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DNA polymorphisms and response to treatment in patients with chronic hepatitis C: Results from the HALT-C trial

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Abstract

Background/Aim—Certain host genetic polymorphisms reportedly affect the likelihood of a sustained virological response (SVR) to interferon treatment in subjects infected with hepatitis C virus (HCV). As part of the HALT-C trial we evaluated genetic associations among patients infected with HCV genotype 1 who had failed previous interferon treatment.

Methods—SVR was determined 24 weeks after completing treatment with pegylated interferon alfa-2a and ribavirin. Eight single nucleotide polymorphisms (SNPs) were selected on the basis of previously reported associations with treatment response. Genotypes were assessed by polymerase chain reaction-based assays. The percentage of patients who achieved SVR was determined for each genotype and for an IL-10 promoter diplotype.

Results—Among 637 non-Hispanic Caucasian patients there were no significant associations between genotype for any individual SNP (*IL10* -1082, *IL10* -592, *TNF* -308, *TNF* -238, *TGFB1* codon 25, *CCL2* -2518, *EPHX1* codon 113 and *AGT* -6) and SVR, but SVR was more common among the patients who were homozygous for the ACC *IL-10* promoter diplotype (adjusted odds ratio, 3.24; 95% confidence interval, 1.33–7.78; p=0.001).

Conclusions—Among non-Hispanic Caucasian patients treated with peginterferon and ribavirin after failing previous treatment with interferon, homozygosity for the ACC *IL-10* promoter diplotype was associated with SVR.

Keywords

hepatitis C; chronic/genetics; polymorphism; genetic; interferon-alpha/therapeutic use; gene frequency

Introduction

Sequencing of the human genome has brought the promise of individualized medicine. Inheritable genetic factors influence the risk of development or clinical course of a variety of diseases(1–3), and may affect response to drug treatment (4–6). In the case of chronic hepatitis C, recent papers have suggested that a number of genetic polymorphisms may influence the outcome of chronic hepatitis C infection or a patient's response to antiviral therapy (7–16).

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial is an NIH-sponsored clinical trial designed to improve the management and outcomes for patients with difficult-to-cure, advanced chronic hepatitis C. As part of an ancillary study of the HALT-C trial, we carried out genetic testing of a series of candidate genetic variations which had been reported to be associated with either response to interferon-based therapy (7–16) or with risk of developing hepatic fibrosis (17–20), which is itself a predictor of therapeutic response. Studying these genetic variations in the HALT-C trial presents an opportunity to assess whether previously-reported host genetic factors predict response to treatment with pegylated interferon plus ribavirin among patients who previously failed to respond to interferon-based treatment.

Materials and Methods

The HALT-C Trial

The over-all design of the HALT-C trial, along with the major clinical, biochemical, and virological responses to the 'Lead-in' phase of therapy have been published (21, 22). In brief, patients with advanced chronic hepatitis C (Ishak fibrosis score >2) (23) who had not previously responded to interferon treatment (either with or without ribavirin) and who had a Child-Turcotte-Pugh score <7 were invited to enroll.

Treatment during the Lead-in phase (i.e., first 24 weeks) consisted of pegylated interferon alfa-2a (Pegasys®) 180 mcg/week subcutaneously, plus ribavirin (Copegus®) 1.0–1.2 g orally per day. Subjects with undetectable HCV RNA at week 20 were offered 48 weeks of treatment with pegylated interferon and ribavirin, and were followed for another 24 weeks after treatment was stopped. Subjects were considered to have a sustained virologic response (SVR) if they had undetectable HCV RNA 24 weeks after discontinuing pegylated interferon and ribavirin treatment.

All subjects had a liver biopsy performed within 12 months prior to entry into the HALT-C trial which was scored for fibrosis using the Ishak fibrosis scale (range 0 through 6) by a group of hepatopathologists Steatosis was scored as not present (0), less than 5% of hepatocytes (1), 5–33% of hepatocytes (2), 33–66% (3) or greater than 66% (4). An estimated duration of hepatitis C infection was determined by the study principal investigator. Race was self-classified as White, Black, Asian/Pacific Islander, American Indian/Alaskan Native, other or unknown. Ethnicity was recorded as Latino/Hispanic or not. Subjects who considered themselves as White but not Latino/Hispanic were classified as non-Hispanic Caucasians and those who self-categorized as Black were classified as African American.

