rs2069827										
GG	158	1.00				152	1.00			
GT/TT	7	†		†		31	1.47 (0.50-4.30)	0.49	‡	
IL6 rs1800797										
AA/AG	22	1.00				115	1.00			
GG	144	2.06 (0.61-6.98)	0.25	‡		69	0.45 (0.19-1.05)	0.07	‡	
IL6 rs1800795										
CC/CG	23	1.00				118	1.00			
GG	143	1.78 (0.55-5.73)	0.34	‡		66	0.47 (0.20-1.10)	0.08	‡	
IL6 rs2069830										
CC	133	1.00				182	1.00			
CT/TT	32	0.87 (0.33-2.27)	0.77	‡		1	†		‡	
IL6 rs2069837										
AA	132	1.00				159	1.00			
AG/GG	34	0.81 (0.32-2.04)	0.65	‡		25	0.82 (0.23-2.91)	0.76	‡	
IL6 rs1554606										
GG	79	1.00				60	1.00			
GT/TT	87	0.88 (0.41-1.91)	0.75	‡		124	2.24 (0.94-5.30)	0.07	‡	
IL6 rs2069845										
AA	75	1.00				60	1.00			
AG/GG	92	0.86 (0.40-1.86)	0.70	‡		123	2.52 (1.06-6.00)	0.04	‡	

Table 4-3 (Continued)										
IL10 rs11119474										
AA/AG	2	1.00				27	1.00			
GG	165	†		‡		156	1.46 (0.48-4.48)	0.51	‡	
IL10 rs3024505										
CC	148	1.00				138	1.00			
CT/TT	19	0.36 (0.11-1.23)	0.10	‡		44	0.50 (0.21-1.22)	0.13	‡	
IL10 rs3024498										
AA	128	1.00				96	1.00		7.53 (2.34-24.26)	0.001
AG/GG	39	0.56 (0.23-1.37)	0.20	‡		87	0.85 (0.34-2.16)	0.74	1.62 (0.68-3.87)	0.28
IL10 rs3024496										
CC	28	1.00		0.27 (0.05-1.31)	0.10	50	1.00		1.46 (0.52-4.15)	0.47
CT	82	2.02 (0.64-6.36)	0.23	3.39 (1.31-8.78)	0.01	86	3.27 (1.06-10.09)	0.04	7.66 (2.31-25.42)	0.001
TT	57	3.98 (1.15-13.77)	0.03	2.24 (0.80-6.28)	0.13	48	1.69 (0.48-5.92)	0.41	9.30 (1.45-59.53)	0.02
IL10 rs1554286										
CC	61	1.00				131	1.00		2.15 (1.00-4.60)	0.05
CT/TT	106	1.41 (0.64-3.14)	0.40	‡		52	3.01 (0.87-10.40)	0.08	15.30 (2.64-88.51)	0.002
IL10 rs2222202										
CC	84	1.00		3.02 (1.18-7.73)	0.02	48	1.00		9.30 (1.45-59.53)	0.02
CT	68	0.55 (0.23-1.29)	0.17	3.21 (1.16-8.85)	0.03	86	1.94 (0.50-7.56)	0.34	7.66 (2.31-25.42)	0.001
TT	15	0.85 (0.07-10.00)	0.90	0.02 (0.01-3.14)	0.12	50	0.59 (0.17-2.07)	0.41	1.46 (0.52-4.15)	0.47
IL10 rs1800890										
AA/AT	70	1.00				116	1.00			
TT	97	1.60 (0.73-3.48)	0.24	‡		67	1.00 (0.41-2.43)	0.99	‡	
LEPR rs6673324										
AA	42	1.00				51	1.00			
AG	87	2.43 (0.97-6.05)	0.057	‡		90	1.64 (0.58-4.62)	0.35	‡	
GG	37	1.82 (0.57-5.79)	0.31	‡		41	1.18 (0.34-4.06)	0.79	‡	
LEPR rs1137100										
AA	112	1.00				100	1.00			
AG/GG	55	0.25 (0.11-0.58)	0.001	‡		83	0.90 (0.40-2.05)	0.81	‡	
LEPR rs1343982										
AA/AG	91	1.00				85	1.00			
GG	76	1.66 (0.77-3.58)	0.19	‡		98	1.11 (0.49-2.53)	0.75	‡	

Table 4-3 (Continued)											
LEPR rs1137101											
AA	42	1.00				53	1.00				
AG	73	0.92 (0.35-2.42)	0.86	‡		91	1.58 (0.58-4.30)	0.37	‡		
GG	52	0.67 (0.24-1.86)	0.44	‡		39	0.31 (0.09-1.10)	0.07	‡		
LEPR rs2376018											
AA	115	1.00				124	1.00				
AG/GG	52	1.38 (0.61-3.12)	0.45	‡		59	2.09 (0.84-5.22)	0.11	‡		
LEPR rs1805096											
CC	52	1.00				74	1.00		2.01 (0.75-5.40)	0.17	
CT	83	2.11 (0.87-5.13)	0.10	‡		70	4.36 (1.21-15.73)	0.03	29.60 (4.27-205.2)	0.001	
TT	32	0.63 (0.21-1.90)	0.42	‡		38	2.36 (0.76-7.33)	0.14	1.01 (0.31-3.32)	0.98	
LEPR rs1892534											
AA	33	1.00				40	1.00		1.20 (0.37-3.90)	0.76	
AG	83	2.98 (1.07-8.33)	0.04	‡		69	1.79 (0.45-7.16)	0.41	26.22 (3.81-180.4)	0.001	
GG	51	1.55 (0.52-4.62)	0.43	‡		74	0.44 (0.15-1.34)	0.15	1.97 (0.74-5.25)	0.18	
TGF-B1 rs2278422											
CC/CG	85	1.00				130	1.00				
GG	82	4.42 (1.84-10.65)	0.001	‡		54	1.50 (0.62-3.60)	0.37	‡		
TGF-B1 rs2241716											
AA/AG	16	1.00		0.65 (0.22-1.94)	0.44	0	1.00				
GG	151	1.48 (0.47-4.62)	0.50	3.34 (1.61-6.91)	0.001	183	†		†		
TGF-B1 rs1800471											
CC/CG	23	1.00				18	1.00				
GG	144	0.57 (0.18-1.76)	0.33	‡		165	1.61 (0.37-6.95)	0.52	‡		

* Model adjusted for the genetic variant, centered Ishak fibrosis score, centered weekly alcohol consumption, centered ln HOMA2-IR score, centered body mass index, centered $\log_{10}$ baseline viral levels and interaction between the genetic variant and ln HOMA2-IR score (where significant)

‡ Odds ratios from the main effects model adjusting for the genetic variant, centered Ishak fibrosis score, centered weekly alcohol consumption, centered log ln HOMA2-IR score, centered body mass index and centered $\log_{10}$ baseline viral levels were reported because the log likelihood test for the interaction between the genetic variant and ln HOMA2-IR scores were not significant at an alpha level of 0.05.

† Minor allele frequency less then 5% in one population

§ Homozygote genotype combined with heterozygote genotype to estimate associations

Table 4-4: Raw Data Comparing Steatosis and Insulin Resistance and the Frequency of *Il10 rs3024496* variant genotypes

	African Americans		Caucasian Americans	
	No Steatosis	Steatosis ≥ 5%	No Steatosis	Steatosis ≥ 5%
HOMA2-IR < 2	CC: 6 CT: 25 TT: 9	CC: 3 (33.3) CT: 23 (47.9) TT: 17 (65.4)	CC: 12 CT: 21 TT: 8	CC: 15 (55.7) CT: 32 (60.4) TT: 16 (66.7)
HOMA2-IR ≥ 2	CC: 7 CT: 4 TT: 4	CC: 4 (36.4) CT: 18 (81.8) TT: 22 (84.6)	CC: 6 CT: 2 TT: 2	CC: 11 (64.7) CT: 20 (90.1) TT: 11 (84.7)

Table 4-5: Frequencies of *LEPR rs1805096* Genotypes for African Americans and Caucasian Americans by Steatosis and Insulin Resistance

	African Americans		Caucasian Americans	
	No Steatosis	Steatosis ≥ 5%	No Steatosis	Steatosis ≥ 5%
HOMA2-IR < 2	CC: 12 CT: 18 TT: 10	CC: 12 (50.0) CT: 27 (60.0) TT: 4 (28.6)	CC: 18 CT: 19 TT: 4	CC: 22 (55.0) CT: 24 (55.8) TT: 16 (80.0)
HOMA2-IR ≥ 2	CC: 7 CT: 4 TT: 4	CC: 13 (65.0) CT: 19 (82.6) TT: 12 (75.0)	CC: 7 CT: 0 TT: 3	CC: 15 (68.2) CT: 15 (100.0) TT: 11 (78.6)

Table 4-6: Adjusted Odds Ratios for Insulin Resistance in African Americans and Caucasian Americans

	African Americans* N = 142				Caucasian Americans* N = 156			
Single Nucleotide Polymorphism	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
IL6 rs1880242								
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
IL6 rs2056576								
CC	47	1.00			58	1.00		
CT	65	0.48	0.20-1.14	0.10	80	1.22	0.57-2.61	0.62
TT	30	0.51	0.17-1.47	0.21	17	0.35	0.07-1.81	0.21
IL6 rs2069827								
GG	134	1.00			130	1.00		
GT/TT	6	5.19	0.65-41.52	0.12	25	0.62	0.20-1.91	0.41
IL6 rs1800797								
AA/AG	19	1.00			99	1.00		
GG	122	0.55	0.18-1.69	0.30	57	0.60	0.28-1.32	0.20
IL6 rs1800795								
CC/CG	20	1.00			99	1.00		
GG	121	0.62	0.29-1.36	0.23	57	0.48	0.16-1.44	0.19
IL6 rs2069830								
CC	113	1.00			155	1.00		
CT/TT	27	0.61	0.23-1.65	0.33	0	†		
IL6 rs2069837								
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
IL6 rs1554606								
GG	66	1.00			52	1.00		
GT/TT	75	1.45	0.69-3.15	0.35	104	1.71	0.76-3.85	0.20
IL6 rs2069845								
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
IL10 rs11119474								
AA/AG	2	1.00			23	1.00		
GG	140	†			132	1.00	0.33-2.94	0.98
IL10 rs3024505								
CC	126	1.00			113	1.00		
CT/TT	16	0.86	0.25-2.97	0.81	41	1.16	0.49-2.73	0.73
IL10 rs3024498								
AA	112	1.00			79	1.00		
AG/GG	30	1.71	0.68-4.33	0.26	76	1.77	0.85-3.70	0.13
IL10 rs3024496								
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

Table 4-6 (Continued)								
IL10 rs1554286								
CC	49	1.00			109	1.00		
CT/TT	93	0.59	0.26-1.31	0.19	46	0.48	0.20-1.11	0.09
IL10 rs2222202								
CC	74	1.00			37	1.00		
CT	57	0.69	0.30-1.57	0.38	75	1.10	0.43-2.84	0.85
TT	11	5.07	1.10-23.45	0.04	44	2.11	0.75-5.94	0.16
IL10 rs1800890								
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
LEPR rs6673324								
AA	33	1.00			41	1.00		
AG	81	0.97	0.39-2.37	0.94	76	0.33	0.14-0.79	0.01
GG	28	0.66	0.20-2.12	0.48	37	0.75	0.28-2.00	0.56
LEPR rs1137100								
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
LEPR rs1343982								
AA/AG	79	1.00			69	1.00		
GG	63	0.95	0.44-2.05	0.90	86	0.75	0.36-1.55	0.44
LEPR rs1137101								
AA	36	1.00			49	1.00		
AG	62	1.60	0.60-4.22	0.35	73	0.86	0.36-2.06	0.74
GG	44	1.77	0.63-4.95	0.28	33	2.25	0.80-6.32	0.12
LEPR rs2376018								
AA	98	1.00			104	1.00		
AG/GG	44	1.16	0.52-2.61	0.72	51	0.57	0.25-1.30	0.18
LEPR rs1805096								
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
LEPR rs1892534								
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
TGF-B1 rs2278422								
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
TGF-B1 rs2241716								
AA/AG	16	1.00			0	1.00		
GG	126	1.32	0.41-4.29	0.64	155	†		
TGF-B1 rs1800471								
CC/CG	16	1.00			16	1.00		
GG	126	1.68	0.56-5.00	0.35	139	0.77	0.25-2.39	0.65

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

† Model could not be estimated because minor allele frequency < 5% for the SNP

‡ Homozygote genotype combined with heterozygote genotype to estimate association

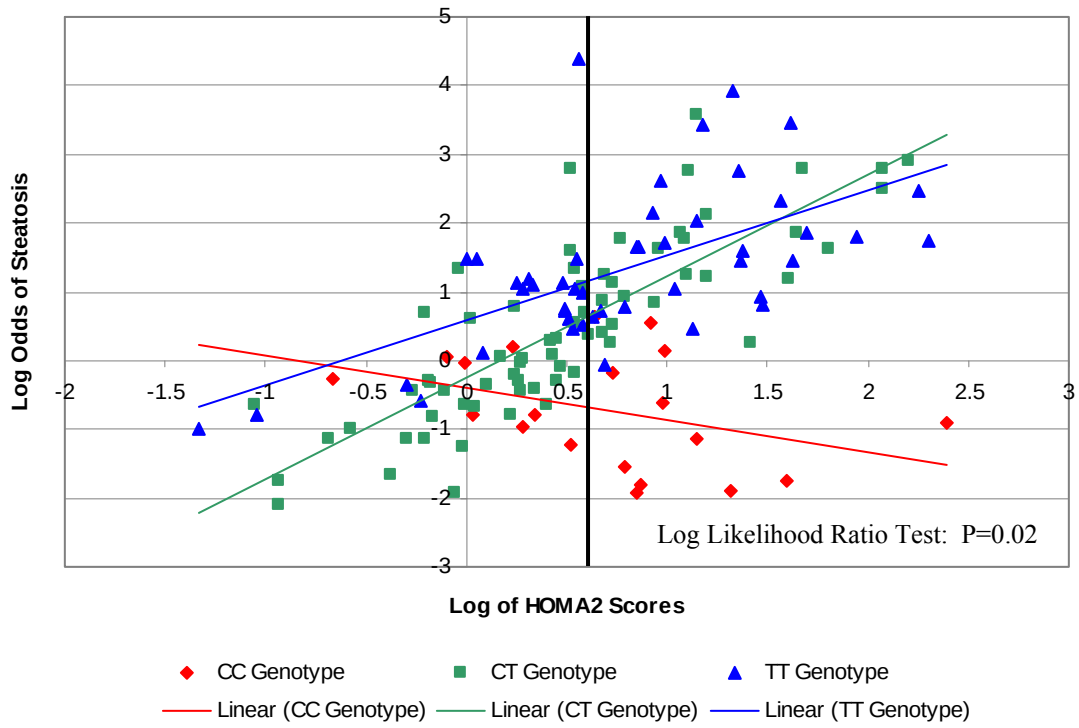

Figure 4-1A: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *IL10 rs3024496* in African Americans

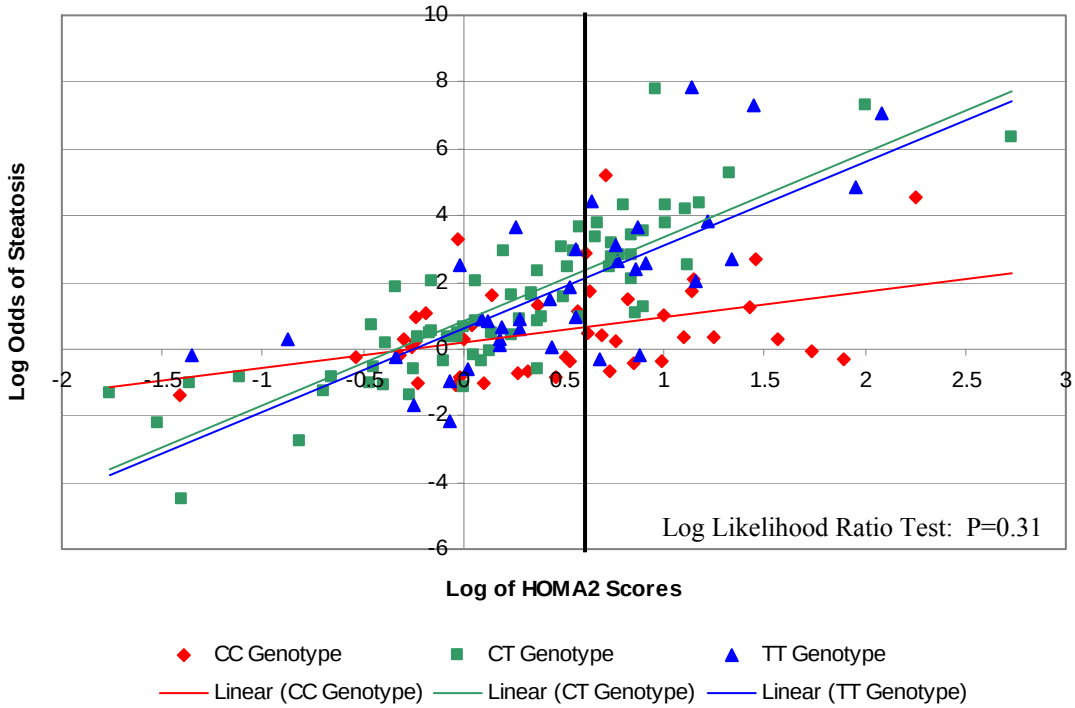

Figure 4-1B: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *IL10 rs3024496* in Caucasian Americans

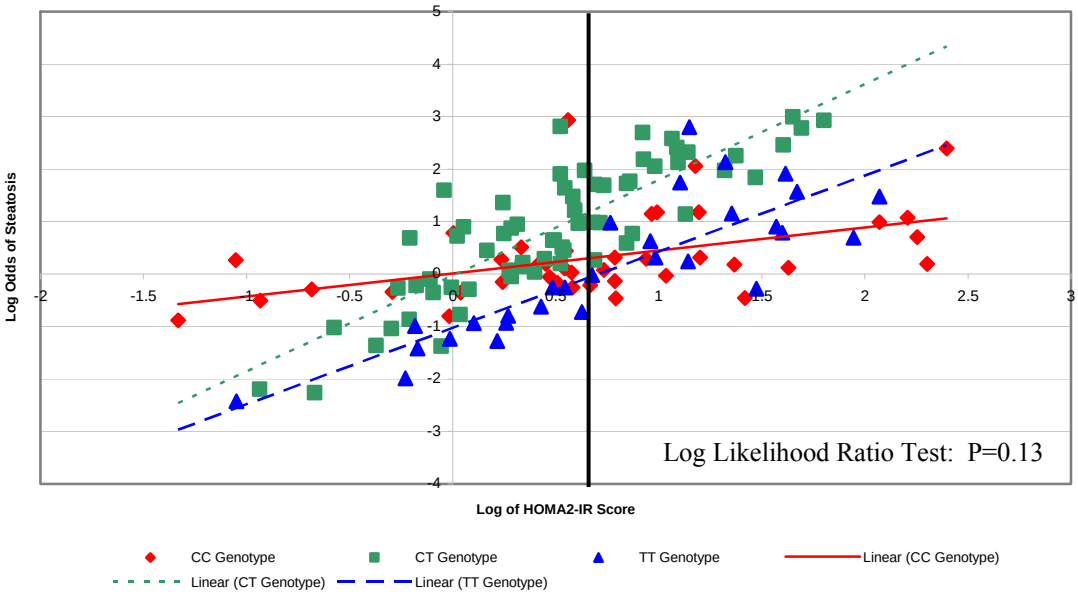

Figure 4-2A: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *LEPR rs1805096* in African Americans

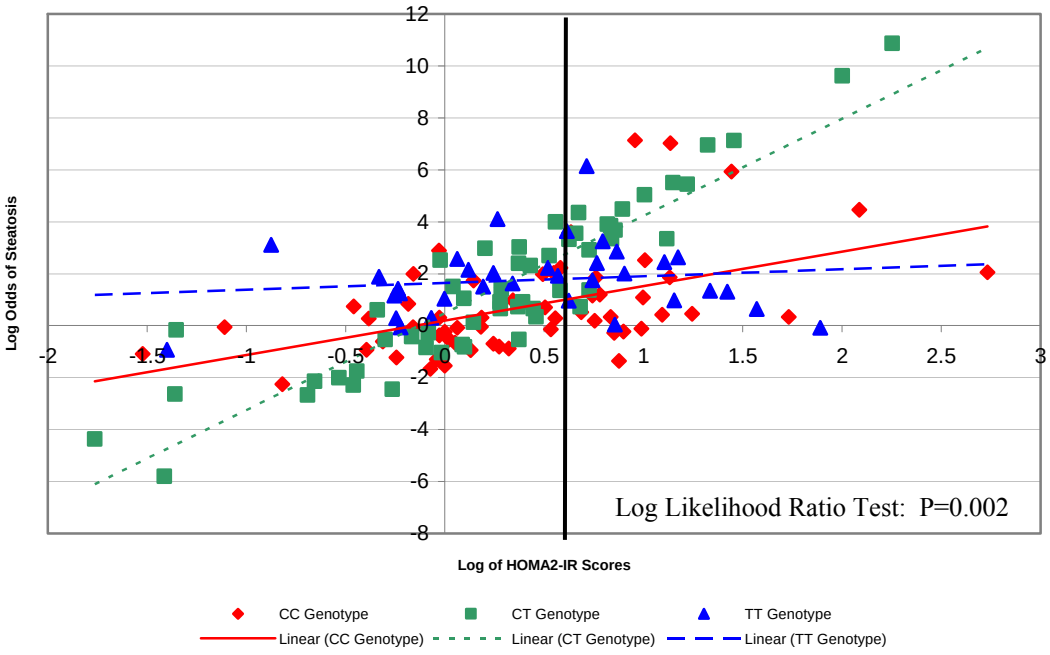

Figure 4-2B: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *LEPR rs1805096* in Caucasian Americans

5.0 RESEARCH ARTICLE 3:

POLYMORPHISMS IN *ADIPONECTIN RECEPTOR 1* (*ADIPOR1*) AND *3-HYDROXY-3-METHYLGLUTARYL-COENZYME A SYNTHASE 2* (*HMGCS2*) AND STEATOSIS AND INSULIN RESISTANCE IN HEPATITIS C VIRUS GENOTYPE-1 INFECTION

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5.1 ABSTRACT

Steatosis is fat deposition in liver cells and is prevalent in 30-84% of chronic hepatitis C virus (HCV) patients. Insulin resistance (IR) occurs when normal amounts of insulin do not produce a typical response from cells. Both are common in HCV infection and are thought to be biologically related.

This study examined associations between host genetic variants, steatosis and IR among 163 African Americans (AA) and 179 Caucasian Americans (CA) infected with HCV genotype-1. Steatosis was defined as having at least 5% of fat in cells on liver biopsy. The Homeostasis Model Assessment (HOMA) Version 2.2 was used to quantify IR and IR was categorized as being present with a value of at least 2. Associations between *ADIPOR1* and *HMGCS2* polymorphisms and steatosis or IR were investigated separately by race using logistic regression models.

Statistically significant associations ($p<0.05$) were observed between *ADIPOR1 rs6666089* and *rs1539355* and steatosis in Caucasian Americans. *HMGCS2 rs12123085* was significantly associated with steatosis and IR. Statistically significant interactions between *ADIPOR1 rs6666089*-AG and *rs1539355*-AG genotypes and higher HOMA2-IR scores were observed in Caucasian Americans when examining steatosis and indicated higher odds of steatosis compared to what would be expected from the main effects of the genotypes and the HOMA2-IR scores.

ADIPOR1 and *HMGCS2* may be important to understanding the occurrence of steatosis and IR in African Americans and Caucasian Americans with HCV genotype-1 infection. Results indicate that some *ADIPOR1* polymorphisms may modify an association between IR and steatosis. The function of these genetic variants is still being studied and identifying the function

may contribute to understanding the mechanisms of steatosis and IR in HCV genotype-1 infection.

5.2 INTRODUCTION

Steatosis is characterized by the accumulation of fat in the liver and diagnosis is made by calculating the percentage of fat in liver cells by examining liver biopsy.(Teli, 1995) Steatosis is prevalent in as few as 30%, or as many as 84%, of patients with chronic hepatitis C virus (HCV) infection.(Adinolfi, 2001; Asselah, 2006; Castera, 2003; Conjeevaram, 2006; Conjeevaram, 2007; Czaja, 1998; Hourigan, 1999; Hui, 2002; Monto, 2002; Patton, 2004; Poynard, 2003; Rubbia-Brandt, 2004; Rubbia-Brandt, 2001; Serfaty, 2001; Westin, 2002) The mechanisms of hepatic steatosis are thought to be multifactorial and the presence of insulin resistance may be associated with the development of steatosis.(Adinolfi, 2001; Castera, 2003; Hourigan, 1999; Rubbia-Brandt, 2000; Serfaty, 2001; Serfaty, 2002)

Factors previously identified to be associated with steatosis in HCV genotype-1 patients include alcohol consumption, higher body mass index (BMI), older age, male gender, Caucasian American race, presence of hepatic inflammation, hyperlipidaemia, increased triglyceride levels, higher cholesterol levels, increased alanine aminotransferase (ALT) levels, increased aspartate aminotransferase (AST) levels, higher fibrosis scores and the presence of insulin resistance.(Asselah, 2006; Browning, 2004; Conjeevaram, 2007; Fabris, 2004; Leandro, 2006; Matos, 2006; Ruhl, 2004; Solis-Herruzo, 2005; Younossi, 2004) African Americans have a lower prevalence of steatosis than Caucasian Americans despite having a generally higher BMI, which is also associated with steatosis.(Browning, 2004; Ruhl, 2004) The presence of steatosis

may influence other HCV conditions or outcomes of treatment. Steatosis was previously identified as being associated with progression of fibrosis in HCV patients.(Adinolfi, 2001; Castera, 2003; Hourigan, 1999; Serfaty, 2002; Westin, 2002) The presence of steatosis may also negatively impact sustained virologic response (SVR).(Fabris, 2005; Guidi, 2005; Jian Wu, 2006; Patton, 2004; Soresi, 2006; Westin, 2007) HCV genotype-1 patients achieved SVR less frequently (29-46%) if steatosis was present compared to those without steatosis (62-65%).(Jian Wu, 2006; Soresi, 2006; Westin, 2007)

Insulin resistance (IR) is a condition in which normal amounts of insulin are insufficient to stimulate cells to use blood glucose for energy and metabolism, specifically fat, muscle and liver cells.(Rao, 2001; Romero-Gomez, 2006) The Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR) can be used to quantify IR.(Matthews, 1985) IR has been shown to occur early in the HCV infection.(Petit, 2001) Additionally, patients with chronic HCV infection were observed in one study to have higher HOMA-IR scores compared to healthy controls.(Hui, 2003) Studies have also shown that IR was predictive of fibrosis progression (D'souza, 2005; Fartoux, 2005; Hui, 2003; Lonardo, 2004; Muzzi, 2005; Sud, 2004) and hepatic inflammation in patients with chronic HCV.(Chitturi, 2002) Presence of IR may reduce the function of interferon therapy and the ability to achieve SVR in HCV patients especially those infected with genotype-1.(Romero-Gomez, 2006; Romero-Gomez, 2005) Clearance of HCV through treatment has been shown to improve insulin sensitivity.(Kawaguchi, 2007) Risk factors associated with IR include African American race, obesity, older age, fibrosis and cirrhosis.(Heathcote, 2002; Petit, 2001; Romero-Gomez, 2005)

The roles of *ADIPOR1* and *HMGCS2* polymorphisms have not been examined with regard to steatosis or IR in HCV infection. Most studies have examined *Adiponectin Receptor 1*

(*ADIPOR1*) and *3-hydroxy-3-methylglutaryl-CoA Synthase 2* (*HMGCS2*) expression or polymorphism associations with steatosis or IR in healthy, diabetic or obese patients (Crimmins, 2007; Sanyal, 2001; Siitonen, 2006; Stefan, 2005; Stefan, 2002; Younossi, 2005; Younossi, 2004) and only one study included African Americans.(Crimmins, 2007) *ADIPOR1* encodes adiponectin and low levels were associated with higher HOMA-IR scores in two studies.(Chandran, 2003; Weyer, 2001) Jonsson et al. found that adiponectin levels varied by HCV genotype and low adiponectin levels were associated with steatosis.(Jonsson, 2005) These results indicate that *ADIPOR1* may influence the occurrence of steatosis or IR. Other studies have also examined *ADIPOR1* polymorphism associations with IR or steatosis.(Siitonen, 2006; Stefan, 2005) In a sample of people of European decent, the *ADIPOR1 rs6666089*-A allele was associated with higher HOMA-IR scores and a greater percent of fatty liver.(Stefan, 2005) Crimmins, et al. observed a statistically significant association between the *ADIPOR1 rs1342387*-A allele and lower HOMA-IR scores in a non-lean subset of African American children.(Crimmins, 2007) These results indicate that *ADIPOR1* polymorphisms may be important in understanding the mechanisms of steatosis or IR, but no studies have examined these associations in HCV infection.

3-hydroxy-3-methylglutaryl-CoA Synthase 2 (*HMGCS2*) is a rate-limiting enzyme of the HMG-CoA pathway of fatty acid metabolism or ketogenesis. Younossi, et al. concluded that insulin may influence the expression of *HMGCS2* suggesting that insulin resistance may participate in the regulation of ketogenesis pathway.(Younossi, 2005) Other studies indicated that people with steatosis and IR have higher *HMGCS2* expression compared to those with steatosis and without IR.(Sanyal, 2001; Younossi, 2005; Younossi, 2004) Few studies have

examined the role of *HMGCS2* in the occurrence of steatosis or IR and no studies tested the association between *HMGCS2* polymorphisms and these conditions.

HCV infection may contribute to occurrence or severity of steatosis or IR and genetic associations may contribute to understanding the occurrence these conditions. This study aims to test associations of *ADIPOR1* and *HMGCS2* polymorphisms with steatosis and with insulin resistance in a sample of African Americans and Caucasian Americans infected with HCV genotype-1.

5.3 MATERIALS AND METHODS

5.3.1 Study Population and Clinical Data

Data were from the Study of Viral Resistance of Antiviral Therapy of Chronic Hepatitis C (Virahep-C). The Virahep-C study design and primary outcomes have been described elsewhere.(Conjeevaram, 2006) Briefly, there were 401 people enrolled with chronic untreated HCV genotype-1 infection. Of those, 374 (194 CA and 180 AA) provided consent for a genetics ancillary study and 365 had DNA available for genotyping. Twelve self-identified Hispanics and 11 individuals taking exogenous insulin were excluded from the analysis. Therefore, 342 individuals were included in the analyses.

5.3.2 Measurement of Steatosis and Insulin Resistance

Patients without cirrhosis were scheduled to have a liver biopsy within 18 months of study enrollment.(Conjeevaram, 2007; Yee, 2007) Liver biopsies were scored by a single pathologist, who was unaware of patient outcome and clinical status.(Conjeevaram, 2007; Yee, 2007) Biopsies were assessed for the severity of HCV by grading inflammation and staging fibrosis using the modified histologic activity index (HAI) scoring system.(Ishak, 1995) Steatosis was also scored on a scale of 0 to 4 according to the percentage of cells with fat where: 0 = none, 0.5 = <5%, 1 = 5-<25%, 2 = 25-<50%, 3 = 50-<75%, 4 = ≥75%.(Conjeevaram, 2007) For this study, IR was quantified by using the HOMA-IR Calculator Version 2.2 released in 2004 and downloaded from http://www.dtu.ox.ac.uk/.(Levy, 1998; Wallace, 2004) The HOMA2-IR model estimates insulin sensitivity as a percentage of a normal reference population and is calibrated to current insulin assays.(Levy, 1998; Wallace, 2004)

5.3.3 Single Nucleotide Polymorphism (SNP) Selection and Genotyping

ADIPOR1 and *HMGCS2* were selected as candidate genes for steatosis and IR based on literature describing expression or genetic variant associations with steatosis and insulin resistance in mainly obese, diabetic or healthy populations.(Crimmins, 2007; Jonsson, 2005; Sanyal, 2001; Siitonen, 2006; Stefan, 2005; Stefan, 2002; Younossi, 2005; Younossi, 2004) SNPs were selected using the International HapMap Project Phase II (www.hapmap.org). SNP selection for the Virahep-C Caucasian American sample was based on data from a sample of Utah residents with ancestry from northern and western Europe, Centre d'Etude du Polymorphisme Humain (CEPH). To select tag SNPs for the African American sample, a pooled sample was created by

combining data from the CEPH population and a sample of Yoruba Africans in Ibadan, Nigeria (YRI) to simulate an African American population. Tag SNPs were selected using HClust (http://www.wpic.pitt.edu/WPICCompGen/hclust.htm), a pairwise tagging program, with an r^2 value that would account for 80% of the common variation in the gene in both race groups.(Rinaldo, 2005; Roeder, 2005) The region of the gene that was tagged included the transcript plus 2 kilobases (kb) upstream and 2kb downstream. Polymorphisms were selected if the minor allele frequency was greater than 10% in both the CEPH and pooled population. An optimization technique to select a SNP for genotyping was utilized if two suggested SNPs were perfectly correlated in the CEPH population. The correlated SNPs were compared to the selected tag SNPs for the pooled African Americans. If one of the correlated SNPs was selected to be tagged in the pooled African American sample that SNP was used in the Caucasian American tag selection. Using this linkage disequilibrium tag SNP selection method, 12 SNPs per gene were identified in an effort to represent at least 80% of the common variation in each gene.

SNPs were genotyped by the Molecular Epidemiology Core Lab at the Graduate School of Public Health, University of Pittsburgh. To complete the SNP genotyping, TaqMan® methodology (Applied Biosystems, Foster City, CA) was used with the 7900HT Real-time PCR Instrument. Genotype calls were made by two independent callers and only concordant calls were used. Of the 365 samples, 96-99% had genotypes assigned to the SNPs. Quality control measures were conducted to ensure that the lab techniques used for genotyping resulted in correct data. Replication genotyping of a select number of samples was completed for each SNP and the successful replication rate varied from 98-100%. Negative controls consisting of TaqMan reaction and no DNA material were also genotyped.

5.3.4 Variable Categorization

Steatosis was categorized into a dichotomous variable with the presence of steatosis (fat score greater than 0) versus no steatosis (fat score equal to 0), HOMA2-IR scores were categorized into the presence of IR (HOMA2-IR at least 2) versus no IR (HOMA2-IR less than 2) for analyses. In general, a HOMA-IR score of at least 1.5 is thought to indicate decreased insulin sensitivity.(Conjeevaram, 2007) For this study, IR was defined as HOMA2-IR score of at least 2.0 based on a previous study of the Virahep-C cohort.(Conjeevaram, 2007) For each SNP, indicator variables were created for the genotypes to test for genotype associations with steatosis or IR. 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. Haplotypes were categorized as either having at least one copy of the haplotype or no copies.

5.3.5 Risk Factor Variables and Model Building

Ishak fibrosis score, weekly alcohol consumption, age, BMI, baseline viral level, HAI score, ALT levels, AST levels, cholesterol levels and triglyceride levels were continuous factors centered at their mean values and examined as risk factors for steatosis and IR. Diabetes status and HCV subtype were categorical risk factors examined in this study. Self-reported race was used since previous reports from the Virahep-C study found that the individual admixture strongly agreed with self-reported race.(Yee, 2007) Steatosis was assessed as a risk factor for IR and continuous HOMA2-IR scores were assessed as a risk factor for steatosis. HOMA2-IR scores were transformed using the natural log and centered at the mean.

5.3.6 Genetic Analytical Methods

Genotype and allele frequencies as well as Hardy Weinberg Equilibrium (HWE) chi square tests were calculated by race for each SNP. The 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 (MAF) were examined by race and SNPs with a MAF less than 5% were not analyzed. Haplotypes were estimated using the EM algorithm for *ADIPOR1* and *HMGCS2* separately by race.(Excoffier, 1995) Twenty-three of the 24 SNPs were used to estimate haplotypes. *RS667246* did not conform to the expectations of HWE and was excluded from haplotype estimation.(Kirk, 2002; Yang, 2003) Estimated haplotypes with a probability of at least 0.7 of being the true haplotype were retained and used in analyses. If estimated haplotypes had a probability less than 0.7, no haplotypes were assigned to the study patient. Common haplotypes with a frequency of at least 5% in either Caucasian Americans or African Americans were investigated for an association with steatosis or IR. SAS® Genetics Version 9.1.3 was used to conduct analyses (SAS Institute Inc., Cary, NC, 2002-2003). The Tagger Program in the Haploview Software Suite version 4.0 was used to calculate the amount of common variation accounted for in the gene (r^2) by the tagged SNPs separately by race.(Barrett, 2005) This analysis was done to evaluate how well the SNP selection methods captured the common genetic variation in the genes.

5.3.7 Statistical Analyses

Demographic characteristics and risk factors for steatosis and IR were assessed by race using appropriate association tests. Genotype association chi square tests and haplotype trait chi square tests were completed to test for an association with steatosis or IR (Appendix C).(Nielsen, 1999; Zhao, 2000)

Odds ratios were used to quantify the association between steatosis or IR and the genetic variants. Adjusted models were built using backwards elimination that included possible confounding variables and removing those that did not significantly contribute to the prediction of the outcome. The elimination method first removed variables with p-values greater than 0.25. The second elimination removed variables with p-values greater than 0.15 and the final elimination removed those with a p-value greater than 0.05. To avoid problems with multicollinearity with significantly correlated variables, only one of the related variables was used in the model building and was chosen because there was more support in the literature for an association. For example, steatosis was significantly correlated with ALT levels and steatosis was used because the literature commonly describes associations between steatosis and IR. Steatosis was retained in the model predicting IR because steatosis and IR are thought to be biologically related and it is unclear if steatosis contributes to the occurrence of IR or vice versa. All possible interaction terms between the main effects variables remaining in the model after the three elimination steps were tested to determine their contribution to the prediction of the outcome. A significant log likelihood ratio test ($p<0.05$) was used to determine if an interaction term significantly contributed to the prediction of the outcome.

In the prediction of steatosis, an interaction between the natural log transformed HOMA2-IR scores and each genetic variant was tested separately by race. In the prediction of

IR, an interaction between steatosis and each genetic variant was tested separately. The log likelihood ratio test was used to determine the significance of these interactions. For log likelihood ratio tests with p-values greater than 0.05, the interaction was not included in the model. Odds ratio (OR) estimates and 95% Confidence Intervals (CI) were estimated for each genetic variant in both unadjusted (Appendix C) and adjusted models. An alpha level of 0.05 was used to determine statistical significance of the analytic tests. The SAS/STAT® software system version 9.1.3 was used for all analyses (SAS Institute Inc., Cary, NC, 2002-2003).

5.4 RESULTS

5.4.1 Population Characteristics

Comparisons of demographic characteristics by race are shown in Table 5-1. African American and Caucasian American patients did not differ significantly by gender, age, baseline viral levels, hepatic inflammation score, Ishak fibrosis score, steatosis, insulin resistance, cholesterol levels, triglyceride levels, or weekly alcohol consumption. African Americans had significantly higher BMI, ALT levels and AST levels compared to Caucasian Americans. HOMA2-IR scores were missing for 52 (25 African Americans; 27 Caucasian Americans) study participants because their insulin or glucose levels were not fasting or not available.

5.4.2 SNP Genotyping and Estimation of Haplotypes

The genotype call rate ranged from 95-99% in African Americans and 97-100% in Caucasian Americans. Table 5-2 presents SNP genotype frequencies, call rate and the p-value from the HWE tests. Overall, the SNPs selected for *ADIPOR1* and *HMGCS2* accounted for 71% (82% and 64%) of the variation in African Americans and 96% (100% and 93%) of the variation in Caucasian Americans. Haplotypes were estimated with a 0.7 probability of being true haplotype in 154 of 163 African Americans and 172 of 179 Caucasian Americans for *ADIPOR1* and 154 of 163 African Americans and 178 of 179 Caucasian Americans for *HMGCS2*. Common haplotypes are presented in Appendix C.

5.4.3 Associations with Steatosis

The final model for steatosis was adjusted for Ishak fibrosis score, weekly alcohol consumption, baseline viral level, natural log transformed HOMA2-IR scores, and BMI. The interaction term between the HOMA2-IR scores and the genetic variant was statistically significant for *ADIPOR1 rs1539355* and *rs6666089*. Results from these models are reported in Table 5-3.

Statistically significant associations were observed between two *ADIPOR1* SNPs and steatosis. Caucasian Americans with the GG genotypes for *ADIPOR1 rs1539355* (OR=0.13: 95% CI=0.02-0.75) or *rs6666089* (OR=0.13: 95% CI=0.02-0.90) had statistically significant lower odds of steatosis compared to those with the AA genotype. Statistically significant interactions were also observed between these SNPs and HOMA2-IR scores in the prediction of steatosis. The odds of steatosis for a one unit higher HOMA2-IR score for Caucasian Americans with the *ADIPOR1 rs1539355*-AG genotype (OR=16.4: 95% CI=2.4-110.8) were significantly

higher than the odds for a one unit higher HOMA2-IR score for those with the AA genotype (OR=1.6: 95% CI=0.6-4.1). Table 5-4 shows the *ADIPOR1 rs1539355* genotype frequencies for those with and without steatosis and with and without IR and may be useful for understanding the observed interaction. The percentage of Caucasian Americans with the *rs1539355*-AG genotype with IR and with steatosis (90%) was higher than the percentage without IR and with steatosis (60%). Figure 5-1A graphically shows the interaction between the genotypes of *ADIPOR1 rs1539355* and HOMA2-IR scores in the prediction of steatosis for Caucasian Americans. The graph shows the steepest increasing slope for the log odds of steatosis was among those with the AG genotype and the different slower increasing slopes for log odds of steatosis were observed for the other genotypes. The different slopes for the three genotypes indicate the interaction. A statistically significant interaction between *ADIPOR1 rs6666089* and HOMA2-IR scores was also observed in Caucasian Americans. For a one unit increase in HOMA2-IR scores, Caucasian Americans with the AG genotype had 41.6 (95% CI=2.8-611.8) times the odds of steatosis compared to those with the AA genotype (OR=1.92: 95% CI=0.71-5.21).

ADIPOR1 polymorphisms were not significantly associated with steatosis in African Americans and the interaction between the HOMA2-IR scores and *ADIPOR1 rs1539355* did not contribute to the prediction of steatosis (p=0.31). Table 5-4 helps to explain the non-significant interaction. The percentage of individuals with IR and with steatosis were similar for the *ADIPOR1 rs1539355* genotypes (AA: 71%, AG: 82%, GG: 79%) and also similar for those with steatosis and without IR (AA: 52%, AG: 51%, GG: 50%). Figure 5-1B is a graphic depiction of the log odds of steatosis by the natural log transformed HOMA2-IR scores for *ADIPOR1 rs1539355* genotypes. The log odds of steatosis for the genotypes were similar showing that as

the HOMA2-IR score increased the log odds of steatosis also increased consistently for each genotype. *ADIPOR1* haplotypes were analyzed, but did not provide additional information about the *ADIPOR1* association with steatosis that was not observed in single SNP associations.

A statistically significant association was observed between one *HMGCS2* polymorphism and steatosis, but only in African Americans. African Americans possessing either the *HMGCS2 rs12123085* AG or GG genotype had 3.1 (95% CI=1.1-8.6) times the odds of steatosis compared to those with the AA genotype. *HMGCS2* haplotypes were analyzed, but the haplotypes did not provide further information about the possible association between steatosis and *HMGCS2* that was not observed with single SNP associations.

5.4.4 Associations with Insulin Resistance

The final model for the prediction of IR was adjusted for age, body mass index, steatosis, Ishak fibrosis score and triglyceride levels. Adjusted odds ratios are shown in Table 5-5. No significant associations were observed between *ADIPOR1* polymorphisms and IR for African Americans or Caucasian Americans. In Caucasian Americans, one *HMGCS2* polymorphism was significantly associated with IR. Caucasian Americans possessing either the *HMGCS2 rs12123085* AG or GG genotype had significantly lower odds of IR (OR=0.3: 95% CI=0.1-0.9) compared to those with the AA genotype. No statistically significant associations between *HMGCS2* polymorphisms and IR were observed in African Americans. No statistically significant interactions were observed between the genetic variant and steatosis in the prediction of IR.

5.5 DISCUSSION

This study investigated associations between genetic markers in *ADIPOR1* and *HMGCS2* with steatosis and with insulin resistance among African American and Caucasian American patients infected with HCV genotype-1. Statistically significant associations for *ADIPOR1 rs1539355*, *rs6666089* and *HMGCS2 rs12123085* with steatosis were observed. *HMGCS2 rs12123085* was also significantly associated with IR.

Statistically significant interactions between *ADIPOR1* polymorphisms and natural log HOMA2-IR scores were observed in the prediction of steatosis. These results imply that the association between steatosis and IR may be moderated by some *ADIPOR1* polymorphisms. More specifically, people with either the *ADIPOR1 rs1539355*-AG or *rs6666089*-AG genotype and higher HOMA2-IR scores had significantly higher odds of steatosis compared to what would be expected from the main effects of the genotype and HOMA2-IR scores alone. Understanding the function of associated polymorphisms may indicate how the polymorphism influences steatosis or IR. *ADIPOR1 rs1539355* is located in the intron region and is predicted to be an intronic enhancer which could change the way that the protein encoded by this genetic variant is produced.(Yuan, 2006) *ADIPOR1 rs6666089* is located in the 5' upstream region of the gene and is predicted to be a promoter which could regulate gene expression.(Yuan, 2006) These two polymorphisms may influence expression of the gene or the production of the protein and these two activities could be related to the mechanisms for steatosis and IR in HCV genotype-1 infection.

The *HMGCS2 rs12123085* AG or GG genotypes were significantly associated with lower odds of IR compared to those with the AA genotype in Caucasian Americans. No statistically significant association was observed between this genetic variant and IR in African Americans,

but the direction of the odds ratio was the same. *HMGCS2 rs12123085* is located in the intron region and was predicted to be an intronic enhancer.(Yuan, 2006) As an intronic enhancer, this genetic variant may contribute to the occurrence of IR by changing how the protein encoded for this genetic variant is produced (Yuan, 2006).

A few previous studies described associations between the same *ADIPOR1* polymorphisms in the current study and IR.(Crimmins, 2007; Stefan, 2005) Specifically, one study described an association between the *ADIPOR1 rs6666089*-A allele IR.(Stefan, 2005) In the present study, no statistically significant association between *ADIPOR1 rs6666089* and IR was observed. The contradictory findings may be due to differences in sample size, study population studied or measurement of IR. The current study included a smaller sample size of Caucasian Americans (n=152) compared to the Stefan et al. study which included approximately 500 Caucasian individuals of European descent.(Stefan, 2005) With regards to study population, participants in the previous study were healthy (Stefan, 2005) compared to the present study which included HCV infected patients. IR is a common condition in HCV infection and it is possible that the virus may contribute to the occurrence of this condition. Therefore, this study described associations in HCV infection adding to the understanding of IR in HCV infection, specifically genotype-1. Exclusion criteria also varied between the studies such that the Stefan et al. study excluded individuals with diabetes or those individuals taking medications that impair glucose levels. (Stefan, 2005) In comparison, the current study only excluded patients taking exogenous insulin. Further, the current study utilized HOMA2-IR to quantify IR which is a more accurate measure of IR compared to the previous study which used HOMA-IR.(Wallace, 2004)

Another study examined the association between *ADIPOR1* polymorphisms and IR in a non-lean group of African American children and found a statistically significant association between *rs1342387*-A allele and lower risk of IR.(Crimmins, 2007) No statistically significant association was observed between this *ADIPOR1* polymorphism and IR in the current study. The contradictory findings may be attributed to differences in sample size, populations examined and phenotype measures. Crimmins et al. examined a sample of African American children aged 10-19 with no chronic illnesses (n=483) (Crimmins, 2007) whereas the current study included only adults infected with HCV (n=142). Since IR commonly occurs in HCV infected patients, it is possible that virus infection may contribute to the occurrence of this condition. Additionally, the inconsistent results could be related to different quantification methods of IR. The previous study also used continuous HOMA-IR scores in the analyses (Crimmins, 2007) and the current study used the HOMA2-IR score as a categorical outcome. The use of HOMA2-IR provides a more accurate measure of insulin sensitivity because it is consistent with current insulin assays compared to HOMA-IR which is calibrated to older insulin assays.(Wallace, 2004)

This study stratified all data by race for the purpose of detecting gene associations with steatosis and IR. The decision to complete the analyses separately by race was based on an *a priori* genetic expectation of different effects of SNPs in different race groups. Even if the same gene is affecting the outcome in Caucasian Americans and African Americans, there is an expectation that different SNPs within a gene for each race will show an association because of 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 SNPs were not directly affecting steatosis or IR, but rather were in linkage disequilibrium or correlated with functional genetic variants. If this were

the case, the different patterns of results may be explained by different linkage disequilibrium patterns in the populations and 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 even present in the other population. Alternatively, if the functional genetic variants are newer or more recent in the population history and the associated genetic variants are old, the associations may differ in race groups because of differences in migration out of Africa.