Genetic Ancillary Study

All subjects entering the HALT-C trial were offered participation in an ancillary study to evaluate genetic polymorphisms associated with hepatitis C disease severity and response to treatment. Of the 1145 subjects enrolled in the Lead-in phase of the HALT-C trial, 1051 (91.7%) agreed to participate in the genetics study (Fig 1). Since genetic polymorphisms can

vary by race/ethnicity, we analyzed data from non-Hispanic Caucasians and African Americans separately. Because only 9 African Americans participants achieved an SVR, *a priori* statistical power was low in this group. Other groups (e.g., Hispanics, Asians, other) were present in too few numbers to permit any meaningful statistical analysis and were, therefore, excluded from this analysis.

The analysis of SVR was further limited to patients with HCV genotype 1 infection who were enrolled in the Lead-in phase of the HALT-C trial and who completed follow-up through week 72 (n=774). Patients with other HCV genotypes were excluded because of different SVR rates among genotype 1 and non-1 subjects in the HALT-C trial (22). Because severity of liver fibrosis may affect SVR (22), we also evaluated the association of selected SNPs with liver fibrosis, measured both as Ishak fibrosis score at entry into the trial and as a fibrosis rate, which was determined by dividing the Ishak fibrosis score by the estimated number of years of infection.

DNA Extraction and Genotyping

DNA was extracted at SeraCare (Gaithersburg, MD) from frozen whole blood using the Gentra Systems Puregene kit (n=117) and from either Epstein-Barr transformed B-lymphocytes (n=636) or frozen peripheral blood mononuclear cells (n=21) using Qiagen DNA purification columns (Qiagen Inc, Valencia, CA). Most patients (62.4%) who achieved SVR had DNA extracted by the Gentra Systems method, whereas 96.8% of patients who did not achieve SVR had DNA extracted by the Qiagen method. Eight single nucleotide polymorphisms (SNPs) from six genes (*IL10* -1082 A/G; *IL10* -592 A/C; *TNF* -308 A/G; *TNF* -238 A/G; *TGFB1* codon 25 R/P [Arg/Pro]; *CCL2* -2518 G/A; *EPHX1* codon 113 Y/H [Tyr/His]; *AGT* -6 A/G) were measured by polymerase chain reaction-based assays performed at the University of Connecticut Health Center. Details of these assays are shown in Supplemental Table 1.

Data Analysis

All data were analyzed by the New England Research Institutes Data Coordinating Center using SAS (Statistical Analysis Software, version 9.1, SAS Institute, Cary, NC, USA). All analyses were stratified by race. For each SNP, we used Pearson's Chi-sq to compare observed genotype proportions to those expected under Hardy-Weinberg equilibrium. For each genotype, we determined the proportion of patients who achieved SVR. The odds ratio (OR) and corresponding 95% confidence interval (CI) were computed using logistic regression models. We considered as potential covariates factors previously shown to be associated with SVR among HALT-C subjects (i.e., prior treatment with interferon monotherapy, cirrhosis, pretreatment HCV RNA level, HFE H63D genotype) (22, 24) or other populations (e.g., age, gender, BMI, steatosis, etc) (25, 26). Our final models included five variables that were independently associated with SVR among our patients (pre-treatment HCV RNA level, presence of cirrhosis, AST/ALT ratio, baseline viral load, HFE H63D genotype, and whether the patient had received ribavirin prior to entering the HALT-C trial).

IL10 (-1082/-819/-592) promoter haplotypes were determined based on genotype results for *IL10* -1082 (A/G) and *IL10* -592 (C/A) as well as the previously reported linkage between *IL10* -819 (T/C) and *IL10* -592 (C/A) (10). The three observed *IL10* promoter haplotypes are GCC, ACC or ATA. We determined the proportion of patients who achieved SVR by *IL10* promoter diplotype, along with the OR and 95% CI. 'Statistical significance' was based on $p<0.05$. To evaluate the association of host genotype with fibrosis progression rate and Ishak fibrosis score, t-tests were used to compare mean differences between genotypes.