One limitation of this study was that the Virahep-C study had a relatively small sample size to test genetic associations with steatosis and IR. However, even with the small sample size this study was able to detect statistically significant associations between genetic variants and steatosis or IR. Another limitation of this study was the inability to confirm the study findings with a validation sample. A similar sample of HCV infected patients was not available to repeat and confirm the observed associations. These findings should also be validated since no adjustment for multiple comparisons was made. Although this study was one of the first to look specifically at African Americans, it was only able to account for 64% of the common variation in *HMGCS2*. This study did not have adequate funding to select and genotype enough SNPs to capture more of the common variation in this gene for African Americans, who are more genetically diverse than Caucasian Americans.(Costas, 2005) Despite these limitations, the results contribute to the literature by identifying *ADIPOR1* and *HMGCS2* polymorphism associations with steatosis and insulin resistance in HCV genotype-1 infection which has not been previously reported.

The findings in this study indicate directions for future research. Since no similar sample was available to validate these results and there was no adjustment for multiple comparisons,

replication of this study is necessary to support the findings. Further, since this study accounted for only 64% of the *HMGCS2* common variation in African Americans additional SNPs in this gene should be selected for a more in depth examination of associations with these conditions in that race group. Additional research could also try to understand the function of the associated SNPs and how they contribute to the occurrence of steatosis and insulin resistance in African- and Caucasian-Americans with HCV genotype-1 infection. Studies could also examine associations between these genetic variants and steatosis and IR in other samples of HCV patients or other risk populations which were unavailable at the time of this study to determine if the genetic associations are specific these conditions in HCV infection or if the genetic variants are associated with the conditions regardless of infectious status. Although, it may be difficult to examine steatosis in other populations because liver biopsy is an invasive procedure and would be unethical in healthy populations, ultrasound technology is currently being validated and could be used in future research.

In conclusion, *ADIPOR1* and *HMGCS2* SNP associations were observed with steatosis or IR and may be important in understanding the mechanisms of steatosis and IR. Based on the results, some *ADIPOR1* SNPs may modify an association between steatosis and IR and may contribute to understanding the biological pathway of these outcomes.

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Table 5-1: Demographic Characteristics of the Virahep-C Sample

Characteristics	African American N = 163	Caucasian American N = 179	p-value
	N (%)	N (%)	
Gender			
Male	103 (63.2)	115 (64.2)	
Female	60 (36.8)	60 (36.8)	0.84†
Portal Inflammation Score (HAI)			
Mild	27 (16.6)	30 (16.8)	
Moderate	104 (63.8)	98 (54.8)	
Severe	32 (19.6)	51 (28.5)	0.14†
Steatosis			
No Steatosis	63 (38.7)	60 (33.5)	
Steatosis Present	100 (61.4)	119 (66.5)	0.32†
Insulin Resistance			
HOMA2-IR < 2	82 (59.4)	102 (67.1)	
HOMA2-IR ≥ 2	56 (40.6)	50 (32.9)	0.18†
	Mean (SD)	Mean (SD)	
Homeostasis Model Assessment 2 (ln HOMA2-IR)	0.6 (0.7)	0.4 (0.8)	0.007‡
Alanine aminotransferase (ALT)	70.3 (45.9)	108.7 (92.2)	<0.0001‡
Aspartate aminotransferase (AST)	59.7 (42.1)	73.7 (59.3)	0.05‡
Age (years)	48.8 (6.9)	47.1 (8.4)	0.08‡
Body Mass Index (BMI)	30.8 (6.4)	28.1 (5.2)	<0.0001‡
Baseline Viral Level (log_{10} IU/mL)	6.3 (0.6)	6.3 (0.8)	0.10‡
Total Inflammation (HAI)	10.0 (3.2)	10.4 (3.5)	0.23‡
Triglycerides (mg/dL)	131.1 (100.0)	114.6 (69.0)	0.17‡
Cholesterol (mg/dL)	177.6 (37.1)	179.5 (5.3)	0.55‡
Ishak Fibrosis Score	2.2 (1.4)	2.3 (1.5)	0.38‡
Alcohol Consumption (Week)	3.6 (10.9)	2.4 (6.3)	0.81‡

† Chi-square test
‡ Wilcoxon Two Sample Test

Table 5-2: Frequencies of Genotypes for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans N = 163 Genotype Frequency	Call Rate	HWE*	Caucasian Americans N = 179 Genotype Frequency	Call Rate	HWE*
ADIPOR1 rs10753929						
CC	101 (0.63)			145 (0.83)		
CT	53 (0.34)			29 (0.17)		
TT	5 (0.03)	0.98	0.49	0 (0)	0.97	0.61
ADIPOR1 rs10920531						
AA	37 (0.23)			62 (0.35)		
AC	77 (0.48)			95 (0.54)		
CC	45 (0.28)	0.98	0.72	20 (0.11)	0.99	0.07
ADIPOR1 rs12045862						
CC	128 (0.80)			92 (0.52)		
CT	30 (0.19)			73 (0.41)		
TT	1 (0.01)	0.98	1.00	11 (0.06)	0.98	0.49
ADIPOR1 rs12733285						
CC	105 (0.68)			84 (0.48)		
CT	41 (0.27)			71 (0.41)		
TT	9 (0.06)	0.95	0.08	20 (0.11)	0.98	0.40
ADIPOR1 rs1342387						
AA	40 (0.25)			36 (0.21)		
AG	75 (0.47)			81 (0.46)		
GG	44 (0.28)	0.98	0.48	59 (0.34)	0.99	0.40
ADIPOR1 rs1539355						
AA	45 (0.29)			80 (0.46)		
AG	77 (0.49)			76 (0.44)		
GG	35 (0.22)	0.96	0.85	17 (0.10)	0.97	0.87
ADIPOR1 rs16850799						
AA	140 (0.87)			100 (0.57)		
AG	21 (0.13)			69 (0.39)		
GG	0 (0)	0.99	1.00	8 (0.05)	0.99	0.36
ADIPOR1 rs2275736						
AA	12 (0.08)			0 (0)		
AT	44 (0.28)			6 (0.04)		
TT	104 (0.65)	0.98	0.03	171 (0.97)	0.99	1.00
ADIPOR1 rs4336908						
AA	142 (0.87)			106 (0.60)		
AG	20 (0.12)			66 (0.37)		
GG	1 (0.01)	1.0	0.75	5 (0.03)	0.99	0.16
ADIPOR1 rs6666089						
AA	124 (0.77)			85 (0.48)		
AG	34 (0.21)			73 (0.42)		
GG	4 (0.02)	0.99	0.32	18 (0.10)	0.98	0.69
ADIPOR1 rs7514221						
CC	54 (0.33)			64 (0.36)		
CT	81 (0.50)			82 (0.46)		
TT	27 (0.17)	0.99	0.72	33 (0.18)	1.00	0.46

Table 5-2 (Continued)

ADIPOR1 rs7539542						
CC	27 (0.17)			75 (0.42)		
CG	74 (0.46)			89 (0.50)		
GG	59 (0.37)	0.99	0.65	13 (0.07)	0.99	0.05
HMGCS2 rs12123085						
AA	125 (0.77)			140 (0.78)		
AG	34 (0.21)			37 (0.21)		
GG	3 (0.02)	0.99	0.73	2 (0.01)	1.00	1.00
HMGCS2 rs12563433						
CC	115 (0.72)			71 (0.40)		
CT	43 (0.27)			85 (0.48)		
TT	2 (0.01)	0.98	0.56	21 (0.12)	0.99	0.56
HMGCS2 rs1441008						
CC	1 (0.01)			18 (0.10)		
CT	26 (0.16)			77 (0.44)		
TT	133 (0.83)	0.98	1.00	82 (0.46)	0.99	0.99
HMGCS2 rs1441010						
AA	35 (0.22)			65 (0.37)		
AG	78 (0.49)			82 (0.46)		
GG	47 (0.29)	0.98	0.81	30 (0.17)	0.99	0.63
HMGCS2 rs2241868						
CC	135 (0.85)			150 (0.85)		
CT	22 (0.14)			27 (0.15)		
TT	1 (0.01)	0.97	1.00	0 (0)	0.99	0.60
HMGCS2 rs3790693						
AA	8 (0.05)			25 (0.14)		
AT	58 (0.36)			80 (0.45)		
TT	94 (0.59)	0.98	0.81	71 (0.41)	0.99	0.72
HMGCS2 rs4659233						
AA	5 (0.03)			2 (0.01)		
AT	43 (0.28)			39 (0.22)		
TT	108 (0.69)	0.96	0.78	133 (0.76)	0.97	1.00
HMGCS2 rs536662						
AA	70 (0.43)			42 (0.24)		
AG	69 (0.43)			86 (0.48)		
GG	22 (0.14)	0.99	0.45	50 (0.28)	0.99	0.83
HMGCS2 rs619167						
AA	80 (0.50)			42 (0.24)		
AG	66 (0.41)			87 (0.49)		
GG	14 (0.09)	0.98	0.94	48 (0.27)	0.99	0.67
HMGCS2 rs649733						
AA	95 (0.59)			95 (0.54)		
AG	58 (0.36)			68 (0.31)		
GG	7 (0.04)	0.98	0.62	14 (0.08)	0.99	0.71
HMGCS2 rs667226						
CC	134 (0.85)			118 (0.67)		
CT	23 (0.15)			55 (0.31)		
TT	1 (0.01)	0.97	1.00	3 (0.02)	0.98	0.31

Table 5-2 (Continued)							
HMGCS2 rs667246							
	CC	69 (0.44)			95 (0.54)		
	CT	65 (0.41)			57 (0.32)		
	TT	23 (0.15)	0.96	0.24	25 (0.14)	0.99	0.002

* P-value from test of Hardy Weinberg Equilibrium

Table 5-3: Adjusted Odds Ratios for Steatosis for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

	African Americans* N = 163				Caucasian Americans* N = 179			
	SNP Main Effects		HOMA2-IR		SNP Main Effects		HOMA2-IR	
Genetic variant	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**
ADIPOR1 rs10753929										
CC	101	1.00				145	1.00			
CT/TT	59	0.71 (0.32-1.59)	0.41	‡		29	0.45 (0.16-1.28)	0.13	‡	
ADIPOR1 rs10920531										
AA	37	1.00				62	1.00			
AC	77	0.67 (0.24-1.88)	0.44	‡		95	2.03 (0.80-5.16)	0.14	‡	
CC	45	0.50 (0.16-1.58)	0.24	‡		20	2.83 (0.59-13.62)	0.20	‡	
ADIPOR1 rs12045862										
CC	128	1.00				92	1.00			
CT/TT	31	2.51 (0.92-6.83)	0.07	‡		84	1.16 (0.50-2.70)	0.73	‡	
ADIPOR1 rs12733285										
CC	105	1.00				84	1.00			
CT	41	0.86 (0.34-2.17)	0.75	‡		71	2.19 (0.87-5.52)	0.10	‡	
TT	9	1.69 (0.32-8.98)	0.54	‡		20	3.26 (0.70-15.38)	0.14	‡	
ADIPOR1 rs1342387										
AA	40	1.00				36	1.00			
AG	75	1.78 (0.66-4.81)	0.25	‡		81	0.63 (0.20-2.03)	0.44	‡	
GG	44	1.63 (0.55-4.80)	0.37	‡		59	0.37 (0.11-1.28)	0.12	‡	
ADIPOR1 rs1539355										
AA	45	1.00				80	1.00		1.55 (0.58-4.12)	0.38
AG	77	1.05 (0.42-2.62)	0.91	‡		76	1.42 (0.44-4.65)	0.56	16.37 (2.42-110.70)	0.004
GG	35	1.01 (0.35-2.92)	0.98	‡		17	0.13 (0.02-0.75)	0.02	3.44 (0.50-23.58)	0.21
ADIPOR1 rs16850799										
AA	140	1.00				100	1.00			
AG/GG	21	1.26 (0.41-3.91)	0.69	‡		77	1.34 (0.57-3.14)	0.50	‡	
ADIPOR1 rs2275736										
AA/AT	56	1.00				6	1.00			
TT	104	0.84 (0.38-1.89)	0.68	‡		171	2.10 (0.14-31.90)	0.59	‡	

Table 5-3 (Continued)

ADIPOR1 rs4336908									
AA	142	1.00			106	1.00			
AG/GG	21	1.49 (0.49-4.56)	0.49	‡	71	1.33 (0.55-3.21)	0.52	‡	
ADIPOR1 rs6666089									
AA	124	1.00			85	1.00		1.92 (0.71-5.21)	0.20
AG or AG/GG	38	0.70 (0.30-1.67)	0.43	‡	73	0.47 (0.16-1.42)	0.18	41.45 (2.81-611.81)	0.01
GG	§	§			18	0.13 (0.02-0.90)	0.04	0.64 (0.05-8.29)	0.73
ADIPOR1 rs7514221									
CC	54	1.00			64	1.00			
CT	81	1.39 (0.59-3.27)	0.45	‡	82	1.48 (0.59-3.71)	0.41	‡	
TT	27	0.61 (0.19-1.93)	0.40	‡	33	2.03 (0.58-7.11)	0.27	‡	
ADIPOR1 rs7539542									
CC	27	1.00			75	1.00			
CG	74	1.07 (0.35-3.33)	0.90	‡	89	2.34 (0.95-5.81)	0.07	‡	
GG	59	1.26 (0.39-4.03)	0.70	‡	13	3.72 (0.52-26.78)	0.19	‡	
HMGCS2 rs12123085									
AA	125	1.00			140	1.00			
AG/GG	37	3.13 (1.14-8.63)	0.03	‡	39	0.71 (0.25-2.02)	0.52	‡	
HMGCS2 rs12563433									
CC	115	1.00			71	1.00			
CT	§	§			85	1.00 (0.41-2.42)	0.99	‡	
CT/TT or TT	45	0.71 (0.29-1.73)	0.45	‡	21	1.55 (0.33-7.28)	0.58	‡	
HMGCS2 rs1441008									
CC/CT	27	1.00			95	1.00			
TT	133	1.87 (0.69-5.10)	0.22	‡	82	0.55 (0.22-1.38)	0.21	‡	
HMGCS2 rs1441010									
AA	25	1.00			65	1.00			
AG	78	0.55 (0.20-1.49)	0.24	‡	82	0.50 (0.19-1.35)	0.17	‡	
GG	47	1.02 (0.34-3.10)	0.97	‡	30	0.38 (0.10-1.47)	0.16	‡	
HMGCS2 rs2241868									
CC	135	1.00			150	1.00			
CT/TT	23	1.73 (0.60-5.00)	0.31	‡	27	0.75 (0.23-2.42)	0.63	‡	

Table 5-3 (Continued)

HMGCS2 rs3790693								
AA or AA/AT	66	1.00			25	1.00		
AT	§	§			80	0.60 (0.15-2.45)	0.47	‡
TT	94	0.60 (0.27-1.35)	0.22	‡	72	0.82 (0.19-3.61)	0.79	‡
HMGCS2 rs4659233								
AA/AT	48	1.00			41	1.00		
TT	108	0.54 (0.23-1.32)	0.18	‡	133	2.05 (0.75-5.61)	0.16	‡
HMGCS2 rs536662								
AA	70	1.00			42	1.00		
AG	69	0.46 (0.20-1.08)	0.08	‡	87	0.93 (0.33-2.61)	0.88	‡
GG	22	0.63 (0.19-2.10)	0.45	‡	48	3.09 (0.83-11.50)	0.09	‡
HMGCS2 rs619167								
AA	80	1.00			42	1.00		
AG	66	0.51 (0.22-1.17)	0.11	‡	86	0.89 (0.31-2.49)	0.82	‡
GG	14	0.36 (0.09-1.46)	0.15	‡	50	3.10 (0.84-11.51)	0.09	‡
HMGCS2 rs649733								
AA	95	1.00			95	1.00		
AG/GG	65	1.10 (0.50-2.42)	0.80	‡	82	0.58 (0.24-1.40)	0.23	‡
HMGCS2 rs667226								
CC	134	1.00			118	1.00		
CT/TT	24	0.35 (0.11-1.16)	0.09	‡	58	1.68 (0.67-4.21)	0.27	‡
HMGCS2 rs667246								
CC	69	1.00			95	1.00		
CT	65	0.46 (0.20-1.08)	0.08	‡	57	0.93 (0.33-2.61)	0.88	‡
TT	23	0.63 (0.19-2.10)	0.45	‡	25	3.10 (0.83-11.50)	0.09	‡

* Model adjusted for the genetic variant, centered Ishak fibrosis score, centered weekly alcohol consumption, centered ln HOMA2-IR score, centered body mass index, centered log of baseline viral level and interaction between the genetic variant and ln HOMA2-IR score (where significant)

‡ Odds ratios from the main effects model adjusting for the genetic variant, centered Ishak fibrosis score, centered weekly alcohol consumption, centered ln HOMA2-IR score, centered body mass index and centered log of baseline viral level were reported because the log likelihood test for the interaction between the genetic variant and ln HOMA2-IR scores were not significant at an alpha level of 0.05.

† Minor allele frequency less then 5% in one population

§ Homozygote genotype combined with heterozygote genotype to estimate association

Table 5-4: Raw Data Comparing Steatosis and Insulin Resistance and the Frequency of *ADIPOR1 rs1539355* variant genotypes

	African Americans		Caucasian Americans	
	No Steatosis	Steatosis ≥ 5%	No Steatosis	Steatosis ≥ 5%
HOMA2-IR < 2	AA: 11 AG: 19 GG: 9	AA: 12 (52.2) AG: 20 (51.3) GG: 9 (50.0	AA: 13 AG: 18 GG: 6	AA: 32 (71.1) AG: 27 (60.0) GG: 3 (33.3)
HOMA2-IR ≥ 2	AA: 5 AG: 4 GG: 3	AA: 12 (70.6) AG: 18 (81.8) GG: 11 (78.6)	AA: 5 AG: 2 GG: 2	AA: 17 (77.3) AG: 18 (90.0) GG: 4 (66.7)

Table 5-5: Adjusted Odds Ratios for Insulin Resistance in African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans* N = 138 N	Odds Ratio	95% Confidence Interval	p-value	Caucasian Americans* N = 152 N	Odds Ratio	95% Confidence Interval	p-value
ADIPOR1 rs10753929								
CC	86	1.00			121	1.00		
CT/TT	50	0.88	0.40-1.97	0.76	27	0.84	0.30-2.34	0.74
ADIPOR1 rs10920531								
AA	30	1.00			54	1.00		
AC	68	1.08	0.39-2.98	0.88	82	1.08	0.47-2.48	0.85
CC	37	0.41	0.13-1.30	0.13	14	1.46	0.37-5.67	0.59
ADIPOR1 rs12045862								
CC	107	1.00			80	1.00		
CT/TT	28	0.72	0.27-1.93	0.52	70	1.29	0.60-2.77	0.51
ADIPOR1 rs12733285								
CC	91	1.00			73	1.00		
CT	33	1.12	0.45-2.80	0.81	59	0.97	0.43-2.20	0.95
TT	7	1.73	0.30-9.91	0.54	16	1.22	0.36-4.17	0.75
ADIPOR1 rs1342387								
AA	32	1.00			31	1.00		
AG	64	0.81	0.31-2.10	0.66	68	0.86	0.32-2.33	0.76
GG	39	0.78	0.27-2.23	0.64	50	1.03	0.36-2.89	0.96
ADIPOR1 rs1539355								
AA	40	1.00			67	1.00		
AG	61	0.88	0.35-2.17	0.78	65	0.80	0.36-1.77	0.58
GG	32	0.88	0.29-2.63	0.81	15	1.26	0.32-4.97	0.75
ADIPOR1 rs16850799								
AA	118	1.00			87	1.00		
AG/GG	19	0.46	0.14-1.50	0.20	63	1.03	0.48-2.21	0.94
ADIPOR1 rs2275736								
AA/AT	46	1.00			6	1.00		
TT	90	2.06	0.88-4.84	0.10	144	0.10	0.01-1.10	0.06
ADIPOR1 rs4336908								
AA	119	1.00			92	1.00		
AG/GG	19	1.00	0.34-2.97	0.99	58	0.92	0.42-2.01	0.83
ADIPOR1 rs6666089								
AA	103	1.00			71	1.00		
AG or AG/GG	35	1.41	0.60-3.35	0.43	62	0.62	0.27-1.41	0.26
GG	‡				16	1.06	0.27-4.06	0.94
ADIPOR1 rs7514221								
CC	47	1.00			55	1.00		
CT	67	1.12	0.47-2.68	0.80	69	0.96	0.42-2.20	0.93
TT	23	2.18	0.71-6.74	0.18	28	0.79	0.27-2.34	0.68
ADIPOR1 rs7539542								
CC	22	1.00			67	1.00		
CG	64	0.90	0.30-2.74	0.85	73	1.14	0.52-2.50	0.75
GG	50	0.47	0.15-1.52	0.21	10	1.54	0.35-6.83	0.57

Table 5-5 (Continued)								
HMGCS2 rs12123085								
AA	106	1.00			121	1.00		
AG/GG	31	0.92	0.37-2.27	0.86	31	0.31	0.10-0.92	0.04
HMGCS2 rs12563433								
CC	101	1.00			55	1.00		
CT	‡				75	0.86	0.37-1.97	0.71
CT/TT or TT	35	1.98	0.43-2.71	0.87	20	2.42	0.75-7.83	0.14
HMGCS2 rs1441008								
CC/CT	24	1.00			79	1.00		
TT	112	1.17	0.41-3.39	0.77	71	0.81	0.37-1.73	0.58
HMGCS2 rs1441010								
AA	32	1.00			59	1.00		
AG	64	2.03	0.71-5.80	0.19	69	0.74	0.32-1.68	0.47
GG	40	1.69	0.55-5.14	0.36	22	0.97	0.32-2.96	0.96
HMGCS2 rs2241868								
CC	112	1.00			128	1.00		
CT/TT	22	0.57	0.19-1.67	0.30	22	0.95	0.33-2.78	0.93
HMGCS2 rs3790693								
AA or AA/AT	55	1.00			17	1.00		
AT	‡				70	0.89	0.25-3.11	0.85
TT	80	0.75	0.34-1.68	0.49	63	1.35	0.39-4.63	0.64
HMGCS2 rs4659233								
AA/AT	39	1.00			34	1.00		
TT	93	0.57	0.24-1.36	0.20	114	1.92	0.72-5.10	0.19
HMGCS2 rs536662								
AA	62	1.00			32	1.00		
AG	54	0.67	0.28-1.60	0.37	73	1.40	0.52-3.78	0.51
GG	20	0.98	0.30-3.19	0.98	45	1.20	0.41-3.54	0.74
HMGCS2 rs619167								
AA	71	1.00			32	1.00		
AG	53	0.57	0.24-1.35	0.20	72	1.37	0.50-3.74	0.54
GG	12	1.04	0.26-4.09	0.96	47	1.21	0.41-3.53	0.73
HMGCS2 rs649733								
AA	83	1.00			83	1.00		
AG/GG	53	1.06	0.49-2.33	0.88	67	1.52	0.70-3.31	0.29
HMGCS2 rs667226								
CC	117	1.00			99	1.00		
CT/TT	18	0.35	0.09-1.45	0.15	50	0.87	0.39-1.94	0.73
HMGCS2 rs667246								
CC	60	1.00			83	1.00		
CT	55	1.17	0.51-2.69	0.72	49	1.44	0.62-3.35	0.40
TT	18	1.22	0.36-4.10	0.75	18	1.90	0.58-6.28	0.29

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

‡ Homozygote genotype combined with heterozygote genotype to estimate association

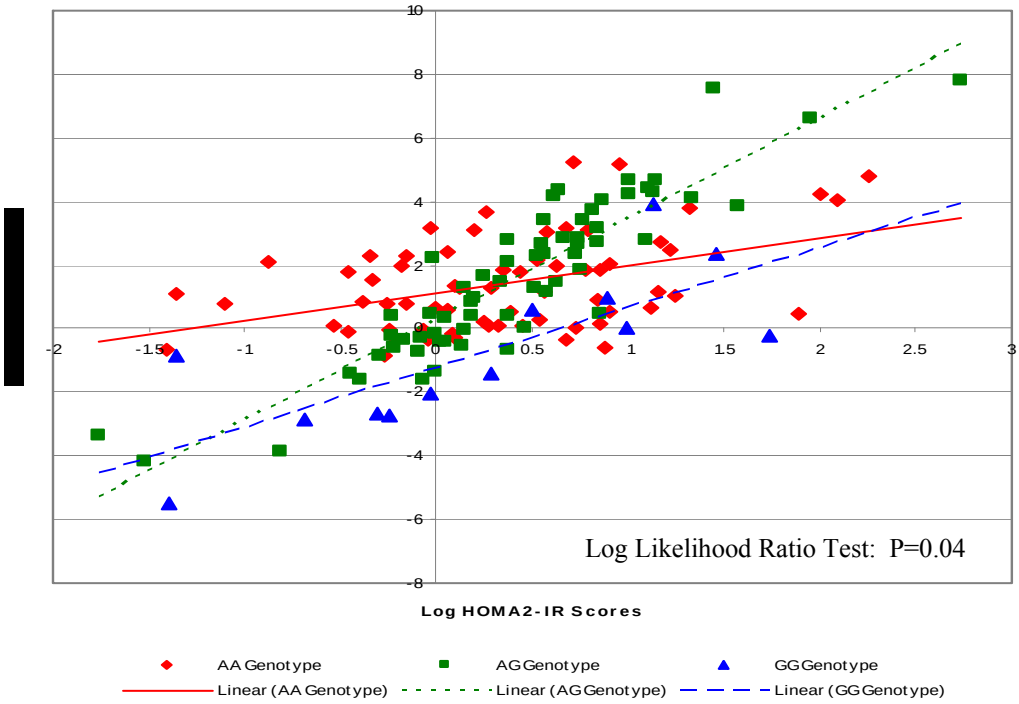


Figure 5-1A: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *ADIPOR1 rs1539355* in Caucasian Americans

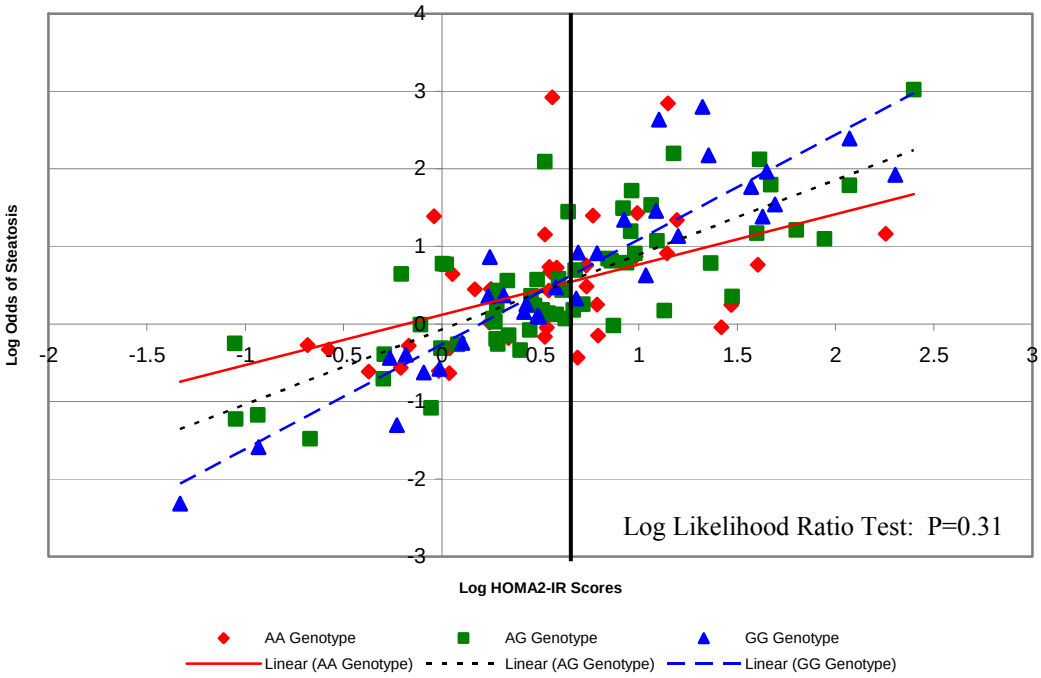


Figure 5-1B: Comparison of Log Odds of Steatosis vs. Natural Log Transformed HOMA2-IR Scores for *ADIPOR1 rs1539355* in African Americans

6.0 GENERAL DISCUSSION

This dissertation aimed to examine host genetic relationships with viral decline in the first 28 days of treatment, steatosis, and insulin resistance using a sample of patients infected with hepatitis C virus (HCV) genotype-1. To address these objectives, data were obtained from The Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C), a study that recruited nearly equal numbers of African American and Caucasian American patients with chronic HCV genotype-1 and no prior history of treatment. (Conjeevaram, 2006) Patients with decompensated cirrhosis were excluded.(Conjeevaram, 2006) In Virahep-C, participants were treated for up to 48 weeks with pegylated-interferon α-2a and weight-based dosing of ribavirin.(Conjeevaram, 2006)

6.1 SUMMARY OF FINDINGS

The study reported in Chapter 3 aimed to determine if viral decline in the first 28 days of treatment was different by host genetic variants of Interferon Stimulated Genes (ISGs). This was the first study that examined the selected 16 ISG SNP associations with 28 day viral decline in HCV treatment research. This study contributes to knowledge gaps in HCV treatment research

by testing for associations between 28 day viral decline and ISG SNPs among two populations that traditionally do not respond well to treatment, African Americans and HCV genotype-1 infected patients. This study identified statistically significant differences in viral decline by ISG SNP genotypes in *MX1, MX2, OASL, STAT1* and *STAT2*. Statistically significant differences in viral decline by the presence or absence of *PKR* haplotypes were observed in African Americans. There were three non-significant differences in viral decline for *IFNAR1 rs1041868, OAS3 rs1981557* and *IRF1 ATCCATCC* with the same pattern of decline observed in both race groups.

The study reported in Chapter 3 identified different patterns of 28 day viral decline for the ISG variant genotypes *MX2 rs443099, rs369908* and *OASL rs1169279* between the two race groups. In these genetic variants, a given genotype was associated with greater 28 day viral decline in one race, but a different genotype was associated with greater decline in the other race and was not necessarily statistically significant. This could indicate that the causal genetic variant related to 28 day viral decline may be in linkage disequilibrium with the associated genetic variant observed in this study. Linkage disequilibrium is a correlation between genetic variants along a chromosome and linkage disequilibrium patterns between genetic variants differ by racial group.(Costas, 2005) Since African Americans and Caucasian Americans have different allele frequencies and different linkage disequilibrium patterns, it is possible that an observed statistically significant association may or may not occur in both races or may not be the same in both races. For example, there was a statistically significant difference in viral decline in African Americans for *MX2 rs369908* genotypes such that those with the AA genotype had greater decline in 28 days compared to those with the AG or GG genotype. In Caucasian Americans, no statistically significant difference in viral decline for this *MX2* SNP was observed. Given the lack of consistent significant associations in both race groups, it is

difficult to positively conclude whether the associated ISGs are important to HCV treatment induced 28 day viral decline.

Prior examination of ISGs with treatment response has focused exclusively on the association between genetic variants or the expression of the ISG protein with achieving a sustained virologic response (SVR).(Giannelli, 2004; Hijikata, 2001; Hijikata, 2000; MacQuillan, 2002; H Saito, 2002; Su, 2008; Tena-Tomas, 2007; Wietzke-Braun, 2006) No studies found tested the association between the selected ISG genetic variants and 28 day viral decline. A study testing ISG SNP associations with SVR in the Virahep-C cohort found associations between *OASL rs1169279*-A allele, *rs3213545*-T allele and *rs2859398*-C allele and a SVR in African Americans and Caucasian Americans.(Su, 2008) The study in Chapter 3 found differences in viral level decline in the first 28 days for two of these *OASL* SNPs but, these associations were not consistent across race. Significant differences in viral decline by *OASL* variant genotypes in the first 28 days were observed among Caucasian Americans such that those carrying the *OASL rs1169279*-GG genotype or the *OASL rs3213545*-CT or TT genotype showed greater decline compared to the other genotypes. No statistically significant differences were observed between the *OASL* variant genotypes and 28 day viral decline in African Americans. It may be the case that some ISGs could take more than 28 days to effectively enhance immune response and work with pegIFNα to reduce HCV viral levels.

The study reported in Chapter 4 aimed to identify associations between selected genetic variants for *COL1A1, CYP2E1, IL6, IL10, IL1R1, LEPR, MCP1/CCL2, MCP2/CCL8, TNF-α* and *TGF-β1* with steatosis and Insulin Resistance (IR). Previous work on insulin resistance identified genetic variant or gene expression relationships in obese, diabetic or healthy populations.(Sartipy, 2003; Scarpelli, 2006; Schattenberg, 2005; Siitonen, 2006; Simeoni, 2004;

Stefan, 2005; Testa, 2006; X Yang, 2005) Few studies have examined genetic variant associations with steatosis.(Sanchez-Munoz, 2004; Stefan, 2005) No studies were found to have tested genetic variant associations with the polymorphisms selected for this dissertation with either steatosis or IR in HCV infection. This project contributes to knowledge gaps in the literature by testing genetic associations with steatosis and IR in an HCV infected population. By examining these relationships, this study helps to develop a greater understanding of the mechanisms of steatosis and IR as well as racial differences in their occurrence.

Statistically significant associations for genetic variants in *IL6, IL10, LEPR and TGF-β1* with steatosis or IR were observed in both race groups. In African Americans, *LEPR rs1137100*-AG or GG genotype was associated with lower odds of steatosis and the *LEPR rs1892534*-AG genotype was associated with higher odds of steatosis in both African Americans and Caucasian Americans. In Caucasian Americans, the *IL6 rs2069845*-AG or GG genotype was associated with higher odds of steatosis compared to having the AA genotype. In Caucasian Americans, the *IL6 rs1880242*-TT genotype was associated with lower odds of IR compared to having GG or GT genotype. *TGFβ rs2278422*-GG genotype was associated with statistically significant higher odds of steatosis in African Americans and lower odds of IR in both race groups compared to possessing the CC or CG genotype.

Statistically significant interactions between HOMA2-IR scores and *IL10, LEPR* and *TGF-β1* genetic variants were observed in the prediction of steatosis. Statistically significant interactions were observed between HOMA2-IR scores and the *IL10 rs3024496*-CT or -TT, *LEPR rs1805096*-CT or *rs1892354*-AG such that there were higher odds of steatosis among Caucasian Americans with high HOMA2-IR scores and any of these genotypes than would be expected by the main effects of HOMA2-IR and genotype alone. In African Americans,

statistically significant interactions were observed for those possessing the *IL10 rs3024496*-CT or *TGF-β1 rs2241716*-GG indicating higher odds of steatosis than would be expected by the main effects or HOMA2-IR and the genotype alone. The interactions observed between *IL10, LEPR* and *TGF-β1* genetic variants may imply that these genetic variants moderate an association between steatosis and IR.

Three previous studies described associations between the *IL6 rs1800795-G* allele and the higher HOMA-IR scores in Caucasian European, healthy or diabetic populations.(Cardellini, 2005; Testa, 2006; X Yang, 2005) The study reported in Chapter 4 found no statistically significant association with either steatosis or IR and this *IL6* SNP. Reasons for the contradictory results may be related to different phenotype measures, statistical methods and different populations. Also the previous studies examined Caucasians who were healthy or diabetic compared to the current study that examined both Caucasian Americans and African Americans infected with HCV genotype-1. HCV infection may contribute to the occurrence of IR and the mechanisms for the development of IR may be different in those with or without HCV.

The study described in Chapter 5 aimed to identify associations of *ADIPOR1* and *HMGCS2* polymorphisms with steatosis and IR among African Americans and Caucasian Americans. This study utilized tag SNP selection methods to choose genetic variants. The selected genetic variants attempted to capture 80% of the common variation in these genes to test for associations with steatosis and IR. Statistically significant associations between two *ADIPOR1* polymorphisms and steatosis were observed in Caucasian Americans. In African Americans *HMGCS2 rs12123085* was associated with steatosis and in Caucasian Americans the same SNP was associated with IR. Statistically significant interactions in Caucasian Americans

were observed between the *ADIPOR1 rs1539355* or *rs6666089* heterozygote genotype and HOMA2-IR scores such that individuals who have higher HOMA2-IR scores and possess the AG genotype for either of these polymorphisms have significantly higher odds of steatosis compared to what would be expected from the main effects of the heterozygote genotype and HOMA2-IR scores alone. These results imply that the heterozygote genotype in the two *ADIPOR1* genetic variants could moderate the association between steatosis and IR. Few studies have tested *ADIPOR1* and *HMGCS2* SNP associations with steatosis or with IR.(Crimmins, 2007; Stefan, 2005) The observed statistically significant associations between *ADIPOR1* and *HMGCS2* genetic variants help to explain the occurrence and mechanism of these conditions in HCV infection.

Previous studies have identified statistically significant associations between *ADIPOR1 rs6666089* or *rs1342387* and IR in African American children or healthy Caucasian adults.(Crimmins, 2007; Stefan, 2005) No statistically significant associations were observed between IR and those *ADIPOR1* polymorphisms in the study reported in Chapter 5. One previous study examined IR in 483 healthy African American children aged 10-19 using continuous HOMA-IR scores.(Crimmins, 2007) The other study included 500 German participants from a family study of type 2 diabetes, which measured IR with the hyperinsulinemic euglycemic clamp and measured liver fat with magnetic resonance spectroscopy (MRI) and analyzed continuous values for steatosis and IR.(Stefan, 2005) The study in Chapter 5 examined 138 African American and 152 Caucasian American adults with chronic HCV and utilized biopsy to measure liver fat and the HOMA2-IR calculator to quantify IR. The most important difference in these studies was the inclusion of patients infected with HCV. It is possible that HCV could influence the occurrence and severity of these conditions

and that the mechanisms for development could be different in those infected with HCV and those without. The different analytical methods and measurement techniques for steatosis and IR could also contribute to different findings because the techniques and definitions may not be consistent.

6.2 DISSERTATION STRENGTHS

The studies completed for this dissertation have several strengths and provide important contributions to the HCV literature. These dissertation studies are the first studies to examine the selected genetic variant associations with 28 day viral decline, steatosis and IR in HCV genotype-1 infection. Genetic associations could contribute to understanding mechanisms of HCV treatment response and improving treatment outcomes which may also reduce the occurrence of steatosis and IR.

Chapter 3 showed associations with ISG polymorphisms and 28 day viral decline. Studies of viral dynamics generally include relatively few participants because these studies require frequent viral level measures in the first few hours and days after treatment initiation.(Herrmann, 2003; Neumann, 2000; Neumann, 1998) Virahep-C collected fewer viral level measurements during the first week of treatment compared to traditional viral dynamics studies, but these measures still allowed for examining 28 day viral decline.(Conjeevaram, 2006; Herrmann, 2003; Neumann, 2000; Neumann, 1998) The fewer measurements in the first 72 hours of treatment most likely caused the finding of two phases of viral decline in the Virahep-C population which differs from previous studies on decline with pegylated interferon α-2a plus ribavirin combination therapy.(Hoofnagle, 2008) However, the inclusion of more patients (401

in Virahep-C, 10 in rigorous viral dynamics study with frequent blood draws in the first few days) and African Americans in Virahep-C may also have contributed to the difference.

The Virahep-C study recruited nearly equal numbers of African Americans (n=196) and Caucasian Americans (n=205) so the study reported in Chapter 3 utilized a sample of HCV genotype-1 infected patients with almost equal numbers of African Americans and Caucasian Americans. Including African Americans in HCV research is important because this group is typically under-represented in HCV treatment studies (Strader, 2002) and generally do not respond as well to HCV treatment as Caucasian Americans.(Conjeevaram, 2006) Examining both African- and Caucasian-Americans with HCV genotype-1 enables observing genetic variants that are associated with viral decline in both race groups or in one race group.

The studies reported in Chapters 4 and 5 found associations between genetic variants and steatosis or IR in HCV infection. African Americans have not been commonly included in studies examining genetic associations with steatosis and IR and genetic associations with these conditions have not been studied extensively in HCV infection.(Crimmins, 2007; Sanchez-Munoz, 2004) As above with viral decline, including African Americans when examining genetic associations with steatosis and IR may contribute to understanding the racial differences in the occurrence of these conditions. These studies also described genetic associations with steatosis which has not been examined extensively in the literature because the diagnosis of steatosis requires a biopsy, an invasive procedure.(Sanchez-Munoz, 2004; Stefan, 2005) The study of genetic associations with steatosis and IR in HCV infection is important because these associations could contribute to understanding whether these conditions are influenced by virus infection or associated with the conditions in a more general population experiencing these conditions.

6.3 DISSERTATION LIMITATIONS

Limitations for the studies of this dissertation should be addressed so that the results may be interpreted in the appropriate contexts. One limitation was that the Virahep-C cohort was relatively small for genetics studies. In addition, the studies described in Chapters 4 and 5 had further reduced sample size because of missing HOMA2-IR scores. Despite the small sample, the studies detected statistically significant main effects associations in the models. Some statistically significant interactions between gene variants and host factors were also identified.

Another possible limitation to these studies was the use of three different methods to select and genotype polymorphisms for the genes. Each of these methods used the best technology available at the time they were completed and accounted for different percentages of the common genetic variation in the genes. Common genetic variation is made up of the differences in the DNA code that exist within a population at an appreciable frequency (greater than 5-10%) compared to the reference DNA code within a given population. Genetic variants are often inherited together creating a pattern of correlation across the genome. The pattern of correlation created by inheritance contributes to describing the common genetic variation. The common genetic variation accounted for in a gene by selected polymorphisms refers to a measure of the percent of genetic variation captured with a correlation or r^2=0.80 reflecting polymorphisms cataloged in the International HapMap Project, Phase II. This refers to the percent of known polymorphisms that are at least 80% correlated with one or more tag selected polymorphisms. In the study reported in Chapter 3, the haplotype-block method accounted for 39% and 56% of the variation and the two-stage approach accounted for 29% and 54% of the variation in the genes for Caucasian Americans and African Americans, respectively. In the study described in Chapter 4, the haplotype-block method accounted for 38% and 47% and the

second approach accounted for 19% and 39% of the variation in the genes for Caucasian Americans and African Americans, respectively. The linkage disequilibrium SNP selection method utilized in the study reported in Chapter 5 accounted for 71% and 96% of the variation in the genes for African Americans and Caucasian Americans, respectively. The overall association for some of the selected genes with respect to 28 day viral decline, steatosis or IR cannot be determined because the selected genetic variants for many of these genes captured less than 80% of the variability for that gene.

The limitations with respect to generalizability to the general population of people with HCV infection are due to the inclusion criteria for Virahep-C. The results of the three studies in this dissertation can be generalized to African American and Caucasian American HCV genotype-1 patients who do not have end stage liver disease because of the exclusion of people with decompensated liver disease and the inclusion requirement of no prior treatment, eliminating the probability of advanced disease in the Virahep-C cohort. Further affecting generalizability, recruitment occurred in eight US cities and arguably did not capture a representative sample of HCV infected individuals. At the time of screening, Virahep-C participants had knowledge of their infection status, may have already been experiencing symptoms or disease progression or may have been under the care of a physician. In the general population, some individuals may be unaware that they have HCV infection, may be asymptomatic, have mild or minimal disease progression and may not be seeking medical care or treatment. It may be difficult to generalize Virahep-C results to a more general population of HCV infection because individuals who seek medical care and volunteer for studies may be experiencing infection differently than individuals who do not know their infection status. Further, there may be participation bias in that individuals who volunteered to participate in

Virahep-C in that they may be more likely to consistently take medication and follow recommended guidelines compared to individuals who did not volunteer. The results from this dissertation may over estimate true viral decline in HCV genotype-1 patients because enrolled study patients may have been more likely to follow treatment guidelines. The Virahep-C cohort also differs from hospital based cohorts of HCV infected patients. In hospital based cohorts, HCV infected patients are generally experiencing more severe complications and illness. Virahep-C recruited a relatively healthy cohort of HCV infected individuals. The results of the Virahep-C study are also only generalizable to HCV patients infected with genotype-1 because the viral mechanisms of different genotypes of HCV are thought to differ in treatment outcomes as well as disease progression.

Another limitation was the lack of a validation sample to confirm the observed results. Validation studies to confirm genetic associations are an important component to genetic research to reduce Type I error due to repeated tests. Validation of the results proved to be problematic because no sample was available that included the same measurements among HCV patients. Future studies could be designed to examine these outcomes in a very similar or larger sample of African Americans and Caucasian Americans with HCV genotype-1 infection to confirm the findings.

Adjustment for multiple comparisons was not made for any of the three projects that make up this dissertation. The decision to not adjust for multiple comparisons was based on an *a priori* decision that the studies were exploratory and took first looks at associations with treatment outcomes and metabolic conditions in an HCV infected population. The genes selected for examination with the 28 day viral decline, steatosis or IR were chosen based on possible biological plausibility of associations. This information regarding the selection of genes

is found in Chapters 3, 4, and 5. Although the large number of comparisons increases the likelihood of a Type I error, appropriate correction for multiple comparisons is difficult because of the unknown correlation structure between polymorphisms within each gene. Cautious interpretation of the findings should be made until additional studies can confirm the results through validation studies and lend support to the observed associations.

6.4 PUBLIC HEALTH SIGNIFICANCE

Recent reports suggest that 3.2 million people in the US have chronic HCV infection.(Armstrong, 2006) However, this estimate does not include incarcerated or homeless individuals and is likely an underestimate of the true number of people with chronic infection.(Armstrong, 2006) Direct and indirect costs associated with HCV infection are estimated to be approximately $5.46 billion annually.(Leigh, 2001) The majority of these costs are related to liver complications, morbidity or mortality associated with infection.(Leigh, 2001) The cost of HCV therapy is estimated to range from $8,000-$22,000 annually for one patient.(Salomon, 2003) HCV treatment is expensive, can have severe side effects and has only been effective in reducing the HCV RNA to undetectable levels in about 54-56% of those treated.(MW Fried, 2002; Manns, 2001) Research that contributes to understanding factors associated with HCV treatment response could lead to new therapies, improved treatment response and ultimately reduced morbidity and mortality related to HCV infection.

Steatosis and insulin resistance are common conditions among individuals infected with HCV. African Americans have lower prevalence of steatosis compared to Caucasian Americans.(Browning, 2004; Conjeevaram, 2007) In contrast, African Americans were

observed to have higher IR scores compared to Caucasian Americans.(Conjeevaram, 2007; Heathcote, 2002; Hui, 2003; Petit, 2001; Romero-Gomez, 2005; Shaheen, 2007) Research has been unable to conclusively identify what factors influence the racial differences in these conditions. Genetic associations with steatosis and insulin resistance in people with HCV may help to understand the mechanisms of these conditions and also may explain these racial differences. Further, understanding the biology of these conditions may provide methods for prevention, management and treatment.

The results of the dissertation may help to explain some of the biological mechanisms in the occurrence of steatosis, IR and HCV treatment response. Understanding the biology of a condition or disease through genetic epidemiology is helpful in figuring out how to prevent, manage and treat it. The results of the study reported in Chapter 3 may be useful for understanding mechanisms of viral decline which could be utilized in the development of novel therapies. Ultimately, these novel therapies could improve treatment response and reduce the occurrence of co-morbidities. Results of the Chapter 3 study could also assist in explaining the racial differences in treatment response and why African Americans have lower response rates to treatment by helping to identify biological mechanisms associated with viral decline. The studies in Chapters 4 and 5 identified host genetic variants associated with steatosis and IR in a population of HCV genotype-1 infected patients. These associations may help to understand the mechanism of the occurrence for these conditions which could lead to methods to prevent or treat the conditions.

6.5 FUTURE RESEARCH

The results from the studies that comprise this dissertation provide ideas for possible future directions of research on host genetic associations with HCV, including 28 day viral decline, steatosis and IR. Statistically significant associations were observed for genetic variants with steatosis or IR in HCV genotype-1 infected patients. These genetic variants may be specifically associated with the occurrence of these conditions in HCV infection or they could be related to the conditions in one race group or they could be associated with steatosis and IR in a general population who experience these conditions. Future research could help to understand the importance of these genetic variants in a more general population of individuals experiencing the conditions as well as in HCV infection.

Results from the three studies could not be validated because a comparable sample of African Americans and Caucasian Americans with HCV genotype-1 infection was not available. Thus, future research could replicate the current studies in other HCV genotype-1 populations to add support to the associated findings. Additionally, validation could be completed in a slightly different population, for example different racial groups, those with more advanced disease or individuals experiencing these conditions without HCV could be studied. Validation in a similar or a slightly different sample could provide different biological information, but could extend the general understanding of these conditions in all populations that experience these conditions. However, it is possible that with a different validation sample the results of the original study may not be replicated because of population differences.

Further, a subsequent research step for associated genetic variants could be to examine additional genetic variants on the gene that are close to the associated variant and that may be in high linkage disequilibrium with the associated variant. Several methods exist to further explore

the genetic associations such as sequencing or fine mapping techniques. In the studies reported in Chapters 3 and 4, the selected genetic variants did not account for the majority of the common variation in most of the genes examined. Since much of the common variation in the genes was not accounted for, the studies cannot conclude on the importance of the gene to the outcome examined. Future studies could select additional genetic variants in the examined genes to account for more of the common genetic variation and to possibly identify additional associations within these genes. To account for the more of the common genetic variation, available public databases such as HapMap Phase II can be used to identify polymorphisms that are not highly correlated with the selected polymorphisms in the current study and cover a larger part of the gene region. This strategy could improve the common genetic variation coverage of a gene like *MX2* from 25% to at least 80% as was attained for *ADIPOR1* (90%).

This dissertation examined associations between 16 ISGs and 28 day viral decline and 12 genes with steatosis and IR. Additional genes have been identified in the literature that may be important to HCV treatment response, steatosis, or IR such as *microsomal triglyceride transfer protein* or *interleukin 12* and could be examined with these outcomes.(Bernard, 2000; Houldsworth, 2005; Mentuccia, 2005; Mirandola, 2006; Namikawa, 2004) Further, the genes examined in this dissertation could be utilized to test for associations with other outcomes such as early virologic response at 12 weeks of treatment, fibrosis or cirrhosis.

6.6 CONCLUSIONS

Twenty-eight day viral decline may be important to understanding differences in HCV long-term treatment outcomes. Steatosis and IR are common conditions related to HCV infection that also

negatively impact the ability to achieve SVR.(Fabris, 2005; Guidi, 2005; Jian Wu, 2006; Patton, 2004; Romero-Gomez, 2006; Romero-Gomez, 2005; Soresi, 2006; Westin, 2007) In these analyses, we examined genetic variant associations with 28 day viral decline and steatosis and IR in both African Americans and Caucasian Americans. In doing so, we wanted to determine if the observed associations were in similar or different directions in the two race groups. Observing different patterns in the associations may help to explain the racial differences in treatment non-response or in the occurrence of steatosis and IR. Based on the results from the three studies, host genetic factors are associated with 28 day viral decline, steatosis and IR in HCV infection. These results indicate that the mechanisms for the occurrence of the outcomes may differ by race. Future research should validate the findings observed in these studies and attempt to further understand the functions of the variants. Once these results are confirmed and additional research is conducted on genetic variant functions, new therapeutic approaches could be developed to improve treatment response and potentially reduce or reverse the occurrence of steatosis and IR.

APPENDIX A

SUPPLEMENTARY TABLES AND FIGURES

FOR CHAPTER 3

A.1 SUPPLEMENTARY MATERIAL FOR INTERFERON STIMULATED GENETIC VARIANTS AND THE EARLY VIRAL DECLINE DURING TREATMENT OF CHRONIC HEPATITIS C

Table A-1 Baseline Demographic and Viral Characteristics for Virahep-C Study Patients Participating in the Genetics Ancillary Study by Race (N = 374)

Characteristic	African Americans (N=180)	Caucasian American (N=194)	P-Value
Gender, n (%)			
Men	118 (65.6)	126 (65.9)	
Women	62 (34.4)	68 (35.1)	0.90
Age (years), mean (SD)	48.7 (7.1)	47.0 (8.6)	0.03†
Weight (kg), mean (SD)	91.0 (19.2)	83.9 (17.3)	0.0002†
HCV Subtype, n(%)			
1	10 (5.6)	16 (8.3)	
1a	86 (48.8)	111 (56.4)	
1a/b	2 (1.1)	12 (6.2)	
1b	81 (59.6)	55 (40.4)	0.002
Source of Infection			
Blood or Blood Products	37 (23.9)	45 (27.0)	
Sexual Transmission	2 (1.3)	1 (0.6)	
Injection Drug Use	86 (55.5)	101 (54.0)	
Intra-nasal Illicit Drug Use	7 (4.5)	5 (3.0)	
Occupational/Medical	14 (9.0)	7 (4.2)	
Other	9 (5.8)	8 (4.8)	0.47
Duration of HCV Infection (yrs)‡, mean (SD)	24.4 (9.4)	25.5 (10.0)	0.33†
Baseline ALT Levels†, mean (SD)	71.3 (45.8)	107.9 (91.9)	<0.0001
Baseline AST Levels†, mean (SD)	60.4 (42.1)	73.7 (60.5)	0.02
Ishak Fibrosis Score†, mean (SD)	2.2 (1.4)	2.3 (1.6)	0.46
HCV RNA Level, (log_{10}IU/ml), mean (SD)			
Baseline	6.2 (0.7)	6.3 (0.8)	0.51†
Day 1	5.8 (0.8)	5.6 (1.2)	0.046
Day 2	5.6 (1.0)	5.3 (1.2)	0.02
Day 7	5.7 (1.1)	5.2 (1.4)	<0.0001
Day 14	5.3 (1.3)	4.6 (1.7)	<0.0001
Day 28	4.6 (1.6)	3.5 (2.0)	<0.0001

† Analysis of Variance

‡ Estimated duration of HCV infection was obtained for 148 Caucasian Americans and 134 African Americans

Table A-2: Genotype Frequencies for Single Nucleotide Polymorphisms African Americans and Caucasian Americans

Single Nucleotide Polymorphism Genotypes	African Americans N = 180	Genotype Call Rate	HWE*	Caucasian Americans N = 194	Genotype Call Rate	HWE*
ISG15 G1P2 rs1921						
AA	28 (0.16)			27 (0.14)		
AG	96 (0.53)			96 (0.50)		
GG	56 (0.31)	1.0	0.21	70 (0.36)	0.99	0.52
ISG15 G1P2 rs9331223						
CC	15 (0.08)			65 (0.34)		
CT	78 (0.44)			92 (0.48)		
TT	86 (0.48)	0.99	0.65	36 (0.19)	0.99	0.73
G1P3 rs11247653						
AA	143 (0.79)			61 (0.32)		
AG	36 (0.20)			92 (0.48)		
GG	1 (0.01)	1.00	0.43	40 (0.21)	0.99	0.66
G1P3 rs1141746						
CC	0 (0)			0 (0)		
CT	0 (0)			0 (0)		
TT	180 (1.0)	1.0	-	193 (1.0)	0.99	-
G1P3 rs1316896						
CC	0 (0)			0 (0)		
CG	0 (0)			0 (0)		
GG	193 (1.00	0.99	-	193 (1.0)	0.99	-
IFI35 rs8076790						
CC	17 (0.09)			5 (0.03)		
CT	89 (0.49)			62 (0.32)		
TT	74 (0.81)	1.0	0.18	126 (0.65)	0.99	0.42
IFI35 rs692692						
AA	12 (0.07)			5 (0.03)		
AG	74 (0.41)			59 (0.31)		
GG	94 (0.52)	1.0	0.62	129 (0.67)	0.99	0.57
IFI35 rs10840						
AA	12 (0.7)			2 (0.01)		
AG	53 (0.29)			29 (0.15)		
GG	115 (0.64)	1.0	0.10	162 (0.84)	0.99	0.59
IFI35 rs455055						
GG	89 (0.49)			12 (0.01)		
GT	66 (0.37)			76 (0.40)		
TT	24 (0.13)	0.99	0.04	103 (0.54)	0.99	0.68
IFNAR1 rs2834190						
AA	142 (0.80)			99 (0.51)		
AT	35 (0.20)			77 (0.40)		
TT	1 (0.006)	0.99	0.69	17 (0.09)	0.99	0.72
IFNAR1 rs2856968						
AA	68 (0.38)			72 (0.37)		
AG	87 (0.48)			94 (0.49)		
GG	25 (0.14)	1.0	0.74	27 (0.14)	0.99	0.68
IFNAR1 rs2252930						
CC	143 (0.79)			99 (0.51)		
CG	36 (0.20)			77 (0.40)		
GG	1 (0.01)	1.0	0.70	17 (0.09)	0.99	0.72

Table A-2 (Continued)							
IFNAR1 rs2243592							
	GG	25 (0.14)			27 (0.14)		
	GT	87 (0.48)			94 (0.49)		
	TT	68 (0.38)	1.0	0.74	72 (0.37)	0.99	0.68
IFNAR1 rs2253923							
	AA	67 (0.37)			72 (0.37)		
	AT	90 (0.50)			97 (0.50)		
	TT	23 (0.13)	1.0	0.39	24 (0.12)	0.99	0.32
IFNAR1 rs2257167							
	CC	8 (0.04)			2 (0.01)		
	CG	55 (0.31)			45 (0.23)		
	GG	117 (0.65)	1.0	0.64	145 (0.76)	0.99	0.73
IFNAR1 rs2834195							
	AA	1 (0.01)			0 (0)		
	AG	14 (0.08)			1 (0.01)		
	GG	165 (0.92)	1.0	0.32	192 (0.99)	0.99	0.70
IFNAR1 rs2243599							
	GG	83 (0.46)			25 (0.13)		
	GT	77 (0.43)			99 (0.51)		
	TT	20 (0.11)	1.0	0.74	69 (0.36)	0.99	0.25
IFNAR1 rs1041868							
	AA	8 (0.05)			4 (0.02)		
	AG	65 (0.36)			55 (0.29)		
	GG	106 (0.59)	0.99	0.62	134 (0.69)	0.99	0.55
IFNAR1 rs2834202							
	AA	116 (0.64)			108 (0.56)		
	AG	58 (0.32)			75 (0.39)		
	GG	6 (0.03)	1.0	0.70	10 (0.05)	0.99	0.51
IFNAR2 rs1476415							
	AA	46 (0.26)			47 (0.24)		
	AC	106 (0.59)			86 (0.45)		
	TT	28 (0.16)	1.0	0.01	60 (0.31)	0.99	0.15
IFNAR2 rs9636866							
	CC	12 (0.07)			10 (0.05)		
	CT	94 (0.52)			62 (0.32)		
	TT	74 (0.41)	1.0	0.01	121 (0.63)	0.99	0.58
IFNAR2 rs2300370							
	AA	6 (0.03)			25 (0.13)		
	AG	68 (0.38)			73 (0.38)		
	GG	106 (0.59)	1.0	0.21	95 (0.49)	0.99	0.07
IFNAR2 rs2248420							
	CC	131 (0.73)			105 (0.55)		
	CT	45 (0.25)			64 (0.32)		
	TT	4 (0.02)	1.0	1.0	25 (0.13)	0.99	0.003
IFNAR2 rs4986956							
	CC	0 (0)			2 (0.01)		
	CT	22 (0.12)			62 (0.32)		
	TT	158 (0.88)	1.0	1.0	121 (0.63)	0.99	0.16
IFNAR2 rs2252650							
	AA	11 (0.06)			25 (0.13)		
	AT	73 (0.41)			72 (0.37)		
	TT	96 (0.53)	1.0	0.56	96 (0.50)	0.99	0.06

Table A-2 (Continued)							
IFNAR2 rs2834165							
	AA	39 (0.22)			49 (0.25)		
	AG	107 (0.59)			85 (0.44)		
	GG	34 (0.19)	1.0	0.01	59 (0.31)	0.99	0.11
IFNAR2 rs2834166							
	AA	6 (0.03)			27 (0.14)		
	AC	59 (0.33)			79 (0.41)		
	TT	115 (0.64)	1.0	0.83	87 (0.45)	0.99	0.19
IFNAR2 rs2250226							
	AA	33 (0.18)			95 (0.49)		
	AG	94 (0.52)			73 (0.38)		
	GG	53 (0.29)	1.0	0.44	25 (0.13)	0.99	0.07
IFNAR2 rs2834167							
	AA	129 (0.72)			109 (0.57)		
	AG	45 (0.25)			77 (0.40)		
	GG	6 (0.03)	1.0	0.69	7 (0.04)	0.99	0.14
IRF1 rs839							
	AA	48 (0.27)			24 (0.12)		
	AG	81 (0.45)			92 (0.48)		
	GG	50 (0.28)	0.99	0.20	77 (0.40)	0.99	0.67
IRF1 rs2070726							
	GG	50 (0.28)			79 (0.41)		
	GT	82 (0.46)			86 (0.45)		
	TT	48 (0.27)	1.0	0.23	28 (0.15)	0.99	0.56
IRF1 rs2070723							
	CC	47 (0.26)			24 (0.12)		
	CT	82 (0.46)			91 (0.47)		
	TT	48 (0.27)	1.0	0.30	79 (0.41)	1.0	0.78
IRF1 rs2070721							
	AA	34 (0.19)			55 (0.28)		
	AG	78 (0.43)			101 (0.52)		
	GG	68 (0.38)	1.0	0.17	38 (0.20)	1.0	0.49
IRF1 rs2549009							
	AA	47 (0.26)			27 (0.14)		
	AG	89 (0.50)			97 (0.51)		
	GG	43 (0.24)	0.99	0.95	68 (0.35)	0.99	0.42
IRF1 rs2549006							
	CC	58 (0.32)			80 (0.41)		
	CT	85 (0.47)			90 (0.46)		
	TT	27 (0.21)	1.0	0.57	24 (0.12)	1.0	0.87
IRF1 rs2549003							
	CC	54 (0.30)			23 (0.41)		
	CT	82 (0.46)			90 (0.47)		
	TT	44 (0.24)	1.0	0.25	79 (0.41)	0.99	0.73
IRF1 rs736801							
	CC	142 (0.79)			76 (0.39)		
	CT	35 (0.20)			93 (0.48)		
	TT	2 (0.01)	0.99	0.92	25 (0.13)	1.0	0.68
IRF7 rs12421158							
	CC	54 (0.30)			22 (0.11)		
	CT	99 (0.55)			88 (0.46)		
	TT	26 (0.15)	0.99	0.07	83 (0.43)	0.99	0.86

Table A-2 (Continued)							
IRF7 rs7932167							
	AA	79 (0.44)			118 (0.61)		
	AC	73 (0.41)			62 (0.32)		
	CC	28 (0.16)	1.0	0.11	13 (0.07)	0.99	0.23
Mx1 rs462903							
	AA	131 (0.73)			65 (0.34)		
	AG	46 (0.26)			92 (0.47)		
	GG	53 (0.29)	1.0	0.65	37 (0.19)	1.0	0.66
Mx1 rs17000900							
	AA	10 (0.06)			5 (0.03)		
	AC	62 (0.35)			31 (0.16)		
	CC	105 (0.59)	0.98	0.83	156 (0.81)	0.99	0.03
Mx1 rs455816							
	AA	123 (0.68)			55 (0.28)		
	AG	53 (0.29)			90 (0.46)		
	GG	4 (0.02)	1.0	0.79	49 (0.25)	1.0	0.32
Mx1 rs469390							
	AA	40 (0.22)			72 (0.37)		
	AG	87 (0.48)			90 (0.46)		
	GG	53 (0.29)	1.0	0.71	32 (0.17)	1.0	0.67
Mx1 rs456298							
	AA	67 (0.37)			144 (0.74)		
	TA	89 (0.50)			48 (0.25)		
	TT	23 (0.13)	0.99	0.43	2 (0.01)	1.0	0.53
Mx2 rs757368							
	CC	57 (0.32)			138 (0.72)		
	CG	84 (0.47)			53 (0.28)		
	GG	29 (0.22)	1.0	0.59	10 (0.05)	0.99	0.21
Mx2 rs2838029							
	AA	41 (0.23)			2 (0.01)		
	AG	82 (0.46)			48 (0.25)		
	GG	57 (0.32)	1.0	0.27	143 (0.74)	0.99	0.53
Mx2 rs443099							
	GG	116 (0.64)			28 (0.15)		
	GT	57 (0.32)			94 (0.49)		
	TT	7 (0.04)	1.0	0.99	71 (0.37)	0.99	0.73
Mx2 rs116422							
	GG	79 (0.44)			127 (0.66)		
	GT	79 (0.44)			60 (0.31)		
	TT	21 (0.12)	0.99	0.85	7 (0.04)	1.0	0.98
Mx2 rs9305739							
	CC	8 (0.04)			0 (0)		
	CT	58 (0.32)			16 (0.08)		
	TT	114 (0.63)	1.0	0.85	177 (0.92)	0.99	1.0
Mx2 rs369908							
	AA	9 (0.05)			128 (0.66)		
	AG	68 (0.38)			55 (0.29)		
	GG	102 (0.57)	0.99	0.59	10 (0.05)	0.99	0.21
Mx2 rs11537891							
	GG	145 (0.81)			191 (0.99)		
	GT	32 (0.18)			3 (0.01)		
	TT	2 (0.01)	0.99	0.71	0 (0)	1.0	1.0

Table A-2 (Continued)							
Mx2 rs464090							
	CC	57 (0.32)			130 (0.67)		
	CT	89 (0.49)			54 (0.28)		
	TT	34 (0.19)	1.0	0.94	9 (0.05)	0.99	0.55
Oas1 rs4766662							
	AA	23 (0.13)			7 (0.04)		
	AC	89 (0.49)			98 (0.51)		
	CC	68 (0.38)	1.0	0.46	80 (0.42)	0.99	0.46
Oas1 rs3741981							
	CC	92 (0.51)			29 (0.15)		
	CT	81 (0.45)			98 (0.51)		
	TT	7 (0.04)	1.0	0.03	65 (0.34)	0.99	0.42
Oas1 rs2285934							
	AA	27 (0.15)			15 (0.08)		
	AC	104 (0.58)			98 (0.51)		
	CC	49 (0.27)	1.0	0.02	80 (0.42)	0.99	0.04
Oas1 rs12298890							
	CC	179 (0.99)			0 (0)		
	CT	1 (0.01)			0 (0)		
	TT	0 (0)	1.0	1.0	193 (1.0)	0.99	-
Oas1 rs2660							
	AA	153 (0.85)			80 (0.42)		
	AG	27 (0.15)			100 (0.52)		
	GG	0 (0)	1.0	0.60	13 (0.07)	0.99	0.01
Oas1 rs6489865							
	AA	0 (0)			13 (0.07)		
	AG	19 (0.11)			98 (0.51)		
	GG	161 (0.89)	1.0	1.0	65 (0.34)	0.99	0.02
Oas2 rs2010604							
	CC	1 (0.01)			10 (0.05)		
	CG	37 (0.20)			85 (0.44)		
	GG	142 (0.79)	1.0	0.69	98 (0.51)	0.99	0.12
Oas2 rs2072138							
	CC	13 (0.07)			13 (0.07)		
	CG	60 (0.34)			81 (0.42)		
	GG	106 (0.59)	0.99	0.27	97 (0.51)	0.98	0.48
Oas2 rs1293762							
	AA	2 (0.01)			32 (0.17)		
	AC	47 (0.26)			108 (0.56)		
	CC	131 (0.73)	1.0	0.55	53 (0.28)	0.99	0.07
Oas2 rs1293739							
	AA	11 (0.06)			9 (0.05)		
	AG	69 (0.38)			74 (0.38)		
	GG	100 (0.56)	1.0	0.84	110 (0.57)	0.99	0.44
Oas3 rs1981557							
	CC	4 (0.02)			15 (0.08)		
	CG	17 (0.10)			98 (0.51)		
	GG	157 (0.88)	0.99	0.73	80 (0.42)	0.99	0.04
Oas3 rs6489879							
	AA	161 (0.89)			80 (0.42)		
	AG	19 (0.11)			99 (0.51)		
	GG	0 (0)	1.00	1.0	14 (0.07)	0.99	0.03

Table A-2 (Continued)							
Oas3 rs2269899							
	AA	92 (0.51)			84 (0.44)		
	AG	80 (0.44)			95 (0.49)		
	GG	8 (0.04)	1.0	0.09	14 (0.07)	0.99	0.06
Oas3 rs2285933							
	CC	27 (0.15)			10 (0.05)		
	CG	83 (0.86)			85 (0.44)		
	GG	70 (0.39)	1.0	0.77	98 (0.51)	0.99	0.12
Oas3 rs2107418							
	GG	39 (0.22)			33 (0.17)		
	GT	71 (0.39)			106 (0.55)		
	TT	70 (0.39)	1.0	0.01	54 (0.28)	0.99	0.12
Oas3 rs2240189							
	CC	123 (0.68)			99 (0.51)		
	CT	51 (0.28)			84 (0.44)		
	TT	6 (0.03)	1.0	0.80	10 (0.05)	0.99	0.14
Oas3 rs757404							
	CC	71 (0.39)			98 (0.51)		
	CT	82 (0.46)			84 (0.44)		
	TT	27 (0.15)	1.0	0.68	11 (0.06)	0.99	0.20
OASL rs1169279							
	AA	20 (0.11)			29 (0.15)		
	AG	80 (0.44)			82 (0.43)		
	GG	80 (0.44)	1.0	1.0	82 (0.83)	0.99	0.26
OASL rs7134141							
	AA	4 (0.02)			0 (0)		
	AG	45 (0.25)			10 (0.05)		
	GG	130 (0.73)	0.99	1.0	184 (0.95)	1.0	1.0
OASL rs2259697							
	CC	23 (0.13)			8 (0.04)		
	CT	89 (0.49)			63 (0.33)		
	TT	68 (0.38)	1.0	0.99	123 (0.63)	1.0	0.46
OASL rs12819210							
	CC	160 (0.89)			124 (0.64)		
	CT	20 (0.11)			63 (0.33)		
	TT	0 (0)	1.0	1.0	7 (0.04)	1.0	0.77
OASL rs3861793							
	CC	0 (0)			0 (0)		
	CG	0 (0)			0 (0)		
	GG	176 (1.0)	0.98	-	194 (1.0)	1.0	-
OASL rs11307154							
	AA	45 (0.25)			10 (0.05)		
	A-	91 (0.51)			65 (0.34)		
	--	43 (0.24)	0.99	0.82	119 (0.61)	1.0	0.77
OASL rs7969180							
	AA	0 (0)			0 (0)		
	AG	4 (0.02)			0 (0)		
	GG	176 (0.98)	1.0	1.0	193 (1.0)	0.99	-
OASL rs2260399							
	CC	71 (0.39)			45 (0.23)		
	CT	90 (0.50)			103 (0.53)		
	TT	19 (0.11)	1.0	0.22	45 (0.23)	0.99	0.35

Table A-2 (Continued)							
OASL rs10849829							
	AA	19 (0.11)			46 (0.24)		
	AG	90 (0.50)			104 (0.54)		
	GG	71 (0.39)	1.0	0.22	44 (0.23)	1.0	0.31
OASL rs3213546							
	CC	7 (0.04)			0 (0)		
	CG	47 (0.26)			11 (0.06)		
	GG	136 (0.70)	1.0	0.33	183 (0.94)	1.0	1.0
OASL rs3213545							
	CC	125 (0.69)			95 (0.50)		
	CT	52 (0.29)			74 (0.39)		
	TT	3 (0.02)	1.0	0.56	23 (0.12)	0.99	0.15
OASL rs28360476							
	AA	0 (0)			0 (0)		
	AC	0 (0)			0 (0)		
	CC	178 (1.0)	0.98	-	194 (1.0)	1.0	-
OASL rs10849832							
	CC	10 (0.06)			6 (0.03)		
	CT	58 (0.29)			37 (0.19)		
	TT	112 (0.62)	1.0	0.49	150 (0.78)	0.99	0.06
OASL rs12315068							
	AA	0 (0)			0 (0)		
	AG	0 (0)			0 (0)		
	GG	179 (1.0)	0.99	-	194 (1.0)	1.0	-
OASL rs10849833							
	AA	10 (0.06)			0 (0)		
	AG	57 (0.32)			18 (0.09)		
	GG	113 (0.63)	1.0	0.43	176 (0.91)	1.0	1.0
OASL rs2859394							
	CC	4 (0.02)			3 (0.02)		
	CT	31 (0.17)			54 (0.28)		
	TT	112 (0.62)	0.99	0.15	136 (0.71)	0.99	0.61
OASL rs2859398							
	CC	5 (0.03)			29 (0.15)		
	CT	57 (0.32)			84 (0.43)		
	TT	118 (0.66)	1.0	0.54	81 (0.42)	1.0	0.35
OASL rs7134069							
	AA	116 (0.65)			177 (0.91)		
	AC	51 (0.29)			17 (0.09)		
	CC	12 (0.07)	0.99	0.06	0 (0)	1.0	1.0
PKR rs2307478							
	CC	0 (0)			0 (0)		
	CT	15 (0.08)			0 (0)		
	TT	165 (0.92)	1.0	1.0	194 (1.0)	1.0	-
PKR rs2307479							
	AA	142 (0.79)			185 (0.95)		
	AC	33 (0.18)			9 (0.05)		
	CC	4 (0.02)	0.99	0.26	0 (0)	1.0	1.0
PKR rs2287350							
	AA	129 (0.73)			70 (0.36)		
	AG	45 (0.25)			90 (0.47)		
	GG	3 (0.02)	1.0	0.78	33 (0.17)	0.99	0.66

Table A-2 (Continued)							
PKR rs2254958							
	CC	129 (0.73)			64 (0.34)		
	CT	45 (0.25)			91 (0.48)		
	TT	4 (0.02)	0.99	1.0	34 (0.18)	0.97	0.87
STAT1 rs2066797							
	AA	123 (0.68)			168 (0.88)		
	AG	51 (0.28)			23 (0.12)		
	GG	6 (0.03)	1.0	0.78	1 (0.01)	0.99	0.83
STAT1 rs3088307							
	CC	12 (0.07)			42 (0.22)		
	CG	68 (0.38)			99 (0.51)		
	GG	100 (0.56)	1.0	0.92	52 (0.27)	0.99	0.69
STAT1 rs1400657							
	AA	110 (0.61)			156 (0.81)		
	AC	61 (0.34)			27 (0.19)		
	CC	9 (0.05)	1.0	0.89	0 (0)	0.99	0.23
STAT1 rs1914408							
	AA	7 (0.04)			9 (0.05)		
	AG	46 (0.26)			59 (0.31)		
	GG	127 (0.71)	1.0	0.28	124 (0.65)	0.99	0.57
STAT1 rs2280234							
	CC	27 (0.15)			83 (0.43)		
	CT	83 (0.46)			84 (0.44)		
	TT	70 (0.39)	1.0	0.77	26 (0.14)	0.99	0.52
STAT1 rs12693590							
	AA	139 (0.77)			167 (0.87)		
	AC	28 (0.21)			23 (0.12)		
	CC	3 (0.02)	1.0	0.71	3 (0.02)	0.99	0.07
STAT1 rs2066802							
	CC	1 (0.01)			1 (0.01)		
	CT	25 (0.14)			23 (0.12)		
	TT	154 (0.86)	1.0	1.0	169 (0.88)	0.99	0.55
STAT1 rs1467199							
	CC	84 (0.47)			124 (0.64)		
	CG	78 (0.43)			61 (0.32)		
	GG	18 (0.10)	1.0	0.99	8 (0.04)	0.99	0.89
STAT2 rs2066808							
	CC	47 (0.26)			0 (0)		
	CT	96 (0.53)			31 (0.16)		
	TT	27 (0.21)	1.0	0.35	162 (0.84)	0.99	0.36
STAT2 rs2066807							
	CC	0 (0)			0 (0)		
	CG	2 (0.01)			31 (0.16)		
	GG	178 (0.99)	1.0	0.94	162 (0.84)	0.99	0.64
STAT2 rs2066811							
	AA	125 (0.69)			192 (0.99)		
	AG	49 (0.27)			1 (0.01)		
	GG	6 (0.03)	1.0	0.66	0 (0)	0.99	1.0
STAT2 rs2228259							
	CC	0 (0)			0 (0)		
	CG	1 (0.01)			0 (0)		
	GG	179 (0.99)	1.0	1.0	193 (1.0)	0.99	-

Table A-2 (Continued)							
STAT2 rs2066816							
	GG	0 (0)			0 (0)		
	TG	0 (0)			0 (0)		
	TT	180 (1.0)	1.0	-	193 (1.0)	0.99	-
STAT2 rs2066819							
	AA	0 (0)			0 (0)		
	AG	2 (0.01)			32 (0.17)		
	GG	178 (0.99)	1.0	1.0	161 (0.83)	0.99	0.38
STAT2 rs11171812							
	AA	45 (0.25)			0 (0)		
	AG	94 (0.52)			2 (0.01)		
	GG	41 (0.23)	1.0	0.55	191 (0.99)	0.99	1.0
STAT2 rs4301822							
	CC	54 (0.30)			0 (0)		
	CT	90 (0.50)			2 (0.01)		
	TT	35 (0.20)	0.99	0.82	191 (0.99)	0.99	1.0

* P-value from test of Hardy Weinberg Equilibrium

Table A-3: Haplotype Frequencies for Interferon Stimulating Genes Among African Americans and Caucasian Americans

Haplotype	SNPs*	African Americans N = 180	Caucasian Americans N = 194
G1P2	*rs1921, rs9331223*		
AT		0.39	0.38
GC		0.26	0.56
GT		0.31	0.05
IFI35	*rs8076790, rs692692, rs10840*		
CAG		0.27	0.18
TGA		0.21	0.09
TGG		0.44	0.73
IFNAR1	*rs2834190, rs2856968, rs2252930, rs2243592, rs2253923, rs2257167, rs2243599, rs1041868, rs2834202*		
AACTAGGGA		0.27	0.01
AACTAGTGA		0.21	0.32
AGCGTCGAA		0.19	0.13
AGCGTGGGG		0.17	0.24
TAGTAGTGA		0.09	0.25
IFNAR2	*rs9636866, rs2300370, rs4986956, rs2252650, rs2834165, rs2834166, rs2250226, rs2834167*		
CGTTACAA		0.03	0.15
CGTTACGA		0.17	0.01
TATAACGA		0.09	0.16
TATAACGG		0.03	0.09
TGTTGAAA		0.17	0.25
TGTTGAAG		0.02	0.07
TGTTGCAA		0.17	0.13
TGTTGCGA		0.09	0.01

Table A-3 (Continued)			
IRF1	*rs839, rs2070726, rs2070723, rs2070721, rs2549009, rs2549006, rs2549003, rs736801*		
	ATCCATCC	0.38	0.35
	ATCCGCCC	0.05	0.01
	GGTAATCC	0.05	0.00
	GGTAGCTC	0.25	0.17
	GGTAGCTT	0.09	0.34
	GGTCGCTC	0.08	0.07
IRF7	*rs12421158, rs7932167*		
	CA	0.42	0.30
	CC	0.16	0.04
	TA	0.22	0.47
	TC	0.20	0.19
Mx1	*rs462903, rs455816, rs469390, rs256928*		
	AAAA	0.26	0.13
	AAGA	0.21	0.32
	AAGT	0.29	0.03
	AGAA	0.04	0.07
	GGAA	0.09	0.31
OAS1	*rs4766662, rs3741981*		
	AC	0.37	0.16
	AT	0.10	0.05
	CC	0.37	0.25
	CT	0.25	0.54
OAS2	*rs2010604, rs2072138, rs1293762, rs1293739*		
	CGAG	0.05	0.25
	GCCG	0.18	0.26
	GGAA	0.03	0.07
	GGAG	0.06	0.11
	GGCA	0.18	0.16
	GGCG	0.41	0.11

Table A-3 (Continued)			
OAS3	*rs2269899, rs2285933, rs2240189, rs757404*		
	ACCT	0.05	0.00
	ACTT	0.15	0.26
	AGCC	0.52	0.42
	GCCT	0.14	0.01
	GGCC	0.09	0.31
OASL	*rs1169279, rs7134141, rs2259697, rs12819210, rs7969180, rs2260399, rs10849829, rs3213546, rs3213545, rs10849832, rs10849833, rs2859394, rs2589398, rs7134069*		
	AATCGTACCCATTC	0.11	0.03
	AGTCGTAGTTGTCA	0.13	0.27
	GGCCGCGGCTGTTA	0.27	0.01
	GGCTGCGGCTGCTA	0.00	0.16
	GGTCGCGGCCGTTA	0.02	0.07
	GGTCGCGGCTGTTA	0.14	0.20
	GGTCGTAGCTGTTA	0.04	0.13
PKR	*rs2307479, rs2287350, rs2254958*		
	AAC	0.71	0.53
	AGT	0.08	0.38
	AGC	0.06	0.03
	AAT	0.05	0.04
	CAC	0.09	0.02
STAT1	*rs2066797, rs3088307, rs1400657, rs1914408, rs2280234, rs12693950, rs2066802, rs1467199*		
	ACAGCATC	0.11	0.44
	ACAGCATG	0.08	0.02
	AGAATATG	0.09	0.15
	AGAGCATC	0.09	0.10
	AGAGCCTC	0.02	0.07
	AGAGTATC	0.09	0.01
	AGCGTATC	0.08	0.07
	AGCGTATG	0.09	0.02
	GGAGTATC	0.07	0.01

Table A-3 (Continued)			
STAT2	*rs2066808, rs2068807, rs2066811, rs2228259, rs2066816, rs2066819*		
	CCAAGT	0.00	0.08
	CGAGAC	0.32	0.01
	CGGGAC	0.16	0.01
	TGAGGC	0.05	0.00
	TGAGGT	0.42	0.91

* SNPs are listed in order that they appear in the haplotype and along the chromosome

Table A-4: Multivariable Model Estimating Differences in Viral Level by Interferon Stimulating Gene Single Nucleotide Polymorphisms During the First 28 Days of Treatment Among Caucasian Americans and African Americans

	African Americans (N = 180) Estimated Change in Viral Level by Treatment Day*								Caucasian Americans (N = 194) Estimated Change in Viral Level by Treatment Day*							
Genetic Marker	N	0**	1	2	7	14	28	p-value	N	0**	1	2	7	14	28	p-value
ISG15 G1P2 rs1921																
AA	28	6.05							27	6.37						
AG	96	6.26	0.03	0.04	-0.01	0.07	0.06		96	6.36	0.14	0.10	0.21	0.34	0.87	
GG	56	6.22	0.13	0.13	-0.03	-0.04	0.10	0.77	70	6.24	0.01	-0.07	0.01	0.04	0.28	0.19
ISG15/G1P2 rs9331223																
CC	15	6.06							65	6.22						
CT	78	6.20	0.10	0.30	0.18	-0.001	-0.05		92	6.38	0.14	0.16	0.15	0.19	0.47	
TT	86	6.25	0.04	0.29	0.20	0.12	-0.03	0.81	36	6.33	-0.02	-0.02	-0.01	-0.02	-0.23	0.19
G1P3 rs11247653																
AA	143	6.23							61	6.30						
AG/GG	37	6.16	0.001	0.001	0.18	0.14	0.34	0.29	132	6.32	-0.07	0.01	-0.11	-0.19	-0.16	0.83
G1P3 rs1141746[§]																
G1P3 rs1316896[§]																
IFI35 rs10840																
AA/AG	65	6.40							32	6.17						
GG	115	6.11	-0.01	-0.08	-0.09	-0.19	-0.13	0.83	162	6.35	0.07	0.15	0.15	-0.14	-0.25	0.49
IFI35 rs455055																
GG	89	6.24							12	6.30						
GT	66	6.26	-0.11	-0.21	-0.22	-0.34	-0.41		76	6.22	0.01	-0.14	-0.07	-0.31	-0.44	
TT	24	6.02	-0.08	-0.08	-0.08	-0.13	0.03	0.59	103	6.39	0.002	-0.11	-0.18	-0.49	-0.90	0.29
IFI35 rs692692																
AA/AG	86	6.16							62	6.30						
GG	94	6.26	-0.01	0.05	0.01	0.06	0.01	0.91	129	6.33	-0.03	-0.03	-0.12	-0.02	-0.25	0.44
IFI35 rs8076790																
CC/CT	106	6.18							67	6.31						
TT	74	6.26	-0.08	0.01	-0.01	0.10	0.10	0.69	126	6.32	-0.01	-0.02	-0.16	-0.06	-0.32	0.26
IFNAR1 rs2834190																
AA	142	6.24							99	6.29						
AT/TT	36	6.09	0.06	0.05	0.21	0.32	0.36	0.56	94	6.35	0.02	0.02	-0.04	-0.20	-0.12	0.77
IFNAR1 rs2856968																
AA	68	6.27							72	6.39						
AG/GG	112	6.18	-0.01	-0.11	-0.08	-0.28	-0.23	0.25	121	6.27	0.10	0.06	0.01	0.09	0.19	0.84

Table A-4 (Continued)

IFNAR1 rs2252930																
CC	143	6.24							99	6.29						
CG/GG	37	6.11	0.04	0.03	0.18	0.30	0.32	0.59	94	6.35	0.02	0.02	-0.04	-0.02	-0.12	0.77
IFNAR1 rs2243592																
GG/GT	112	6.18							121	6.27						
TT	68	6.27	0.01	0.11	0.08	0.28	0.23	0.25	72	6.39	-0.10	-0.06	-0.01	-0.09	-0.19	0.84
IFNAR1 rs2253923																
AA	67	6.28							72	6.40						
AT/TT	113	6.18	-0.01	-0.10	-0.07	-0.28	-0.24	0.26	121	6.27	0.11	0.07	0.04	0.10	0.20	0.82
IFNAR1 rs2257167																
CC/CG	63	6.20							47	6.19						
GG	117	6.22	0.01	0.03	-0.01	0.14	-0.09	0.15	145	6.36	-0.08	0.01	-0.11	-0.19	-0.34	0.63
IFNAR1 rs2834195																
AA/AG	15	6.16							1	†						
GG	165	6.23	-0.12	-0.18	-0.22	-0.34	-0.24	0.88	192							
IFNAR1 rs2243599																
GG	83	6.29							99	6.22						
GT	77	6.08	0.03	-0.02	-0.08	-0.15	-0.03		26	6.29	-0.23	-0.17	0.12	0.15	0.21	
TT	20	6.40	-0.07	-0.03	0.04	0.27	0.45	0.58	69	6.39	-0.29	-0.16	0.11	0.11	0.03	0.73
IFNAR1 rs1041868																
AA/AG	73	6.20							59	6.18						
GG	106	6.23	0.01	0.09	0.06	0.31	0.18	0.07	134	6.37	0.03	0.17	0.17	0.06	-0.14	0.47
IFNAR1 rs2834202																
AA	116	6.22							108	6.35						
AG/GG	64	6.20	-0.16	-0.22	-0.20	-0.11	-0.27	0.17	85	6.28	0.13	0.15	0.01	0.06	0.06	0.74
IFNAR2 rs1476415																
AA	46	6.34							48	6.20						
AC	106	6.22	0.05	-0.05	-0.01	-0.15	-0.24		86	6.41	0.19	0.09	0.04	-0.02	-0.14	
CC	28	6.02	0.02	-0.09	-0.15	-0.43	-0.43	0.13	60	6.28	0.17	-0.01	-0.21	-0.33	-0.14	0.38
IFNAR2 rs9636866																
CC/CT	106	6.22							72	6.34						
TT	74	6.21	0.08	0.10	0.12	0.06	0.10	0.89	121	6.30	-0.09	-0.05	-0.04	0.14	0.06	0.65
IFNAR2 rs2300370																
AA/AG	74	6.17							98	6.35						
GG	106	6.24	0.01	0.06	0.06	0.24	0.35	0.26	95	6.28	-0.16	-0.09	-0.05	-0.04	-0.09	0.77
IFNAR2 rs2248420																
CC	131	6.23							105	6.27						
CT/TT	49	6.16	-0.05	-0.04	-0.15	-0.27	-0.47	0.16	87	6.36	0.09	-0.01	-0.05	-0.16	-0.14	0.80

Table A-4 (Continued)

IFNAR2 rs4986956																
CC/CT	22	6.16							22	6.37						
TT	158	6.22	-0.06	-0.13	0.10	0.17	0.30	0.46	171	6.31	-0.06	-0.11	0.15	0.27	0.38	0.28
IFNAR2 rs2252650																
AA/AT	84	6.20							97	6.37						
TT	96	6.23	0.02	0.08	0.09	0.15	0.27	0.63	96	6.27	-0.17	-0.11	-0.06	-0.05	-0.13	0.68
IFNAR2 rs2831465																
AA	39	6.10							80	6.26						
AG	107	6.25	0.05	0.10	0.07	0.20	0.11		85	6.45	0.06	0.17	0.34	0.38	-0.002	
GG	34	6.23	-0.05	-0.02	0.02	0.14	0.26	0.77	59	6.17	-0.10	0.03	0.20	0.27	0.07	0.37
IFNAR2 rs28334166																
AA	65	6.21							106	6.26						
AC/CC	115	6.22	0.14	0.14	0.04	0.05	-0.09	0.36	87	6.38	0.02	0.02	-0.08	-0.05	-0.001	0.98
IFNAR2 rs2250226																
AA	33	6.15							96	6.27						
AG	94	6.30	0.12	0.14	0.06	0.08	-0.22		73	6.35	0.20	0.16	0.20	0.14	0.12	
GG	53	6.10	0.11	0.09	-0.01	0.04	-0.27	0.57	25	6.39	-0.02	-0.17	-0.56	-0.64	-0.46	0.31
IFNAR2 rs2834167																
AA	129	6.23							109	6.25						
AG/GG	51	6.18	-0.05	-0.09	-0.16	-0.18	-0.44	0.11	84	6.40	-0.01	-0.01	-0.03	0.03	-0.14	0.81
IRF1 rs839																
AA	48	6.31							25	6.45						
AG	81	6.19	0.004	-0.18	-0.12	-0.27	-0.21		92	6.39	-0.01	-0.13	-0.19	-0.33	0.03	
GG	50	6.15	0.003	-0.13	0.10	-0.03	0.01	0.55	77	6.19	-0.19	-0.26	-0.20	-0.46	0.14	0.09
IRF1 rs2070726																
GG	50	6.15							79	6.20						
GT	82	6.24	0.003	-0.05	-0.21	-0.23	-0.21		86	6.39	0.19	0.13	0.03	0.14	-0.07	
TT	48	6.24	-0.01	0.13	-0.14	0.002	-0.03	0.55	28	6.45	0.12	0.18	0.14	0.36	-0.25	0.08
IRF1 rs2070723																
CC	47	6.31							24	6.45						
CT	83	6.20	-0.02	-0.19	-0.11	-0.26	-0.20		91	6.39	-0.03	-0.15	-0.21	-0.36	-0.001	
TT	50	6.15	-0.004	-0.14	0.11	-0.03	-0.01	0.55	79	6.20	-0.18	-0.25	-0.22	-0.46	0.15	0.11
IRF1 rs2070721																
AA	34	6.23							55	6.17						
AC	78	6.15	0.12	0.22	-0.01	0.04	0.08		101	6.37	-0.003	-0.04	-0.07	-0.08	-0.50	
CC	68	6.28	0.06	0.26	-0.10	0.03	-0.06	0.19	38	6.41	0.10	0.14	0.08	0.23	-0.33	0.11

Table A-4 (Continued)

IRF1 rs2549009																
AA	47	6.35							27	6.32						
AG	89	6.17	0.12	0.04	0.05	0.01	-0.01		97	6.43	0.02	-0.09	-0.02	-0.23	0.09	
GG	43	6.15	0.04	-0.06	0.07	0.10	0.17	0.93	68	6.18	-0.09	-0.18	-0.08	-0.38	0.16	0.27
IRF1 rs2549006																
CC	58	6.18							80	6.19						
CT	85	6.20	0.04	0.10	0.03	-0.02	-0.23		90	6.40	0.14	0.09	-0.004	0.10	-0.09	
TT	37	6.29	0.03	0.11	0.03	0.02	-0.06	0.82	24	6.45	0.17	0.24	0.21	0.46	-0.12	0.19
IRF1 rs2549003																
CC	54	6.30							23	6.44						
CT	82	6.18	0.002	-0.09	-0.04	-0.15	-0.24		90	6.38	-0.06	-0.16	-0.21	-0.37	0.03	
TT	44	6.17	-0.03	-0.10	0.10	0.07	0.17	0.61	79	6.20	-0.21	-0.27	-0.23	-0.48	0.15	0.11
IRF1 rs736801																
CC	142	6.22							76	6.31						
CT/TT	37	6.16	-0.09	-0.17	0.06	0.07	0.06	0.44	118	6.33	0.08	0.14	0.05	-0.04	0.03	0.82
IRF7 rs12421158																
CC	54	6.15							22	6.41						
CT	99	6.23	-0.09	-0.06	0.10	-0.05	0.10		88	6.22	-0.10	-0.15	-0.36	-0.57	-0.55	
TT	26	6.26	0.04	0.10	0.30	0.12	0.14	0.33	83	6.40	-0.19	-0.25	-0.32	-0.47	-0.49	0.90
IRF7 rs7932167																
AA	79	6.17							118	6.38						
AC	73	6.33	-0.05	-0.12	-0.11	-0.07	-0.17		62	6.26	-0.08	-0.08	-0.10	-0.007	-0.07	
CC	28	6.03	-0.19	-0.27	-0.07	-0.01	-0.08	0.79	13	6.01	0.09	0.20	-0.16	-0.16	-0.49	0.82
Mx1 rs462903																
AA	131	6.25							65	6.26						
AG/GG	49	6.13	-0.01	-0.06	0.05	-0.12	-0.21	0.42	129	6.36	0.19	0.25	0.45	0.41	0.13	0.07
Mx1 rs17000900																
AA/AC	72	6.26							36	6.22						
CC	105	6.17	-0.02	-0.09	-0.07	-0.15	-0.11	0.90	156	6.35	0.05	0.06	0.11	0.25	0.27	0.93
Mx1 rs455816																
AA	123	6.24							55	6.33						
AG	53	6.14	0.03	-0.05	0.07	-0.09	-0.001		90	6.23	0.22	0.19	0.33	0.14	-0.002	
GG	4	6.53	-0.40	-0.52	-0.34	-0.39	-0.18	0.67	49	6.48	0.12	0.23	0.33	0.42	0.24	0.43
Mx1 rs469390																
AA	40	6.17							72	6.34						
AG	87	6.26	0.19	0.21	0.26	0.43	0.46		90	6.30	0.11	0.02	0.13	-0.13	0.04	
GG	53	6.16	0.19	0.22	0.29	0.36	0.48	0.58	32	6.34	0.13	0.22	0.32	0.11	0.23	0.57