RESULTS

Characteristics of Subjects Studied

Selected demographic and clinical information is summarized in Table 1. The 1051 genetic study participants did not differ from the overall group of participants in any meaningful way. Because the current analysis was restricted to subjects who were infected with HCV genotype 1 and who reported their race as Caucasian, non-Hispanic or African American, subjects in our report differ from the overall HALT-C participants with regard to those variables. Among subjects included in the present analysis, the SVR rate was 16% among non-Hispanic Caucasians and 7% among African Americans. Data from African American subjects is made available for potential meta-analyses in supplemental tables 2 and 3.

Genetic Polymorphisms and Sustained Virological Response

Host genotype was successfully obtained for each of the eight SNPs from all specimens tested (Table 2). For all 8 alleles examined, the distribution of genotypes was consistent with the proportions expected under Hardy-Weinberg equilibrium. Among non-Hispanic Caucasians, SVR was somewhat less common among carriers of the *IL10* -1082 G (OR, 0.87) or the *IL10* -592 A (OR, 0.78) polymorphisms, but neither difference was statistically significant (Table 2). Analysis of four polymorphisms in three additional cytokine genes (*TNF* -308 A/G promoter, *TNF* -238 A/G promoter, *TGFB1* codon 25 R/P and *CCL2* -2518 G/A promoter) also failed to show an association between genotype and SVR rate among non-Hispanic Caucasians, as did our analysis for the variant that alters *EPHX1* codon 113. For the *AGT* -6 A/G promoter genotype, the adjusted analysis yielded an OR of 0.62 (95% CI, 0.38–1.01; p=0.05). Because the *AGT* -6 promoter was previously associated with fibrosis, we repeated the multivariate analysis excluding variables correlated with cirrhosis (i.e., histological cirrhosis and AST/ALT ratio). In this model the association of *AGT* -6 with SVR was slightly less (OR=0.69; 95% CI 0.44 – 1.11; p=0.13).

IL10 Promoter Haplotypes and Sustained Virological Response

Among non-Hispanic Caucasians, the GCC haplotype was more frequent (48.7%) than ACC (26.8%) or ATA (24.5%) (Table 3). The frequency of SVR was highest (32%) among patients who were homozygous for the ACC haplotype (who comprised 5.8% [37/637] of our study population) and there was a significant difference when ACC homozygotes were compared to GCC homozygotes (OR, 2.59; 95% CI, 1.14 5.87; p=0.02). SVR was not more common among those who were heterozygous for ACC. Patients who were homozygous for the ATA haplotype had the lowest rate of SVR (8%), but this difference was not statistically significant. In a logistic regression model that controlled for pre-treatment HCV RNA level, presence of cirrhosis, prior treatment with ribavirin, AST/ALT ratio and HFE H63D genotype (all of which were independently associated with SVR) (22, 24), the association with the ACC/ACC diplotype became stronger (adjusted OR 3.24; CI: 1.33 – 7.78; p=0.001), but results for other diplotypes did not change meaningfully (Table 3). Patients with the ACC/ACC IL10 diplotype also had the greatest decline in HCV RNA at week 12 (2.66 $\log_{10}$ IU/mL vs. approximately 2.3 $\log_{10}$ for the other diplotypes) and the highest frequency of end-of-treatment response (43% of subjects had undetectable HCV RNA; OR: 1.62, 95% CI: 0.78 – 3.39). However, neither finding reached statistical significance.

Genetic Polymorphisms and Fibrosis

Because advanced fibrosis has been associated with several of the SNPs that we studied (17– 20, 27) and with reduced response to antiviral therapy (22), fibrosis stage was a potential confounder in our analysis of response to interferon therapy. We examined host genotype results for their relationship to mean Ishak fibrosis score and fibrosis progression

rate among all subjects for whom these data were available (fibrosis score, n=1128; fibrosis rate, n=1063) as well as in the 774 subjects participating in the SVR analysis. No significant associations were observed in either racial group for any of the eight SNPs (data not shown).