Table A-4 (Continued)

Mx1 rs456298																
AA	67	6.21							144	6.29						
AT/TT	112	6.21	0.04	0.04	-0.05	0.02	0.17	0.49	50	6.39	-0.08	0.05	0.03	0.05	-0.29	0.16
Mx2 rs757368																
CC	57	6.20							138	6.30						
CG/GG	123	6.22	0.0003	0.04	0.03	0.09	-0.08	0.64	55	6.36	-0.13	-0.13	-0.08	-0.11	-0.14	0.93
Mx2 rs2838029																
AA	41	6.33							2	5.60						
AG	82	6.13	-0.01	-0.05	-0.19	-0.16	-0.17		48	6.40	0.44	0.46	-0.26	-0.09	-0.35	
GG	57	6.24	-0.10	-0.14	-0.21	-0.19	-0.26	0.97	143	6.30	0.58	0.60	-0.19	-0.05	-0.35	0.93
Mx2 rs443099																
GG	116	6.24							28	6.33						
GT	57	6.18	0.10	-0.01	-0.04	-0.07	0.04		94	6.35	0.30	0.45	-0.03	-0.10	-0.29	
TT	7	6.02	-0.76	-0.83	-0.62	-0.91	-0.99	0.04	71	6.27	0.17	0.38	-0.10	-0.10	0.04	0.03
Mx2 rs116422																
GG	79	6.17							127	6.33						
GT/TT	100	6.24	0.13	0.13	0.21	0.13	0.29	0.21	67	6.30	0.17	0.22	0.12	0.30	0.19	0.34
Mx2 rs9305739																
CC/CT	66	6.24							16	6.43						
TT	114	6.20	-0.04	-0.07	0.02	0.11	0.26	0.39	177	6.31	0.35	0.46	0.39	0.68	1.00	0.12
Mx2 rs369908																
AA	9	6.18							128	6.35						
AG	68	6.19	0.77	0.88	0.64	0.61	0.55		55	6.25	-0.30	-0.44	-0.50	-0.61	-0.97	
GG	102	6.23	0.69	0.83	0.56	0.54	0.36	0.06	10	6.32	0.18	0.10	-0.11	-0.40	0.10	0.003
Mx2 rs11537891[†]																
GG/GT	145	6.22							192							
TT	34	6.16	-0.01	-0.004	0.02	0.04	0.14	0.97	2	†						
Mx2 rs464090																
CC	57	6.25							130	6.38						
CT/TT	123	6.20	0.16	0.23	0.03	0.17	0.29	0.045	63	6.18	-0.20	-0.31	-0.43	-0.59	-0.63	0.14
OAS1 rs4766662																
AA/AC	112	6.24							75	6.34						
CC	68	6.17	-0.03	-0.10	0.03	0.05	0.15	0.53	118	6.30	0.02	-0.03	0.08	0.06	0.16	0.89
OAS1 rs3741981																
CC	92	6.20							29	6.52						
CT	81	6.26	0.06	0.05	0.01	0.20	0.03		98	6.17	0.03	0.16	0.12	0.20	0.39	
TT	7	5.88	-0.36	-0.66	-0.32	-0.003	0.12	0.08	65	6.43	0.24	0.26	0.48	0.62	0.67	0.35

Table A-4 (Continued)

OAS1 rs2285934																
AA/AC	131	6.20							113	6.27						
CC	49	6.24	-0.02	-0.002	0.05	0.11	0.12	0.98	80	6.39	0.20	0.16	0.39	0.48	0.44	0.13
OAS1 rs12298890[§]																
OAS1 rs2660																
AA	152	6.18							80	6.40						
AG/GG	27	6.38	0.07	0.10	0.18	0.28	0.18	0.83	113	6.26	-0.20	-0.14	-0.37	-0.48	-0.42	0.11
OAS1 rs6489865																
AA/AG	19	6.34							111	6.26						
GG	161	6.20	-0.11	-0.07	-0.07	-0.19	-0.07	0.85	82	6.40	0.22	0.17	0.37	0.47	0.41	0.14
OAS2 rs2010604																
CC/CG	38	6.36							95	6.23						
GG	142	6.17	0.01	0.10	-0.01	0.17	0.10	0.54	98	6.40	0.12	0.13	0.22	0.31	0.12	0.45
OAS2 rs2072138																
CC/CG	73	6.18							94	6.36						
GG	106	6.25	-0.15	-0.15	-0.21	-0.20	-0.20	0.64	97	6.26	-0.22	-0.34	-0.43	-0.44	-0.33	0.25
OAS2 rs1293762																
AA/AC	49	6.34							140	6.29						
CC	131	6.17	-0.12	-0.20	-0.22	-0.39	-0.33	0.34	53	6.38	0.12	0.15	0.27	0.26	0.17	0.80
OAS2 rs1293739																
AA/AG	80	6.18							83	6.31						
GG	100	6.24	-0.07	0.01	0.11	0.19	0.23	0.55	110	6.32	0.23	0.25	0.21	0.21	0.25	0.52
OAS3 rs1981557																
CC/CG	21	6.20							113	6.25						
GG	157	6.22	-0.04	-0.001	0.11	-0.01	0.17	0.67	80	6.41	0.22	0.16	0.39	0.51	0.46	0.09
OAS3 rs6489879																
AA	161	6.20							80	6.41						
AG/GG	19	6.34	0.11	0.07	0.07	0.19	0.07	0.85	113	6.25	-0.22	-0.16	-0.39	-0.51	-0.46	0.09
OAS3 rs2269899																
AA	92	6.15							84	6.36						
AG/GG	88	6.28	-0.14	-0.14	-0.22	-0.23	-0.42	0.12	109	6.28	-0.10	-0.13	-0.32	-0.41	-0.34	0.42
OAS3 rs2285933																
CC/CG	110	6.18							95	6.38						
GG	70	6.27	-0.04	-0.07	-0.03	-0.03	0.08	0.88	98	6.26	-0.15	-0.16	-0.22	-0.24	-0.05	0.49
OAS3 rs2107418																
GG	39	6.27							33	6.37						
GT	71	6.14	-0.05	0.10	-0.08	-0.07	-0.18		106	6.24	0.10	0.28	0.23	0.67	0.77	
TT	70	6.26	-0.09	-0.08	0.05	0.07	-0.02	0.97	54	6.45	0.20	0.32	0.35	0.49	0.36	0.06

Table A-4 (Continued)

OAS3 rs2240189																
CC	123	6.27							99	6.27						
CT/TT	57	6.10	0.20	0.19	0.09	0.21	0.06	0.11	94	6.36	0.11	0.10	0.17	0.17	-0.02	0.57
OAS3 rs757404																
CC	71	6.29							98	6.26						
CT/TT	109	6.16	-0.01	0.03	-0.03	-0.01	-0.12	0.81	95	6.37	0.13	0.12	0.18	0.20	0.02	0.63
OASL rs1169279																
AA/AG	100	6.20							111	6.34						
GG	80	6.23	0.07	0.16	0.12	0.05	0.15	0.58	82	6.28	-0.08	-0.11	-0.26	-0.19	0.24	0.01
OASL rs7134141																
AA/AG	49	6.24							10	6.64						
GG	130	6.21	0.09	0.12	0.08	0.15	0.11	0.86	184	6.30	0.04	0.11	-0.02	0.05	0.23	0.97
OASL rs2259697																
CC/CT	112	6.22							71	6.43						
TT	68	6.20	-0.13	0.04	-0.05	0.12	0.13	0.25	123	6.26	-0.13	-0.10	-0.11	-0.14	-0.35	0.46
OASL rs12819210																
CC	160	6.20							124	6.26						
CT/TT	20	6.29	0.17	0.28	0.29	0.39	0.37	0.71	70	6.44	0.13	0.10	0.12	0.16	0.42	0.24
OASL rs3861793[§]																
OASL rs11307154																
AA/A-	136	6.20							75	6.13						
--	43	6.24	-0.08	-0.16	-0.11	0.01	-0.09	0.72	119	6.44	-0.06	-0.04	-0.01	-0.06	0.13	0.70
OASL rs7969180[§]																
OASL rs2260399																
CC	71	6.27							45	6.29						
CT	90	6.17	-0.03	-0.07	0.02	0.16	-0.02		103	6.25	-0.10	-0.18	-0.05	-0.19	-0.55	
TT	19	6.19	0.05	-0.04	0.11	0.18	0.17	0.67	45	6.50	-0.19	-0.08	-0.03	-0.24	-0.66	0.25
OASL rs10849829																
AA	19	6.19							46	6.51						
AG	90	6.17	-0.08	-0.04	-0.08	-0.02	-0.18		104	6.26	0.07	0.08	-0.01	0.04	0.07	
GG	71	6.27	-0.05	0.03	-0.11	-0.18	-0.17	0.67	44	6.27	0.18	0.16	0.01	0.24	0.62	0.30
OASL rs3213546																
CC/CG	54	6.20							11	6.58						
GG	126	6.22	0.05	0.06	0.12	0.20	0.15	0.88	183	6.30	0.03	0.09	-0.09	-0.04	0.02	0.95
OASL rs3213545																
CC	125	6.20							95	6.28						
CT/TT	55	6.24	-0.05	-0.10	-0.12	0.05	0.01	0.63	97	6.35	-0.01	0.08	0.18	0.05	-0.33	0.02
OASL rs28360476[§]																

Table A-4 (Continued)

OASL rs10849832																
CC/CT	68	6.18							43	6.23						
TT	112	6.23	0.08	0.08	-0.01	-0.08	-0.04	0.83	150	6.34	0.05	0.11	0.10	0.03	0.09	0.98
OASL rs12315068[§]																
OASL rs10849833																
AA/AG	67	6.16							18	6.48						
GG	113	6.24	0.10	0.08	0.07	0.06	0.11	0.91	176	6.30	-0.09	-0.08	-0.27	-0.21	-0.23	0.94
OASL rs2859394																
CC/CT	35	6.28							57	6.45						
TT	144	6.20	0.01	-0.09	-0.13	-0.09	-0.15	0.92	136	6.27	-0.16	-0.05	-0.09	-0.16	-0.35	0.40
OASL rs2859398																
CC/CT	62	6.26							113	6.38						
TT	118	6.19	0.01	0.03	0.01	-0.15	-0.14	0.67	81	6.23	-0.02	-0.10	-0.17	-0.11	0.19	0.20
OASL rs7134069																
AA	116	6.24							177	6.30						
AC/CC	63	6.18	-0.11	-0.10	-0.05	-0.001	-0.08	0.74	17	6.47	0.05	0.10	0.22	0.15	0.17	0.99
PKR rs2307478																
CC/CT	15	6.24							0	§						
TT	165	6.21	0.20	0.32	0.07	0.09	-0.15	0.28	194							
PKR rs2307479																
AA	142	6.20							185	6.30						
AC/CC	37	6.25	-0.22	-0.34	-0.32	-0.57	-0.57	0.045	9	6.64	0.10	0.06	-0.16	-0.20	0.06	0.90
PKR rs2287350																
AA	129	6.23							70	6.34						
AG	45	6.18	-0.07	-0.15	-0.13	-0.20	-0.04		90	6.27	0.14	0.26	0.17	-0.05	-0.22	
GG	4	5.99	0.12	0.15	0.28	0.03	-0.50	0.68	33	6.42	0.06	0.09	0.23	0.09	-0.03	0.54
PKR rs2254958																
CC	129	6.21							64	6.28						
CT	48	6.18	-0.21	-0.33	-0.24	-0.43	-0.26		91	6.29	0.18	0.32	0.17	-0.08	-0.25	
TT	3	6.60	-0.02	0.35	0.14	0.01	0.12	0.14	34	6.42	0.07	0.15	0.28	0.10	-0.08	0.31
STAT1 rs2066797																
AA	123	6.25							168	6.31						
AG/GG	57	6.14	-0.08	-0.12	-0.10	-0.10	0.02	0.78	24	6.32	0.22	0.20	0.44	0.42	-0.11	0.04
STAT1 rs3088307																
CC/CG	80	6.27							141	6.37						
GG	100	6.17	0.19	0.22	0.09	0.16	0.23	0.15	52	6.18	0.17	-0.07	0.02	0.04	-0.15	0.18
STAT1 rs1400657																
AA	110	6.27							156	6.33						
AC/CC	70	6.12	-0.03	0.02	-0.12	-0.15	-0.23	0.59	37	6.27	-0.05	-0.10	-0.06	-0.02	-0.15	0.95

Table A-4 (Continued)

STAT1 rs1914408																
AA/AG	53	6.15							68	6.25						
GG	127	6.24	0.14	0.17	0.20	0.30	0.19	0.50	124	6.35	-0.02	0.19	0.01	0.05	-0.02	0.39
STAT1 rs2280234																
CC	27	6.05							83	6.35						
CT	83	6.29	-0.21	-0.09	-0.06	0.07	-0.16		84	6.33	-0.05	-0.15	-0.04	-0.16	-0.27	
TT	70	6.19	-0.11	-0.04	-0.13	-0.09	-0.31	0.50	26	6.14	0.01	-0.17	0.27	0.23	-0.20	0.20
STAT1 rs12693590																
AA	139	6.25							167	6.33						
AC/CC	41	6.10	0.02	0.08	-0.04	-0.10	-0.15	0.81	26	6.26	-0.07	-0.23	-0.42	-0.44	-0.66	0.40
STAT1 rs2066802																
CC/CT	26	6.13							24	6.26						
TT	154	6.23	0.24	0.21	0.20	0.24	0.09	0.41	169	6.32	-0.25	-0.21	-0.49	-0.60	-0.32	0.19
STAT1 rs1467199																
CC	84	6.18							124	6.37						
CG/GG	96	6.24	-0.17	-0.12	0.09	0.03	-0.15	0.02	69	6.21	-0.12	-0.26	-0.17	-0.25	-0.10	0.43
STAT2 rs2066808																
CC/CT	143	6.21							34	6.37						
TT	37	6.23	-0.16	-0.15	0.12	0.07	0.20	0.10	160	6.31	0.20	0.21	0.09	0.07	-0.003	0.80
STAT2 rs2066807†																
CC/CG	2								31	6.47						
GG	178	†							162	6.39	0.13	0.03	-0.04	-0.08	-0.22	0.83
STAT2 rs2066811																
AA	125	6.21							192							
AG/GG	55	6.23	0.21	0.21	0.01	0.01	0.23	0.02	1	†						
STAT2 rs2228259§																
STAT2 rs2066816§																
STAT2 rs2066819																
AA/AG	2	5.53							32	6.39						
GG	178	6.22	-0.90	-0.83	-0.75	0.09	0.18	0.18	161	6.30	0.14	0.06	-0.004	-0.02	-0.18	0.82
STAT2 rs11171812†																
AA/AG	139	6.21							2							
GG	41	6.21	-0.10	-0.1	0.15	0.10	0.19	0.17	191	†						
STAT2 rs4201822†																
	144	6.24							2							
	35	6.14	0.11	0.14	0.23	0.08	0.00	0.64	191	†						

* Model adjusted for the genetic variant, age, time, and the interaction between time and the genetic variant

** Reflects the mean HCV RNA levels

§ Monomorphic SNP, † Minor allele frequency less than 5%

Table A-5: Multivariable Model Estimating Differences in Viral Level for Interferon Stimulated Gene Haplotypes During the First 28 Days of Treatment Among Caucasian Americans and African Americans

	African Americans (N = 180) Estimated Change in Viral Level by Treatment Day*								Caucasian Americans (N = 194) Estimated Change in Viral Level by Treatment Day*							
Genetic Marker	N	0	1	2	7	14	28	p- value	N	0	1	2	7	14	28	p- value
ISG15 G1P2																
AT	119	6.22	-0.10	-0.07	0.06	0.11	-0.04	0.35	120	6.36	0.11	0.14	0.15	0.21	0.32	0.79
GC	88	6.20	0.06	-0.02	0.002	-0.07	0.08	0.52	156	6.32	0.07	0.09	0.14	0.16	0.55	0.15
GT	95	6.28	0.07	0.18	0.007	0.03	0.001	0.40	18	6.27	-0.07	-0.21	-0.22	-0.23	-0.22	0.98
IFI35																
CAG	85	6.16	0.02	-0.06	-0.02	-0.08	-0.02	0.85	64	6.30	0.03	0.03	0.12	0.02	0.25	0.44
TGA	65	6.40	0.01	0.08	0.09	0.19	0.13	0.83	31	6.15	-0.02	-0.11	-0.12	0.18	0.29	0.47
TGG	123	6.17	0.01	-0.08	-0.09	-0.17	-0.17	0.87	179	6.32	-0.11	-0.27	-0.26	-0.55	-0.92	0.26
IFNAR1																
AACTAGGGA	78	6.25	0.11	0.18	0.15	0.15	0.04	0.61	3	†						
AACTAGTGA	64	6.19	-0.03	-0.06	-0.17	-0.21	-0.07	0.56	104	6.38	-0.20	-0.16	-0.11	-0.10	-0.20	0.56
AGCGTCGAA	62	6.21	-0.01	-0.06	-0.01	-0.16	0.08	0.13	47	6.19	0.08	-0.02	0.10	0.18	0.33	0.66
AGCGTGGGG	54	6.16	-0.08	-0.12	-0.05	0.002	-0.17	0.48	84	6.28	0.11	0.13	-0.02	0.03	0.008	0.78
TAGTAGTGA	32	6.13	0.05	0.02	0.20	0.39	0.50	0.20	81	6.30	0.007	0.08	0.09	-0.13	-0.15	0.61
IFNAR2																
CGTTACAA	9	6.39	0.01	0.16	0.12	0.18	0.49	0.65	54	6.36	0.12	0.11	0.20	0.08	0.07	0.86
CGTTACGA	59	6.14	0.05	0.04	-0.06	-0.06	-0.15	0.75	1	†						
TATAACGA	29	6.17	-0.03	-0.07	-0.07	-0.09	-0.27	0.74	46	6.32	0.15	0.10	0.14	0.17	0.43	0.41
TATAACGG	11	6.25	-0.02	-0.21	-0.18	-0.50	-0.82	0.12	23	6.38	0.01	-0.07	-0.19	-0.10	0.01	0.95
TGTTGAAA	54	6.25	-0.18	-0.16	-0.06	-0.08	0.13	0.10	72	6.19	-0.02	-0.05	0.03	-0.02	0.24	0.46
TGTTGAAG	4	†							23	6.59	-0.20	-0.08	0.06	0.12	-0.32	0.17
TGTTGCGA	29	6.21	0.11	0.10	0.15	0.28	0.30	0.73	3	†						
IRF1																
ATCCATCC	113	6.24	0.02	0.10	-0.001	0.02	-0.04	0.84	113	6.41	0.16	0.16	0.07	0.22	-0.09	0.07
ATCCGCCC	15	6.32	0.09	-0.01	-0.11	0.09	0.04	0.75	1	†						
GGTAATCC	79	6.15	0.02	-0.04	0.09	0.05	0.16	0.50	58	6.14	-0.13	-0.16	0.01	0.05	0.36	0.12
GGTAGCTT	30	6.23	-0.08	-0.17	0.05	0.12	0.10	0.46	108	6.32	0.07	0.10	0.04	-0.07	0.02	0.87
GGTCGCTC	29	6.10	0.03	0.13	0.02	-0.07	-0.23	0.56	27	6.25	-0.003	0.04	-0.02	-0.11	-0.04	0.99
IRF7																
CA	131	6.23	0.09	0.10	-0.09	-0.08	-0.10	0.54	107	6.26	0.08	0.09	0.05	0.07	0.10	0.99
CC	39	6.21	-0.20	-0.27	-0.22	-0.07	0.04	0.22	9	†						
TA	60	6.25	-0.02	0.03	0.10	-0.02	0.20	0.20	130	6.35	-0.09	-0.25	-0.08	-0.11	0.02	0.43
TC	78	6.24	-0.06	-0.10	0.03	-0.04	-0.12	0.53	69	6.25	-0.07	-0.05	-0.20	-0.13	-0.22	0.72

Table A-5 (Continued)

Mx1																
AAAA	81	6.24	0.001	0.01	-0.08	-0.01	-0.11	0.78	37	6.19	-0.15	-0.27	-0.44	-0.17	-0.15	0.35
AAGA	61	6.16	0.05	0.01	0.20	0.16	0.14	0.53	95	6.27	0.04	-0.04	0.04	-0.15	0.04	0.47
AAGT	90	6.21	0.10	0.15	0.06	0.16	0.31	0.29	5	†						
AGAA	8	†							23	6.15	0.13	0.10	-0.01	0.03	0.09	0.97
GGAA	32	6.09	0.03	0.02	0.07	-0.15	-0.06	0.60	95	6.33	0.12	0.14	0.25	0.13	-0.05	0.50
OAS1																
AC	141	6.19	-0.01	-0.001	-0.05	-0.16	-0.14	0.94	129	6.36	-0.001	-0.05	0.04	-0.06	-0.23	0.63
AT	2	†							15	6.34	0.23	0.11	0.24	0.45	0.41	0.72
CC	110	6.20	0.02	0.04	0.07	0.02	0.10	0.82	78	6.30	-0.09	-0.09	-0.20	-0.19	-0.002	0.37
CT	86	6.21	-0.01	-0.09	-0.04	0.14	0.12	0.24	159	6.31	0.10	0.11	0.24	0.27	0.26	0.51
OAS2																
CGAG	19	6.37	0.05	0.08	0.03	0.13	-0.003	0.92	88	6.21	-0.08	-0.11	-0.23	-0.30	-0.08	0.43
GCCG	61	6.21	0.18	0.19	0.25	0.35	0.32	0.37	91	6.34	0.26	0.34	0.44	0.49	0.38	0.20
GGAA	5	†							24	6.50	-0.10	-0.15	0.01	0.06	-0.46	0.09
GGAG	15	6.37	-0.01	0.18	0.20	0.28	0.18	0.83	33	6.22	0.07	0.16	-0.05	-0.09	0.24	0.31
GGCA	56	6.16	-0.06	-0.15	-0.27	-0.34	-0.48	0.27	54	6.23	-0.23	-0.23	-0.28	-0.27	-0.14	0.53
GGCG	108	6.23	-0.13	-0.09	-0.06	-0.07	-0.05	0.84	37	6.42	-0.06	-0.14	-0.12	-0.04	-0.03	0.98
OAS3																
ACTT	45	6.07	0.21	0.19	0.12	0.19	0.13	0.35	92	6.36	0.12	0.13	0.20	0.22	0.06	0.66
ACCT	15	6.34	-0.04	0.14	0.17	0.38	0.36	0.61	0	†						
AGCC	133	6.22	0.05	0.02	0.06	0.02	-0.05	0.97	134	6.28	-0.21	-0.19	-0.16	-0.17	-0.09	0.68
GCCT	50	6.22	-0.21	-0.19	-0.24	-0.30	-0.40	0.20	2	†						
GGCC	22	6.31	-0.10	-0.15	-0.18	-0.37	-0.38	0.65	106	6.27	-0.13	-0.16	-0.33	-0.44	-0.33	0.36
OASL																
AATCGTACCCATTC	36	6.18	-0.09	-0.07	0.06	0.06	0.07	0.86	10	6.64	-0.03	-0.11	0.03	-0.05	-0.22	0.97
AGTCGTAGTTGTCA	43	6.20	-0.01	-0.11	-0.05	0.13	0.03	0.47	85	6.33	0.01	0.06	0.17	0.12	-0.24	0.057
GGCCGCGGCTGTTA	82	6.19	-0.11	-0.08	-0.09	-0.20	-0.23	0.64	1	†						
GGCTGCGGCTGCTA	14	6.31	0.17	0.35	0.28	0.36	0.34	0.72	57	6.45	0.16	0.05	0.08	0.16	0.35	0.38
GGTCGCGGCCGTTA	5	†	6.24						28	6.04	-0.09	-0.21	-0.33	-0.18	-0.27	0.75
GGTCGCGGCTGTTA	47	6.22	0.05	0.02	-0.005	0.003	-0.02	0.99	73	6.15	0.04	0.08	0.04	0.14	0.27	0.78
GGTCGTAGCTGTTA	12	5.92	0.10	0.04	0.07	0.15	-0.21	0.45	47	6.24	-0.17	-0.28	-0.44	-0.51	-0.39	0.40
PKR																
ACC	153	6.19	0.02	-0.09	-0.24	0.01	0.20	0.62	152	6.28	0.03	0.04	-0.11	-0.05	0.11	0.79
AGT	25	6.09	-0.09	-0.11	-0.10	-0.08	0.08	0.83	119	6.33	0.15	0.23	0.15	-0.04	-0.19	0.26
AGC	15	6.21	-0.04	-0.12	0.09	-0.04	-0.14	0.72	8	†						
AAT	13	6.29	-0.31	-0.27	-0.20	-0.72	-0.76	0.02	14	6.29	0.03	0.21	0.33	0.28	0.28	0.96
CAC	21	6.15	-0.31	-0.42	-0.41	-0.65	-0.95	0.008	8	†						

Table A-5 (Continued)

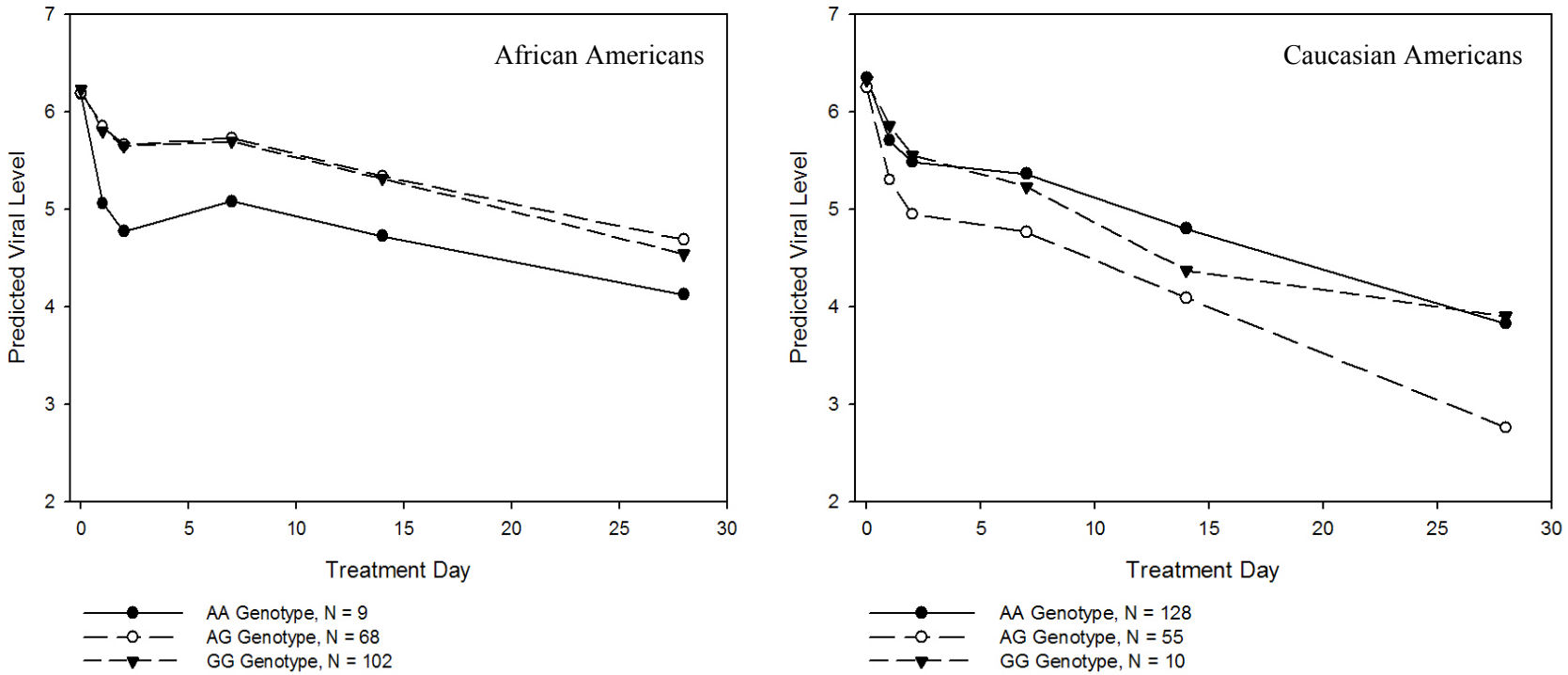
STAT1																
	ACAGCATC	33	6.28	-0.11	-0.14	-0.09	-0.11	-0.20	0.87	135	6.37	-0.18	0.12	0.01	0.005	0.09	0.14
	ACAGCATG	25	6.23	-0.21	-0.24	-0.13	-0.27	-0.32	0.41	5	†						
	AGAATATG	29	6.34	-0.11	0.10	0.16	0.24	0.23	0.53	53	6.21	-0.17	-0.41	-0.21	-0.32	-0.32	0.14
	AGAGCATC	26	6.22	0.25	0.24	0.29	0.44	0.65	0.15	36	6.35	0.28	0.31	0.08	0.23	0.48	0.08
	AGAGCCTC	8	†							23	6.27	-0.09	-0.32	-0.59	-0.65	-0.90	0.14
	AGAGTATC	29	6.32	0.06	-0.004	0.07	0.20	0.32	0.66	2	†						
	AGCGTATC	27	6.13	-0.06	-0.06	-0.31	-0.38	-0.48	0.32	28	6.27	-0.13	-0.16	-0.02	-0.07	-0.42	0.28
	AGCGTATG	28	6.14	0.02	0.02	0.16	0.20	-0.09	0.25	7	†						
	GGAGTATC	22	6.08	0.04	-0.01	0.05	-0.21	-0.22	0.53	2	†						
STAT2																
	CCAAGT	2	†							31	6.39	-0.13	-0.03	0.04	0.08	0.22	0.83
	CGAGAC	103	6.26	0.05	0.09	-0.02	0.09	-0.03	0.44	1	†						
	CGGGAC	52	6.27	0.15	0.17	0.03	0.02	0.24	0.10	1	†						
	TGAGGC	15	6.05	-0.11	-0.17	-0.04	-0.04	0.22	0.56	0	†						
	TGAGGT	122	6.23	-0.17	-0.19	0.05	-0.07	-0.15	0.048	193	‡						

* Model adjusted for age, time, genetic variant and interaction between time and genetic variant

** Reflects the mean HCV RNA levels

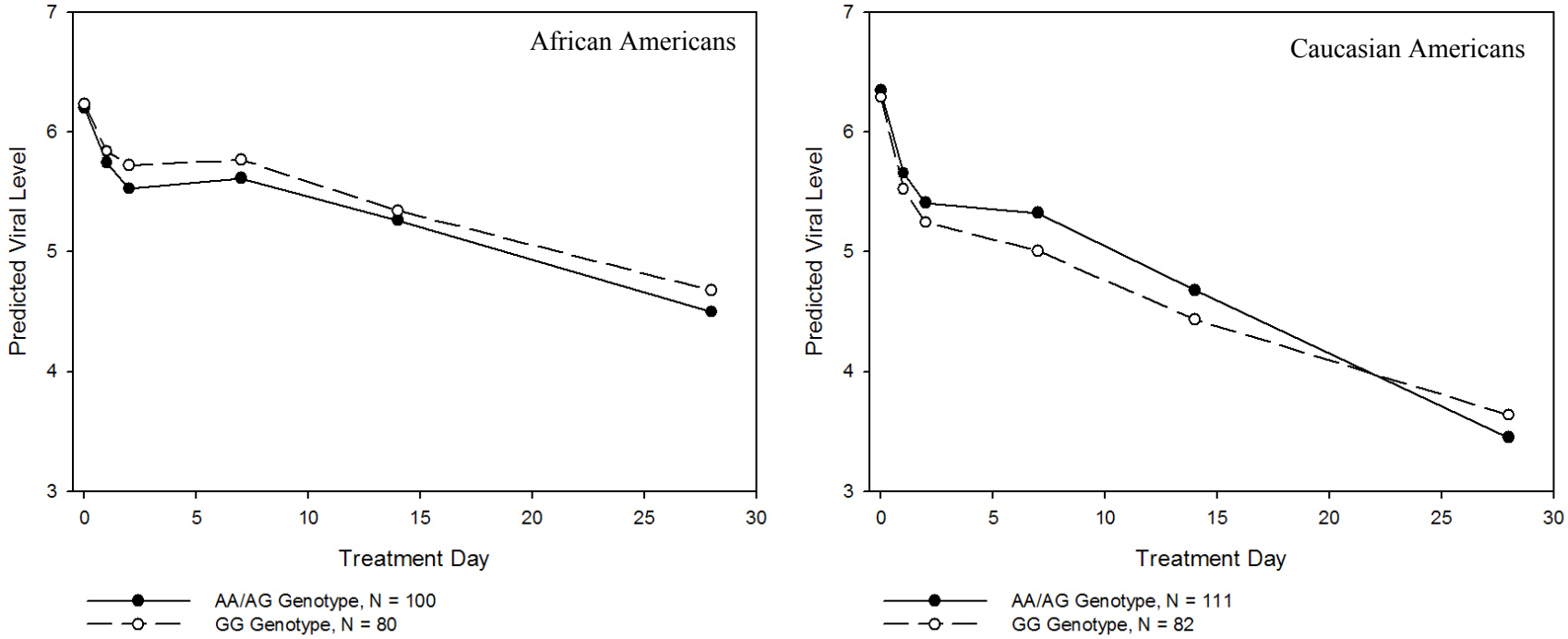
† Haplotype frequency less than 5%

‡ No variation in the haplotype



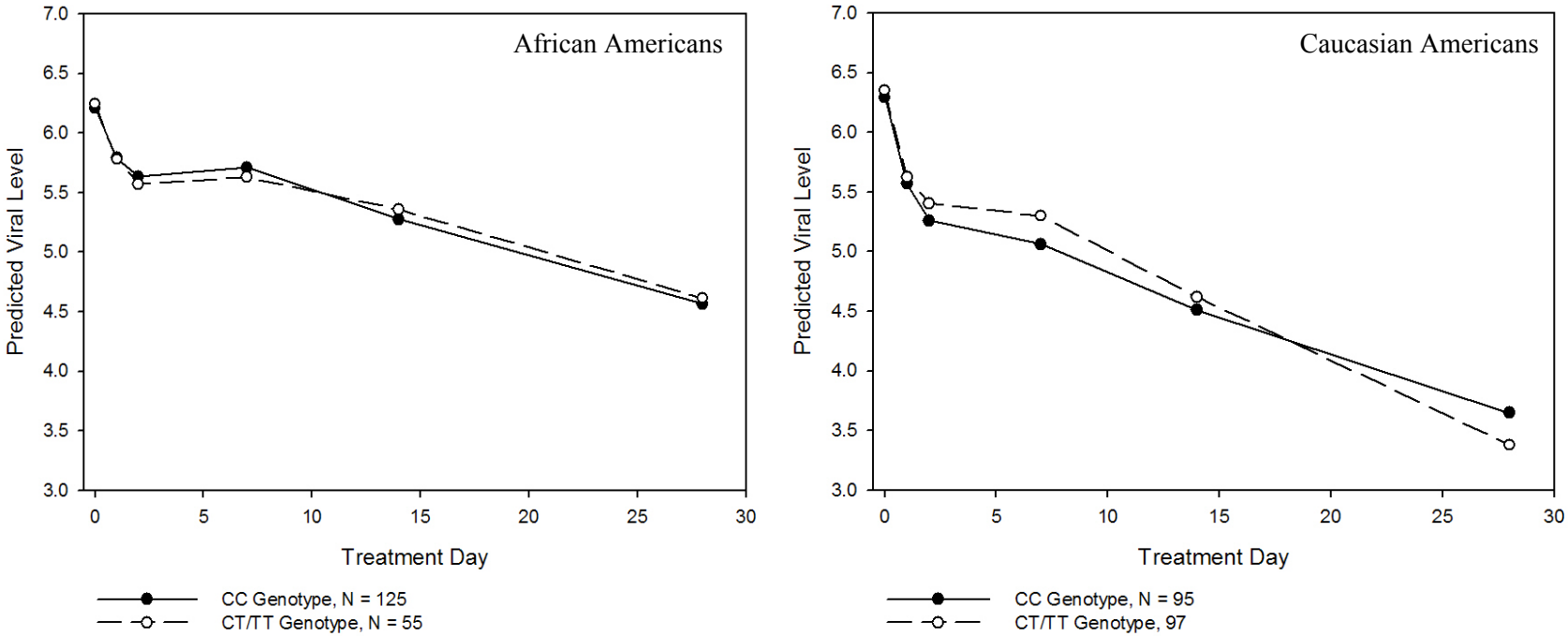
Figures A3-1a and 1b: Predicted Viral Level for *MX2 rs369908* Genotypes Over the First 28 Days of Treatment among African Americans (N=179) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



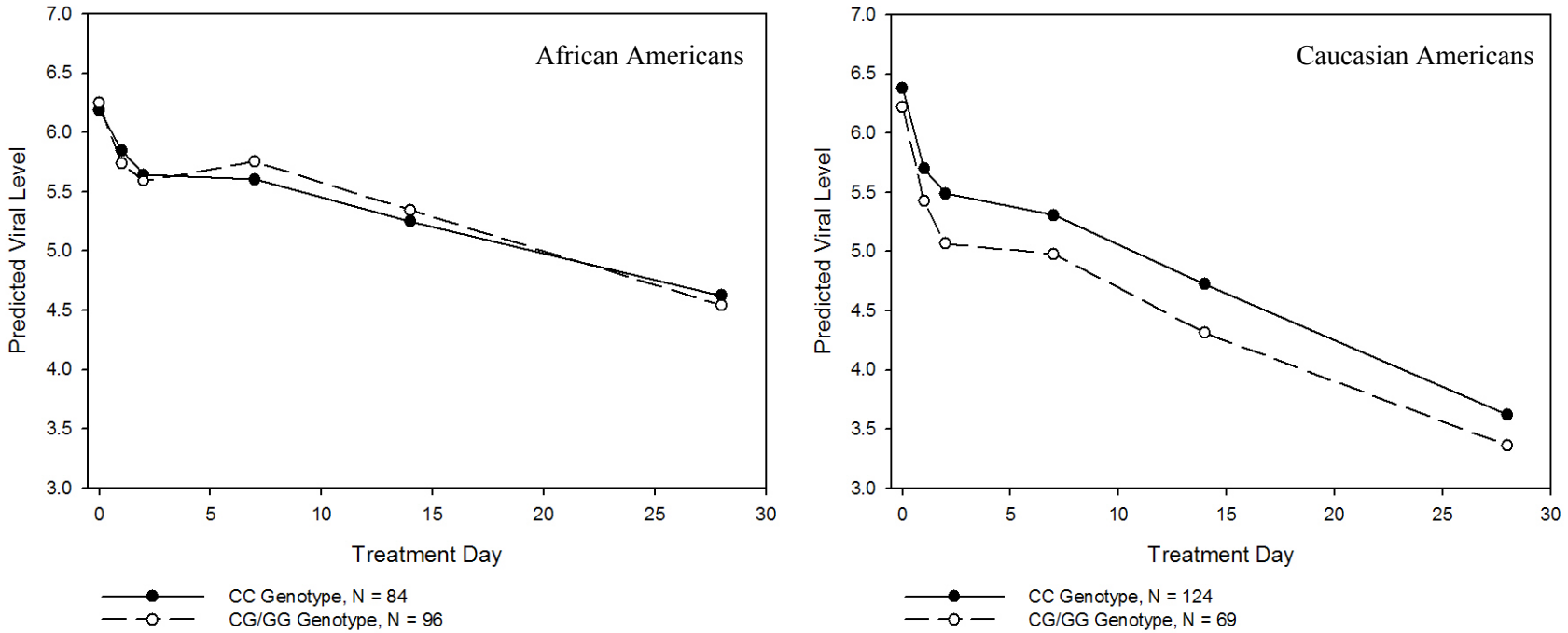
Figures A3-2a and 2b: Predicted Viral Level for *OASL rs1169279* Genotypes Over the First 28 Days of Treatment among African Americans (N=180) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



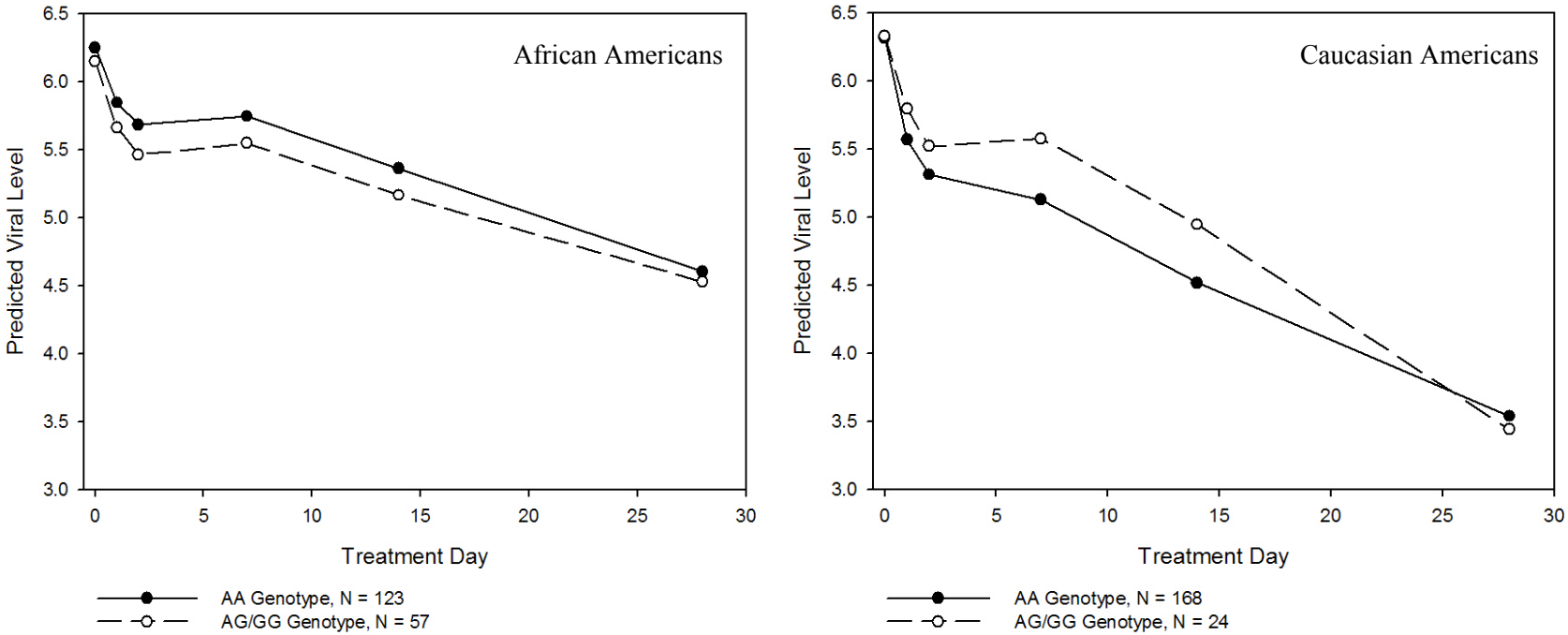
Figures A3-3a and 3b: Predicted Viral Level for *OASL rs3213545* Genotypes over the First 28 Days of Treatment among African Americans (N=180) and Caucasian Americans (N=192)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



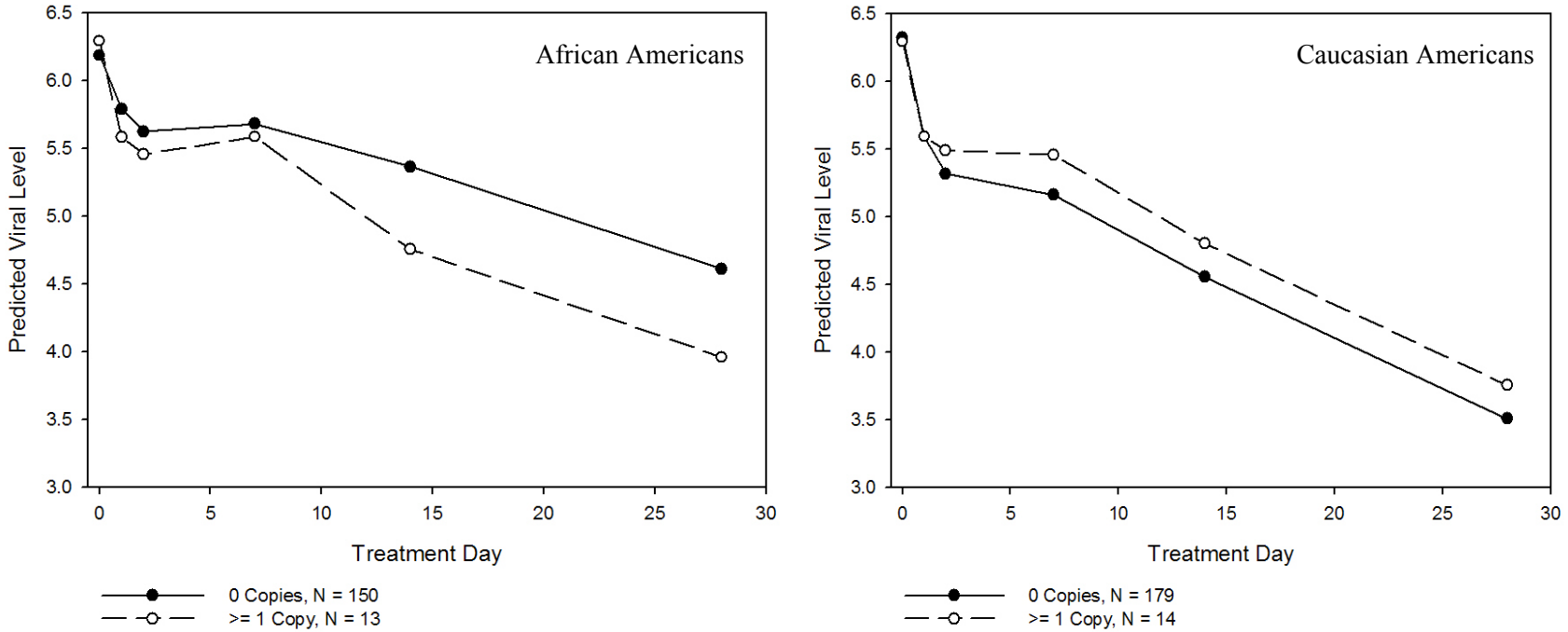
Figures A3-4a and 4b: Predicted Viral Level for *STAT1 rs1467199* Genotypes Over the First 28 Days of Treatment among African Americans (N=180) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