Discussion

This study examined whether genetic variants that had previously been associated with either response to interferon treatment or liver fibrosis predicted response to treatment with pegylated interferon alfa-2a plus ribavirin in a large study of subjects from the United States with advanced chronic hepatitis C who had failed a previous course of interferon-based treatment. Although neither the *IL10* -1082 nor the *IL10* -592 promoter polymorphism alone predicted response to treatment, the *IL-10* ACC/ACC diplotype was associated with SVR and this association was relatively strong, especially after adjustment for other predictors of SVR. We also note that the frequency of ACC/ACC diplotype among the HALT-C population (5.8%) was lower than that observed in the general adult population by Trompet (7.3%), Gowans (7.8%) and Klein (10%) (28–30) suggesting that subjects with this diplotype were underrepresented in the HALT-C cohort, perhaps because HCV-infected subjects with this diplotype responded well to initial treatment with interferon. Some studies of *IL10* ACC function suggest that this haplotype (and the *IL10* ATA haplotype) produces less IL-10 than the GCC haplotype (10, 31), although another study failed to confirm that finding (32). Nelson and colleagues reported that administration of IL-10 resulted in an increase in HCV RNA level and a flare of ALT (33). A possible explanation for the observed association is that persons who are homozygous for *IL10* ACC produce less IL-10 which leads to improved control of HCV.

Results from previous studies of the *IL10* haplotype and response to interferon based treatment for chronic hepatitis C are inconsistent. Among patients who received interferon monotherapy, Edwards-Smith reported higher SVR rates among patients carrying ACC than the GCC haplotype (10), and the highest SVR rates among patients carrying the also putatively low producing ATA haplotype. Therefore, the results from that study are consistent with the hypothesis that haplotypes associated with low IL-10 production might increase the likelihood of SVR. In apparent conflict, however, is a study by Knapp who reported that patients homozygous for GCC, who might be expected to have the highest production of IL-10, were more likely to achieve SVR (11). Yee et al. (15) reported *IL10* haplotype results that are not directly comparable to other studies because they included additional genetic variants in extended *IL10* haplotypes. One of the two extended *IL10* haplotypes that included ATA was associated with SVR and one of the two extended *IL10* haplotypes that included ACC had the opposite association. Finally, Mangia et al. (12) found no statistically significant associations between any *IL10* haplotype and response to treatment, but that study had low statistical power because it was limited to 95 patients. Taken as a whole, the data fail to provide a consistent picture of the relationship between *IL10* haplotypes and response to treatment for HCV.

Prior studies of individual *IL10* promoter polymorphisms are also inconsistent. Edwards-Smith found that carriage of the *IL10* -592A allele was associated with viral clearance during the first 12 weeks of treatment (OR=5.1; 95% CI 1.4–19.1) (10) and Yee found an association between the -592A allele and SVR(15),. Knapp found no association of *IL10* -592A and SVR but reported that the -1082 GG genotype was associated with SVR (OR=2.28; p=0.005), and, somewhat paradoxically, that the -1082 AG heterozygous genotype had the opposite association (11). Three additional reports (two from Europe and one from the United States) found no association between either the -592A allele or the -1082G allele and SVR (8, 12, 14).

The reason for the different results reported from studies of the association of *IL10* promoter variants and virologic response is not clear. The study populations differ with regard to factors that are related to response to interferon-based treatments such as the degree of liver fibrosis, exclusion of HCV non-1 genotypes or type of interferon used (pegylated vs. regular). Furthermore, environmental factors including lower body mass index, smoking and female gender, which have been linked to decreased IL-10 production (34), may vary between studies. It is also possible that the observed differences between studies, including our finding that the ACC/ACC diplotype is associated with SVR, could be due to chance.

We were motivated to study TNF promoter polymorphisms because Dai et al. reported that Taiwanese patients receiving peginterferon and ribavirin were more likely to achieve SVR if they carried *TNF* -308 A (9). However neither the *TNF* -238 nor *TNF* -308 *TNF* was associated with SVR in our analysis. Other studies from the United States (15, 19), Europe (2, 7, 8, 13) and Taiwan (16) also failed to detect an association of either *TNF* promoter polymorphism with viral clearance following interferon treatment. Furthermore, recent studies have cast doubt on the functional significance of the -238 and the -308 polymorphisms (35). Taken together, the cumulative evidence does not indicate that TNF promoter genotype alters response to interferon treatment of chronic HCV.

Because fibrosis is associated with an increased risk of failure of interferon treatment, we also examined polymorphisms that have been associated with an increased risk of fibrosis but have not been assessed for their relationship to SVR (18, 19). We were unable to demonstrate an association of the *TGFB1* codon 25 allele and response to treatment, confirming one prior negative study (14). Alleles at -2518 of the *CCL2* promoter region were not associated with SVR in either Caucasians or in African Americans, which is in agreement with two prior reports (36, 37). We found no association between *EPHX1* Y113H polymorphism and SVR, but the data suggested that the *AGT* -6 GG genotype might be associated with increased response to treatment. Further study of this polymorphism is warranted.

The fact that HALT-C trial participants have advanced fibrosis and are non-responders to prior treatment with interferon raises the question of whether our results can be compared with other studies of patients with chronic hepatitis C. Restriction of enrollment to previous non-responders likely eliminates patients who are most responsive to interferon, but it also enriches for patients who are truly non-responsive to treatment with interferon. It is plausible that epidemiologic associations for treatment response to pegylated interferon plus ribavirin could be weaker among patients who previously failed interferon therapy, but the available data do not support this concern. HALT-C investigators have replicated the reported risk factors for treatment failure (i.e., older age, African American ethnicity, HCV genotype 1, higher HCV RNA level, the presence of cirrhosis) that were found in trials of previously untreated patients (26, 38– 40) and these associations were at least as strong among the HALT-C participants (22).

Enrollment into HALT-C was limited to subjects with bridging fibrosis or cirrhosis (i.e., Ishak fibrosis score of 3 through 6). The exclusion of subjects with minimal fibrosis restricts our ability to examine the relationship between genetic polymorphism and liver fibrosis. Furthermore, because of the lack of data demonstrating that risk factors for fibrosis are similar in HALT-C subjects and in subjects in published trials evaluating SNPs and liver fibrosis, we did not report data on host SNPs and liver fibrosis. None-the-less, we did evaluate association of SNPs and liver fibrosis score and fibrosis rate because of the potential for these SNPs to influence liver fibrosis and thereby confound their effect on SVR. Our failure to demonstrate an association of host SNPs with liver fibrosis makes it unlikely that the SNPs we evaluated affected SVR by influencing liver fibrosis.

We believe that our study represents the largest analysis to date of host genetics and response to treatment for chronic hepatitis C. The statistical power to detect a two-fold association between presence of an allele and SVR ranged from 87–94% for the alleles that we studied with the exception of *TNF* -238 (45%) and *TGFB1* -25 (70%), but the power to find a 1.5 fold association with SVR was low for all genotypes. Other strengths of our study include uniform treatment of patients with the current 'gold standard' regimen (pegylated interferon plus ribavirin) and careful follow-up for treatment outcomes within the context of an NIH-sponsored clinical trial.