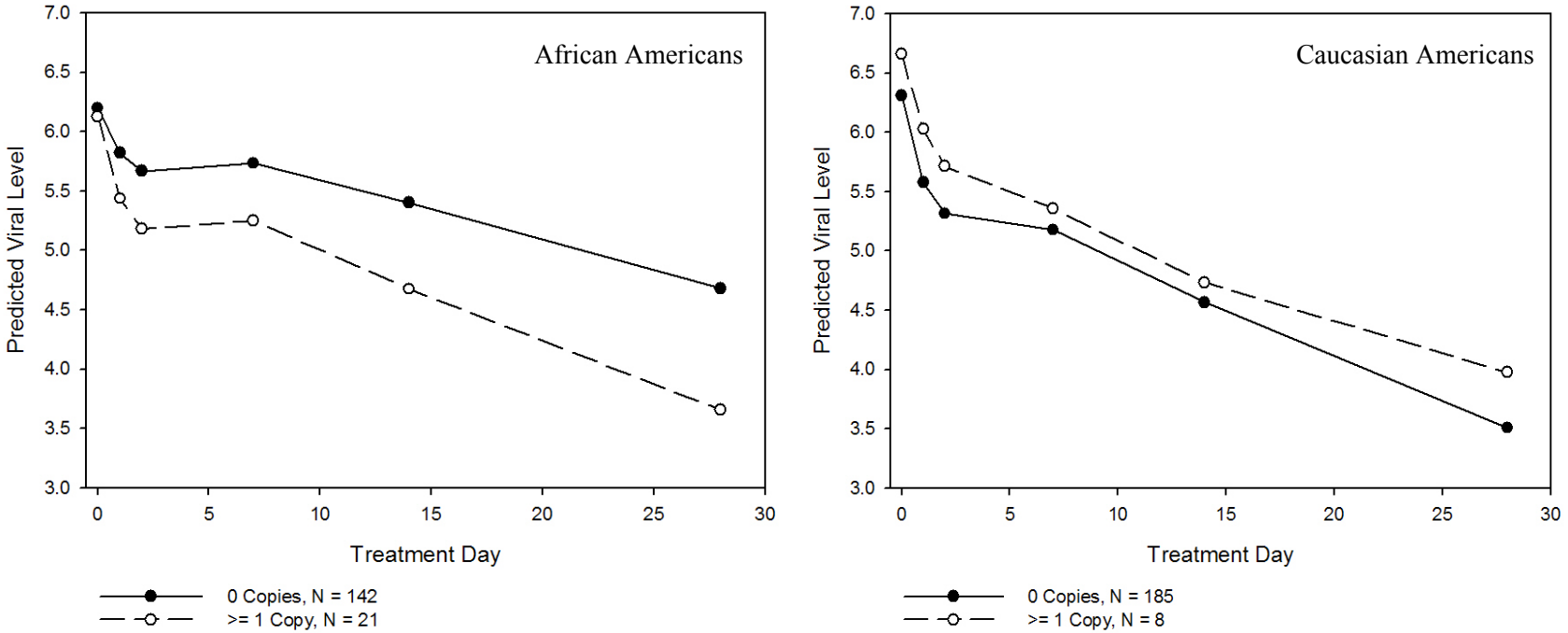
Figures A3-5a and 5b: Predicted Viral Level for *STAT1 rs2966797* Genotypes Over the First 28 Days of Treatment among African Americans (N=180) and Caucasian Americans (N=193)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



Figures A3-6a and 6b – Predicted Viral Level for *PKR AAT* Over the First 28 Days of Treatment among African Americans (N=193) and Caucasian Americans (N=163)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant



Figures A3-7a and 7b: Predicted Viral Level for *PKR CAC* Over the First 28 Days of Treatment among African Americans (N=193) and Caucasian Americans (N=163)

Depictions of viral level over the first 28 days of treatment were completed by graphing the predicted viral levels at each time point for representative individuals at each level of the genetic variant

Table A-6: Common Variation in Genes Accounted for with Selected Single Nucleotide Polymorphisms

SNP Selection Method: Haplotype Block Method **Minor Allele Frequency: 10%**								
			African Americans			**Caucasian Americans**		
Gene	**Virahep-C SNPs**	**Virahep-C SNPs in High LD**	**# SNPs for R2 = 0.8**	**# SNPs Covered**	**% of Variation Covered**	**# SNPs for R2 = 0.8**	**# SNPs Covered**	**% of Variation Covered**
IRF1	8	4	19	18	94%	25	22	88%
Mx1	5	0	61	17	27%	79	39	49%
PKR	4	0	20	4	20%	12	4	33%
AVERAGE			**100**	**39**	**39%**	**116**	**65**	**56%**
SNP Selection Method: Two Stage Tagging **Minor Allele Frequency: 5%**								
			African Americans			**Caucasian Americans**		
Gene	**Virahep-C SNPs**	**Virahep-C SNPs in High LD**	**# SNPs for R2 = 0.8**	**# SNPs Covered**	**% of Variation Covered**	**# SNPs for R2 = 0.8**	**# SNPs Covered**	**% of Variation Covered**
G1P2	2	0	1	1	100%	1	1	100%
G1P3	3	0	10	0	0%	2	1	50%
IFI35	4	0	7	4	57%	8	7	87%
IFNAR1	10	4	41	23	56%	36	27	75%
IFNAR2	10	1	43	20	46%	50	24	48%
IRF7	2	0	6	3	50%	6	2	33%
Mx2	8	2	60	9	15%	50	17	34%
OAS1	6	0	13	3	23%	35	35	100%
OAS2	4	0	36	4	11%	55	13	23%
OAS3	7	3	49	10	20%	59	39	66%

Table A-6 Continued								
OASL	18	5	25	10	40%	21	11	52%
STAT1	8	0	59	11	18%	39	14	35%
STAT2*	8	2	8	5	62%	6	6	100%
AVERAGE			**358**	**103**	**29%**	**368**	**197**	**54%**

APPENDIX B

SUPPLEMENTARY TABLES AND FIGURES

FOR CHAPTER 4

B.1 HOST GENETICS, STEATOSIS AND INSULIN RESISTANCE AMONG AFRICAN AMERICANS AND CAUCASIAN AMERICANS WITH HEPATITIS C VIRUS GENOTYPE-1 INFECTION

Table B-1: Demographic Characteristics of VIRAHEP-C Study Population by Race

Characteristics	African American N = 167	Caucasian American N = 184	p-value
	N (%)	N (%)	
Gender			
Male	107 (64.1)	118 (64.1)	
Female	60 (35.9)	66 (35.9)	0.99‡
HCV Subtype			
1	10 (6.0)	15 (8.2)	
1a	77 (46.1)	104 (56.5)	
1a/b	2 (1.2)	12 (6.5)	
1b	77 (46.1)	53 (28.8)	
Indete	1 (0.6)	0 (0)	0.002‡
Portal Inflammation Score (HAI)			
Mild	27 (16.2)	30 (16.3)	
Moderate	108 (64.7)	101 (54.9)	
Severe	32 (19.2)	53 (28.8)	0.09‡
Steatosis			
No Steatosis	64 (38.3)	63 (34.2)	
Steatosis Present	103 (61.7)	121 (65.8)	0.43‡
Insulin Resistance			
HOMA2-IR < 2	83 (58.5)	104 (66.7)	
HOMA2-IR ≥ 2	59 (41.6)	52 (33.3)	0.14‡
	Mean (SD)	Mean (SD)	
Homeostasis Model Assessment 2 (ln HOMA2-IR)	0.6 (0.7)	0.4 (0.7)	0.006†
Alanine Aminotransferase (ALT)	70.6 (45.8)	108.0 (91.5)	<0.0001†
Aspartate Aminotransferase (AST)	60.0 (43.2)	73.0 (58.7)	0.06†
Age (years)	48.7 (6.9)	47.3 (8.4)	0.13†
Body Mass Index (BMI)	30.8 (6.4)	28.2 (5.2)	<0.0001†
Baseline Viral Level (log_{10} IU/mL)	6.2 (0.6)	6.3 (0.8)	0.08†
Total Inflammation (HAI)	10.0 (3.2)	10.4 (3.5)	0.21†
Triglycerides (mg/dL)	132.4 (100.0)	114.9 (68.4)	0.14†
Cholesterol (mg/dL)	177.7 (36.7)	179.2 (35.5)	0.67†
Ishak Fibrosis Score	2.1 (1.4)	2.3 (1.5)	0.33†
Alcohol Consumption (Week)	3.6 (10.8)	2.3 (6.2)	0.99†

‡ Chi-square Test
† Wilcoxon Two Sample Test

Table B-2: Frequencies of Genotypes for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans N = 167 Genotype Frequency	Call Rate	HWE*	Caucasian Americans N = 184 Genotype Frequency	Call Rate	HWE*
COL1A1 rs2586485						
CC	21 (0.13)			8 (0.04)		
CT	75 (0.45)			60 (0.33)		
TT	71 (0.43)	1.0	0.94	115 (0.63)	0.99	0.96
COL1A1 rs2586494						
AA	5 (0.03)			4 (0.02)		
AC	52 (0.32)			41 (0.22)		
CC	110 (0.66)	1.0	0.70	138 (0.76)	0.99	0.53
COL1A1 rs7406586						
AA	47 (0.28)			12 (0.07)		
AG	83 (0.50)			56 (0.30)		
GG	37 (0.222)	1.0	0.98	115 (0.63)	0.99	0.16
COL1A1 rs2269336						
CC	94 (0.56)			137 (0.75)		
CG	65 (0.39)			44 (0.24)		
GG	8 (0.05)	1.0	0.44	2 (0.01)	0.99	0.73
CYP2E1 rs10857735						
AA	27 (0.17)			1 (0.01)		
AC	73 (0.46)			17 (0.09)		
CC	59 (0.37)	0.94	0.59	169 (0.90)	0.96	0.39
CYP2E1 rs2070673						
AA	76 (0.45)			6 (0.03)		
AT	66 (0.40)			46 (0.25)		
TT	25 (0.15)	1.0	0.10	131 (0.72)	0.99	0.44
CYP2E1 rs915908						
AA	1 (0.01)			3 (0.01)		
AG	9 (0.05)			37 (0.21)		
GG	156 (0.94)	0.99	0.17	140 (0.78)	0.98	0.76
CYP2E1 rs2070676						
CC	22 (0.14)			144 (0.81)		
CG	77 (0.48)			33 (0.18)		
GG	62 (0.39)	0.96	0.81	2 (0.01)	0.97	1.0
IL6 rs1880242						
GG	4 (0.02)			34 (0.19)		
GT	48 (0.29)			106 (0.58)		
TT	115 (0.69)	1.0	1.0	43 (0.24)	0.99	0.03
IL6 rs2056576						
CC	54 (0.32)			69 (0.38)		
CT	79 (0.48)			94 (0.51)		
TT	33 (0.20)	0.99	0.67	20 (0.11)	0.99	0.15

Table B-2 (Continued)

IL6 rs2069827							
	GG	158 (0.96)			152 (0.83)		
	GT	7 (0.04)			30 (0.16)		
	TT	0 (0)	0.99	1.0	1 (0.01)	0.99	1.0
IL6 rs1800797							
	AA	0 (0)			23 (0.12)		
	AG	22 (0.13)			92 (0.50)		
	GG	144 (0.87)	0.99	1.0	69 (0.38)	1.0	0.37
IL6 rs1800795							
	CC	0 (0)			27 (0.15)		
	CG	23 (0.14)			91 (0.49)		
	GG	143 (0.86)	0.99	1.0	66 (0.36)	1.0	0.63
IL6 rs2069830							
	CC	133 (0.81)			182 (0.99)		
	CT	30 (0.18)			1 (0.01)		
	TT	2 (0.01)	0.99	0.69	0 (0)	0.99	1.0
IL6 rs2069837							
	AA	132 (0.80)			159 (0.86)		
	AG	34 (0.20)			25 (0.14)		
	GG	0 (0)	0.99	0.20	0 (0)	1.0	1.0
IL6 rs1554606							
	GG	79 (0.48)			60 (0.33)		
	GT	71 (0.43)			95 (0.52)		
	TT	16 (0.10)	0.99	0.99	29 (0.15)	1.0	0.40
IL6 rs2069845							
	AA	75 (0.45)			60 (0.33)		
	AG	75 (0.45)			95 (0.52)		
	GG	17 (0.10)	1.0	0.78	28 (0.15)	0.99	0.34
IL10 rs11119474							
	AA	0 (0)			0 (0)		
	AG	2 (0.01)			27 (0.15)		
	GG	175 (0.99)	1.0	1.0	156 (0.85)	0.99	0.61
IL10 rs3024505							
	CC	148 (0.89)			138 (0.76)		
	CT	19 (0.11)			40 (0.22)		
	TT	0 (0)	1.0	1.0	4 (0.02)	0.99	0.54
IL10 rs3024498							
	AA	128 (0.77)			96 (0.53)		
	AG	39 (0.23)			67 (0.37)		
	GG	0 (0)	1.0	0.13	20 (0.11)	0.99	0.12
IL10 rs3024496							
	CC	28 (0.17)			50 (0.27)		
	CT	82 (0.49)			86 (0.47)		
	TT	57 (0.34)	1.0	0.87	48 (0.26)	1.0	0.38
IL10 rs1554286							
	CC	61 (0.37)			132 (0.72)		
	CT	79 (0.47)			50 (0.27)		
	TT	27 (0.16)	1.0	0.87	3 (0.02)	1.0	0.76

Table B-2 (Continued)

IL10 rs2222202							
	CC	84 (0.50)			48 (0.26)		
	CT	68 (0.41)			86 (0.47)		
	TT	15 (0.09)	1.0	0.82	50 (0.27)	1.0	0.38
IL10 rs1800890							
	AA	10 (0.06)			29 (0.16)		
	AT	60 (0.36)			87 (0.47)		
	TT	97 (0.59)	1.0	0.86	67 (0.37)	0.99	0.93
IL1R1 rs3917257							
	CC	0 (0)			0 (0)		
	CG	0 (0)			0 (0)		
	GG	167 (1.0)	1.0	-	183 (1.0)	0.99	-
IL1R1 rs3917275							
	AA	153 (0.92)			182 (0.99)		
	AG	13 (0.07)			1 (0.01)		
	GG	1 (0.01)	1.0	0.23	0 (0)	0.99	1.0
IL1R1 rs2110726							
	CC	136 (0.81)			70 (0.38)		
	CT	30 (0.18)			94 (0.52)		
	TT	1 (0.01)	1.0	1.0	19 (0.10)	0.99	0.12
IL1R1 rs3917332							
	AA	4 (0.02)			7 (0.04)		
	AT	40 (0.24)			60 (0.33)		
	TT	123 (0.74)	1.0	0.73	116 (0.63)	0.99	0.83
IL1R1 rs871656							
	AA	11 (0.06)			10 (0.05)		
	AT	61 (0.37)			54 (0.30)		
	TT	95 (0.57)	1.0	0.78	118 (0.65)	0.99	0.26
LEPR rs6673324							
	AA	42 (0.25)			51 (0.28)		
	AG	87 (0.52)			90 (0.50)		
	GG	37 (0.22)	0.99	0.53	41 (0.22)	0.99	0.91
LEPR rs1137100							
	AA	112 (0.67)			100 (0.55)		
	AG	49 (0.29)			69 (0.68)		
	GG	6 (0.04)	1.0	0.82	14 (0.08)	0.99	0.66
LEPR rs1343982							
	AA	16 (0.10)			16 (0.09)		
	AG	75 (0.45)			69 (0.38)		
	GG	76 (0.45)	1.0	0.69	99 (0.54)	0.99	0.45
LEPR rs1137101							
	AA	42 (0.25)			53 (0.29)		
	AG	73 (0.44)			91 (0.50)		
	GG	52 (0.31)	1.0	0.11	39 (0.21)	0.99	0.99
LEPR rs2376018							
	AA	115 (0.69)			124 (0.68)		
	AG	49 (0.29)			54 (0.29)		
	GG	3 (0.02)	1.0	0.58	5 (0.03)	0.99	0.76

Table B-2 (Continued)						
LEPR rs1805096						
CC	52 (0.31)			74 (0.41)		
CT	83 (0.50)			70 (0.38)		
TT	32 (0.19)	1.0	0.91	38 (0.21)	0.99	0.01
LEPR rs1892534						
AA	33 (0.20)			40 (0.22)		
AG	83 (0.50)			69 (0.38)		
GG	51 (0.31)	1.0	0.94	74 (0.40)	0.99	0.003
MCP1/CCL2 rs3917879						
GG	0 (0)			0 (0)		
GT	0 (0)			0 (0)		
TT	167 (1.0)	1.0	-	183 (1.0)	0.99	-
MCP1/CCL2 rs1024611						
CC	9 (0.05)			16 (0.09)		
CT	51 (0.31)			72 (0.40)		
TT	106 (0.64)	0.99	0.39	96 (0.52)	1.0	0.64
MCP1/CCL2 rs3760396						
CC	148 (0.89)			96 (0.52)		
CG	17 (0.10)			77 (0.42)		
GG	1 (0.01)	0.99	0.42	11 (0.06)	1.0	0.39
MCP1/CCL2 rs2857657						
CC	144 (0.86)			124 (0.68)		
CG	23 (0.14)			54 (0.29)		
GG	0 (0)	1.0	1.0	5 (0.03)	0.99	0.76
MCP1/CCL2 rs4586						
CC	66 (0.40)			26 (0.14)		
CT	82 (0.49)			86 (0.47)		
TT	18 (0.11)	0.99	0.31	72 (0.39)	1.0	0.97
MCP1/CCL2 rs13900						
CC	115 (0.63)			96 (0.52)		
CT	51 (0.31)			72 (0.39)		
TT	10 (0.06)	0.99	0.27	16 (0.09)	1.0	0.64
MCP1/CCL2 rs991804						
AA	26 (0.15)			16 (0.09)		
AG	75 (0.45)			70 (0.39)		
GG	66 (0.40)	1.0	0.54	96 (0.53)	0.99	0.53
MCP2/CCL8 rs3138036						
AA	150 (0.90)			134 (0.73)		
AG	15 (0.09)			47 (0.25)		
GG	1 (0.01)	0.99	0.44	3 (0.02)	1.0	0.80
MCP2/CCL8 rs3138038						
AA	156 (0.89)			135 (0.73)		
AC	19 (0.11)			45 (0.25)		
CC	1 (0.01)	0.99	0.46	2 (0.02)	1.0	1.0
MCP2/CCL8 rs11575057						
CC	1 (0.01)			5 (0.03)		
CT	19 (0.11)			53 (0.29)		
TT	146 (0.88)	0.99	0.66	126 (0.68)	1.0	0.84

Table B-2 (Continued)							
TGF-B1 rs2278422							
	CC	14 (0.08)			29 (0.16)		
	CG	71 (0.43)			101 (0.55)		
	GG	82 (0.49)	1.0	0.80	54 (0.29)	1.0	0.11
TGF-B1 rs2241716							
	AA	0 (0)			0 (0)		
	AG	16 (0.10)			0 (0)		
	GG	151 (0.90)	1.0	1.0	183 (1.0)	0.99	-
TGF-B1 rs1800471							
	CC	0 (0)			1 (0.01)		
	CG	23 (0.14)			17 (0.09)		
	GG	144 (0.86)	1.0	1.0	165 (0.90)	0.99	0.38
TNFα rs2229094							
	CC	6 (0.04)			13 (0.07)		
	CT	78 (0.47)			57 (0.31)		
	TT	83 (0.50)	1.0	0.02	113 (0.62)	0.99	0.13
TNFα rs3093662							
	AA	138 (0.83)			156 (0.85)		
	AG	28 (0.17)			25 (0.14)		
	GG	1 (0.01)	1.0	1.0	3 (0.01)	1.0	0.11
TNFα rs3093665							
	AA	153 (0.92)			178 (0.97)		
	AC	14 (0.08)			6 (0.03)		
	CC	0 (0)	1.0	1.0	0 (0)	1.0	1.0

* P-value from test of Hardy Weingberg Equilibrium (HWE)

Table B-3: Frequencies of Genotypes for Single Nucleotide Polymorphisms and Association with Steatosis among African Americans and Caucasian Americans

Single Nucleotide Polymorphism		African Americans N = 167 No Steatosis	African Americans N = 167 Steatosis ≥ 5%	African Americans N = 167 p-value*	Caucasian Americans N = 184 No Steatosis	Caucasian Americans N = 184 Steatosis ≥ 5%	Caucasian Americans N = 184 p-value*
COL1A1 rs2586485							
	CC	0.10	0.15		0.02	0.06	
	CT	0.52	0.42		0.33	0.32	
	TT	0.38	0.43	0.42	0.65	0.62	0.33
COL1A1 rs2586494							
	AA	0.02	0.04		0.03	0.02	
	AC	0.29	0.33		0.24	0.22	
	CC	0.69	0.63	0.59	0.73	0.77	0.44
COL1A1 rs7406586							
	AA	0.22	0.30		0.11	0.04	
	AG	0.46	0.51		0.29	0.31	
	GG	0.32	0.18	0.08	0.60	0.65	0.09
COL1A1 rs2269336							
	CC	0.56	0.57		0.75	0.75	
	CG	0.41	0.38		0.24	0.24	
	GG	0.03	0.06	0.91	0.02	0.01	0.99
CYP2E1 rs10857735							
	AA	0.20	0.15		0.0	0.01	
	AC	0.46	0.49		0.08	0.10	
	CC	0.35	0.37	0.73	0.92	0.89	0.64
CYP2E1 rs2070673							
	AA	0.46	0.45		0.03	0.03	
	AT	0.37	0.43		0.19	0.29	
	TT	0.18	0.12	0.59	0.78	0.68	0.37
CYP2E1 rs915908							
	AA	0.0	0.01		0.03	0.01	
	AG	0.09	0.04		0.21	0.20	
	GG	0.91	0.95	0.29	0.76	0.79	0.44
CYP2E1 rs2070676							
	CC	0.26	0.07		0.84	0.78	
	CG	0.41	0.51		0.15	0.21	
	GG	0.33	0.42	0.003	0.02	0.01	0.50
IL6 rs1880242							
	GG	0.02	0.03		0.16	0.20	
	GT	0.31	0.28		0.56	0.59	
	TT	0.68	0.70	0.74	0.29	0.22	0.33
IL6 rs2056576							
	CC	0.26	0.28		0.32	0.42	
	CT	0.45	0.50		0.54	0.50	
	TT	0.19	0.22	0.55	0.14	0.09	0.21
IL6 rs2069827							
	GG	0.93	0.98		0.83	0.84	
	GT	0.08	0.02		0.18	0.16	
	TT	0.0	0.0	0.07	0.0	0.01	0.74

Table B-3 (Continued)							
IL6 rs1800797							
	AA	0.0	0.0		0.13	0.12	
	AG	0.15	0.12		0.41	0.54	
	GG	0.85	0.88	0.48	0.46	0.34	0.20
IL6 rs1800795							
	CC	0.0	0.0		0.18	0.13	
	CG	0.15	0.13		0.38	0.55	
	GG	0.85	0.87	0.44	0.44	0.32	0.09
IL6 rs2069830							
	CC	0.79	0.80		1.0	0.99	
	CT	0.21	0.18		0.0	0.01	
	TT	0.0	0.02	0.49	0.0	0.0	0.47
IL6 rs2069837							
	AA	0.77	0.79		0.87	0.85	
	AG	0.24	0.21		0.13	0.15	
	GG	0.0	0.0	0.64	0.0	0.0	0.51
IL6 rs1554606							
	GG	0.52	0.45		0.41	0.29	
	GT	0.40	0.44		0.40	0.57	
	TT	0.09	0.10	0.73	0.19	0.14	0.08
IL6 rs2069845							
	AA	0.49	0.43		0.43	0.28	
	AG	0.41	0.47		0.40	0.58	
	GG	0.10	0.10	0.76	0.18	0.14	0.07
IL10 rs11119474							
	AA	0.0	0.0		0.0	0.0	
	AG	0.02	0.01		0.19	0.12	
	GG	0.99	0.99	0.75	0.81	0.88	0.38
IL10 rs3024505							
	CC	0.82	0.93		0.69	0.79	
	CT	0.18	0.07		0.29	0.18	
	TT	0.0	0.0	0.04	0.02	0.03	0.31
IL10 rs3024498							
	AA	0.74	0.80		0.52	0.53	
	AG	0.27	0.20		0.33	0.38	
	GG	0.0	0.0	0.30	0.14	0.09	0.56
IL10 rs3024496							
	CC	0.27	0.10		0.38	0.21	
	CT	0.46	0.50		0.40	0.51	
	TT	0.28	0.40	0.096	0.22	0.28	0.07
IL10 rs1554286							
	CC	0.37	0.35		0.73	0.71	
	CT	0.46	0.49		0.24	0.29	
	TT	0.18	0.17	0.93	0.03	0.01	0.60
IL10 rs2222202							
	CC	0.43	0.57		0.22	0.28	
	CT	0.43	0.38		0.40	0.51	
	TT	0.15	0.06	0.04	0.38	0.21	0.07

Table B-3 (Continued)							
IL10 rs1800890							
	AA	0.07	0.05		0.22	0.12	
	AT	0.38	0.34		0.49	0.47	
	TT	0.54	0.62	0.45	0.29	0.41	0.09
IL1R1 rs3917257[§]							
IL1R1 rs3917275							
	AA	0.94	0.91		0.98	1.0	
	AG	0.06	0.08		0.02	0.0	
	GG	0.0	0.01	0.58	0.0	0.0	0.16
IL1R1 rs2110726							
	CC	0.74	0.87		0.46	0.35	
	CT	0.25	0.13		0.44	0.55	
	TT	0.02	0.0	0.02	0.10	0.11	0.21
IL1R1 rs3917332							
	AA	0.02	0.03		0.08	0.02	
	AT	0.22	0.25		0.33	0.33	
	TT	0.77	0.73	0.80	0.59	0.65	0.10
IL1R1 rs871656							
	AA	0.06	0.06		0.03	0.07	
	AT	0.34	0.40		0.24	0.32	
	TT	0.60	0.54	0.74	0.73	0.61	0.21
LEPR rs6673324							
	AA	0.37	0.22		0.25	0.29	
	AG	0.40	0.57		0.51	0.49	
	GG	0.22	0.21	0.09	0.24	0.22	0.91
LEPR rs1137100							
	AA	0.53	0.73		0.56	0.55	
	AG	0.40	0.26		0.38	0.37	
	GG	0.07	0.01	0.008	0.06	0.08	0.80
LEPR rs1343982							
	AA	0.16	0.07		0.06	0.10	
	AG	0.49	0.44		0.40	0.36	
	GG	0.35	0.49	0.10	0.54	0.54	0.57
LEPR rs1137101							
	AA	0.22	0.26		0.27	0.30	
	AG	0.41	0.42		0.49	0.50	
	GG	0.37	0.32	0.86	0.24	0.20	0.76
LEPR rs2376018							
	AA	0.75	0.67		0.75	0.65	
	AG	0.24	0.31		0.25	0.31	
	GG	0.02	0.02	0.46	0.0	0.04	0.11
LEPR rs1805096							
	CC	0.29	0.29		0.49	0.37	
	CT	0.46	0.51		0.37	0.39	
	TT	0.25	0.19	0.60	0.14	0.24	0.12
LEPR rs1892534							
	AA	0.25	0.20		0.16	0.25	
	AG	0.47	0.51		0.35	0.39	
	GG	0.28	0.29	0.77	0.49	0.36	0.14

Table B-3 (Continued)						
MCP1/CCL2 rs3917879[§]						
MCP1/CCL2 rs1024611						
CC	0.06	0.05		0.13	0.07	
CT	0.41	0.25		0.33	0.43	
TT	0.53	0.70	0.09	0.54	0.51	0.15
MCP1/CCL2 rs3760396						
CC	0.94	0.86		0.54	0.52	
CG	0.06	0.13		0.40	0.43	
GG	0.0	0.01	0.22	0.06	0.06	0.93
MCP1/CCL2 rs2857657						
CC	0.88	0.84		0.76	0.64	
CG	0.12	0.16		0.19	0.35	
GG	0.0	0.0	0.43	0.05	0.02	0.07
MCP1/CCL2 rs4586						
CC	0.43	0.35		0.19	0.12	
CT	0.47	0.55		0.41	0.49	
TT	0.10	0.10	0.62	0.40	0.39	0.26
MCP1/CCL2 rs13900						
CC	0.53	0.69		0.54	0.51	
CT	0.41	0.25		0.33	0.43	
TT	0.06	0.06	0.10	0.13	0.07	0.15
MCP1/CCL2 rs991804						
AA	0.13	0.16		0.13	0.07	
AG	0.54	0.40		0.32	0.43	
GG	0.32	0.45	0.15	0.56	0.51	0.20
MCP2/CCL8 rs3138036						
AA	0.88	0.92		0.71	0.73	
AG	0.12	0.07		0.29	0.24	
GG	0.0	0.01	0.36	0.0	0.03	0.82
MCP2/CCL8 rs3138038						
AA	0.85	0.91		0.71	0.74	
AC	0.15	0.08		0.29	0.22	
CC	0.0	0.01	0.23	0.0	0.04	0.64
MCP2/CCL8 rs11575057						
CC	0.0	0.01		0.02	0.04	
CT	0.16	0.08		0.33	0.26	
TT	0.84	0.91	0.15	0.65	0.70	0.74
TGF-B1 rs2278422						
CC	0.12	0.06		0.16	0.16	
CG	0.52	0.39		0.52	0.56	
GG	0.37	0.55	0.06	0.32	0.28	0.92
TGF-B1 rs2241716						
AA	0.0	0.0		0.0	0.0	
AG	0.12	0.07		0.0	0.0	
GG	0.88	0.93	0.35	1.0	1.0	
TGF-B1 rs1800471						
CC	0.0	0.0		0.0	0.01	
CG	0.12	0.16		0.10	0.09	
GG	0.88	0.84	0.43	0.91	0.90	0.77

Table B-3 (Continued)							
TNFα rs2229094							
	CC	0.03	0.04		0.03	0.09	
	CT	0.47	0.47		0.40	0.27	
	TT	0.50	0.50	0.96	0.57	0.65	0.10
TNFα rs3093662							
	AA	0.82	0.82		0.84	0.85	
	AG	0.16	0.18		0.14	0.13	
	GG	0.02	0.0	0.42	0.02	0.02	0.99
TNFα rs3093665							
	AA	0.90	0.93		0.94	0.98	
	AC	0.10	0.07		0.06	0.02	
	CC	0.0	0.0	0.53	0.0	0.0	0.19

* P-value based on genotype association chi square test

† Chi Square could not be estimated because minor allele frequency < 5% for the SNP

§ Monomorphic SNP

Table B-4: Unadjusted Odd Ratios for Steatosis for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

	African Americans N = 167				Caucasian Americans N = 184			
Single Nucleotide Polymorphism	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
COL1A1 rs2586485								
CC	96	1.00			68	1.00		
TT	71	1.23	0.66-2.27	0.52	115	0.88	0.46-1.65	0.68
COL1A1 rs2586494								
AA/AC	57	1.00			45	1.00		
CC	110	0.77	0.40-1.47	0.43	138	1.23	0.61-2.47	0.56
COL1A1 rs7406586								
AA	47	1.00			12	1.00		
AG	83	0.82	0.39-1.74	0.61	56	2.96	0.82-10.60	0.10
GG	37	0.41	0.18-0.98	0.04	115	2.87	0.86-9.65	0.09
COL1A1 rs2269336								
CC	94	1.00			137	1.00		
CG/GG	73	0.96	0.52-1.77	0.90	46	0.97	0.48-1.95	0.93
CYP2E1 rs10857735								
AA/AC	100	1.00			18	1.00		
CC	59	1.09	0.57-2.08	0.79	159	0.71	0.24-2.11	0.54
CYP2E1 rs2070673								
AA	76	1.00			6	1.00		
AT	66	1.19	0.61-2.31	0.61	46	1.46	0.24-9.00	0.69
TT	25	0.70	0.28-1.69	0.41	131	0.84	0.15-4.74	0.84
CYP2E1 rs915908								
AA/AG	10	1.00			40	1.00		
GG	156	1.99	0.58-6.81	0.27	140	1.20	0.58-2.49	0.62
CYP2E1 rs2070676								
CC	22	1.00			144	1.00		
CG	77	4.77	1.76-12.89	0.002	33	1.52	0.66-3.51	0.32
GG	62	4.86	1.76-13.45	0.002	2	†		
IL6 rs1880242								
GG/GT	52	1.00			140	1.00		
TT	115	1.10	0.57-2.11	0.77	43	0.68	0.34-1.38	0.29
IL6 rs2056576								
CC	54	1.00			69	1.00		
CT	79	1.39	0.70-2.79	0.35	94	0.71	0.36-1.38	0.31
TT	33	1.43	0.61-3.38	0.42	20	0.49	0.18-1.36	0.17
IL6 rs2069827								
GG	158	1.00			152	1.00		
GT/TT	7	†			31	0.94	0.42-2.10	0.87
IL6 rs1800797								
AA/AG	22	1.00			115	1.00		
GG	144	1.26	0.52-2.06	0.61	69	0.59	0.32-1.11	0.10
IL6 rs1800795								
CC/CG	23	1.00			118	1.00		
GG	143	1.16	0.48-2.78	0.74	66	0.59	0.31-1.10	0.10

Table B-4 (Continued)

IL6 rs2069830									
	CC	133	1.00			182	1.00		
	CT/TT	32	0.94	0.44-2.01	0.88	1	†		
IL6 rs2069837									
	AA	132	1.00			159	1.00		
	AG/GG	34	0.88	0.43-1.82	0.73	25	1.19	0.49-2.91	0.70
IL6 rs1554606									
	GG	79	1.00			60	1.00		
	GT/TT	87	1.28	0.70-2.35	0.43	124	1.75	0.92-3.30	0.09
IL6 rs2069845									
	AA	75	1.00			60	1.00		
	AG/GG	92	1.24	0.68-2.29	0.48	123	1.92	1.02-3.63	0.045
IL10 rs11119474									
	AA/AG	2	1.00			27	1.00		
	GG	165	†			156	1.66	0.73-3.81	0.23
IL10 rs3024505									
	CC	148	1.00			138	1.00		
	CT/TT	19	0.37	0.14-0.96	0.04	44	0.60	0.30-1.20	0.15
IL10 rs3024498									
	AA	128	1.00			96	1.00		
	AG/GG	39	0.70	0.34-1.43	0.33	87	0.98	0.53-1.80	0.95
IL10 rs3024496									
	CC	28	1.00			50	1.00		
	CT	82	2.85	1.19-6.81	0.02	86	2.29	1.11-4.72	0.03
	TT	57	3.80	1.51-9.54	0.01	48	2.24	0.97-5.16	0.06
IL10 rs1554286									
	CC	61	1.00			131	1.00		
	CT/TT	106	1.09	0.58-2.04	0.80	52	1.15	0.58-2.26	0.69
IL10 rs2222202									
	CC	84	1.00			48	1.00		
	CT	68	0.66	0.35-1.27	0.21	86	1.02	0.47-2.22	0.96
	TT	15	0.28	0.09-0.85	0.02	50	0.45	0.19-1.03	0.06
IL10 rs1800890									
	AA/AT	70	1.00			116	1.00		
	TT	97	1.34	0.72-2.47	0.35	67	1.70	0.88-3.28	0.11
IL1R1 rs3917275									
	AA	153	1.00			182	1.00		
	AG/GG	14	1.62	0.49-5.37	0.43	1	†		
IL1R1 rs2110726									
	CC	136	1.00			70	1.00		
	CT/TT	31	0.41	0.19-0.89	0.02	113	1.60	0.86-1.99	0.14
IL1R1 rs3917332									
	AA/AT	44	1.00			67	1.00		
	TT	123	0.81	0.40-1.63	0.56	116	1.32	0.71-2.47	0.38
IL1R1 rs871656									
	AA/AT	72	1.00			64	1.00		
	TT	95	0.78	0.42-1.44	0.42	118	0.60	0.31-1.16	0.13

Table B-4 (Continued)

LEPR rs6673324								
AA	42	1.00			51	1.00		
AG	87	2.39	1.17-4.91	0.02	90	0.84	0.41-1.75	0.65
GG	37	1.60	0.68-3.77	0.29	41	0.79	0.33-1.89	0.60
LEPR rs1137100								
AA	112	1.00			100	1.00		
AG/GG	55	0.41	0.22-0.77	0.006	83	1.04	0.57-1.92	0.90
LEPR rs1343982								
AA/AG	91	1.00			85	1.00		
GG	76	1.74	0.93-3.24	0.08	98	0.99	0.54-1.82	0.97
LEPR rs1137101								
AA	42	1.00			53	1.00		
AG	73	0.88	0.40-1.93	0.75	91	0.93	0.45-1.91	0.84
GG	52	0.75	0.33-1.69	0.49	39	0.76	0.32-1.80	0.53
LEPR rs2376018								
AA	115	1.00			124	1.00		
AG/GG	52	1.48	0.75-2.92	0.26	59	1.62	0.82-3.19	0.16
LEPR rs1805096								
CC	52	1.00			74	1.00		
CT	83	1.13	0.56-2.30	0.74	70	1.44	0.73-2.84	0.29
TT	32	0.77	0.33-1.81	0.55	38	2.27	0.94-5.46	0.07
LEPR rs1892534								
AA	33	1.00			40	1.00		
AG	83	1.33	0.62-2.86	0.47	69	0.71	0.30-1.71	0.45
GG	51	1.30	0.56-3.05	0.54	74	0.47	0.20-1.11	0.09
MCP1/CCL2 rs3917879[‡]								
MCP1/CCL2 rs1024611								
CC/CT	60	1.00			88	1.00		
TT	106	2.11	1.12-3.97	0.02	96	0.88	0.48-1.62	0.69
MCP1/CCL2 rs3760396								
CC	148	1.00			96	1.00		
CG/GG	18	2.58	0.82-8.13	0.11	88	1.10	0.60-2.02	0.76
MCP1/CCL2 rs2857657								
CC	144	1.00			124	1.00		
CG/GG	23	1.39	0.56-3.41	0.48	59	1.83	0.92-3.64	0.09
MCP1/CCL2 rs4586								
CC	66	1.00			26	1.00		
CT	82	1.41	0.74-2.69	0.30	86	1.85	0.76-4.49	0.18
TT	18	1.20	0.41-3.47	0.74	72	1.50	0.61-3.70	0.38
MCP1/CCL2 rs13900								
CC	105	1.00			96	1.00		
CT/TT	61	0.50	0.26-0.93	0.03	88	1.14	0.62-2.09	0.69
MCP1/CCL2 rs991804								
AA/AG	101	1.00			86	1.00		
GG	66	1.71	0.91-3.22	0.10	96	0.83	0.45-1.53	0.54
MCP2/CCL8 rs3138036								
AA	150	1.00			134	1.00		
AG/GG	16	0.68	0.25-1.86	0.46	50	0.93	0.47-1.82	0.83

Table B-4 (Continued)

MCP2/CCL8 rs3138038								
AA	147	1.00			135	1.00		
AC/CC	19	0.59	0.23-1.51	0.27	49	0.89	0.45-1.75	0.74
MCP2/CCL8 rs11575057								
CC/CT	20	1.00			58	1.00		
TT	146	1.89	0.76-4.73	0.17	126	1.23	0.65-2.35	0.53
TGF-β1 rs2278422								
CC/CG	85	1.00			130	1.00		
GG	82	2.11	1.13-3.92	0.02	54	0.83	0.43-1.61	0.58
TGF-β1 rs2241716								
AA/AG	16	1.00			0	1.00		
GG	151	1.68	0.60-4.72	0.32	183	†		
TGF-β1 rs1800471								
CC/CG	23	1.00			18	1.00		
GG	144	0.72	0.29-1.78	0.48	165	0.96	0.34-2.68	0.93
TNFα rs2229094								
CC/CT	84	1.00			70	1.00		
TT	83	0.98	0.54-1.80	0.95	113	1.36	0.73-2.54	0.33
TNFα rs3093662								
AA	138	1.00			156	1.00		
AG/GG	29	1.05	0.48-2.31	0.91	28	0.92	0.40-2.13	0.84
TNFα rs3093665								
AA	153	1.00			178	1.00		
AC/CC	14	0.69	0.24-2.00	0.49	6	†		

‡ Monomorphic SNP

† Minor allele frequency less then 5% in one population

Table B-5: Adjusted Odds Ratios for Steatosis for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans* N = 167 N	Odds Ratio	Confidence Interval	p-value	Caucasian Americans* N = 184 N	Odds Ratio	Confidence Interval	p-value
COL1A1 rs2586485								
CC	96	1.00			68	1.00		
TT	71	1.41	0.65-3.05	0.38	115	1.04	0.43-2.50	0.93
COL1A1 rs2586494								
AA/AC	57	1.00			45	1.00		
CC	110	0.75	0.33-1.72	0.50	138	0.60	0.23-1.59	0.30
COL1A1 rs7406586								
AA	47	1.00			12	1.00		
AG	83	0.59	0.23-1.52	0.27	56	1.93	0.32-11.73	0.47
GG	37	0.46	0.15-1.39	0.17	115	2.25	0.40-12.72	0.36
COL1A1 rs2269336								
CC	94	1.00			137	1.00		
CG/GG	73	0.80	0.37-1.70	0.56	46	1.55	0.59-4.04	0.37
CYP2E1 rs10857735								
AA/AC	100	1.00			18	1.00		
CC	59	1.14	0.52-2.53	0.74	159	0.99	0.19-5.06	0.99
CYP2E1 rs2070673								
AA	76	1.00			6	1.00		
AT	66	1.11	0.48-2.53	0.81	46	0.48	0.03-7.71	0.60
TT	25	0.60	0.20-1.87	0.37	131	0.46	0.03-6.55	0.57
CYP2E1 rs915908								
AA/AG	10	1.00			40	1.00		
GG	156	2.32	0.34-16.04	0.39	140	0.91	0.34-2.47	0.85
CYP2E1 rs2070676								
CC	22	1.00			144	1.00		
CG	77	3.37	0.90-12.66	0.07	33	0.93	0.30-2.86	0.90
GG	62	2.85	0.76-10.70	0.12	2	1.58	0.08-31.64	0.77
IL6 rs1880242								
GG/GT	52	1.00			140	1.00		
TT	115	1.28	0.57-2.89	0.55	43	0.78	0.29-2.06	0.61
IL6 rs2056576								
CC	54	1.00			69	1.00		
CT	79	1.08	0.47-2.52	0.85	94	0.57	0.23-1.42	0.23
TT	33	1.10	0.38-3.14	0.87	20	0.91	0.23-3.65	0.90
IL6 rs2069827								
GG	158	1.00			152	1.00		
GT/TT	7	†			31	1.47	0.50-4.30	0.49
IL6 rs1800797								
AA/AG	22	1.00			115	1.00		
GG	144	2.06	0.61-6.98	0.25	69	0.45	0.19-1.05	0.07
IL6 rs1800795								
CC/CG	23	1.00			118	1.00		
GG	143	1.78	0.55-5.73	0.34	66	0.47	0.20-1.20	0.08

Table B-5 (Continued)

IL6 rs2069830								
CC	133	1.00			182	1.00		
CT/TT	32	0.87	0.33-2.27	0.78	1	†		
IL6 rs2069837								
AA	132	1.00			159	1.00		
AG/GG	34	0.81	0.32-2.04	0.65	25	0.82	0.23-2.91	0.76
IL6 rs1554606								
GG	79	1.00			60	1.00		
GT/TT	87	0.88	0.41-1.90	0.75	124	2.24	0.94-5.30	0.07
IL6 rs2069845								
AA	75	1.00			60	1.00		
AG/GG	92	0.86	0.40-1.86	0.70	123	2.52	1.06-6.00	0.04
IL10 rs11119474								
AA/AG	2	1.00			27	1.00		
GG	165	1.59	0.09-27.09	0.75	156	1.46	0.48-4.48	0.51
IL10 rs3024505								
CC	148	1.00			138	1.00		
CT/TT	19	0.36	0.11-1.23	0.10	44	0.50	0.21-1.22	0.13
IL10 rs3024498								
AA	128	1.00			96	1.00		
AG/GG	39	0.56	0.23-1.37	0.20	87	1.31	0.58-2.96	0.52
IL10 rs3024496								
CC	28	1.00			50	1.00		
CT	82	2.98	0.93-9.58	0.07	86	2.22	0.81-6.09	0.12
TT	57	6.06	1.73-21.28	0.005	48	1.35	0.43-4.22	0.61
IL10 rs1554286								
CC	61	1.00			131	1.00		
CT/TT	106	1.41	0.64-3.14	0.40	52	1.39	0.57-3.42	0.47
IL10 rs2222202								
CC	84	1.00			48	1.00		
CT	68	0.50	0.22-1.15	0.10	86	1.65	0.56-4.88	0.37
TT	15	0.12	0.03-0.57	0.01	50	0.74	0.24-2.33	0.61
IL10 rs1800890								
AA/AT	70	1.00			116	1.00		
TT	97	1.60	0.73-3.48	0.24	67	1.00	0.41-2.43	0.99
IL1R1 rs3917275								
AA	153	1.00			182	1.00		
AG/GG	14	1.05	0.23-4.83	0.95	1	†		
IL1R1 rs2110726								
CC	136	1.00			70	1.00		
CT/TT	31	0.32	0.12-0.86	0.02	113	2.21	0.92-5.31	0.08
IL1R1 rs3917332								
AA/AT	44	1.00			67	1.00		
TT	123	0.86	0.35-2.11	0.74	116	1.38	0.60-3.17	0.45
IL1R1 rs871656								
AA/AT	72	1.00			64	1.00		
TT	95	0.83	0.39-1.76	0.62	118	0.87	0.37-2.08	0.77

Table B-5 (Continued)

LEPR rs6673324								
AA	42	1.00			51	1.00		
AG	87	2.43	0.97-6.05	0.06	90	1.64	0.58-4.62	0.35
GG	37	1.82	0.57-5.79	0.31	41	1.18	0.34-4.06	0.79
LEPR rs1137100								
AA	112	1.00			100	1.00		
AG/GG	55	0.25	0.11-0.58	0.001	83	0.90	0.40-2.05	0.81
LEPR rs1343982								
AA/AG	91	1.00			85	1.00		
GG	76	1.66	0.77-3.58	0.19	98	1.11	0.49-2.53	0.80
LEPR rs1137101								
AA	42	1.00			53	1.00		
AG	73	0.92	0.35-2.42	0.86	91	1.58	0.58-4.30	0.37
GG	52	0.67	0.24-1.86	0.44	39	0.31	0.09-1.10	0.07
LEPR rs2376018								
AA	115	1.00			124	1.00		
AG/GG	52	1.38	0.61-3.12	0.45	59	2.09	0.84-5.22	0.11
LEPR rs1805096								
CC	52	1.00			74	1.00		
CT	83	2.11	0.87-5.13	0.10	70	1.55	0.62-3.90	0.35
TT	32	0.63	0.21-1.90	0.42	38	2.35	0.73-7.53	0.15
LEPR rs1892534								
AA	33	1.00			40	1.00		
AG	83	2.98	1.07-8.33	0.04	69	0.69	0.22-2.20	0.54
GG	51	1.55	0.52-4.62	0.43	74	0.44	0.14-2.37	0.16
MCP1/CCL2 rs3917879[‡]								
MCP1/CCL2 rs1024611								
CC/CT	60	1.00			88	1.00		
TT	106	2.09	0.94-4.63	0.07	96	1.10	0.49-2.47	0.82
MCP1/CCL2 rs3760396								
CC	148	1.00			96	1.00		
CG/GG	18	2.36	0.59-9.48	0.23	88	1.91	0.82-4.42	0.13
MCP1/CCL2 rs2857657								
CC	144	1.00			124	1.00		
CG/GG	23	1.54	0.49-4.88	0.46	59	1.55	0.60-3.97	0.37
MCP1/CCL2 rs4586								
CC	66	1.00			26	1.00		
CT	82	1.59	0.71-3.56	0.26	86	3.21	0.94-10.95	0.06
TT	18	1.21	0.31-4.70	0.79	72	3.16	0.89-1.28	0.08
MCP1/CCL2 rs13900								
CC	105	1.00			96	1.00		
CT/TT	61	0.52	0.24-1.15	0.11	88	0.91	0.41-2.05	0.82
MCP1/CCL2 rs991804								
AA/AG	101	1.00			86	1.00		
GG	66	1.46	0.67-3.18	0.34	96	1.08	0.48-2.44	0.85
MCP2/CCL8 rs3138036								
AA	150	1.00			134	1.00		
AG/GG	16	0.44	0.12-1.58	0.21	50	1.29	0.49-3.32	0.63

Table B-5 (Continued)								
MCP2/CCL8 rs3138038								
AA	147	1.00			135	1.00		
AC/CC	19	0.36	0.11-1.23	0.11	49	1.27	0.49-3.32	0.63
MCP2/CCL8 rs11575057								
CC/CT	20	1.00			58	1.00		
TT	146	3.16	0.95-10.47	0.06	126	1.03	0.42-2.57	0.94
TGF-βI rs2278422								
CC/CG	85	1.00			130	1.00		
GG	82	4.42	1.84-10.65	0.001	54	1.50	0.62-3.60	0.37
TGF-βI rs2241716								
AA/AG	16	1.00			0	1.00		
GG	151	1.69	0.51-5.65	0.39	183	†		
TGF-βI rs1800471								
CC/CG	23	1.00			18	1.00		
GG	144	0.57	0.18-1.76	0.33	165	1.61	0.37-6.95	0.52
TNFα rs2229094								
CC/CT	84	1.00			70	1.00		
TT	83	0.78	0.37-1.67	0.53	113	1.36	0.58-3.19	0.48
TNFα rs3093662								
AA	138	1.00			156	1.00		
AG/GG	29	0.98	0.37-3.66	0.97	28	1.24	0.41-3.82	0.70
TNFα rs3093665								
AA	153	1.00			178	1.00		
AC/CC	14	1.06	0.29-3.85	0.93	6	0.39	0.06-2.53	0.32

* Model adjusted for the genetic variant, Ishak fibrosis score, $\log_{10}$ baseline viral level, ln HOMA2-IR, weekly alcohol consumption and body mass index and excluded individuals taking exogenous insulin

‡ Monomorphic SNP

† Minor allele frequency less then 5% in one population

Abbreviations: 95% Confidence Interval (Confidence Interval)

Table B-6 Log Likelihood Ratio Test of the Significance of the Interaction Term Between Natural Log Transformed HOMA2-IR Scores and the Genetic Variant in the Prediction of Steatosis

	African Americans					Caucasian Americans				
	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value
COL1A1 rs2586485	1	160.839	160.552	0.287	0.592	1	142.610	142.550	0.060	0.806
COL1A1 rs2586494	1	161.155	161.150	0.005	0.944	1	141.537	136.630	4.907	0.027
COL1A1 rs7406586	2	159.551	158.614	0.937	0.626	2	141.721	130.832	10.889	0.004
COL1A1 rs2269336	1	161.270	160.069	1.201	0.273	1	141.803	140.708	1.095	0.295
CYP2E1 rs10857735	1	158.186	158.182	0.004	0.950	1	139.877	139.486	0.391	0.532
CYP2E1 rs2070673	2	160.522	159.087	1.435	0.488	2	142.266	139.443	2.823	0.244
CYP2E1 rs915908	1	159.798	155.249	4.549	0.033	1	140.544	140.474	0.070	0.791
CYP2E1 rs2070676	2	150.990	147.107	3.883	0.144	2	140.744	138.966	1.778	0.411
IL6 rs1880242	1	161.262	160.132	1.130	0.288	1	142.358	142.158	0.200	0.655
IL6 rs2056576	2	161.572	160.382	1.190	0.552	2	141.013	140.112	0.901	0.637
IL6 rs2069827	1	147.450	147.450	0.000	1.000	1	142.125	142.010	0.115	0.735
IL6 rs1800797	1	159.221	159.220	0.001	0.975	1	140.203	139.579	0.624	0.430
IL6 rs1800795	1	159.652	159.652	0.000	1.000	1	140.597	139.824	0.773	0.379
IL6 rs2069830	1	159.811	159.659	0.152	0.697	1	143.577	143.577	0.000	1.000
IL6 rs2069837	1	160.386	159.897	0.489	0.484	1	143.577	142.492	1.085	0.298
IL6 rs1554606	1	160.483	160.394	0.089	0.766	1	140.294	138.616	1.678	0.195
IL6 rs2069845	1	161.470	161.154	0.316	0.574	1	138.162	135.869	2.293	0.130
IL10 rs11119474	1	161.514	158.237	3.277	0.070	1	142.174	141.730	0.444	0.505
IL10 rs3024505	1	158.843	155.772	3.071	0.080	1	139.318	139.205	0.113	0.737
IL10 rs3024498	1	159.974	159.817	0.157	0.692	1	142.206	137.026	5.180	0.023
IL10 rs3024496	2	152.911	145.239	7.672	0.022	2	141.097	135.272	5.825	0.054
IL10 rs1554286	1	160.896	160.686	0.210	0.647	1	142.098	136.241	5.857	0.016
IL10 rs2222202	2	152.976	140.552	12.424	0.002	2	141.097	135.272	5.825	0.054
IL10 rs1800890	1	160.228	159.789	0.439	0.508	1	142.617	140.556	2.061	0.151

Table B-6 (Continued)

IL1R1 rs3917275	1	161.613	160.529	1.084	0.298	1	141.963	141.963	0.000	1.000
IL1R1 rs2110726	1	156.301	154.626	1.675	0.196	1	139.451	139.431	0.020	0.888
IL1R1 rs3917332	1	161.506	161.175	0.331	0.565	1	142.057	141.806	0.251	0.616
IL1R1 rs871656	1	161.373	161.307	0.066	0.797	1	140.503	138.850	1.653	0.199
LEPR rs6673324	2	157.937	156.344	1.593	0.451	2	139.585	138.481	1.104	0.576
LEPR rs1137100	1	150.364	150.134	0.230	0.632	1	142.556	140.039	2.517	0.113
LEPR rs1343982	1	159.908	159.707	0.201	0.654	1	142.551	140.393	2.158	0.142
LEPR rs1137101	2	160.868	160.668	0.200	0.905	2	134.871	134.759	0.112	0.946
LEPR rs2376018	1	161.030	160.124	0.906	0.341	1	140.012	139.526	0.486	0.486
LEPR rs1805096	2	155.409	151.396	4.013	0.134	2	140.230	127.957	12.273	0.002
LEPR rs1892534	2	156.513	151.997	4.516	0.105	2	140.373	129.746	10.627	0.005
MCP1/CCL2 rs1024611	1	157.269	157.175	0.094	0.759	1	143.622	143.510	0.112	0.738
MCP1/CCL2 rs3760396	1	158.978	158.972	0.006	0.938	1	141.336	140.745	0.591	0.442
MCP1/CCL2 rs2857657	1	161.059	156.115	4.944	0.026	1	141.785	141.545	0.240	0.624
MCP1/CCL2 rs4586	2	159.279	155.750	3.529	0.171	2	139.736	139.437	0.299	0.861
MCP1/CCL2 rs13900	1	157.994	157.901	0.093	0.760	1	143.622	143.510	0.112	0.734
MCP1/CCL2 rs991804	1	160.683	160.675	0.008	0.929	1	142.581	142.293	0.288	0.592
MCP2/CCL8 rs3138036	1	158.963	156.659	2.304	0.129	1	143.436	140.615	2.821	0.093
MCP2/CCL8 rs3138038	1	157.807	155.248	2.559	0.110	1	143.436	140.615	2.821	0.093
MCP2/CCL8 rs11575057	1	156.828	154.079	2.749	0.097	1	143.667	141.727	1.940	0.164
TGF-β1 rs2278422	1	149.478	147.202	2.276	0.131	1	142.853	141.564	1.289	0.256
TGF-β1 rs2241716	1	160.878	154.731	6.147	0.013	1	143.672	143.672	0.000	1.000
TGF-β1 rs1800471	1	160.878	160.199	0.679	0.410	1	142.617	142.197	0.420	0.517
TNFα rs2229094	1	161.210	158.233	2.977	0.084	1	142.125	141.719	0.406	0.524
TNFα rs3093662	1	161.615	158.342	3.273	0.070	1	143.524	143.001	0.523	0.470
TNFα rs3093665	1	161.609	160.065	1.544	0.214	1	142.659	141.539	1.120	0.290

Abbreviation: Degrees of Freedom (df)

Table B-7: Adjusted Odds Ratios for Steatosis of Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

	African Americans* N = 167					Caucasian Americans* N = 184				
	SNP Main Effects			HOMA2-IR		SNP Main Effects			HOMA2-IR	
Single Nucleotide Polymorphism	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**N**	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**
COL1A1 rs2586485										
CC	96	1.00				68	1.00			
TT	71	1.41 (0.65-3.05)	0.38	‡		115	1.04 (0.43-2.50)	0.93	‡	
COL1A1 rs2586494										
AA/AC	57	1.00				45	1.00		19.54(2.32-164.49)	0.01
CC	110	0.75 (0.33-1.72)	0.50	‡		138	0.22 (0.05-1.02)	0.05	2.29 (1.05-4.98)	0.04
COL1A1 rs7406586										
AA	47	1.00				12	1.00		1.00	
AG	83	0.59 (0.23-1.52)	0.27	‡		56	7.75 (0.94-63.95)	0.06	42.80 (3.63-504.40)	0.01
GG	37	0.46 (0.15-1.39)	0.17	‡		115	3.36 (0.58-19.34)	0.18	1.96 (0.88-4.33)	0.10
COL1A1 rs2269336										
CC	94	1.00				137	1.00			
CG/GG	73	0.80 (0.37-1.70)	0.56	‡		46	1.55 (0.59-4.04)	0.37	‡	
CYP2E1 rs10857735										
AA/AC	100	1.00				18	1.00			
CC	59	1.14 (0.52-2.53	0.74	‡		159	0.99 (0.18-5.06)	0.99	‡	
CYP2E1 rs2070673										
AA	76	1.00				6	1.00			
AT	66	1.11 (0.48-2.53)	0.81			46	0.48 (0.03-7.71)	0.54	‡	
TT	25	0.59 (0.19-1.87)	0.37			131	0.46 (0.03-6.55)	0.57	‡	
CYP2E1 rs915908										
AA/AG	10	1.00				40	1.00			
GG	156	2.32 (0.34-16.04)	0.39	‡		140	0.91 (0.34-2.47)	0.85	‡	
CYP2E1 rs2070676										
CC	22	1.00				144	1.00			
CG	77	3.37 (0.90-12.66)	0.07	‡		33	0.93 (0.30-2.86)	0.90	‡	
GG	62	2.85 (0.76-10.70)	0.12	‡		2	†		‡	

Table B-7 (Continued)

IL6 rs1880242									
GG/GT	52	1.00			140	1.00			
TT	115	1.28 (0.57-2.89)	0.55	‡	43	0.76 (0.29-2.06)	0.61	‡	
IL6 rs2056576									
CC	54	1.00			69	1.00			
CT	79	1.08 (0.47-2.52)	0.85	‡	94	0.57 (0.23-1.42)	0.23	‡	
TT	33	1.10 (0.38-1.34)	0.86	‡	20	0.91 (0.23-3.65)	0.90	‡	
IL6 rs2069827									
GG	158	1.00			152	1.00			
GT/TT	7	†		†	31	1.47 (0.50-4.30)	0.49	‡	
IL6 rs1800797									
AA/AG	22	1.00			115	1.00			
GG	144	2.06 (0.61-6.98)	0.25	‡	69	0.45 (0.19-1.05)	0.07	‡	
IL6 rs1800795									
CC/CG	23	1.00			118	1.00			
GG	143	1.78 (0.55-5.73)	0.34	‡	66	0.47 (0.20-1.10)	0.08	‡	
IL6 rs2069830									
CC	133	1.00			182	1.00			
CT/TT	32	0.87 (0.33-2.27)	0.77	‡	1	†		‡	
IL6 rs2069837									
AA	132	1.00			159	1.00			
AG/GG	34	0.81 (0.32-2.04)	0.65	‡	25	0.82 (0.23-2.91)	0.76	‡	
IL6 rs1554606									
GG	79	1.00			60	1.00			
GT/TT	87	0.88 (0.41-1.91)	0.75	‡	124	2.24 (0.94-5.30)	0.07	‡	
IL6 rs2069845									
AA	75	1.00			60	1.00			
AG/GG	92	0.86 (0.40-1.86)	0.70	‡	123	2.52 (1.06-6.00)	0.04	‡	
IL10 rs11119474									
AA/AG	2	1.00			27	1.00			
GG	165	†		‡	156	1.46 (0.48-4.48)	0.51	‡	
IL10 rs3024505									
CC	148	1.00			138	1.00			
CT/TT	19	0.36 (0.11-1.23)	0.10	‡	44	0.50 (0.21-1.22)	0.13	‡	

Table B-7 (Continued)

IL10 rs3024498										
AA	128	1.00				96	1.00		7.53 (2.34-24.26)	0.001
AG/GG	39	0.56 (0.23-1.37)	0.20	‡		87	0.85 (0.34-2.16)	0.74	1.62 (0.68-3.87)	0.28
IL10 rs3024496										
CC	28	1.00		0.27 (0.05-1.31)	0.10	50	1.00		1.46 (0.52-4.15)	0.47
CT	82	2.02 (0.64-6.36)	0.23	3.39 (1.31-8.78)	0.01	86	3.27 (1.06-10.09)	0.04	7.66 (2.31-25.42)	0.001
TT	57	3.98 (1.15-13.77)	0.03	2.24 (0.80-6.28)	0.13	48	1.69 (0.48-5.92)	0.41	9.30 (1.45-59.53)	0.02
IL10 rs1554286										
CC	61	1.00				131	1.00		2.15 (1.00-4.60)	0.05
CT/TT	106	1.41 (0.64-3.14)	0.40	‡		52	3.01 (0.87-10.40)	0.08	15.30 (2.64-88.51)	0.002
IL10 rs2222202										
CC	84	1.00		3.02 (1.18-7.73)	0.02	48	1.00		9.30 (1.45-59.53)	0.02
CT	68	0.55 (0.23-1.29)	0.17	3.21 (1.16-8.85)	0.03	86	1.94 (0.50-7.56)	0.34	7.66 (2.31-25.42)	0.001
TT	15	0.85 (0.07-10.00)	0.90	0.02 (0.01-3.14)	0.12	50	0.59 (0.17-2.07)	0.41	1.46 (0.52-4.15)	0.47
IL10 rs1800890										
AA/AT	70	1.00				116	1.00			
TT	97	1.60 (0.73-3.48)	0.24	‡		67	1.00 (0.41-2.43)	0.99	‡	
IL1R1 rs3917275										
AA	153	1.00				182	1.00			
AG/GG	14	1.05 (0.23-4.83)	0.95	‡		1	†			
IL1R1 rs2110726										
CC	136	1.00				70	1.00			
CT/TT	31	0.32 (0.11-0.86)	0.02	‡		113	2.21 (0.92-5.31)	0.08	‡	
IL1R1 rs3917332										
AA/AT	44	1.00				67	1.00			
TT	123	0.86 (0.35-2.11)	0.74	‡		116	1.38 (0.60-3.17)	0.45	‡	
IL1R1 rs871656										
AA/AT	72	1.00				64	1.00			
TT	95	0.83 (0.29-1.76)	0.62	‡		118	0.88 (0.37-2.08)	0.77	‡	
LEPR rs6673324										
AA	42	1.00				51	1.00			
AG	87	2.43 (0.97-6.05)	0.057	‡		90	1.64 (0.58-4.62)	0.35	‡	
GG	37	1.82 (0.57-5.79)	0.31	‡		41	1.18 (0.34-4.06)	0.79	‡	

Table B-7 (Continued)

LEPR rs1137100										
AA	112	1.00				100	1.00			
AG/GG	55	0.25 (0.11-0.58)	0.001	‡		83	0.90 (0.40-2.05)	0.81	‡	
LEPR rs1343982										
AA/AG	91	1.00				85	1.00			
GG	76	1.66 (0.77-3.58)	0.19	‡		98	1.11 (0.49-2.53)	0.75	‡	
LEPR rs1137101										
AA	42	1.00				53	1.00			
AG	73	0.92 (0.35-2.42)	0.86	‡		91	1.58 (0.58-4.30)	0.37	‡	
GG	52	0.67 (0.24-1.86)	0.44	‡		39	0.31 (0.09-1.10)	0.07	‡	
LEPR rs2376018										
AA	115	1.00				124	1.00			
AG/GG	52	1.38 (0.61-3.12)	0.45	‡		59	2.09 (0.84-5.22)	0.11	‡	
LEPR rs1805096										
CC	52	1.00				74	1.00		2.01 (0.75-5.40)	0.17
CT	83	2.11 (0.87-5.13)	0.10	‡		70	4.36 (1.21-15.73)	0.03	29.60 (4.27-205.2)	0.001
TT	32	0.63 (0.21-1.90)	0.42	‡		38	2.36 (0.76-7.33)	0.14	1.01 (0.31-3.32)	0.98
LEPR rs1892534										
AA	33	1.00				40	1.00		1.20 (0.37-3.90)	0.76
AG	83	2.98 (1.07-8.33)	0.04	‡		69	1.79 (0.45-7.16)	0.41	26.22 (3.81-180.4)	0.001
GG	51	1.55 (0.52-4.62)	0.43	‡		74	0.44 (0.15-1.34)	0.15	1.97 (0.74-5.25)	0.18
MCP1/CCL2 rs3917879[‡]										
MCP1/CCL2 rs1024611										
CC/CT	60	1.00				88	1.00			
TT	106	2.09 (0.94-4.63)	0.07	‡		96	1.10 (0.49-2.47)	0.82	‡	
MCP1/CCL2 rs3760396										
CC	148	1.00				96	1.00			
CG/GG	18	2.36 (0.59-9.48)	0.23	‡		88	1.91 (0.82-4.42)	0.13	‡	
MCP1/CCL2 rs2857657										
CC	144	1.00		1.73 (0.95-3.16)	0.07	124	1.00			
CG/GG	23	2.33 (0.42-12.89)	0.33	24.80 (1.23-500.2)	0.04	59	1.55 (0.60-3.97)	0.37	‡	
MCP1/CCL2 rs4586										
CC	66	1.00				26	1.00			
CT	82	1.59 (0.71-3.56)	0.26	‡		86	3.21 (0.94-10.95)	0.06	‡	
TT	18	1.21 (0.31-4.70)	0.79	‡		72	3.16 (0.89-11.28)	0.08	‡	

Table B-7 (Continued)

MCP1/CCL2 rs13900										
CC	105	1.00				96	1.00			
CT/TT	61	0.52 (0.24-1.15)	0.11	‡		88	0.91 (0.41-2.05)	0.82	‡	
MCP1/CCL2 rs991804										
AA/AG	101	1.00				86	1.00			
GG	66	1.46 (0.67-3.18)	0.34	‡		96	1.08 (0.48-2.44)	0.85	‡	
MCP2/CCL8 rs3138036										
AA	150	1.00				134	1.00			
AG/GG	16	0.44 (0.12-1.58)	0.21	‡		50	1.27 (0.49-3.32)	0.63	‡	
MCP2/CCL8 rs3138038										
AA	147	1.00				135	1.00			
AC/CC	19	0.36 (0.11-1.23)	0.10	‡		49	1.27 (0.49-3.32)	0.63	‡	
MCP2/CCL8 rs11575057										
CC/CT	20	1.00				58	1.00			
TT	146	3.16 (0.95-10.47)	0.06	‡		126	1.03 (0.42-2.57)	0.94	‡	
TGF-βI rs2278422										
CC/CG	85	1.00				130	1.00			
GG	82	4.42 (1.84-10.65)	0.001	‡		54	1.50 (0.62-3.60)	0.37	‡	
TGF-βI rs2241716										
AA/AG	16	1.00		0.65 (0.22-1.94)	0.44	0	1.00			
GG	151	1.48 (0.47-4.62)	0.50	3.34 (1.61-6.91)	0.001	183	†		†	
TGF-βI rs1800471										
CC/CG	23	1.00				18	1.00			
GG	144	0.57 (0.18-1.76)	0.33	‡		165	1.61 (0.37-6.95)	0.52	‡	
TNFα rs2229094										
CC/CT	84	1.00				70	1.00			
TT	83	0.78 (0.37-1.67)	0.53	‡		113	1.36 (0.58-3.19)	0.48	‡	
TNFα rs3093662										
AA	138	1.00				156	1.00			
AG/GG	29	0.98 (0.37-2.66)	0.98	‡		28	1.24 (0.41-3.82)	0.70	‡	
TNFα rs3093665										
AA	153	1.00				178	1.00			
AC/CC	14	1.06 (0.29-3.85)	0.93	‡		6	0.39 (0.06-2.53)	0.32	‡	

* Model adjusted for the genetic variant, Ishak fibrosis score, $\log_{10}$ baseline viral level, ln HOMA2-IR score, weekly alcohol consumption, body mass index and interaction between the genetic variant and ln HOMA2-IR score (where significant)
‡ Odds ratios from the main effects model adjusting for the genetic variant, Ishak fibrosis score, $\log_{10}$ baseline viral level, ln HOMA2-IR score, weekly alcohol consumption and body mass index were reported because the log likelihood test for the interaction between the genetic variant and ln HOMA2-IR scores were not significant at an alpha level of 0.05.
† Minor allele frequency less then 5% in one population

Table B-8: Chi Square Association between Insulin Resistance and Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

Single Nucleotide Polymorphism		African Americans N = 152 HOMA2-IR < 2	African Americans N = 152 HOMA2-IR ≥ 2	p-value*	Caucasian Americans N = 157 HOMA2-IR < 2	Caucasian Americans N = 157 HOMA2-IR ≥ 2	p-value*
COL1A1 rs2586485							
	CC	0.11	0.17		0.04	0.08	
	CT	0.47	0.48		0.29	0.37	
	TT	0.42	0.35	0.44	0.67	0.56	0.37
COL1A1 rs2586494							
	AA	0.02	0.02		0.03	0.0	
	AC	0.28	0.33		0.25	0.15	
	CC	0.70	0.65	0.77	0.72	0.85	0.11
COL1A1 rs7406586							
	AA	0.29	0.26		0.07	0.06	
	AG	0.43	0.55		0.29	0.37	
	GG	0.28	0.19	0.21	0.64	0.58	0.51
COL1A1 rs2269336							
	CC	0.54	0.58		*0.72*	0.83	
	CG	0.41	0.39		0.26	0.17	
	GG	0.05	0.03	0.66	0.02	0.0	0.25
CYP2E1 rs10857735							
	AA	0.20	0.14		*0.0*	0.02	
	AC	0.40	0.56		*0.07*	0.12	
	CC	0.41	0.30	0.17	0.93	0.86	0.11
CYP2E1 rs2070673							
	AA	0.46	0.49		*0.03*	0.04	
	AT	0.40	0.39		0.20	0.37	
	TT	0.15	0.12	0.89	0.77	0.60	0.04
CYP2E1 rs915908							
	AA	0.0	0.0		0.02	0.02	
	AG	0.05	0.04		0.21	0.17	
	GG	0.95	0.96	0.79	0.78	0.81	0.80
CYP2E1 rs2070676							
	CC	0.19	0.09		0.83	0.72	
	CG	0.39	0.49		0.16	0.28	
	GG	0.43	0.42	0.33	0.02	0.0	0.07
IL6 rs1880242							
	GG	0.0	0.03		0.14	0.23	
	GT	0.31	0.29		0.56	0.65	
	TT	0.69	0.68	0.29	0.30	0.12	0.03
IL6 rs2056576							
	CC	0.29	0.35		0.38	0.39	
	CT	0.48	0.44		0.48	0.58	
	TT	0.23	0.22	0.81	0.14	0.04	0.15
IL6 rs2069827							
	GG	0.98	0.94		0.82	0.89	
	GT	0.02	0.06		0.18	0.12	
	TT	0.0	0.0	0.28	0.0	0.0	0.26

Table B-8 (Continued)

IL6 rs1800797							
	AA	0.0	0.0		0.11	0.17	
	AG	0.11	0.16		0.47	0.56	
	GG	0.89	0.84	0.45	0.42	0.27	0.24
IL6 rs1800795							
	CC	0.0	0.0		0.11	0.17	
	CG	0.11	0.18		0.47	0.56	
	GG	0.89	0.82	0.33	0.42	0.27	0.24
IL6 rs2069830							
	CC	0.77	0.84		1.0	1.0	
	CT	0.23	0.13		0.0	0.0	
	TT	0.0	0.03	0.15	0.0	0.0	
IL6 rs2069837							
	AA	0.83	0.71		0.83	0.92	
	AG	0.17	0.29		0.17	0.08	
	GG	0.0	0.0	0.095	0.0	0.0	0.15
IL6 rs1554606							
	GG	0.51	0.43		0.39	0.23	
	GT	0.41	0.43		0.49	0.60	
	TT	0.08	0.15	0.41	0.13	0.17	0.16
IL6 rs2069845							
	AA	0.49	0.39		0.39	0.23	
	AG	0.42	0.46		0.49	0.60	
	GG	0.08	0.15	0.34	0.12	0.17	0.14
IL10 rs11119474							
	AA	0.0	0.0		0.0	0.0	
	AG	0.0	0.03		0.16	0.12	
	GG	1.0	0.97	0.12	0.84	0.89	0.61
IL10 rs3024505							
	CC	0.88	0.90		0.72	0.77	
	CT	0.12	0.10		0.28	0.17	
	TT	0.0	0.0	0.73	0.01	0.06	0.13
IL10 rs3024498							
	AA	0.81	0.78		0.56	0.42	
	AG	0.19	0.22		0.35	0.48	
	GG	0.0	0.0	0.62	0.10	0.10	0.43
IL10 rs3024496							
	CC	0.11	0.17		0.26	0.33	
	CT	0.58	0.36		0.51	0.42	
	TT	0.31	0.46	0.057	0.23	0.25	0.37
IL10 rs1554286							
	CC	0.33	0.35		0.66	0.79	
	CT	0.54	0.41		0.31	0.21	
	TT	0.13	0.25	0.13	0.03	0.0	0.23
IL10 rs2222202							
	CC	0.49	0.58		0.23	0.25	
	CT	0.47	0.29		0.51	0.42	
	TT	0.04	0.13	0.05	0.26	0.33	0.37

Table B-8 (Continued)							
IL10 rs1800890							
	AA	0.02	0.07		0.12	0.23	
	AT	0.31	0.36		0.55	0.42	
	TT	0.66	0.57	0.42	0.34	0.35	0.13
IL1R1 rs3917257[§]							
IL1R1 rs3917275							
	AA	0.94	0.90		0.99	1.0	
	AG	0.06	0.09		0.01	0.0	
	GG	0.0	0.02	0.43	0.0	0.0	0.47
IL1R1 rs2110726							
	CC	0.80	0.87		0.40	0.35	
	CT	0.19	0.13		0.49	0.54	
	TT	0.01	0.0	0.34	0.11	0.12	0.61
IL1R1 rs3917332							
	AA	0.01	0.03		0.03	0.06	
	AT	0.19	0.23		0.37	0.33	
	TT	0.80	0.74	0.67	0.61	0.62	0.69
IL1R1 rs871656							
	AA	0.06	0.07		0.04	0.06	
	AT	0.39	0.39		0.30	0.29	
	TT	0.55	0.54	0.95	0.66	0.65	0.85
LEPR rs6673324							
	AA	0.24	0.29		0.20	0.39	
	AG	0.54	0.55		0.57	0.35	
	GG	0.22	0.16	0.61	0.22	0.27	0.04
LEPR rs1137100							
	AA	0.66	0.61		0.60	0.52	
	AG	0.30	0.35		0.34	0.37	
	GG	0.04	0.04	0.77	0.07	0.12	0.57
LEPR rs1343982							
	AA	0.10	0.13		0.08	0.12	
	AG	0.48	0.45		0.35	0.37	
	GG	0.42	0.42	0.79	0.58	0.52	0.74
LEPR rs1137101							
	AA	0.29	0.19		0.33	0.29	
	AG	0.41	0.42		0.51	0.40	
	GG	0.30	0.39	0.24	0.16	0.31	0.24
LEPR rs2376018							
	AA	0.71	0.70		0.65	0.71	
	AG	0.28	0.29		0.33	0.23	
	GG	0.01	0.02	0.97	0.02	0.06	0.36
LEPR rs1805096							
	CC	0.29	0.29		0.39	0.43	
	CT	0.54	0.39		0.41	0.29	
	TT	0.17	0.32	0.05	0.19	0.28	0.27
LEPR rs1892534							
	AA	0.18	0.32		0.21	0.27	
	AG	0.54	0.39		0.39	0.31	
	GG	0.28	0.29	0.07	0.39	0.42	0.49

Table B-8 (Continued)						
MCP1/CCL2 rs3917879[§]						
MCP1/CCL2 rs1024611						
CC	0.06	0.04		0.06	0.14	
CT	0.33	0.28		0.43	0.46	
TT	0.62	0.68	0.83	0.51	0.40	0.23
MCP1/CCL2 rs3760396						
CC	0.92	0.88		0.48	0.60	
CG	0.08	0.10		0.45	0.39	
GG	0.0	0.02	0.50	0.08	0.02	0.18
MCP1/CCL2 rs2857657						
CC	0.87	0.87		0.70	0.71	
CG	0.13	0.13		0.26	0.27	
GG	0.0	0.0	0.99	0.04	0.02	0.80
MCP1/CCL2 rs4586						
CC	0.45	0.34		0.14	0.15	
CT	0.46	0.56		0.49	0.52	
TT	0.10	0.10	0.39	0.37	0.33	0.76
MCP1/CCL2 rs13900						
CC	0.60	0.68		0.51	0.40	
CT	0.33	0.28		0.43	0.46	
TT	0.07	0.04	0.69	0.06	0.14	0.23
MCP1/CCL2 rs991804						
AA	0.17	0.15		0.06	0.14	
AG	0.46	0.39		0.41	0.45	
GG	0.37	0.46	0.60	0.53	0.41	0.21
MCP2/CCL8 rs3138036						
AA	0.89	0.93		0.70	0.79	
AG	0.11	0.06		0.30	0.17	
GG	0.0	0.02	0.25	0.01	0.04	0.19
MCP2/CCL8 rs3138038						
AA	0.87	0.93		0.70	0.81	
AC	0.13	0.06		0.29	0.16	
CC	0.0	0.02	0.14	0.02	0.04	0.17
MCP2/CCL8 rs11575057						
CC	0.0	0.02		0.03	0.04	
CT	0.15	0.06		0.32	0.19	
TT	0.86	0.93	0.10	0.65	0.77	0.17
TGF-β1 rs2278422						
CC	0.04	0.12		0.13	0.21	
CG	0.45	0.51		0.52	0.64	
GG	0.52	0.38	0.06	0.35	0.15	0.04
TGF-β1 rs2241716						
AA	0.0	0.0		0.0	0.0	
AG	0.13	0.07		0.0	0.0	
GG	0.87	0.93	0.24	1.0	1.0	
TGF-β1 rs1800471						
CC	0.0	0.0		0.01	0.0	
CG	0.17	0.12		0.08	0.14	
GG	0.83	0.88	0.37	0.91	0.87	0.43

Table B-8 (Continued)							
TNFα rs2229094							
	CC	0.01	0.06		0.06	0.08	
	CT	0.46	0.45		0.30	0.33	
	TT	0.53	0.49	0.16	0.64	0.60	0.63
TNFα rs3093662							
	AA	0.83	0.83		0.83	0.87	
	AG	0.17	0.16		0.16	0.10	
	GG	0.0	0.02	0.29	0.01	0.04	0.36
TNFα rs3093665							
	AA	0.90	0.93		0.95	1.0	
	AC	0.10	0.07		0.05	0.0	
	CC	0.0	0.0	0.86	0.0	0.0	0.37

* P-value based on genotype association chi square test

† Chi Square could not be estimated because minor allele frequency < 5% for the SNP

§ Monomorphic SNP

Table B-9: Unadjusted Odd Ratios for Insulin Resistance for Single Nucleotide Polymorphisms in African Americans and Caucasian Americans

Single Nucleotide Polymorphism		African Americans N = 142				Caucasian Americans N = 156			
		N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
COL1A1 rs2586485									
	CC/CT	85	1.00			57	1.00		
	TT	57	0.73	0.38-1.42	0.35	98	0.61	0.31-1.21	0.16
COL1A1 rs2586494									
	AA/AC	45	1.00			37	1.00		
	CC	97	0.81	0.41-1.60	0.54	118	2.13	0.89-5.06	0.09
COL1A1 rs7406586									
	AA	41	1.00			10	1.00		
	AG	70	1.41	0.66-3.02	0.38	49	1.48	0.34-6.24	0.60
	GG	31	0.75	0.30-1.88	0.54	96	1.05	0.25-4.32	0.95
COL1A1 rs2269336									
	CC	79	1.00			117	1.00		
	CG/GG	63	0.86	0.45-1.64	0.64	38	0.54	0.23-1.25	0.15
CYP2E1 rs10857735									
	AA/AC	86	1.00			14	1.00		
	CC	51	0.92	0.58-1.46	0.71	136	0.44	0.16-1.22	0.12
CYP2E1 rs2070673									
	AA	68	1.00			5	1.00		
	AT	54	0.91	0.46-1.82	0.80	39	1.36	0.20-9.02	0.75
	TT	20	0.75	0.27-2.04	0.57	111	0.58	0.09-3.65	0.56
CYP2E1 rs915908									
	AA/AG	6	1.00			33	1.00		
	GG	135	1.13	0.24-5.22	0.88	120	1.22	0.53-2.81	0.64
CYP2E1 rs2070676									
	CC	19	1.00			121	1.00		
	CG	61	2.66	0.92-7.73	0.07	29	2.07	0.91-4.67	0.22
	GG	58	2.06	0.71-6.01	0.19	2	†		
IL6 rs1880242									
	GG/GT	45	1.00			119	1.00		
	TT	97	0.97	0.49-1.94	0.94	36	0.31	0.12-0.79	0.02
IL6 rs2056576									
	CC	47	1.00			58	1.00		
	CT	65	0.75	0.36-1.57	0.45	80	1.17	0.58-2.37	0.66
	TT	30	0.79	0.33-1.91	0.60	17	0.26	0.05-1.25	0.09
IL6 rs2069827									
	GG	134	1.00			130	1.00		
	GT/TT	6	2.50	0.44-14.09		25	0.58	0.22-1.56	0.28
IL6 rs1800797									
	AA/AG	19	1.00			99	1.00		
	GG	122	0.63	0.25-1.62	0.34	57	0.51	0.25-1.06	0.07
IL6 rs1800795									
	CC/CG	20	1.00			99	1.00		
	GG	121	0.57	0.22-1.44	0.23	57	0.51	0.25-1.06	0.07

Table B-9 (Continued)

IL6 rs2069830								
CC	113	1.00			155	1.00		
CT/TT	27	0.66	0.29-1.51	0.33	0	†		
IL6 rs2069837								
AA	112	1.00			135	1.00		
AG/GG	29	2.05	0.95-4.46	0.07	21	0.40	0.13-1.26	0.12
IL6 rs1554606								
GG	66	1.00			52	1.00		
GT/TT	75	1.38	0.95-0.33	0.33	104	2.14	1.00-4.54	0.05
IL6 rs2069845								
AA	63	1.00			52	1.00		
AG/GG	79	1.52	0.80-2.90	0.21	103	2.17	1.02-4.62	0.04
IL10 rs11119474								
AA/AG	2	1.00			23	1.00		
GG	140	†			132	1.50	0.55-4.06	0.43
IL10 rs3024505								
CC	126	1.00			113	1.00		
CT/TT	16	0.82	0.30-2.29	0.71	41	0.76	0.35-1.64	0.48
IL10 rs3024498								
AA	112	1.00			79	1.00		
AG/GG	30	1.16	0.53-2.56	0.71	76	1.72	0.88-3.37	0.11
IL10 rs3024496								
CC	20	1.00			44	1.00		
CT	70	0.39	0.15-1.05	0.06	75	0.65	0.30-1.42	0.28
TT	52	0.92	0.34-2.53	0.88	37	0.86	0.35-2.13	0.75
IL10 rs1554286								
CC	49	1.00			109	1.00		
CT/TT	93	0.90	0.46-1.78	0.77	46	0.51	0.23-1.10	0.09
IL10 rs2222202								
CC	74	1.00			37	1.00		
CT	57	0.53	0.26-1.05	0.07	75	0.75	0.33-1.74	0.51
TT	11	3.08	0.78-12.19	0.11	44	1.16	0.47-2.88	0.75
IL10 rs1800890								
AA/AT	55	1.00			102	1.00		
TT	87	0.66	0.34-1.28	0.22	53	1.04	0.52-2.11	0.91
IL1R1 rs3917275								
AA	130	1.00			154	1.00		
AG/GG	12	1.76	0.53-5.82	0.35	1	†		
IL1R1 rs2110726								
CC	117	1.00			59	1.00		
CT/TT	25	0.58	0.24-1.41	0.23	96	1.28	0.64-2.56	0.49
IL1R1 rs3917332								
AA/AT	33	1.00			60	1.00		
TT	109	0.73	0.34-1.56	0.42	95	1.04	0.53-2.06	0.91
IL1R1 rs871656								
AA/AT	64	1.00			53	1.00		
TT	78	0.93	0.49-1.77	0.83	101	0.93	0.46-1.88	0.84

Table B-9 (Continued)

LEPR rs6673324								
AA	33	1.00			41	1.00		
AG	81	0.84	0.40-1.80	0.66	76	0.32	0.14-0.72	0.006
GG	28	0.61	0.23-1.62	0.32	37	0.64	0.26-1.58	0.33
LEPR rs1137100								
AA	93	1.00			88	1.00		
AG/GG	49	1.26	0.65-2.45	0.49	67	1.37	0.70-2.67	0.36
LEPR rs1343982								
AA/AG	79	1.00			69	1.00		
GG	63	0.99	0.52-1.90	0.99	86	0.79	0.41-1.55	0.49
LEPR rs1137101								
AA	36	1.00			49	1.00		
AG	62	1.58	0.68-3.64	0.29	73	0.90	0.41-1.98	0.79
GG	44	1.99	0.84-4.74	0.12	33	2.13	0.86-5.32	0.10
LEPR rs2376018								
AA	98	1.00			104	1.00		
AG/GG	44	1.08	0.54-2.16	0.84	51	0.77	0.37-1.58	0.47
LEPR rs1805096								
CC	44	1.00			62	1.00		
CT	68	0.72	0.34-1.54	0.40	58	0.65	0.30-1.42	0.28
TT	30	1.89	0.77-4.62	0.17	34	1.31	0.55-3.07	0.54
LEPR rs1892534								
AA	31	1.00			36	1.00		
AG	68	0.41	0.18-0.92	0.03	57	0.61	0.25-1.49	0.28
GG	43	0.59	0.24-1.44	0.25	62	0.84	0.36-1.97	0.69
MCP1/CCL2 rs3917879[‡]								
MCP1/CCL2 rs1024611								
CC/CT	50	1.00			81	1.00		
TT	91	1.31	0.67-2.57	0.43	75	0.64	0.33-1.25	0.19
MCP1/CCL2 rs3760396								
CC	127	1.00			80	1.00		
CG/GG	14	1.45	0.50-4.22	0.50	76	0.62	0.31-1.21	0.16
MCP1/CCL2 rs2857657								
CC	124	1.00			109	1.00		
CG/GG	18	0.98	0.38-2.53	0.97	46	0.96	0.46-1.99	0.90
MCP1/CCL2 rs4586								
CC	59	1.00			22	1.00		
CT	67	1.61	0.81-3.20	0.18	78	0.99	0.37-2.64	0.99
TT	15	1.41	0.45-4.40	0.56	56	0.82	0.29-2.29	0.70
MCP1/CCL2 rs13900								
CC	90	1.00			75	1.00		
CT/TT	51	0.73	0.37-1.42	0.35	81	1.56	0.80-3.06	0.19
MCP1/CCL2 rs991804								
AA/AG	84	1.00			78	1.00		
GG	58	1.45	0.76-2.78	0.26	76	0.62	0.32-1.23	0.17
MCP2/CCL8 rs3138036								
AA	128	1.00			114	1.00		
AG/GG	13	0.65	0.21-2.05	0.46	42	0.61	0.28-1.34	0.22

Table B-9 (Continued)								
MCP2/CCL8 rs3138038								
AA	126	1.00			115	1.00		
AC/CC	15	0.52	0.17-1.58	0.25	41	0.54	0.24-1.22	0.14
MCP2/CCL8 rs11575057								
CC/CT	16	1.00			48	1.00		
TT	125	2.13	0.71-6.38	0.18	108	1.81	0.85-3.87	0.13
TGF-β1 rs2278422								
CC/CG	76	1.00			111	1.00		
GG	66	0.56	0.29-1.08	0.08	45	0.33	0.14-0.78	0.01
TGF-β1 rs2241716								
AA/AG	16	1.00			0	1.00		
GG	126	1.96	0.65-5.93	0.24	155	†		
TGF-β1 rs1800471								
CC/CG	16	1.00			16	1.00		
GG	126	1.55	0.61-3.94	0.36	139	0.61	0.21-1.74	0.35
TNFα rs2229094								
CC/CT	69	1.00			58	1.00		
TT	73	0.86	0.45-1.63	0.65	97	0.82	0.41-1.62	0.56
TNFα rs3093662								
AA	119	1.00			131	1.00		
AG/GG	23	1.04	0.45-2.42	0.93	25	0.75	0.29-1.93	0.55
TNFα rs3093665								
AA	130	1.00			151	1.00		
AC/CC	12	0.73	0.23-2.35	0.60	5	†		

‡ Monomorphic SNP

† Minor allele frequency less then 5% in one population

Table B-10: Adjusted Odds Ratios for Insulin Resistance for Single Nucleotide Polymorphisms among African Americans and Caucasian Americans

	African Americans* N = 142				Caucasian Americans* N = 156			
Single Nucleotide Polymorphism	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**
COL1A1 rs2586485								
CC	85	1.00			57	1.00		
TT	57	0.89	0.41-1.91	0.76	98	0.72	0.34-1.52	0.39
COL1A1 rs2586494								
AA/AC	45	1.00			37	1.00		
CC	97	1.00	0.45-2.22	0.99	118	2.07	0.82-5.17	0.12
COL1A1 rs7406586								
AA	41	1.00			10	1.00		
AG	70	1.88	0.75-4.70	0.18	49	0.87	0.18-4.20	0.86
GG	31	0.87	0.27-2.78	0.82	96	0.69	0.15-3.12	0.63
COL1A1 rs2269336								
CC	79	1.00			117	1.00		
CG/GG	63	0.77	0.36-1.66	0.51	38	0.46	0.19-1.14	0.09
CYP2E1 rs10857735								
AA/CC	86	1.00			14	1.00		
CC	51	0.86	0.50-1.47	0.57	136	0.52	0.14-1.57	0.25
CYP2E1 rs2070673								
AA	68	1.00			5	1.00		
AT	54	0.87	0.39-1.97	0.74	39	1.56	0.21-11.86	0.67
TT	20	0.68	0.21-1.28	0.51	111	0.80	0.11-5.68	0.83
CYP2E1 rs915908								
AA/AG	6	1.00			33	1.00		
GG	135	4.49	0.42-47.89	0.21	120	1.37	0.55-3.42	0.50
CYP2E1 rs2070676								
CC	19	1.00			121	1.00		
CG	61	2.33	0.57-9.79	0.25	29	2.01	0.81-4.98	0.13
GG	58	1.96	0.47-8.25	0.36	2	†		
IL6 rs1880242								
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
IL6 rs2056576								
CC	47	1.00			58	1.00		
CT	65	0.48	0.20-1.14	0.10	80	1.22	0.57-2.61	0.62
TT	30	0.51	0.17-1.47	0.21	17	0.35	0.07-1.81	0.21
IL6 rs2069827								
GG	134	1.00			130	1.00		
GT/TT	6	5.19	0.65-41.52	0.12	25	0.62	0.20-1.91	0.41
IL6 rs1800797								
AA/AG	19	1.00			99	1.00		
GG	122	0.55	0.18-1.69	0.30	57	0.60	0.28-1.32	0.20
IL6 rs1800795								
CC/CG	20	1.00			99	1.00		
GG	121	0.62	0.29-1.36	0.23	57	0.48	0.16-1.44	0.19

Table B-10 (Continued)

IL6 rs2069830								
CC	113	1.00			155	1.00		
CT/TT	27	0.61	0.23-1.65	0.33	0	†		
IL6 rs2069837								
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
IL6 rs1554606								
GG	66	1.00			52	1.00		
GT/TT	75	1.45	0.69-3.15	0.35	104	1.71	0.76-3.85	0.20
IL6 rs2069845								
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
IL10 rs11119474								
AA/AG	2	1.00			23	1.00		
GG	140	†			132	1.00	0.33-2.94	0.98
IL10 rs3024505								
CC	126	1.00			113	1.00		
CT/TT	16	0.86	0.25-2.97	0.81	41	1.16	0.49-2.73	0.73
IL10 rs3024498								
AA	112	1.00			79	1.00		
AG/GG	30	1.71	0.68-4.33	0.26	76	1.77	0.85-3.70	0.13
IL10 rs3024496								
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
IL10 rs1554286								
CC	49	1.00			109	1.00		
CT/TT	93	0.59	0.26-1.31	0.19	46	0.48	0.20-1.11	0.09
IL10 rs2222202								
CC	74	1.00			37	1.00		
CT	57	0.69	0.30-1.57	0.38	75	1.10	0.43-2.84	0.85
TT	11	5.07	1.10-23.45	0.04	44	2.11	0.75-5.94	0.16
IL10 rs1800890								
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
IL1R1 rs3917275								
AA	130	1.00			154	1.00		
AG/GG	12	2.00	0.47-8.60	0.35	1	†		
IL1R1 rs2110726								
CC	117	1.00			59	1.00		
CT/TT	25	0.65	0.23-1.86	0.42	96	1.18	0.55-2.56	0.67
IL1R1 rs3917332								
AA/AT	33	1.00			60	1.00		
TT	109	0.60	0.25-1.43	0.25	95	0.94	0.44-2.00	0.87
IL1R1 rs871656								
AA/AT	64	1.00			53	1.00		
TT	78	1.03	0.49-2.18	0.93	101	1.03	0.48-2.22	0.94

Table B-10 (Continued)								
LEPR rs6673324								
AA	33	1.00			41	1.00		
AG	81	0.97	0.39-2.37	0.94	76	0.33	0.14-0.79	0.01
GG	28	0.66	0.20-2.12	0.48	37	0.75	0.28-2.00	0.56
LEPR rs1137100								
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
LEPR rs1343982								
AA/AG	79	1.00			69	1.00		
GG	63	0.95	0.44-2.05	0.90	86	0.75	0.36-1.55	0.44
LEPR rs1137101								
AA	36	1.00			49	1.00		
AG	62	1.60	0.60-4.22	0.35	73	0.86	0.36-2.06	0.74
GG	44	1.77	0.63-4.95	0.28	33	2.25	0.80-6.32	0.12
LEPR rs2376018								
AA	98	1.00			104	1.00		
AG/GG	44	1.16	0.52-2.61	0.72	51	0.57	0.25-1.30	0.18
LEPR rs1805096								
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
LEPR rs1892534								
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
MCP1/CCL2 rs1024611								
CC/CT	50	1.00			81	1.00		
TT	91	1.04	0.47-2.29	0.93	75	0.83	0.40-1.75	0.63
MCP1/CCL2 rs3760396								
CC	127	1.00			80	1.00		
CG/GG	14	1.40	0.41-4.83	0.60	76	0.61	0.29-1.27	0.18
MCP1/CCL2 rs2857657								
CC	124	1.00			109	1.00		
CG/GG	18	0.79	0.25-2.47	0.68	46	0.85	0.38-1.88	0.68
MCP1/CCL2 rs4586								
CC	59	1.00			22	1.00		
CT	67	1.32	0.58-2.98	0.51	78	0.73	0.25-2.13	0.56
TT	15	1.66	0.47-5.88	0.44	56	0.79	0.26-2.43	0.68
MCP1/CCL2 rs13900								
CC	90	1.00			75	1.00		
CT/TT	51	0.90	0.41-1.97	0.79	81	0.90	0.41-1.97	0.79
MCP1/CCL2 rs991804								
AA/AG	84	1.00			78	1.00		
GG	58	1.15	0.53-2.47	0.73	76	0.79	0.37-1.67	0.53
MCP2/CCL8 rs3138036								
AA	128	1.00			114	1.00		
AG/GG	13	0.69	0.18-2.65	0.59	42	0.59	0.24-1.45	0.25
MCP2/CCL8 rs3138038								
AA	126	1.00			115	1.00		
AC/CC	15	0.59	0.16-2.19	0.43	41	0.59	0.24-1.45	0.25