In summary, among non-Hispanic Caucasians infected with genotype 1 hepatitis C virus and moderate-to-advanced liver fibrosis, SVR was more common among participants who were homozygous for the ACC *IL10* diplotype, which has been linked to low production of IL10. We could not confirm a number of prior associations of DNA polymorphisms with sustained virological response to interferon treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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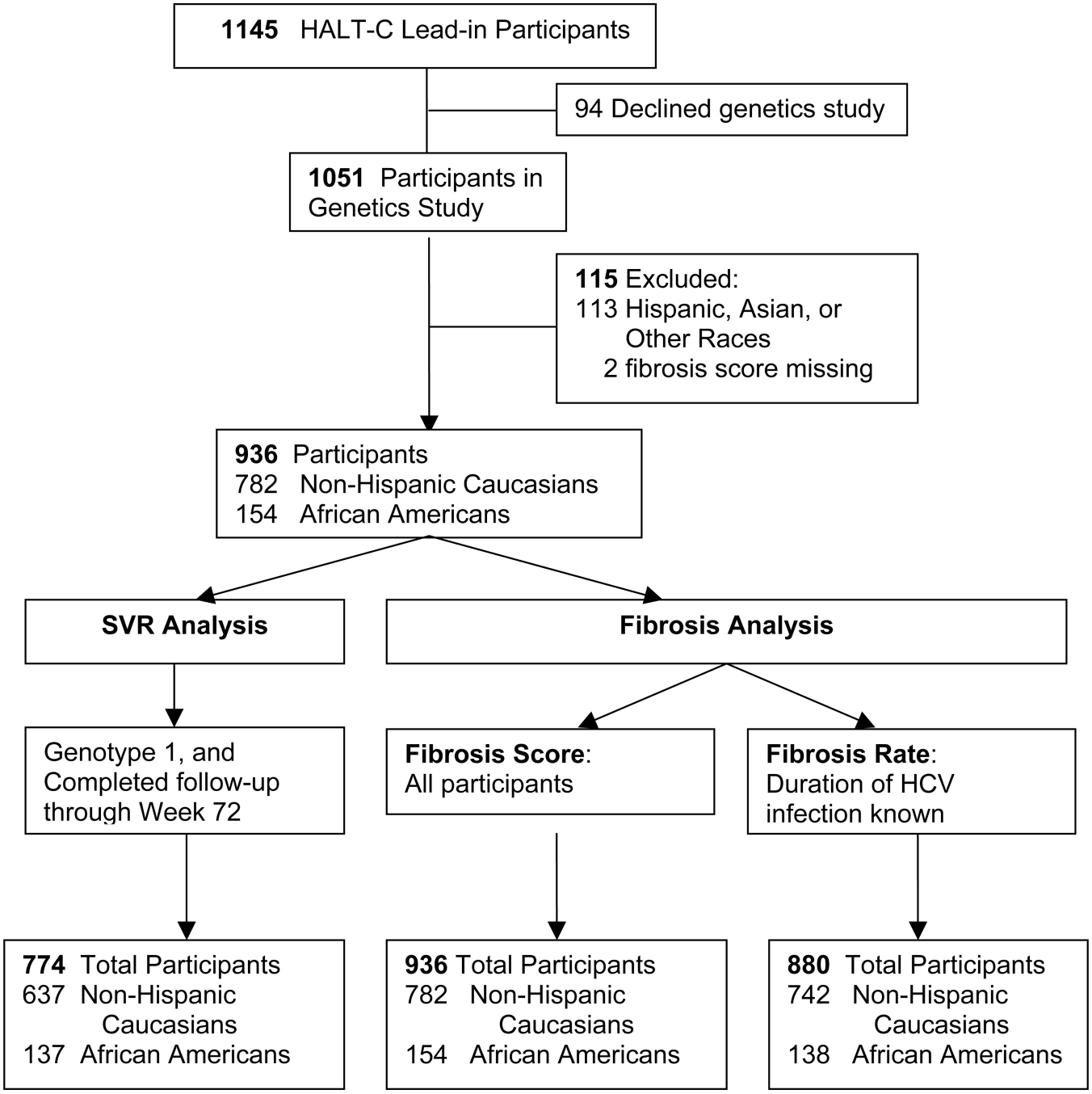

Figure 1.
Overview of patients participating in the Lead-in phase of the HALT-C trial who agreed to participate in the genetics study and who were included in the current report.

Table 1

Selected demographic and clinical features of subjects participating in the Lead-in phase of the HALT-C trial, the genetics ancillary study, and in the current report

Variables	Lead-in Phase of HALT-C trial (N=1145)	Lead-in Participants in Genetics study (N=1051)	Participants in Current Report* (N=774)
Age (mean, sd)	50 (7.30)	50 (7.24)	50.1 (7.04)
Male (n, %)	827 (72%)	760 (72%)	563 (73%)
Race			
Caucasian, non-Hispanic (n,%)	844 (74%)	783 (75%)	637 (82%)
African American (n, %)	175 (15%)	154 (15%)	137 (18%)
Other (n, %)	126 (11%)	114 (11%)	0 (0%)
Estimated years of infection (mean, sd)	28.11 (8.13)	28.27 (8.13)	27.95 (7.77)
BMI (mean, sd)	29.7(5.4)	29.7(5.5)	29.7(5.5)
Ishak Fibrosis Score			
2–4 (n, %)	713 (62%)	653 (62%)	488 (63%)
5–6 (n, %)	430 (38%)	396 (38%)	286 (37%)
Ishak Inflammation Score (mean, sd)	7.5 (2.1)	7.5 (2.1)	7.30 (2.0)
Steatosis score			
0 or 1	694 (61%)	637 (61%)	477 (62%)
2	348 (30%)	321 (31%)	228 (30%)
3	88 (8%)	80 (8%)	59 (8%)
4	15 (1%)	13 (1%)	10 (1%)
AST/ALT ratio (mean, sd)	0.84 (0.29)	0.82 (0.29)	0.85 (0.29)
HCV Genotype 1 (n, %)	1017 (89%)	929 (89%)	774 (100%)
HCV RNA level < 1.5 million IU/mL (n,%)	323 (28%)	302(29%)	207(27%)
HCV RNA level (log 10) (mean, sd)	6.42 (0.53)	6.41 (0.54)	6.44 (0.53)
Prior treatment:			
Interferon alone (n, %)	326 (28%)	298 (28%)	205 (26%)
Interferon and ribavirin (n, %)	819 (72%)	753 (72%)	569 (74%)