Table B-10 (Continued)								
MCP2/CCL8 rs11575057								
CC/CT	16	1.00			48	1.00		
TT	125	2.07	0.63-6.83	0.23	108	1.78	0.75-4.25	0.19
TGF-β1 rs2278422								
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
TGF-β1 rs2241716								
AA/AG	16	1.00			0	1.00		
GG	126	1.32	0.41-4.29	0.64	155	†		
TGF-β1 rs1800471								
CC/CG	16	1.00			16	1.00		
GG	126	1.68	0.56-5.00	0.35	139	0.77	0.25-2.39	0.65
TNFα rs2229094								
CC/CT	69	1.00			58	1.00		
TT	73	0.75	0.35-1.61	0.45	97	0.80	0.37-1.75	0.58
TNFα rs3093662								
AA	119	1.00			131	1.00		
AG/GG	23	0.91	0.34-2.46	0.85	25	0.79	0.26-2.41	0.68
TNFα rs3092665								
AA	130	1.00			151	1.00		
AC/CC	12	0.63	0.17-2.38	0.49	5	†		

***** Model adjusted for the genetic variant, Ishak fibrosis score, steatosis, body mass index, age and triglyceride levels and excluded individuals taking exogenous insulin

† Model could not be estimated because minor allele frequency < 5% for the SNP

§ Monomorphic SNP

Abbreviations: 95% Confidence Interval (Confidence Interval)

Table B-11: Log Likelihood Ratio Test of the Significance of the Interaction Term Between Steatosis and the Genetic Variant in the Prediction of Insulin Resistance

	African Americans					Caucasian Americans				
	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value
COL1A1 rs2586485	1	162.940	162.760	0.180	0.671	1	173.080	172.397	0.683	0.409
COL1A1 rs2586494	1	163.036	159.543	3.493	0.062	1	171.264	171.003	0.261	0.609
COL1A1 rs7406586	2	159.791	159.690	0.101	0.951	2	173.342	168.009	5.333	0.069
COL1A1 rs2269336	1	162.596	162.131	0.465	0.495	1	170.795	170.406	0.389	0.533
CYP2E1 rs10857735	1	156.161	154.397	1.764	0.184	1	168.180	168.559	-0.379	0.538
CYP2E1 rs2070673	2	162.579	162.518	0.061	0.805	2	171.416	168.349	3.067	0.080
CYP2E1 rs915908	1	160.563	159.405	1.158	0.282	1	172.238	172.232	0.006	0.938
CYP2E1 rs2070676	2	158.144	156.441	1.703	0.427	2	166.876	165.625	1.251	0.535
IL6 rs1880242	1	163.018	162.804	0.214	0.644	1	167.222	167.114	0.108	0.742
IL6 rs2056576	2	159.945	159.738	0.207	0.902	2	171.030	169.801	1.229	0.541
IL6 rs2069827	1	158.137	153.791	4.346	<0.05, n=7	1	173.104	173.099	0.005	0.944
IL6 rs1800797	1	161.348	161.347	0.001	0.975	1	172.967	172.966	0.001	0.975
IL6 rs1800795	1	160.711	160.681	0.030	0.863	1	173.182	173.174	0.008	0.929
IL6 rs2069830	1	159.840	159.840	0.000	1.000	1	173.036	173.036	0.000	1.000
IL6 rs2069837	1	160.123	159.372	0.751	0.386	1	169.083	168.575	0.508	0.476
IL6 rs1554606	1	161.553	161.469	0.084	0.772	1	172.914	172.498	0.416	0.519
IL6 rs2069845	1	161.159	161.151	0.008	0.929	1	172.140	171.528	0.612	0.434
IL10 rs11119474	1	159.642	159.642	0.000	1.000	1	173.823	173.729	0.094	0.759
IL10 rs3024505	1	162.979	162.010	0.969	0.325	1	173.360	173.320	0.040	0.842
IL10 rs3024498	1	161.757	161.736	0.021	0.885	1	171.474	171.440	0.034	0.854
IL10 rs3024496	2	157.403	155.933	1.470	0.480	2	171.825	169.978	1.847	0.397
IL10 rs1554286	1	161.317	161.314	0.003	0.956	1	170.698	170.687	0.011	0.917
IL10 rs2222202	2	155.915	152.955	2.960	0.228	2	171.825	169.978	1.847	0.397
IL10 rs1800890	1	157.670	157.664	0.006	0.938	1	172.649	172.387	0.262	0.609

Table B-11 (Continued)

IL1R1 rs3917275	1	162.145	159.355	2.790	0.095	1	173.458	173.458	0.000	1.000
IL1R1 rs2110726	1	162.381	160.705	1.676	0.195	1	173.644	173.590	0.054	0.816
IL1R1 rs3917332	1	161.699	161.672	0.027	0.870	1	173.795	173.768	0.027	0.870
IL1R1 rs871656	1	163.029	163.027	0.002	0.964	1	171.289	170.732	0.557	0.456
LEPR rs6673324	2	162.397	160.877	1.520	0.468	2	166.341	165.476	0.865	0.649
LEPR rs1137100	1	161.142	160.630	0.512	0.474	1	172.880	172.299	0.581	0.446
LEPR rs1343982	1	163.021	162.414	0.607	0.436	1	173.213	172.731	0.482	0.488
LEPR rs1137101	2	161.715	160.163	1.552	0.213	2	169.790	168.795	0.995	0.319
LEPR rs2376018	1	162.908	161.849	1.059	0.303	1	171.971	171.344	0.627	0.429
LEPR rs1805096	2	158.557	157.106	1.451	0.484	2	172.087	171.545	0.542	0.462
LEPR rs1892534	2	159.145	157.511	1.634	0.442	2	173.415	171.385	2.030	0.152
MCP1/CCL2 rs3917879[‡]				0.000					0.000	
MCP1/CCL2 rs1024611	1	162.436	162.118	0.318	0.573	1	174.389	174.259	0.130	0.718
MCP1/CCL2 rs3760396	1	162.162	162.131	0.031	0.860	1	172.836	172.516	0.320	0.572
MCP1/CCL2 rs2857657	1	162.864	160.395	2.469	0.116	1	173.656	173.457	0.199	0.656
MCP1/CCL2 rs4586	2	161.673	161.165	0.508	0.776	2	174.293	174.178	0.115	0.944
MCP1/CCL2 rs13900	1	162.373	161.883	0.490	0.484	1	174.389	174.259	0.130	0.718
MCP1/CCL2 rs991804	1	162.915	162.846	0.069	0.793	1	173.436	173.353	0.083	0.773
MCP2/CCL8 rs3138036	1	162.138	161.572	0.566	0.452	1	173.244	172.788	0.456	0.500
MCP2/CCL8 rs3138038	1	161.796	160.863	0.933	0.344	1	173.244	172.788	0.456	0.500
MCP2/CCL8 rs11575057	1	161.600	160.482	1.118	0.290	1	172.868	172.861	0.007	0.933
TGF-β1 rs2278422	1	157.728	157.727	0.001	0.975	1	168.910	168.453	0.457	0.499
TGF-β1 rs2241716	1	162.817	161.394	1.423	0.233	1	174.626	174.626	0.000	1.000
TGF-β1 rs1800471	1	162.138	162.062	0.076	0.783	1	173.616	173.543	0.073	0.787
TNFα rs2229094	1	162.474	161.383	1.091	0.296	1	173.521	172.405	1.116	0.291
TNFα rs3093662	1	163.001	162.711	0.290	0.590	1	174.457	174.429	0.028	0.876
TNFα rs3093665	1	162.552	162.542	0.010	0.920	1	172.118	172.118	0.000	1.000

Abbreviation: Degrees of Freedom (df)

Table B-12: Haplotype Frequencies and Trait Test for Steatosis by Race

Haplotype	Single Nucleotide Polymorphisms	African Americans N = 167	Caucasian Americans N = 184
COL1A1	*rs2586485, rs2586494, rs7406586, rs2269336*		
CAAC		0.05	0.00
CCAC		0.07	0.02
CCAG		0.07	0.01
CCGC		0.16	0.17
CCGG		0.00	0.01
TAGG		0.03	0.10
TAAC		0.06	0.02
TCAC		0.19	0.18
TCAG		0.07	0.00
TCGC		0.22	0.48
TCGG		0.05	0.01
CYP2E1	*rs10857735, rs2070673, rs915908, rs2070676*		
AAGC		0.18	0.04
AAGG		0.22	0.01
CAGG		0.25	0.10
CTAC		0.03	0.11
CTGC		0.16	0.73
CTGG		0.15	0.00
IL6	*rs2056576, rs2069827, rs1800797, rs1800795, rs2069830, rs2069830, rs2069837, rs1554606, rs2069845*		
CGACCATG		0.03	0.27
CGGGCAGA		0.24	0.18
CGGGCATG		0.13	0.02
CGGGCGGA		0.10	0.06
CTACCATG		0.02	0.08
TGGGCAGA		0.23	0.34
TGGGCATG		0.11	0.01
TGGGTAGA		0.10	0.00

Table B-12 (Continued)			
IL10	*rs11119474, rs3024505, rs3024498, rs3024496, rs1554286, rs1800890, rs2222202*		
	ACACCTT	0.01	0.07
	GCACCCT	0.09	0.00
	GCACCTT	0.07	0.01
	GCATCCT	0.18	0.34
	GCATTCT	0.40	0.15
	GCGCCTA	0.09	0.26
	GTACCTA	0.06	0.14
IL1R1	*rs3917257, rs3917275, rs2110726, rs3917332, rs871656*		
	CAT	0.10	0.20
	CTA	0.20	0.19
	CTT	0.56	0.25
	TTT	0.09	0.35
LEPR	*rs6673324, rsS1137100, rs1343982, rs1137101, rs2376018*		
	AAAGA	0.12	0.00
	AAGAA	0.02	0.06
	AAGGA	0.08	0.18
	AAGGG	0.10	0.00
	AGAGA	0.18	0.26
	GAGAA	0.35	0.29
	GAGAG	0.05	0.16
	GAGGA	0.06	0.02
MCP1/CCL2	*rs1024611, rs3760396, rs2857657, rs4586, rs13900, rs991804*		
	CCCCTA	0.21	0.28
	TCCCCA	0.16	0.00
	TCCCCG	0.27	0.10
	TCCTCG	0.24	0.18
	TCGTCG	0.07	0.17
	TGCTCG	0.06	0.27

Table B-12 (Continued)			
MCP2/CCL8	*rs11575057, rs3138036, rs3138038*		
	CGC	0.05	0.15
	TAA	0.94	0.82
TGF-β1	*rs2278422, rs2241716, rs1800471*		
	CGG	0.28	0.43
	GGC	0.05	0.04
	GGG	0.60	0.52
TNFα	*rs3093662, rs3093665*		
	AA	0.91	0.92
	GA	0.05	0.07

Table B-13: Haplotype Frequencies by Presence of Steatosis and Trait Association Test by Race

Haplotype	Single Nucleotide Polymorphisms*	African Americans		Caucasian Americans	
		No Steatosis	Steatosis ≥ 5%	No Steatosis	Steatosis ≥ 5%
COL1A1	*rs2586485, rs2586494, rs7406586, rs2269336*				
CAAC		0.03	0.04	0.00	0.00
CCAC		0.03	0.09	0.01	0.03
CCAG		0.07	0.08	0.01	0.01
CCGC		0.24	0.13	0.15	0.18
CCGG		0.00	0.00	0.02	0.01
TAGG		0.05	0.03	0.10	0.10
TAAC		0.04	0.09	0.02	0.01
TCAC		0.17	0.20	0.25	0.15
TCAG		0.07	0.08	0.00	0.00
TCGC		0.23	0.19	0.45	0.49
TCGG		0.04	0.05	0.00	0.01
Trait Test		0.61		0.77	
CYP2E1	*rs10857735, rs2070673, rs915908, rs2070676*				
AAGC		0.20	0.17	0.00	0.05
AAGG		0.22	0.23	0.02	0.01
CAGG		0.22	0.29	0.08	0.12
CTAC		0.04	0.01	0.13	0.10
CTGC		0.21	0.13	0.76	0.71
CTGG		0.11	0.17	0.00	0.00
Trait Test		0.95		0.79	

Table B-13 (Continued)						
IL6	*rs2056576, rs2069827, rs1800797, rs1800795, rs2069830, rs2069830, rs2069837, rs1554606, rs2069845*					
CGACCATG		0.04		0.04	0.20	0.30
CGGGCAGA		0.24		0.25	0.19	0.17
CGGGCATG		0.13		0.13	0.02	0.01
CGGGCGGA		0.12		0.09	0.05	0.07
CTACCATG		0.03		0.01	0.09	0.07
TGGGCAGA		0.23		0.23	0.38	0.33
TGGGCATG		0.09		0.13	0.00	0.01
TGGGTAGA		0.09		0.10	0.00	0.00
Trait Test			1.00			1.00
IL10	*rs11119474, rs3024505, rs3024498, rs3024496, rs1554286, rs1800890, rs2222202*					
ACACCTT		0.00		0.01	0.11	0.06
GCACCCT		0.10		0.07	0.00	0.00
GCACCTT		0.11		0.04	0.00	0.01
GCATCCT		0.11		0.24	0.28	0.34
GCATTCT		0.41		0.44	0.15	0.16
GCGCCTA		0.09		0.07	0.24	0.27
GTACCTA		0.09		0.04	0.21	0.13
Trait Test			0.99			1.00
IL1R1	*rs3917257, rs3917275, rs2110726, rs3917332, rs871656*					
CAT		0.07		0.12	0.25	0.18
CTA		0.18		0.22	0.13	0.22
CTT		0.56		0.57	0.31	0.22
TTT		0.14		0.06	0.29	0.35
Trait Test			0.38			0.10

Table B-13 (Continued)						
LEPR	*rs6673324, rsS1137100, rs1343982, rs1137101, rs2376018*					
AAAGA		0.09		0.14	0.00	0.00
AAGAA		0.05		0.01	0.02	0.08
AAGGA		0.06		0.08	0.23	0.16
AAGGG		0.06		0.12	0.00	0.00
AGAGA		0.27		0.12	0.24	0.26
GAGAA		0.31		0.38	0.35	0.25
GAGAG		0.04		0.05	0.13	0.18
GAGGA		0.06		0.07	0.01	0.03
Trait Test			0.23			0.99
MCP1/CCL2	*rs1024611, rs3760396, rs2857657, rs4586, rs13900, rs991804*					
CCCCTA		0.25		0.17	0.29	0.31
TCCCCA		0.15		0.17	0.00	0.00
TCCCCG		0.28		0.27	0.11	0.09
TCCTCG		0.22		0.24	0.17	0.18
TCGTCG		0.06		0.07	0.16	0.17
TGCTCG		0.03		0.07	0.27	0.27
Trait Test			1.00			1.00
MCP2/CCL8	*rs11575057, rs3138036, rs3138038*					
CGC		0.07		0.04	0.14	0.14
TAA		0.91		0.96	0.82	0.83
Trait Test			0.87			0.91
TGF-β1	*rs2278422, rs2241716, rs1800471*					
CGG		0.33		0.23	0.43	0.42
GGC		0.00		0.06	0.05	0.04
GGG		0.56		0.65	0.52	0.53
Trait Test			0.03			0.89

Table B-13 (Continued)								
TNFα		*rs3093662, rs3093665*						
	AA		0.91		0.91	0.91		0.91
	GA		0.04		0.05	0.06		0.08
Trait Test				0.89			0.38	

* SNPs are listed in order that they appear in the haplotype and along the chromosome

Table B-14: Unadjusted Odds Ratios for Steatosis for Gene Haplotypes

Haplotype	African Americans N = 167				Caucasian Americans N = 184			
	N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
COL1A1								
CAAC	11	2.01	0.52-7.73	0.31	0	†		
CCAC	13	3.45	0.73-16.33	0.12	3	†		
CCAG	18	0.96	0.35-2.65	0.94	0	†		
CCGC	28	0.53	0.23-1.18	0.12	60	1.08	0.56-2.07	0.83
TAAC	14	2.24	0.59-8.52	0.24	6	†		
TAGG	7	0.42	0.11-1.66	0.22	37	0.83	0.39-1.76	0.63
TCAC	38	0.86	0.45-1.65	0.65	57	1.41	0.63-3.18	0.41
TCAG	14	1.47	0.43-5.00	0.54	0	†		
TCGC	45	0.71	0.34-1.50	0.37	132	1.81	0.92-3.59	0.09
TCGG	11	1.56	0.39-6.22	0.53	2	†		
CYP2E1								
AAGC	43	0.59	0.29-1.20	0.14	12	1.64	0.43-6.30	0.47
AAGG	52	1.45	0.72-2.90	0.30	3	†		
CAGG	64	2.07	1.05-4.09	0.04	33	1.61	0.70-3.70	0.27
CTAC	10	0.53	0.15-1.82	0.31	36	0.70	0.32-1.45	0.32
CTGC	36	0.57	0.27-1.21	0.15	163	1.38	0.42-4.54	0.60
CTGG	37	1.63	0.75-3.58	0.17	0	†		
IL6								
CGACCATG	12	0.99	0.31-3.19	0.99	86	1.79	0.96-3.37	0.07
CGGGCAGA	64	0.99	0.51-1.91	0.97	57	0.84	0.44-1.62	0.60
CGGGCATG	32	0.94	0.43-2.08	0.89	5	†		
CGGGCGGA	33	0.76	0.36-1.62	0.48	22	1.50	0.56-4.02	0.42
CTACCATG	6	†			28	0.74	0.32-1.70	0.48
TGGGCAGA	55	1.26	0.64-2.47	0.50	108	0.83	0.44-1.56	0.57
TGGGCATG	24	1.98	0.78-5.02	0.15	1	†		
TGGGTAGA	31	1.00	0.46-2.20	0.99	0	†		
IL10								
ACACCTT	2	†			27	0.60	0.26-1.38	0.23
GCACCCT	31	0.84	0.38-1.84	0.66	0	†		
GCACCTT	22	0.39	0.16-0.94	0.04	2	†		
GCATCCT	48	3.41	1.64-7.07	0.001	78	1.78	0.96-3.30	0.07
GCATTCT	105	1.04	0.56-1.96	0.89	51	1.24	0.63-2.48	0.53
GCGCCTA	32	0.81	0.38-1.76	0.60	79	0.91	0.49-1.68	0.78
GTACCTA	19	0.37	0.14-0.96	0.04	45	0.59	0.30-1.17	0.13
IL1R1								
CAT	24	1.50	0.60-3.70	0.38	66	0.79	0.42-1.49	0.46
CTA	55	1.19	0.62-2.29	0.61	64	1.68	0.86-3.28	0.13
CTT	125	0.91	0.40-2.07	0.81	75	0.65	0.35-1.22	0.18
TTT	31	0.44	0.20-0.95	0.04	110	1.70	0.91-3.18	0.09

Table B-14 (Continued)								
LEPR								
AAAGA	33	1.97	0.89-4.39	0.096	0	†		
AAGAA	7	†			22	3.76	1.07-13.25	0.04
AAGGA	22	1.36	0.55-3.36	0.50	63	0.81	0.43-1.53	0.52
AAGGG	34	1.92	0.83-4.42	0.13	0	†		
AGAGA	51	0.32	0.16-0.62	0.001	81	1.09	0.59-2.02	0.78
GAGAA	101	1.81	0.96-3.39	0.07	85	0.54	0.29-0.99	0.047
GAGAG	12	0.98	0.31-3.13	0.97	55	1.41	0.71-2.80	0.32
GAGGA	18	1.50	0.55-4.11	0.43	8	1.61	0.31-8.19	0.57
MCP1/CCL2								
CCCCTA	60	0.47	0.25-0.89	0.02	87	1.21	0.66-2.23	0.54
TCCCCA	49	1.32	0.67-2.62	0.43	0	†		
TCCCCG	49	0.93	0.51-1.72	0.83	32	0.98	0.44-2.19	0.97
TCCTCG	68	1.06	0.57-1.96	0.85	62	0.91	0.48-1.73	0.77
TCGTCG	21	1.52	0.59-3.90	0.39	58	1.74	0.88-3.47	0.11
TGCTCG	18	2.58	0.82-8.13	0.11	88	1.10	0.60-2.02	0.76
MCP2/CCL8								
CGC	16	0.68	0.25-1.86	0.46	49	0.89	0.45-1.75	0.73
TAA	165	§			178	0.31	0.04-2.65	0.29
TGF-β1								
CGG	75	0.43	0.23-0.83	0.01	129	1.16	0.60-2.24	0.67
GGG	137	2.61	0.99-6.91	0.05	143	0.96	0.46-1.99	0.91
GGC	11	6.45	0.81-51.70	0.08	18	1.04	0.37-2.91	0.95
TNFα								
AA	166	§			181	0.99	0.09-10.88	0.98
GA	16	1.29	0.46-3.58	0.64	22	1.43	0.53-3.86	0.48

† Haplotype not common enough in population to estimate the odds ratio
§ No variation in the haplotype in the population

Table B-15: Adjusted Odds Ratios for Steatosis for Haplotypes among African Americans and Caucasian Americans

	African Americans* N = 167				Caucasian Americans* N = 184			
Haplotype	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**
COL1A1								
CAAC	11	0.87	0.14-5.42	0.88	0	†		
CCAC	13	2.66	0.52-13.67	0.24	3	†		
CCAG	18	0.77	0.22-2.65	0.68	0	†		
CCGC	28	0.45	0.17-1.24	0.12	60	1.02	0.41-2.55	0.97
TAAC	14	2.22	0.41-12.05	0.36	6	0.55	0.06-5.13	0.60
TAGG	7	0.17	0.02-1.30	0.09	37	1.88	0.66-5.36	0.24
TCAC	38	2.01	0.67-6.03	0.21	57	0.86	0.36-2.04	0.74
TCAG	14	1.98	0.46-8.53	0.36	0	†		
TCGC	45	0.92	0.35-2.40	0.86	132	1.97	0.76-5.10	0.16
TCGG	11	1.42	0.31-6.53	0.66	2	†		
CYP2E1								
AAGC	43	0.95	0.39-2.34	0.91	12	1.27	0.13-12.03	0.84
AAGG	52	0.92	0.40-2.13	0.84	3	†		
CAGG	64	2.10	0.91-4.88	0.08	33	1.24	0.41-3.76	0.71
CTAC	10	0.39	0.06-2.73	0.34	36	0.96	0.35-2.64	0.94
CTGC	36	0.79	0.31-2.01	0.62	163	1.28	0.23-6.97	0.78
CTGG	37	1.33	0.50-3.50	0.57	0	†		
IL6								
CGACCATG	12	1.10	0.25-4.89	0.90	86	1.58	0.69-3.65	0.28
CGGGCAGA	64	1.51	0.66-3.45	0.33	57	0.78	0.33-1.84	0.57
CGGGCATG	32	1.09	0.43-2.78	0.85	5	†		
CGGGCGGA	33	0.75	0.29-1.93	0.55	22	0.85	0.20-3.58	0.83
CTACCATG	6	†			28	1.31	0.44-3.87	0.63
TGGGCAGA	55	1.20	0.52-2.79	0.67	108	0.69	0.29-1.63	0.40
TGGGCATG	24	1.35	0.44-4.14	0.60	1	†		
TGGGTAGA	31	0.87	0.33-2.30	0.77	0	†		
IL10								
ACACCTT	2	†			27	0.68	0.22-2.09	0.51
GCACCCT	31	0.74	0.27-2.01	0.55	0	†		
GCACCTT	22	0.31	0.10-0.98	0.046	2	†		
GCATCCT	48	2.03	0.83-5.01	0.12	78	1.95	0.78-4.79	0.14
GCATTCT	105	1.41	0.64-3.14	0.40	51	1.39	0.57-3.42	0.47
GCGCCTA	32	0.57	0.22-1.49	0.25	79	1.48	0.65-3.38	0.36
GTACCTA	19	0.36	0.11-1.23	0.10	45	0.48	0.20-1.16	0.11
IL1R1								
CAT	24	2.40	0.67-8.61	0.18	66	0.77	0.33-1.79	0.55
CTA	55	1.13	0.50-2.55	0.78	64	1.14	0.48-2.70	0.77
CTT	125	1.30	0.47-3.58	0.61	75	0.78	0.33-1.83	0.57
TTT	31	0.34	0.12-0.93	0.04	110	2.30	0.96-5.52	0.06

Table B-15 (Continued)								
LEPR								
AAAGA	33	5.30	1.57-17.84	0.01	0	†		
AAGAA	7	†			22	6.88	0.83-57.34	0.08
AAGGA	22	0.88	0.29-2.65	0.82	63	0.81	0.34-1.95	0.63
AAGGG	34	1.80	0.67-4.84	0.25	0	†		
AGAGA	51	0.20	0.09-0.47	0.001	81	1.01	0.44-2.32	0.98
GAGAA	101	2.10	0.95-4.67	0.07	85	0.82	0.34-1.96	0.66
GAGAG	12	0.73	0.23-4.25	0.99	55	1.61	0.64-4.08	0.31
GAGGA	18	1.81	0.49-6.63	0.37	8	†		
MCP1/CCL2								
CCCCTA	60	0.48	0.22-1.06	0.07	87	0.96	0.43-2.15	0.91
TCCCCA	49	1.29	0.56-2.98	0.57	0	†		
TCCCCG	49	1.06	0.52-2.19	0.87	32	0.89	0.31-2.58	0.83
TCCTCG	68	1.32	0.60-2.91	0.49	62	0.69	0.29-1.65	0.40
TCGTCG	21	1.39	0.43-4.51	0.58	58	1.51	0.59-3.87	0.39
TGCTCG	18	2.36	0.59-9.48	0.23	88	1.91	0.82-4.42	0.13
MCP2/CCL8								
CGC	16	0.44	0.12-1.58	0.21	49	1.27	0.49-3.32	0.63
TAA	165	§			178	0.12	0.01-2.01	0.14
TGF-β1								
CGG	75	0.18	0.07-0.46	0.0003	129	0.67	0.28-1.60	0.36
GGG	137	8.89	2.10-37.70	0.003	143	1.19	0.45-3.19	0.72
GGC	11	†			18	0.61	0.16-2.42	0.48
TNFα								
AA	166	§			181	1.47	0.10-21.995	0.78
GA	16	0.75	0.20-2.76	0.66	22	2.21	0.56-8.63	0.26

* Model adjusted for the haplotype, Ishak fibrosis score, weekly alcohol consumption, ln HOMA2-IR scores, $\log_{10}$ baseline viral level and body mass index

† Haplotype not common enough in population to estimate the odds ratio

§ No variation in the haplotype in the population

Table B-16: Haplotype Frequencies by Insulin Resistance Category and Trait Association Test by Race

		Homeostasis Model Assessment of Insulin Resistance			
		African Americans		Caucasian Americans	
Haplotype	Single Nucleotide Polymorphisms*	HOMA2-IR < 2	HOMA2-IR ≥ 2	HOMA2-IR < 2	HOMA2-IR ≥ 2
COL1A1	*rs2586485, rs2586494, rs7406586, rs2269336*				
CAAC		0.02	0.07	0.00	0.00
CCAC		0.05	0.10	0.01	0.00
CCAG		0.07	0.08	0.01	0.03
CCGC		0.18	0.17	0.15	0.00
TAAC		0.08	0.06	0.02	0.20
TAGG		0.03	0.05	0.12	0.04
TCAC		0.19	0.17	0.17	0.19
TCAG		0.09	0.05	0.00	0.00
TCGC		0.21	0.20	0.49	0.47
TCGG		0.05	0.05	0.01	0.00
Trait Test			0.89		0.45
CYP2E1	*rs10857735, rs2070673, rs915908, rs2070676*				
AAGC		0.17	0.19	0.06	0.02
AAGG		0.22	0.22	0.01	0.01
CAGG		0.26	0.27	0.09	0.14
CTAC		0.03	0.02	0.12	0.10
CTGC		0.18	0.13	0.75	0.68
CTGG		0.13	0.16	0.00	0.00
Trait Test			0.99		0.88
IL6	*rs2056576, rs2069827, rs1800797, rs1800795, rs2069830, rs2069830, rs2069837, rs1554606, rs2069845*				
CGACCATG		0.04	0.03	0.23	0.37
CGGGCAGA		0.28	0.19	0.19	0.17
CGGGCATG		0.11	0.16	0.01	0.05
CGGGCGGA		0.08	0.13	0.07	0.04
CTACCATG		0.01	0.03	0.09	0.05
TGGGCAGA		0.23	0.21	0.37	0.31

Table B-16 (Continued)						
IL6 (Continued)						
TGGGCATG		0.13		0.11	0.01	0.00
TGGGTAGA		0.11		0.08	0.00	0.00
Trait Test			1.00			1.00
IL10	*rs11119474, rs3024505, rs3024498, rs3024496, rs1554286, rs1800890, rs2222202*					
ACACCTT		0.00		0.02	0.08	0.06
GCACCCT		0.11		0.02	0.00	0.00
GCACCTT		0.08		0.05	0.00	0.01
GCATCCT		0.20		0.18	0.31	0.35
GCATTCT		0.40		0.45	0.18	0.11
GCGCCTA		0.06		0.11	0.24	0.29
GTACCTA		0.06		0.05	0.16	0.14
Trait Test			1.00			0.99
IL1R1	*rs3917257, rs3917275, rs2110726, rs3917332, rs871656*					
CAT		0.08		0.09	0.21	0.22
CTA		0.22		0.21	0.18	0.18
CTT		0.57		0.58	0.26	0.21
TTT		0.10		0.07	0.34	0.36
Trait Test			0.59			0.91
LEPR	*rs6673324, rsS1137100, rs1343982, rs1137101, rs2376018*					
AAAGA		0.11		0.13	0.00	0.00
AAGAA		0.01		0.02	0.07	0.06
AAGGA		0.07		0.10	0.17	0.19
AAGGG		0.09		0.09	0.00	0.00
AGAGA		0.18		0.20	0.23	0.28
GAGAA		0.40		0.30	0.32	0.24
GAGAG		0.04		0.06	0.17	0.16
GAGGA		0.04		0.07	0.02	0.04
Trait Test			0.99			0.99

Table B-16 (Continued)						
MCP1/CCL2	*rs1024611, rs3760396, rs2857657, rs4586, rs13900, rs991804*					
CCCCTA		0.22		0.18	0.27	0.37
TCCCCA		0.16		0.16	0.00	0.00
TCCCCG		0.28		0.27	0.11	0.05
TCCTCG		0.22		0.26	0.15	0.22
TCGTCG		0.07		0.07	0.17	0.15
TGCTCG		0.04		0.07	0.30	0.21
Trait Test			1.00			1.00
MCP2/CCL8	*rs11575057, rs3138036, rs3138038*					
CGC		0.05		0.04	0.16	0.12
TAA		0.93		0.96	0.81	0.89
Trait Test			0.80			0.54
TGF-β1	*rs2278422, rs2241716, rs1800471*					
CGG		0.26		0.30	0.37	0.53
GGC		0.08		0.01	0.03	0.07
GGG		0.59		0.61	0.58	0.40
Trait Test			0.008			0.03
TNFα	*rs3093662, rs3093665*					
AA		0.92		0.91	0.91	0.91
GA		0.04		0.06	0.07	0.09
Trait Test			0.79			0.04

* SNPs are listed in order that they appear in the haplotype and along the chromosome

Table B-17: Unadjusted Odds of Insulin Resistance for Gene Haplotypes among Virahep-C Study Patients

Single Nucleotide Polymorphism	African Americans N = 142				Caucasian Americans N = 156			
	N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
COL1A1								
CAAC	7	2.87	0.68-12.18	0.15	0	†		
CCAC	13	2.34	0.71-7.70	0.16	3	†		
CCAG	16	1.20	0.42-3.41	0.73	0	†		
CCGC	26	1.03	0.44-2.38	0.95	49	1.29	0.63-2.63	0.49
TAAC	11	1.11	0.32-3.88	0.88	5	†		
TAGG	6	1.34	0.32-5.68	0.69	29	0.36	0.13-1.01	0.05
TCAC	33	0.88	0.38-2.02	0.76	49	1.29	0.63-2.63	0.49
TCAG	12	0.40	0.10-1.56	0.19	0	†		
TCGC	37	0.75	0.34-1.67	0.48	110	1.08	0.50-2.32	0.85
TCGG	9	1.05	0.27-4.17	0.94	2	†		
CYP2E1								
AAGC	37	1.04	0.49-2.22	0.93	9	2.85	0.73-11.13	0.13
AAGG	47	1.23	0.60-2.51	0.58	3	†		
CAGG	58	1.54	0.76-3.11	0.23	29	1.86	0.82-4.23	0.14
CTAC	6	1.00	0.21-4.64	0.99	30	0.73	0.30-1.78	0.49
CTGC	31	0.58	0.25-1.33	0.20	129	0.69	0.31-0.58	0.58
CTGG	32	1.15	0.52-2.54	0.11	0	†		
IL6								
CGACCATG	10	0.67	0.19-2.42	0.55	75	2.81	1.40-5.63	0.004
CGGGCAGA	53	0.57	0.28-1.16	0.12	51	0.82	0.40-1.67	0.58
CGGGCATG	28	1.41	0.62-3.21	0.42	4	†		
CGGGCGGA	28	1.81	0.81-4.03	0.15	18	0.48	0.15-1.54	0.22
CTACCATG	5	†			24	0.47	0.16-1.33	0.15
TGGGCAGA	45	0.82	0.40-1.66	0.58	93	0.95	0.48-1.88	0.89
TGGGCATG	22	1.41	0.59-3.36	0.44	1	†		
TGGGTAGA	27	0.64	0.28-1.47	0.29	0	†		
IL10								
ACACCTT	2	†			23	0.67	0.25-1.81	0.43
GCACCCT	25	0.41	0.16-1.04	0.06	0	†		
GCACCTT	18	0.61	0.23-1.62	0.32	2	†		
GCATCCT	42	0.93	0.4-1.83	0.84	65	1.08	0.55-2.11	0.82
GCATTCT	93	0.90	0.46-1.78	0.77	46	0.51	0.23-1.10	0.09
GCGCCTA	25	1.82	0.77-4.27	0.17	69	1.42	0.73-2.77	0.31
GTACCTA	16	0.82	0.30-2.29	0.71	42	0.71	0.33-1.53	0.38
IL1R1								
CAT	17	1.06	0.39-2.86	0.91	59	0.91	0.46-1.82	0.80
CTA	51	0.91	0.46-1.80	0.78	53	1.08	0.53-2.17	0.84
CTT	108	1.33	0.54-3.29	0.53	62	0.72	0.36-1.43	0.34
TTT	25	0.64	0.26-1.56	0.33	93	1.19	0.60-2.36	0.63

Table B-17 (Continued)								
LEPR								
AAAGA	27	1.28	0.58-2.79	0.54	0	†		
AAGAA	5	†			19	0.90	0.32-2.53	0.85
AAGGA	20	1.39	0.57-3.39	0.47	52	1.17	0.58-2.35	0.66
AAGGG	28	1.26	0.56-2.88	0.58	0	†		
AGAGA	46	1.19	0.61-2.34	0.61	65	1.30	0.66-2.54	0.45
GAGAA	88	0.69	0.36-1.33	0.27	75	0.41	0.21-0.82	0.01
GAGAG	12	1.46	0.47-4.57	0.13	48	0.75	0.36-1.56	0.44
GAGGA	15	1.86	0.67-5.17	0.14	7	2.78	0.60-12.90	0.19
MCP1/CCL2								
CCCCTA	50	0.76	0.39-1.50	0.43	80	1.62	0.83-3.18	0.16
TCCCCA	43	0.90	0.44-1.83	0.77	0	†		
TCCCCG	43	0.98	0.51-1.61	0.93	26	0.42	0.16-1.12	0.09
TCCTCG	57	1.67	0.87-3.20	0.13	51	1.92	0.96-3.86	0.08
TCGTCG	17	0.87	0.33-2.31	0.78	46	0.99	0.47-2.01	0.93
TGCTCG	14	1.45	0.50-4.22	0.50	76	0.62	0.31-1.21	0.16
MCP2/CCL8								
CGC	13	0.65	0.21-2.05	0.47	41	0.54	0.24-1.22	0.14
TAA	140	1.65	0.61-4.44	0.32	151	1.53	0.80-2.93	0.20
TGF-β1								
CGG	66	1.67	0.85-3.27	0.14	110	3.12	1.33-7.31	0.009
GGG	116	0.26	0.08-0.87	0.03	122	0.50	0.23-1.07	0.08
GGC	8	0.16	0.02-1.33	0.09	16	1.66	0.58-4.74	0.34
TNFα								
AA	141	†			153	0.24	0.02-2.71	0.25
GA	12	1.68	0.55-5.11	0.36	20	1.10	0.41-2.95	0.85

† Haplotype not common enough in population to estimate the odds ratio
§ No variation in the haplotype in the population

Table B-18: Adjusted Odds Ratios for Insulin Resistance for Haplotypes among African Americans and Caucasian Americans

	African Americans* N = 142				Caucasian Americans* N = 156			
Haplotype	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**
COL1A1								
CAAC	7	4.83	0.82-28.29	0.08	0	†		
CCAC	13	2.63	0.70-9.91	0.15	3	†		
CCAG	16	1.05	0.29-3.76	0.95	0	†		
CCGC	26	0.61	0.20-1.90	0.39	49	1.05	0.48-2.31	0.90
TAAC	11	0.99	0.25-3.88	0.98	5	†		
TAGG	6	†			29	0.34	0.12-1.02	0.05
TCAC	33	0.66	0.22-1.93	0.44	49	1.19	0.54-2.62	0.68
TCAG	12	0.26	0.06-1.22	0.09	0	†		
TCGC	37	0.98	0.36-2.66	0.97	110	1.06	0.45-2.49	0.89
TCGG	9	1.46	0.31-6.79	0.63	2	†		
CYP2E1								
AAGC	37	1.31	0.53-3.22	0.56	9	2.11	0.46-9.61	0.34
AAGG	47	0.99	0.42-2.31	0.98	3	†		
CAGG	58	1.46	0.64-3.35	0.37	29	1.66	0.67-4.13	0.28
CTAC	6	0.25	0.02-3.63	0.25	30	0.65	0.24-1.72	0.38
CTGC	31	0.52	0.19-1.38	0.19	129	0.62	0.15-2.60	0.51
CTGG	32	1.32	0.53-3.28	0.55	0	†		
IL6								
CGACCATG	10	0.49	0.09-2.79	0.42	75	2.42	1.13-5.19	0.02
CGGGCAGA	53	0.65	0.28-1.50	0.31	51	1.01	0.47-2.18	0.99
CGGGCATG	28	1.91	0.75-4.91	0.18	4	†		
CGGGCGGA	28	2.07	0.77-5.56	0.15	18	0.27	0.07-1.03	0.06
CTACCATG	5	†			24	0.46	0.14-1.54	0.21
TGGGCAGA	45	0.65	0.27-1.53	0.32	93	1.10	0.52-2.32	0.80
TGGGCATG	22	0.82	0.28-2.39	0.72	1	†		
TGGGTAGA	27	0.59	0.21-1.62	0.30	0	†		
IL10								
ACACCTT	2	†			23	1.01	0.34-3.02	0.98
GCACCCT	25	0.60	0.21-1.70	0.34	0	†		
GCACCTT	18	0.59	0.17-2.02	0.40	2	†		
GCATCCT	42	0.79	0.34-1.82	0.58	65	0.64	0.28-1.42	0.27
GCATTCT	93	0.59	0.26-1.31	0.19	46	0.48	0.20-1.11	0.09
GCGCCTA	25	3.00	1.09-8.26	0.03	69	1.56	0.75-3.22	0.24
GTACCTA	16	0.86	0.25-2.97	0.81	42	1.14	0.49-2.68	0.76
IL1R1								
CAT	17	0.99	0.30-3.24	0.99	59	1.01	0.47-2.17	0.98
CTA	51	0.74	0.32-1.68	0.47	53	0.99	0.45-2.09	0.94
CTT	108	1.23	0.43-3.48	0.70	62	0.74	0.35-1.58	0.44
TTT	25	0.70	0.24-2.04	0.52	93	1.02	0.47-2.21	0.95

Table B-18 (Continued)

LEPR								
AAAGA	27	0.71	0.27-1.87	0.49	0	†		
AAGAA	5	1.25	0.17-9.00	0.83	19	0.74	0.25-2.23	0.59
AAGGA	20	1.00	0.33-3.05	0.99	52	1.01	0.46-2.22	0.97
AAGGG	28	1.35	0.53-3.45	0.53	0	†		
AGAGA	46	1.67	0.71-3.95	0.24	65	1.35	0.65-2.81	0.43
GAGAA	88	0.72	0.33-1.59	0.42	75	0.51	0.22-1.09	0.08
GAGAG	12	1.29	0.34-4.85	0.71	48	0.56	0.24-1.30	0.18
GAGGA	15	1.54	0.43-5.54	0.51	7	3.29	0.63-17.24	0.16
MCP1/CCL2								
CCCCTA	50	0.97	0.44-2.13	0.93	80	1.23	0.59-2.60	0.58
TCCCCA	43	0.99	0.43-2.27	0.98	0	†		
TCCCCG	43	0.95	0.47-1.91	0.88	26	0.31	0.10-1.02	0.05
TCCTCG	57	1.62	0.75-3.51	0.22	51	2.15	0.99-4.67	0.053
TCGTCG	17	0.72	0.22-2.34	0.58	46	0.86	0.39-1.91	0.71
TGCTCG	14	1.40	0.41-4.83	0.60	76	0.61	0.29-1.27	0.18
MCP2/CCL8								
CGC	13	0.69	0.18-2.65	0.59	41	0.59	0.24-1.45	0.25
TAA	140	§			151	1.27	0.11-14.89	0.85
TGF-β1								
CGG	66	2.43	1.01-5.84	0.047	110	3.09	1.24-7.71	0.02
GGG	116	0.13	0.03-0.52	0.004	122	0.50	0.21-1.16	0.10
GGC	8	0.16	0.02-1.48	0.11	16	1.32	0.42-4.12	0.63
TNFα								
AA	141	§			153	0.18	0.01-2.32	0.17
GA	12	1.94	0.52-7.29	0.33	20	1.12	0.35-3.62	0.84

Comparison of having one or more copies of a haplotype compared to no copies of the haplotype
* Model adjusted for the haplotype, Ishak fibrosis score, body mass index, steatosis, age and triglyceride levels
† Haplotype not common enough in population to estimate the odds ratio
§ No variation in the haplotype in the population
Abbreviation: 95% Confidence Interval (Confidence Interval)

Table B-19a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL10 rs2222202* Genotypes in Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	CC: 8 CT: 21 TT: 12	CC: 16 CT: 32 TT: 15	CC: 24 CT: 53 TT: 27
	HOMA2-IR ≥ 2	CC: 2 CT: 2 TT: 6	CC: 11 CT: 20 TT: 11	CC: 13 CT: 22 TT: 17
	Column Total	CC: 10 CT: 23 TT: 18	CC: 27 CT: 52 TT: 26	TOTAL CC: 37 CT: 75 TT: 44

Table B-19b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL10 rs2222202* Genotypes in African Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	CC: 17 CT: 22 TT: 1	CC: 24 CT: 17 TT: 2	CC: 41 CT: 39 TT: 3
	HOMA2-IR ≥ 2	CC: 5 CT: 4 TT: 6	CC: 28 CT: 14 TT: 2	CC: 33 CT: 18 TT: 8
	Column Total	CC: 22 CT: 26 TT: 7	CC: 52 CT: 31 TT: 4	TOTAL CC: 74 CT: 57 TT: 11

Table B-20a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL10 rs1800890* Genotypes in Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 6 AT: 23 TT: 12	AA: 6 AT: 33 TT: 23	AA: 12 AT: 56 TT: 35
	HOMA2-IR ≥ 2	AA: 3 AT: 4 TT: 3	AA: 9 AT: 18 TT: 15	AA: 12 AT: 22 TT: 18
	Column Total	AA: 10 AT: 27 TT: 15	AA: 27 AT: 51 TT: 38	TOTAL AA: 24 AT: 78 TT: 53

Table B-20b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL10 rs1800890* Genotypes in African Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 2 AT: 14 TT: 24	AA: 0 AT: 12 TT: 31	AA: 2 AT: 26 TT: 55
	HOMA2-IR ≥ 2	AA: 2 AT: 6 TT: 7	AA: 3 AT: 16 TT: 25	AA: 5 AT: 22 TT: 32
	Column Total	AA: 4 AT: 20 TT: 31	AA: 3 AT: 28 TT: 56	TOTAL AA: 7 AT: 48 TT: 87

Table B-21a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs6673324* Genotypes in Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 9 AG: 21 GG: 11	AA: 12 AG: 37 GG: 12	AA: 21 AG: 58 GG: 23
	HOMA2-IR ≥ 2	AA: 4 AG: 4 GG: 2	AA: 16 AG: 14 GG: 12	AA: 20 AG: 18 GG: 14
	Column Total	AA: 13 AG: 25 GG: 13	AA: 28 AG: 51 GG: 24	TOTAL AA: 41 AG: 76 GG: 37

Table B-21b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs6673324* Genotypes in African Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 11 AG: 19 GG: 10	AA: 9 AG: 26 GG: 8	AA: 20 AG: 45 GG: 18
	HOMA2-IR ≥ 2	AA: 6 AG: 8 GG: 1	AA: 7 AG: 28 GG: 9	AA: 13 AG: 36 GG: 10
	Column Total	AA: 17 AG: 27 GG: 11	AA: 16 AG: 54 GG: 17	TOTAL AA: 33 AG: 81 GG: 28

Table B-22a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs1137100* Genotypes in Caucasian Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 25 AG: 13 GG: 3	AA: 36 AG: 22 GG: 4	AA: 61 AG: 35 GG: 7
HOMA2-IR ≥ 2	AA: 4 AG: 5 GG: 1	AA: 23 AG: 14 GG: 5	AA: 27 AG: 19 GG: 6
Column Total	AA: 29 AG: 18 GG: 4	AA: 59 AG: 36 GG: 9	TOTAL AA: 88 AG: 54 GG: 13

Table B-22b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs1137100* Genotypes in African Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 21 AG: 16 GG: 3	AA: 34 AG: 9 GG: 0	AA: 55 AG: 25 GG: 3
HOMA2-IR ≥ 2	AA: 6 AG: 7 GG: 2	AA: 32 AG: 11 GG: 1	AA: 38 AG: 18 GG: 3
Column Total	AA: 27 AG: 23 GG: 5	AA: 66 AG: 20 GG: 1	TOTAL AA: 93 AG: 43 GG: 6

Table B-23a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs1892534* Genotypes in Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 5 AG: 18 GG: 18	AA: 17 AG: 23 GG: 22	AA: 22 AG: 41 GG: 40
	HOMA2-IR ≥ 2	AA: 3 AG: 0 GG: 7	AA: 11 AG: 16 GG: 15	AA: 14 AG: 16 GG: 22
	Column Total	AA: 8 AG: 18 GG: 25	AA: 28 AG: 39 GG: 37	TOTAL AA: 36 AG: 57 GG: 62

Table B-23b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *LEPR rs1892534* Genotypes in African Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 10 AG: 19 GG: 11	AA: 5 AG: 26 GG: 12	AA: 15 AG: 45 GG: 23
	HOMA2-IR ≥ 2	AA: 4 AG: 4 GG: 7	AA: 12 AG: 19 GG: 13	AA: 16 AG: 23 GG: 20
	Column Total	AA: 14 AG: 23 GG: 18	AA: 17 AG: 45 GG: 25	TOTAL AA: 31 AG: 68 GG: 43

Table B-24a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *TGF-β1 rs2278422* Genotypes in Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	CC: 6 CG: 21 GG: 14	CC: 6 CG: 34 GG: 23	CC: 12 CG: 55 GG: 37
	HOMA2-IR ≥ 2	CC: 2 CG: 7 GG: 1	CC: 9 CG: 26 GG: 7	CC: 11 CG: 33 GG: 8
	Column Total	CC: 8 CG: 28 GG: 15	CC: 15 CG: 60 GG: 30	TOTAL CC: 28 CG: 88 GG: 45

Table B-24b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *TGF-β1 rs2278422* Genotypes in African Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	CC: 3 CG: 23 GG: 14	CC: 0 CG: 14 GG: 29	CC: 3 CG: 37 GG: 43
	HOMA2-IR ≥ 2	CC: 3 CG: 9 GG: 3	CC: 4 CG: 20 GG: 20	CC: 7 CG: 29 GG: 23
	Column Total	CC: 6 CG: 32 GG: 17	CC: 4 CG: 34 GG: 49	TOTAL CC: 10 CG: 66 GG: 66

Table B-25a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL6 rs2069845* Genotypes in Caucasian Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 22 AG: 14 GG: 5	AA: 18 AG: 37 GG: 7	AA: 40 AG: 51 GG: 12
HOMA2-IR ≥ 2	AA: 3 AG: 5 GG: 2	AA: 9 AG: 36 GG: 7	AA: 12 AG: 51 GG: 9
Column Total	AA: 25 AG: 19 GG: 7	AA: 27 AG: 63 GG: 14	TOTAL AA: 52 AG: 82 GG: 21

Table B-25b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *IL6 rs2069845* Genotypes in African Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 19 AG: 17 GG: 4	AA: 22 AG: 18 GG: 3	AA: 41 AG: 35 GG: 7
HOMA2-IR ≥ 2	AA: 6 AG: 7 GG: 2	AA: 16 AG: 21 GG: 7	AA: 22 AG: 28 GG: 9
Column Total	AA: 25 AG: 24 GG: 6	AA: 38 AG: 39 GG: 10	TOTAL AA: 63 AG: 63 GG: 16

Table B-26: Amount of CommonVariation in Each Gene Accounted for by Selected Single Nucleotide Polymorphisms Using Different Methods

SNP Selection Method: Haplotype Block Method **Minor Allele Frequency: 10%**								
			African Americans			**Caucasian Americans**		
Gene	**Virahep-C SNPs**	**Virahep-C SNPs in High LD**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation Covered**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation Covered**
IL6	9	2	15	4	26%	13	10	76%
IL10	7	1	14	12	85%	16	13	81%
TGF-β1	3	1	9	1	11%	13	1	7%
TNF-a	3	0	18	4	22%	15	3	20%
AVERAGE	**22**		**56**	**21**	**38%**	**57**	**27**	**47%**
SNP Selection Method: Two Stage Tagging **Minor Allele Frequency: 5%**								
			African Americans			**Caucasian Americans**		
Gene	**Virahep-C SNPs**	**Virahep-C SNPs in High LD**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation Covered**
COL1A1	4	0	21	5	23%	20	14	70%
CYP2E1	4	1	44	7	15%	32	9	28%
IL1R1	5	0	48	2	4%	48	8	16%
LEPR	7	2	234	51	21%	220	89	40%
MCP1	7	2	10	4	40%	6	5	83%
MCP2	3	3	6	0	0%	18	8	44%
AVERAGE	**30**		**363**	**69**	**19%**	**344**	**133**	**39%**

Abbreviations: Linkage Disequilibrium (LD)

APPENDIX C

SUPPLEMENTARY TABLES AND FIGURES

FOR CHAPTER 5

C.1 A POLYMORPHISMS IN *ADIPONECTIN RECEPTOR 1* (*ADIPOR1*) AND *3-HYDROXY-3-METHYLGLUTARYL-COENZYME A SYNTHASE 2* (*HMGCS2*) AND STEATOSIS AND INSULIN RESISTANCE IN HEPATITIS C VIRUS GENOTYPE-1 INFECTION

Table C-1: Genotype Frequencies for *ADIPOR1* and *HMGCS2* Single Nucleotide Polymorphisms and Association with Steatosis in African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans N = 163 No Steatosis	African Americans N = 163 Steatosis ≥ 5%	African Americans p-value*	Caucasian Americans N = 179 No Steatosis	Caucasian Americans N = 179 Steatosis ≥ 5%	Caucasian Americans p-value*
ADIPOR1 rs10753929						
CC	0.66	0.61		0.79	0.85	
CT	0.29	0.37		0.21	0.15	
TT	0.05	0.02	0.41	0.0	0.0	0.31
ADIPOR1 rs10920531						
AA	0.22	0.24		0.44	0.31	
AC	0.45	0.51		0.46	0.58	
CC	0.34	0.26	0.51	0.10	0.12	0.20
ADIPOR1 rs12045862						
CC	0.86	0.78		0.53	0.53	
CT	0.14	0.22		0.42	0.41	
TT	0.0	0.01	0.32	0.05	0.07	0.90
ADIPOR1 rs12733285						
CC	0.64	0.70		0.55	0.44	
CT	0.28	0.25		0.36	0.43	
TT	0.08	0.05	0.67	0.09	0.13	0.38
ADIPOR1 rs1342387						
AA	0.28	0.22		0.17	0.22	
AG	0.42	0.52		0.44	0.47	
GG	0.30	0.26	0.49	0.39	0.31	0.50
ADIPOR1 rs1539355						
AA	0.29	0.28		0.43	0.48	
AG	0.45	0.52		0.41	0.45	
GG	0.26	0.20	0.66	0.16	0.07	0.20
ADIPOR1 rs16850799						
AA	0.89	0.86		0.59	0.55	
AG	0.11	0.14		0.37	0.40	
GG	0.0	0.0	0.51	0.03	0.05	0.80
ADIPOR1 rs2275736						
AA	0.08	0.07		0.0	0.0	
AT	0.28	0.29		0.02	0.04	
TT	0.65	0.64	0.96	0.98	0.96	0.38
ADIPOR1 rs4336908						
AA	0.89	0.86		0.63	0.59	
AG	0.11	0.13		0.33	0.39	
GG	0.0	0.01	0.63	0.03	0.03	0.75
ADIPOR1 rs6666089						
AA	0.76	0.77		0.44	0.50	
AG	0.21	0.20		0.39	0.43	
GG	0.03	0.03	0.98	0.17	0.07	0.11
ADIPOR1 rs7514221						
CC	0.37	0.31		0.40	0.33	
CT	0.43	0.55		0.43	0.48	
TT	0.19	0.14	0.33	0.17	0.19	0.68

Table C-1 (Continued)						
ADIPOR1 rs7539542						
CC	0.19	0.16		0.51	0.39	
CG	0.42	0.49		0.42	0.54	
GG	0.40	0.36	0.67	0.07	0.08	0.30
HMGCS2 rs12123085						
AA	0.80	0.75		0.80	0.77	
AG	0.18	0.23		0.20	0.22	
GG	0.02	0.02	0.74	0.0	0.02	0.57
HMGCS2 rs12563433						
CC	0.72	0.73		0.48	0.36	
CT	0.27	0.26		0.44	0.50	
TT	0.02	0.01	0.94	0.09	0.14	0.31
HMGCS2 rs1441008						
CC	0.0	0.01		0.14	0.09	
CT	0.23	0.14		0.41	0.45	
TT	0.77	0.85	0.22	0.46	0.47	0.56
HMGCS2 rs1441010						
AA	0.18	0.23		0.27	0.42	
AG	0.50	0.49		0.54	0.42	
GG	0.32	0.28	0.71	0.19	0.16	0.17
HMGCS2 rs2241868						
CC	0.89	0.83		0.83	0.85	
CT	0.11	0.16		0.17	0.15	
TT	0.0	0.01	0.46	0.0	0.0	0.81
HMGCS2 rs3790693						
AA	0.06	0.06		0.12	0.15	
AT	0.36	0.36		0.51	0.42	
TT	0.58	0.58	0.99	0.37	0.42	0.55
HMGCS2 rs4659233						
AA	0.03	0.04		0.0	0.02	
AT	0.25	0.28		0.24	0.22	
TT	0.72	0.68	0.84	0.76	0.77	0.58
HMGCS2 rs536662						
AA	0.42	0.45		0.27	0.22	
AG	0.46	0.42		0.54	0.47	
GG	0.12	0.14	0.84	0.19	0.31	0.20
HMGCS2 rs619167						
AA	0.48	0.51		0.27	0.22	
AG	0.42	0.43		0.55	0.45	
GG	0.11	0.07	0.66	0.18	0.33	0.12
HMGCS2 rs649733						
AA	0.57	0.59		0.42	0.59	
AG	0.37	0.37		0.48	0.34	
GG	0.06	0.04	0.79	0.10	0.07	0.10
HMGCS2 rs667226						
CC	0.83	0.85		0.68	0.67	
CT	0.15	0.15		0.30	0.32	
TT	0.02	0.0	0.45	0.02	0.02	0.98

* P-value based on genotype association chi square test

† Chi Square could not be estimated

Table C-2: Unadjusted Odd Ratios for Steatosis for Single Nucleotide Polymorphisms

	African Americans N = 163				Caucasian Americans N = 179			
Single Nucleotide Polymorphism	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
ADIPOR1 rs10753929								
CC	106	1.00			145	1.00		
CT/TT	62	1.24	0.65-2.37	0.51	29	0.66	0.29-1.49	0.32
ADIPOR1 rs10920531								
AA	38	1.00			62	1.00		
AC	81	1.05	0.47-2.33	0.91	95	1.82	0.93-3.57	0.08
CC	48	0.69	0.29-1.65	0.40	20	1.69	0.57-4.97	0.34
ADIPOR1 rs12045862								
CC	135	1.00			93	1.00		
CT/TT	32	1.81	0.78-4.21	0.17	84	1.00	0.54-1.87	0.99
ADIPOR1 rs12733285								
CC	110	1.00			84	1.00		
CT	43	0.83	0.40-1.69	0.60	71	1.47	0.75-2.87	0.27
TT	10	0.59	0.16-2.18	0.43	20	1.85	0.61-5.57	0.28
ADIPOR1 rs1342387								
AA	41	1.00			36	1.00		
AG	80	1.54	0.71-3.23	0.28	81	0.81	0.34-1.93	0.64
GG	46	1.11	0.48-2.61	0.81	59	0.60	0.25-1.48	0.27
ADIPOR1 rs1539355								
AA	47	1.00			80	1.00		
AG	81	1.18	0.56-2.48	0.67	76	0.99	0.50-1.94	0.97
GG	37	0.82	0.34-1.96	0.65	17	0.40	0.14-1.17	0.10
ADIPOR1 rs16850799								
AA	148	1.00			100	1.00		
AG/GG	22	1.38	0.53-3.59	0.51	77	1.19	0.63-2.24	0.59
ADIPOR1 rs2275736								
AA/AT	60	1.00			6	1.00		
TT	108	0.98	0.51-1.87	0.94	171	0.39	0.04-3.41	0.40
ADIPOR1 rs4336908								
AA	149	1.00			107	1.00		
AG/GG	22	1.41	0.54-3.62	0.49	71	1.23	0.65-2.33	0.53
ADIPOR1 rs6666089								
AA	131	1.00			85	1.00		
AG or AG/GG	35	0.93	0.43-1.99	0.84	74	0.98	0.50-1.92	0.95
GG	5	0.93	0.15-5.74	0.93	18	0.35	0.13-1.00	0.049
ADIPOR1 rs7514221								
CC	57	1.00			64	1.00		
CT	86	1.54	0.77-3.06	0.22	83	1.32	0.66-2.61	0.43
TT	28	0.90	0.36-2.24	0.82	33	1.38	0.56-3.39	0.48
ADIPOR1 rs7539542								
CC	28	1.00			76	1.00		
CG	77	1.39	0.57-3.36	0.47	89	1.67	0.87-3.21	0.12
GG	63	1.07	0.43-2.63	0.89	13	1.47	0.41-5.20	0.55

Table C-2 (Continued)								
HMGCS2 rs12123085								
AA	132	1.00			140	1.00		
AG/GG	39	1.34	0.63-2.84	0.44	40	1.22	0.57-2.61	0.61
HMGCS2 rs12563433								
CC	122	1.00			75	1.00		
CT	44	0.96	0.47-1.95	0.91	85	1.49	0.76-2.87	0.25
TT	2	0.61	0.04-9.91	0.73	21	2.08	0.69-6.33	0.20
HMGCS2 rs1441008								
CC	1	1.00			18	1.00		
CT	29				77	1.77	0.62-5.04	0.29
TT	138	1.76	0.79-3.90	0.16	82	1.63	0.58-4.60	0.36
HMGCS2 rs1441010								
AA	36	1.00			65	1.00		
AG	83	0.76	0.33-1.72	0.51	82	0.51	0.25-1.05	0.07
GG	50	0.69	0.28-1.69	0.42	30	0.56	0.22-1.43	0.23
HMGCS2 rs2241868								
CC	142	1.00			150	1.00		
CT/TT	24	1.68	0.65-4.30	0.28	28	0.90	0.39-2.09	0.81
HMGCS2 rs3790693								
AA	10	1.00			25	1.00		
AT	61	1.03	0.26-4.03	0.97	80	0.65	0.24-1.73	0.39
TT	98	1.05	0.28-3.98	0.94	72	0.88	0.32-2.42	0.81
HMGCS2 rs4659233								
AA/AT	50	1.00			41	1.00		
TT	113	0.82	0.41-1.63	0.57	133	1.01	0.48-2.12	0.97
HMGCS2 rs536662								
AA	74	1.00			42	1.00		
AG	74	0.84	0.44-1.63	0.62	87	1.06	0.50-2.27	0.89
GG	22	1.07	0.40-2.86	0.90	48	2.07	0.83-5.18	0.12
HMGCS2 rs619167								
AA	83	1.00			42	1.00		
AG	71	0.97	0.51-1.87	0.93	86	0.99	0.46-2.11	0.98
GG	14	0.60	0.19-1.86	0.37	50	2.18	0.88-5.44	0.09
HMGCS2 rs649733								
AA	98	1.00			95	1.00		
AG/GG	70	0.91	0.49-1.71	0.77	82	0.50	0.27-0.95	0.03
HMGCS2 rs667226								
CC	141	1.00			119	1.00		
CT/TT	26	0.85	0.36-1.98	0.70	58	1.08	0.55-2.10	0.82

† Minor allele frequency less then 5% in one population

Table C-3: Log Likelihood Ratio Test of the Significance of the Interaction Term Between Natural Log Transformed HOMA2-IR Scores and the Genetic Variant in the Prediction of Steatosis

	African Americans					Caucasian Americans				
	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value
ADIPOR1 rs10753929	1	154.505	154.502	0.003	0.960	1	128.176	126.176	2.000	0.157
ADIPOR1 rs10920531	2	153.166	151.506	1.660	0.436	2	132.502	129.117	3.385	0.184
ADIPOR1 rs12045862	1	151.201	150.841	0.360	0.549	1	135.408	135.250	0.158	0.691
ADIPOR1 rs12733285	2	150.598	148.693	1.905	0.386	2	130.503	126.264	4.239	0.120
ADIPOR1 rs1342387	2	150.762	148.360	2.402	0.301	2	132.659	130.286	2.373	0.305
ADIPOR1 rs1539355	2	150.215	149.549	0.666	0.305	2	126.322	119.720	6.602	0.037
ADIPOR1 rs16850799	1	155.855	155.790	0.065	0.799	1	135.156	135.139	0.017	0.896
ADIPOR1 rs2275736	1	155.173	153.861	1.312	0.252	1	135.122	131.201	3.921	n=6
ADIPOR1 rs4336908	1	156.129	156.057	0.072	0.788	1	135.920	135.727	0.193	0.660
ADIPOR1 rs6666089	1	155.941	156.057	-0.116	0.733	2	126.314	113.276	13.038	0.001
ADIPOR1 rs7514221	2	153.833	153.304	0.529	0.768	2	135.142	131.197	3.945	0.139
ADIPOR1 rs7539542	2	155.145	152.179	2.966	0.227	2	131.121	130.716	0.405	0.817
HMGCS2 rs12123085	1	149.614	149.585	0.029	0.865	1	136.133	135.854	0.279	0.597
HMGCS2 rs12563433	1	154.467	153.309	1.158	0.282	2	135.023	134.665	0.358	0.836
HMGCS2 rs1441008	1	153.845	153.178	0.667	0.414	1	133.736	133.556	0.180	0.109
HMGCS2 rs1441010	2	151.615	151.371	0.244	0.855	2	132.729	132.227	0.502	0.778
HMGCS2 rs2241868	1	152.597	151.637	0.960	0.327	1	135.273	129.412	5.861	no est
HMGCS2 rs3790693	1	152.192	148.951	3.241	0.072	2	134.582	131.131	3.451	0.178
HMGCS2 rs4659233	1	149.165	147.886	1.279	0.258	1	132.198	131.949	0.249	0.618
HMGCS2 rs536662	2	152.107	152.035	0.072	0.965	2	130.627	129.622	1.005	0.605
HMGCS2 rs619167	2	151.699	150.077	1.622	0.444	2	131.244	130.355	0.889	0.641
HMGCS2 rs649733	1	155.288	155.092	0.196	0.658	1	133.915	133.509	0.406	0.524
HMGCS2 rs667226	1	150.238	148.838	1.400	0.237	1	134.688	132.912	1.776	0.183
HMGCS2 rs667246	2	148.282	146.987	1.295	0.523	2	134.988	134.387	0.601	0.740

Abbreviations: Degrees of Freedom (df)

Table C-4: Genotype Frequencies for *ADIPOR1* and *HMGCS2* Single Nucleotide Polymorphisms and Association with Insulin Resistance among African Americans and Caucasian Americans

Single Nucleotide Polymorphism	African Americans N = 138 HOMA2-IR < 2	African Americans N = 138 HOMA2-IR ≥ 2	p-value*	Caucasian Americans N = 152 HOMA2-IR < 2	Caucasian Americans N = 152 HOMA2-IR ≥ 2	p-value*
ADIPOR1 rs10753929						
CC	0.62	0.65		0.81	0.84	
CT	0.37	0.29		0.19	0.16	
TT	0.01	0.06	0.17	0.0	0.0	0.67
ADIPOR1 rs10920531						
AA	0.19	0.26		0.37	0.35	
AC	0.49	0.52		0.55	0.55	
CC	0.32	0.23	0.36	0.09	0.10	0.95
ADIPOR1 rs12045862						
CC	0.78	0.82		0.55	0.52	
CT	0.21	0.18		0.38	0.44	
TT	0.01	0.0	0.59	0.08	0.04	0.56
ADIPOR1 rs12733285						
CC	0.70	0.67		0.50	0.48	
CT	0.25	0.26		0.40	0.40	
TT	0.05	0.07	0.86	0.10	0.13	0.90
ADIPOR1 rs1342387						
AA	0.22	0.25		0.21	0.21	
AG	0.48	0.48		0.46	0.46	
GG	0.30	0.27	0.83	0.34	0.33	0.99
ADIPOR1 rs1539355						
AA	0.29	0.31		0.46	0.46	
AG	0.49	0.43		*0.46*	0.42	
GG	0.23	0.26	0.76	0.09	0.13	0.79
ADIPOR1 rs16850799						
AA	0.83	0.91		0.57	0.59	
AG	0.17	0.09		0.37	0.39	
GG	0.0	0.0	0.16	0.06	0.02	0.57
ADIPOR1 rs2275736						
AA	0.09	0.06		0.0	0.0	
AT	0.30	0.24		0.01	0.10	
TT	0.62	0.70	0.59	0.99	0.90	0.007
ADIPOR1 rs4336908						
AA	0.87	0.86		0.62	0.61	
AG	0.12	0.14		0.35	0.37	
GG	0.01	0.0	0.65	0.03	0.02	0.94
ADIPOR1 rs6666089						
AA	0.76	0.74		0.45	0.52	
AG	0.23	0.20		0.45	0.35	
GG	0.01	0.06	0.25	0.10	0.13	0.53
ADIPOR1 rs7514221						
CC	0.35	0.33		0.36	0.36	
CT	0.51	0.47		0.45	0.48	
TT	0.13	0.20	0.54	0.19	0.16	0.86

Table C-4 (Continued)						
ADIPOR1 rs7539542						
CC	0.14	0.19		0.45	0.45	
CG	0.44	0.49		0.49	0.47	
GG	0.42	0.32	0.40	0.06	0.08	0.87
HMGCS2 rs12123085						
AA	0.78	0.77		0.75	0.88	
AG	0.20	0.22		0.24	0.12	
GG	0.03	0.02	0.90	0.01	0.0	0.16
HMGCS2 rs12563433						
CC	0.75	0.75		0.38	0.35	
CT	0.25	0.22		0.53	0.45	
TT	0.0	0.03	0.27	0.10	0.20	0.20
HMGCS2 rs1441008						
CC	0.0	0.02		0.09	0.04	
CT	0.21	0.14		0.43	0.51	
TT	0.79	0.84	0.32	0.49	0.45	0.44
HMGCS2 rs1441010						
AA	0.26	0.19		0.36	0.47	
AG	0.44	0.52		0.51	0.37	
GG	0.30	0.30	0.55	0.14	0.16	0.28
HMGCS2 rs2241868						
CC	0.81	0.87		0.85	0.84	
CT	0.19	0.11		0.15	0.16	
TT	0.0	0.02	0.26	0.0	0.0	0.80
HMGCS2 rs3790693						
AA	0.03	0.09		0.11	0.12	
AT	0.39	0.33		0.52	0.37	
TT	0.59	0.58	0.19	0.38	0.51	0.22
HMGCS2 rs4659233						
AA	0.04	0.05		0.01	0.0	
AT	0.23	0.28		0.25	0.17	
TT	0.73	0.67	0.75	0.74	0.83	0.40
HMGCS2 rs536662						
AA	0.44	0.47		0.23	0.18	
AG	0.42	0.39		0.48	0.51	
GG	0.14	0.14	0.94	0.30	0.31	0.82
HMGCS2 rs619167						
AA	0.49	0.54		0.23	0.18	
AG	0.42	0.38		0.47	0.49	
GG	0.09	0.08	0.86	0.30	0.33	0.84
HMGCS2 rs649733						
AA	0.61	0.59		0.56	0.53	
AG	0.33	0.37		0.36	0.45	
GG	0.06	0.05	0.88	0.08	0.02	0.26
HMGCS2 rs667226						
CC	0.83	0.91		0.66	0.69	
CT	0.16	0.09		0.33	0.29	
TT	0.01	0.0	0.31	0.01	0.02	0.77

* P-value based on genotype association chi square test

† Chi Square could not be estimated

Table C-5: Unadjusted Odds Ratios for Insulin Resistance for Single Nucleotide Polymorphisms

Single Nucleotide Polymorphism	African Americans N = 138				Caucasian Americans N = 152			
	N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
ADIPOR1 rs10753929								
CC	91	1.00			121	1.00		
CT/TT	53	0.87	0.44-1.72	0.68	27	0.82	0.33-2.04	0.67
ADIPOR1 rs10920531								
AA	31	1.00			54	1.00		
AC	72	0.50	0.32-1.74	0.50	82	1.07	0.51-2.23	0.86
CC	40	0.16	0.19-1.32	0.16	14	1.21	0.35-4.16	0.76
ADIPOR1 rs12045862								
CC	114	1.00			81	1.00		
CT/TT	29	0.76	0.33-1.74	0.51	70	1.10	0.56-2.18	0.78
ADIPOR1 rs12733285								
CC	96	1.00			73	1.00		
CT	35	1.10	0.50-2.40	0.82	59	1.03	0.50-2.16	0.93
TT	8	1.46	0.35-6.20	0.61	16	1.30	0.42-4.02	0.64
ADIPOR1 rs1342387								
AA	33	1.00			31	1.00		
AG	69	0.87	0.38-1.99	0.74	68	1.00	0.41-2.49	0.99
GG	41	0.75	0.30-1.89	0.55	50	0.99	0.38-2.58	0.98
ADIPOR1 rs1539355								
AA	42	1.00			67	1.00		
AG	65	0.81	0.37-1.77	0.59	65	0.91	0.44-1.89	0.80
GG	34	1.08	0.43-2.67	0.87	15	1.36	0.43-4.32	0.60
ADIPOR1 rs16850799								
AA	126	1.00			87	1.00		
AG/GG	20	0.49	0.18-1.35	0.17	63	0.93	0.47-1.86	0.84
ADIPOR1 rs2275736								
AA/AT	50	1.00			6	1.00		
TT	94	1.44	0.71-2.89	0.31	144	0.09	0.01-0.78	0.03
ADIPOR1 rs4336908								
AA	126	1.00			93	1.00		
AG/GG	20	1.06	0.41-2.73	0.91	58	1.02	0.51-2.06	0.95
ADIPOR1 rs6666089								
AA	110	1.00			71	1.00		
AG or AG/GG	37	1.10	0.52-2.32	0.81	63	0.68	0.33-1.42	0.31
GG					16	1.10	0.36-3.39	0.86
ADIPOR1 rs7514221								
CC	50	1.00			55	1.00		
CT	72	0.99	0.48-2.05	0.97	70	1.07	0.51-2.27	0.86
TT	24	1.63	0.61-4.35	0.33	28	0.82	0.30-2.22	0.70
ADIPOR1 rs7539542								
CC	23	1.00			68	1.00		
CG	67	0.79	0.31-2.04	0.63	73	0.96	0.47-1.95	0.91
GG	54	0.54	0.20-1.45	0.22	10	1.39	0.36-5.45	0.63

Table C-5 (Continued)								
HMGCS2 rs12123085								
AA	113	1.00			121	1.00		
AG/GG	33	1.05	0.48-2.29	0.90	32	0.40	0.15-1.06	0.07
HMGCS2 rs12563433								
CC	108	1.00			55	1.00		
CT					75	0.93	0.44-1.98	0.85
TT	36	1.00	0.47-2.14	0.99	20	2.24	0.79-6.37	0.13
HMGCS2 rs1441008								
CC	27	1.00			11	1.00		
CT					68	2.62	0.52-13.08	0.24
TT	117	1.41	0.60-3.33	0.44	71	2.02	0.40-10.13	0.39
HMGCS2 rs1441010								
AA	33	1.00			59	1.00		
AG	69	1.60	0.68-3.76	0.28	69	0.55	0.26-1.17	0.12
GG	43	1.39	0.55-3.51	0.49	22	0.89	0.32-2.47	0.83
HMGCS2 rs2241868								
CC	119	1.00			128	1.00		
CT/TT	23	0.64	0.25-1.63	0.35	23	1.13	0.44-2.88	0.80
HMGCS2 rs3790693								
AA	8	1.00			17	1.00		
AT	52	0.23	0.04-1.23	0.09	70	0.64	0.21-1.97	0.43
TT	84	0.26	0.05-1.38	0.11	63	1.21	0.40-3.68	0.74
HMGCS2 rs4659233								
AA/AT	41	1.00			34	1.00		
TT	98	0.76	0.36-1.57		114	1.76	0.73-4.24	0.21
HMGCS2 rs536662								
AA	66	1.00			32	1.00		
AG	59	0.88	0.44-1.79	0.73	73	1.33	0.54-3.31	0.54
GG	20	0.98	0.36-2.68	0.97	45	1.29	0.48-3.44	0.63
HMGCS2 rs619167								
AA	74	1.00			32	1.00		
AG	58	0.83	0.42-1.66	0.60	72	1.28	0.51-3.19	0.60
GG	12	0.84	0.24-2.89	0.78	47	1.32	0.50-3.51	0.58
HMGCS2 rs649733								
AA	86	1.00			83	1.00		
AG/GG	58	1.08	0.55-2.11	0.83	67	1.15	0.58-2.27	0.70
HMGCS2 rs667226								
CC	124	1.00			100	1.00		
CT/TT	20	0.49	0.18-1.35	0.17	50	0.87	0.42-1.81	0.71

Table C-6: Log Likelihood Ratio Test of the Significance of the Interaction Term Between Natural Log Transformed HOMA2-IR Scores and the Genetic Variant in the Prediction of Steatosis

	African Americans					Caucasian Americans				
	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value	df	Main Effects Log Likelihood	Interaction Log Likelihood	Chi Square	p-value
ADIPOR1 rs10753929	1	153.784	152.621	1.163	0.281	1	165.221	160.767	4.454	est ns
ADIPOR1 rs10920531	2	148.918	146.682	2.236	0.327	2	165.744	164.253	1.491	0.474
ADIPOR1 rs12045862	1	153.457	149.361	4.096	no est	1	166.498	165.508	0.990	0.320
ADIPOR1 rs12733285	2	148.124	144.846	3.278	0.194	2	163.807	160.941	2.866	0.239
ADIPOR1 rs1342387	2	155.286	153.642	1.644	0.440	2	165.837	163.087	2.750	0.253
ADIPOR1 rs1539355	2	147.642	146.733	0.909	0.635	2	162.973	160.343	2.630	0.269
ADIPOR1 rs16850799	1	154.651	152.533	2.118	0.146	1	165.743	165.708	0.035	0.852
ADIPOR1 rs2275736	1	151.920	150.755	1.165	0.280	1	161.347	158.858	2.489	0.115
ADIPOR1 rs4336908	1	158.239	157.729	0.510	0.475	1	167.160	167.022	0.138	0.710
ADIPOR1 rs6666089	1	157.621	157.621	0.000	1.000	2	162.784	156.882	5.902	0.052
ADIPOR1 rs7514221	2	155.250	153.815	1.435	0.488	2	168.476	165.989	2.487	0.288
ADIPOR1 rs7539542	2	152.062	150.686	1.376	0.503	2	165.689	164.547	1.142	0.565
HMGCS2 rs12123085	1	157.727	156.796	0.931	0.335	1	163.553	163.526	0.027	0.870
HMGCS2 rs12563433	1	156.126	155.713	0.413	0.520	2	162.764	161.704	1.060	0.589
HMGCS2 rs1441008	1	154.684	151.170	3.514	0.061	1	164.524	162.381	2.143	0.343
HMGCS2 rs1441010	2	154.274	153.980	0.294	0.863	2	165.445	161.672	3.773	0.152
HMGCS2 rs2241868	1	152.136	151.979	0.157	0.692	1	165.870	161.313	4.557	no est
HMGCS2 rs3790693	1	153.829	151.776	2.053	0.152	2	164.947	161.513	3.434	0.180
HMGCS2 rs4659233	1	146.110	144.641	1.469	0.226	1	161.866	159.845	2.021	0.155
HMGCS2 rs536662	2	153.888	153.882	0.006	0.997	2	165.576	164.746	0.830	0.660
HMGCS2 rs619167	2	152.993	151.981	1.012	0.603	2	166.141	165.395	0.746	0.689
HMGCS2 rs649733	1	154.749	152.317	2.432	0.119	1	164.885	163.458	1.427	0.232
HMGCS2 rs667226	1	152.517	152.464	0.053	0.818	1	161.515	161.351	0.164	0.686
HMGCS2 rs667246	2	151.257	149.949	1.308	0.520	2	165.109	161.728	3.381	0.184

Abbreviations: Degrees of Freedom (df)

Table C-7: Haplotype Frequencies and Trait Test for Steatosis by Race

Haplotype	Single Nucleotide Polymorphisms	African Americans N = 163		Caucasian Americans N = 179	
		No Steatosis	Steatosis ≥ 5%	No Steatosis	Steatosis ≥ 5%
ADIPOR1					
CACCAGATAACC	*rs10753929, rs10920531, rs12045862,*	0.08	0.06	0.00	0.00
CACCGGAAAACC	*rs12744285, rs1342387, rs1539355,*	0.02	0.07	0.00	0.02
CACCGGATAGCC	*rs16850799, rs2275736, rs4336908, rs6666089,*	0.10	0.11	0.33	0.25
CACTAAATAATC	*rs7514221, rs7539542*	0.05	0.06	0.17	0.19
CACTAAATAATG		0.05	0.05	0.00	0.02
CCCCGGAAAACG		0.16	0.13	0.01	0.00
CCCTAAATAATG		0.09	0.06	0.07	0.10
CCTCGAGTGACG		0.02	0.04	0.16	0.18
TACCAAATAATC		0.04	0.04	0.10	0.08
TCCCAAATAATG		0.13	0.16	0.00	0.00
Trait Test		1.00		1.00	
HMGCS2					
ACCATTTAAAC	*rs12123085, rs12563433, rs1441008,*	0.03	0.03	0.07	0.07
ACCGCATAAGC	*rs1441010, rs2241868,*	0.07	0.05	0.25	0.22
ACTACTTGGAC	*rs3790693, rs4659233, rs536662, rs619167,*	0.07	0.08	0.01	0.01
ACTACTTGGAT	*rs649733,*	0.09	0.07	0.14	0.15
ACTGCAAAAAC	*rs667226*	0.05	0.05	0.03	0.01
ACTGCTTAAAC		0.15	0.12	0.00	0.01
ACTGCTTAAGC		0.17	0.16	0.08	0.01
ATTACTTGGAC		0.14	0.12	0.29	0.36
ATTATTTAAAC		0.01	0.01	0.00	0.01
GCTGCAAAAAC		0.09	0.13	0.10	0.13
Trait Test		1.00		1.00	

* SNPs are listed in order that they appear in the haplotype and along the chromosome

Table C-8: Unadjusted Odds Ratio Estimates of Steatosis for Gene Haplotypes

Haplotype	African Americans N = 163				Caucasian Americans N = 179			
	N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
ADIPOR1								
CACCAGATAACC	21	1.04	0.41-2.69	0.93	0	†		
CACCGGAAAACC	10	1.53	0.38-6.16	0.55	4	†		
CACCGGATAGCC	31	1.01	0.45-2.27	0.97	83	0.86	0.45-1.61	0.63
CACTAAATAATC	18	1.00	0.37-2.75	0.99	56	1.37	0.68-2.73	0.38
CACTAAATAATG	18	1.00	0.37-2.75	0.99	3	†		
CCCCGGAAAACG	42	0.80	0.39-1.65	0.54	1	†		
CCCTAAATAATG	21	0.66	0.26-1.67	0.38	30	1.45	0.60-3.49	0.41
CCTCGAGTGACG	11	1.77	0.45-6.94	0.42	60	1.25	0.64-2.45	0.52
TACCAAATAATC	11	0.75	0.22-2.58	0.65	31	0.63	0.28-1.39	0.25
TCCCAAATAATG	44	1.17	0.57-2.40	0.68	0	†		
HMGCS2								
ACCATTTAAAC	8	0.62	0.15-2.58	0.51	24	1.01	0.41-2.51	0.98
ACCGCATAAGC	20	0.75	0.29-1.93	0.55	72	0.82	0.44-1.55	0.55
ACTACTTGGAC	23	0.99	0.40-2.44	0.98	2	†		
ACTACTTGGAT	23	0.80	0.33-1.96	0.63	51	1.01	0.51-2.01	0.97
ACTGCAAAAAC	14	1.16	0.37-2.63	0.80	4	†		
ACTGCTTAAAC	39	0.77	0.37-1.61	0.49	1	†		
ACTGCTTAAGC	49	0.89	0.45-1.77	0.74	11	0.10	0.02-0.46	0.004
ATTACTTGGAC	41	0.99	0.48-2.05	0.98	103	1.59	0.85-2.97	0.15
CGTGCAAAAAC	34	1.70	0.75-3.84	0.21	40	1.23	0.58-2.64	0.59

† Haplotype not common enough in population to estimate odds

Table C-9: Adjusted Odds Ratios for Steatosis for Gene Haplotype among African Americans and Caucasian Americans

	African Americans* N = 163				Caucasian Americans* N = 179			
Haplotype	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**
ADIPOR1								
CACCAGATAACC	20	1.31	0.37-4.56	0.77	0	†		
CACCGGAAAACC	10	2.47	0.37-16.32	0.23	4	†		
CACCGGATAGCC	30	0.56	0.21-1.48	0.36	83	0.67	0.28-1.62	0.37
CACTAAATAATC	17	1.71	0.39-7.42	0.48	56	2.81	1.00-7.92	0.05
CACTAAATAATG	17	1.39	0.38-5.11	0.62	3	†		
CCCCGGAAAACG	40	0.76	0.31-1.83	0.54	1	†		
CCCTAAATAATG	21	0.74	0.24-2.28	0.72	30	2.30	0.69-7.71	0.18
CCTCGAGTGACG	10	1.90	0.33-10.90	0.47	60	1.47	0.59-3.67	0.41
TACCAAATAATC	11	0.52	0.11-2.37	0.44	31	0.47	0.17-1.28	0.14
TCCCAAATAATG	41	0.53	0.21-1.32	0.23	0	†		
HMGCS2								
ACCATTTAAAC	8	0.45	0.09-2.30	0.36	23	1.26	0.36-4.43	0.72
ACCGCATAAGC	18	0.86	0.25-2.96	0.82	72	1.13	0.47-2.76	0.79
ACTACTTGGAC	21	0.91	0.31-2.64	0.86	2	†		
ACTACTTGGAT	21	0.39	0.12-1.32	0.13	51	1.53	0.59-3.94	0.38
ACTGCAAAAAC	13	1.06	0.25-4.54	0.94	4	†		
ACTGCTTAAAC	38	0.61	0.25-1.51	0.29	1	†		
ACTGCTTAAGC	47	1.21	0.52-2.78	0.66	11	0.05	0.01-0.50	0.01
ATTACTTGGAC	40	0.65	0.26-1.63	0.36	103	1.26	0.54-2.95	0.59
ATTATTTAAAC	1	†			2	†		
CGTGCAAAAAC	34	3.59	1.24-10.36	0.02	39	0.72	0.25-2.03	0.53

* Model adjusted for Ishak fibrosis score, weekly alcohol consumption, baseline viral level, homeostasis model of insulin resistance 2, and body mass index

† Haplotype not common enough or too common to estimate the odds ratio

Abbreviations: 95% Confidence Interval (Confidence Interval)

Table C-10: Haplotype Frequencies and Trait Test for Insulin Resistance by Race

Haplotype	SNPs	African Americans N = 138 HOMA2-IR < 2	African Americans N = 138 HOMA2-IR ≥ 2	Caucasian Americans N = 152 HOMA2-IR < 2	Caucasian Americans N = 152 HOMA2-IR ≥ 2
ADIPOR1					
CACCAGATAACC	*rs10753929, rs10920531, rs12045862, rs12744285, rs1342387, rs1539355, rs16850799, rs2275736, rs4336908, rs6666089, rs7514221, rs7539542*	0.06	0.05	0.00	0.00
CACCGGAAAACC		0.05	0.05	0.00	0.04
CACCGGATAGCC		0.10	0.12	0.29	0.28
CACTAAATAATC		0.05	0.06	0.18	0.18
CACTAAATAATG		0.04	0.08	0.01	0.01
CCCCGGAAAACG		0.17	0.12	0.01	0.00
CCCTAAATAATG		0.07	0.05	0.08	0.02
CCTCGAGTGACG		0.00	0.04	0.17	0.15
TACCAAATAATC		0.03	0.07	0.10	0.08
TCCCAAATAATG		0.17	0.13	0.00	0.00
Trait Test			1.00		1.00
HMGCS2					
ACCATTTAAAC	*rs12123085, rs12563433, rs1441008, rs1441010, rs2241868, rs3790693, rs4659233, rs536662, rs619167, rs649733, rs667226*	0.04	0.02	0.06	0.06
ACCGCATAAGC		0.05	0.07	0.22	0.21
ACTACTTGGAC		0.09	0.09	0.01	0.00
ACTACTTGGAT		0.08	0.04	0.15	0.16
ACTGCAAAAAC		0.03	0.07	0.01	0.02
ACTGCTTAAAC		0.12	0.14	0.00	0.01
ACTGCTTAAGC		0.17	0.16	0.03	0.02
ATTACTTGGAC		0.12	0.13	0.34	0.40
ATTATTTAAAC		0.01	0.00	0.00	0.01
GCTGCAAAAAC		0.12	0.11	0.13	0.06
Trait Test			1.00		1.00

Table C-11: Unadjusted Odds Ratios for Insulin Resistance for Gene Haplotypes

Single Nucleotide Polymorphism	African Americans N = 138				Caucasian Americans N = 152			
	N	Odds Ratio	95% Confidence Interval	p-value	N	Odds Ratio	95% Confidence Interval	p-value
ADIPOR1								
CACCAGATAACC	15	0.97	0.34-2.79	0.96	0	†		
CACCGGAAAACC	8	1.27	0.31-5.32	0.74	4	†		
CACCGGATAGCC	28	1.22	0.54-2.79	0.63	72	0.90	0.45-1.80	0.77
CACTAAATAATC	12	0.76	0.24-2.47	0.65	46	0.97	0.46-2.04	0.93
CACTAAATAATG	15	1.72	0.60-4.94	0.31	2	†		
CCCCGGAAAACG	34	0.74	0.34-1.60	0.44	1	†		
CCCTAAATAATG	17	0.65	0.23-1.87	0.42	23	0.86	0.33-2.27	0.77
CCTCGAGTGACG	9	1.28	0.35-4.64	0.71	48	0.88	0.42-1.85	0.74
TACCAAATAATC	11	3.71	0.94-14.68	0.06	29	0.72	0.29-1.78	0.48
TCCCAAATAATG	34	0.81	0.37-1.74	0.58	0	†		
HMGCS2								
ACCATTTAAAC	8	0.17	0.02-1.39	0.10	18	0.97	0.34-2.72	0.95
ACCGCATAAGC	15	1.14	0.41-3.14	0.81	60	1.09	0.54-2.17	0.82
ACTACTTGGAC	20	0.85	0.34-2.14	0.73	2	†		
ACTACTTGGAT	16	0.59	0.21-1.67	0.32	45	0.93	0.44-1.97	0.85
ACTGCAAAAAC	11	1.29	0.39-4.20	0.68	4	†		
ACTGCTTAAAC	32	1.25	0.57-2.73	0.58	1	†		
ACTGCTTAAGC	39	0.85	0.41-1.78	0.67	8	0.69	0.13-3.54	0.66
ATTACTTGGAC	32	1.06	0.49-2.33	0.88	93	1.30	0.64-2.63	0.47
GCTGCAAAAAC	28	0.93	0.40-2.15	0.87	31	0.41	0.16-1.08	0.07

† Unable to estimate odds because haplotype not common enough in population

Table C-12: Adjusted Odds Ratios for Insulin Resistance for *ADIPOR1* and *HMGCS2* Haplotypes among African Americans and Caucasian Americans

	African Americans* N = 138				Caucasian Americans* N = 152			
Haplotype	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**	**N**	**Odds Ratio**	**Confidence Interval**	**p-value**
ADIPOR1								
CACCAGATAACC	15	0.75	0.21-2.74	0.67	0	†		
CACCGGAAAACC	8	0.86	0.14-5.31	0.87	4	†		
CACCGGATAGCC	28	1.55	0.60-4.03	0.37	72	0.82	0.38-1.78	0.62
CACTAAATAATC	12	0.68	0.17-2.75	0.59	46	0.90	0.40-2.04	0.81
CACTAAATAATG	15	1.79	0.50-6.35	0.38	2	†		
CCCCGGAAAACG	34	0.74	0.29-1.90	0.53	1	†		
CCCTAAATAATG	17	0.79	0.24-2.66	0.71	23	1.05	0.37-2.97	0.93
CCTCGAGTGACG	9	1.22	0.28-5.33	0.80	48	0.87	0.38-1.97	0.74
TACCAAATAATC	11	5.94	1.23-18.65	0.03	29	0.72	0.26-2.00	0.53
TCCCAAATAATG	34	0.78	0.31-1.94	0.59	0	†		
HMGCS2								
ACCATTTAAAC	8	0.22	0.03-1.97	0.18	18	0.91	0.28-2.99	0.87
ACCGCATAAGC	15	1.96	0.55-6.92	0.48	60	1.26	0.58-2.73	0.57
ACTACTTGGAC	20	0.86	0.29-2.54	0.79	2	†		
ACTACTTGGAT	16	0.36	0.09-1.48	0.16	45	0.81	0.36-1.83	0.61
ACTGCAAAAAC	11	1.92	0.52-7.11	0.33	4	†		
ACTGCTTAAAC	32	1.32	0.54-3.25	0.54	1	†		
ACTGCTTAAGC	39	0.75	0.32-1.77	0.51	8	1.45	0.24-8.76	0.68
ATTACTTGGAC	32	1.13	0.43-2.96	0.80	93	1.23	0.57-2.67	0.60
GCTGCAAAAAC	28	0.94	0.37-2.42	0.90	31	0.32	0.11-0.96	0.04

* Model adjusted for Ishak fibrosis score, body mass index, age, steatosis and triglyceride levels

† Haplotype not common enough or too common to estimate the odds ratio

Table C-13a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *ADIPOR1 rs666089* Genotypes Among Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 14 AG: 18 GG: 6	AA: 32 AG: 27 GG: 4	AA: 46 AG: 45 GG: 10
	HOMA2-IR ≥ 2	AA: 5 AG: 1 GG: 3	AA: 20 AG: 16 GG: 3	AA: 25 AG: 17 GG: 6
	Column Total	AA: 19 AG: 19 GG: 9	AA: 52 AG: 43 GG: 7	TOTAL AA: 71 AG: 62 GG: 16

Table C-13b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *ADIPOR1 rs666089* Genotypes Among Caucasian Americans

		Steatosis		
		No Steatosis	Steatosis ≥ 5%	Row Total
Insulin Resistance	HOMA2-IR < 2	AA: 29 AG: 10 GG: 1	AA: 33 AG: 19 GG: 0	AA: 62 AG: 29 GG: 1
	HOMA2-IR ≥ 2	AA: 10 AG: 4 GG: 0	AA: 31 AG: 8 GG: 3	AA: 41 AG: 12 GG: 3
	Column Total	AA: 39 AG: 14 GG: 1	AA: 64 AG: 17 GG: 3	TOTAL AA: 103 AG: 31 GG: 4

Table C-14a: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *HMGCS2 rs12123085* Genotypes Among Caucasian Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 30 AG: 9 GG: 0	AA: 47 AG: 15 GG: 1	AA: 77 AG: 24 GG: 1
HOMA2-IR ≥ 2	AA: 8 AG: 1 GG: 0	AA: 36 AG: 5 GG: 0	AA: 44 AG: 6 GG: 0
Column Total	AA: 38 AG: 10 GG: 0	AA: 83 AG: 20 GG: 1	TOTAL AA: 121 AG: 30 GG: 1

Table C-14b: Descriptive Comparison of Individuals by Steatosis and Insulin Resistance for *HMGCS2 rs12123085* Genotypes Among Caucasian Americans

Insulin Resistance	Steatosis: No Steatosis	Steatosis: Steatosis ≥ 5%	Row Total
HOMA2-IR < 2	AA: 32 AG: 6 GG: 1	AA: 31 AG: 10 GG: 1	AA: 63 AG: 16 GG: 2
HOMA2-IR ≥ 2	AA: 13 AG: 1 GG: 0	AA: 30 AG: 11 GG: 1	AA: 43 AG: 12 GG: 1
Column Total	AA: 45 AG: 7 GG: 1	AA: 61 AG: 21 GG: 2	TOTAL AA: 106 AG: 28 GG: 3

Table C-15: Amount of Common Variation in Each Gene Accounted for by Selected Single Nucleotide Polymorphisms (SNPs)

SNP Selection Method: Linkage Disequilibrium Tagging **Minor Allele Frequency: 10%**								
			African Americans			**Caucasian Americans**		
Gene	**ADIPOR1 & HMGCS2 SNPs**	**SNPs in High LD**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation**	**# SNPs for R2 = 0.8**	**# SNPs Covered with Genotyped SNPs**	**% of Variation Covered**
ADIPOR1	12	0	17	14	82%	21	21	100%
HMGCS2	12	0	28	18	64%	31	29	93%
AVERAGE			**45**	**32**	**71%**	**52**	**50**	**96%**

Abbreviations: Linkage Disequilibrium (LD)

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