* Subjects enrolled in Lead-in phase, infected with HCV genotype 1 who reported race as Caucasian, non-Hispanic or as African American and who had HCV RNA results available at Week 20 and at Week 72. Because the current analysis was restricted to non-Hispanic Caucasians and African Americans who were infected with HCV genotype 1, these groups differ from the overall HALT-C participants ($p<0.05$).

Table 2

Genotype frequency and frequency of sustained virological response among 637 non-Hispanic Caucasian patients infected with genotype 1 hepatitis C who completed follow-up through week 72 (odds ratios [OR] and 95% confidence intervals [CI]).

Gene / Variant	Genotype	Total	SVR	% SVR	OR (95% CI)	Adjusted OR**
IL10						
rs 1800896	AA	164	28	17%	1	
−1082 A/G promoter	AG	326	49	15%	0.86 (0.52,1.43)	
	GG	147	23	16%	0.90 (0.49,1.65)	
	AG+GG	473	72	15%	0.87 (0.54,1.41)	0.74 (0.44, 1.24)
rs 1800872	CC	363	62	17%	1	
−592 A/C promoter	CA	236	35	15%	0.85 (0.54,1.33)	
	AA	38	3	8%	0.42 (0.12,1.4)	
	CA + AA	274	38	14%	0.78 (0.50,1.21)	0.84 (0.52, 1.34)
TNF	GG	427	67	16%	1	
rs 1800629	GA	184	27	15%	0.92 (0.57,1.50)	
−308 A/G promoter	AA	26	6	23%	1.61 (0.62,4.17)	
	GA + AA	210	33	16%	1.00 (0.64,1.58)	1.22 (0.75, 2.01)
rs 361525	GG	579	90	16%	1	
−238 A/G promoter	GA	57	10	18%	1.16 (0.56,2.37)	
	AA	1	0	0%	ND	
	GA + AA	58	10	17%	1.13 (0.55,2.32)	1.03 (0.48, 2.21)
TGFB1	GG	533	85	16%	1	
rs 1800471	GC	102	15	15%	0.91 (0.50,1.65)	
Codon 25 R/P	CC	2	0	0%	ND	
	GC + CC	104	15	14%	0.89 (0.49,1.61)	0.85 (0.45, 1.62)
CCL2	AA	337	57	17%	1	
rs 1024611	AG	248	33	13%	0.75 (0.47,1.2)	
−2518 G/A promoter	GG	52	10	19%	1.17 (0.55,2.47)	
	AG+GG	300	43	14%	0.82 (0.53,1.26)	0.78 (0.49, 1.24)
AGT						

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Gene / Variant	Genotype	Total	SVR	% SVR	OR (95% CI)	Adjusted OR**
rs 5051	GG	208	38	18%	1	
−6 A/G promoter	GA	314	48	15%	0.81 (0.51,1.29)	
	AA	115	14	12%	0.62 (0.32,1.20)	
	GA+AA	429	62	15%	0.76 (0.49,1.18)	0.62 (0.38, 1.01)
EPHX1						
rs 1051740	YY	320	53	17%	1	
Codon 113 Y/H	YH	265	38	14%	0.84 (0.54,1.33)	
	HH	52	9	17%	1.05 (0.48,2.29)	
	YH + HH	317	47	15%	0.88 (0.57,1.34)	0.95 (0.60, 1.50)

** Adjusted for pre-treatment HCV RNA level, presence of cirrhosis, AST/ALT ratio, baseline viral load, HFE H63D genotype, and prior treatment with ribavirin.

Table 3

IL-10 promoter diplotype and frequency of sustained virological response (odds ratios [OR]and 95% confidence intervals [CI]) among 637 non-Hispanic Caucasian patients infected with genotype 1 hepatitis C who completed follow-up through week 72

Diplotype	Total (n=637)	%	SVR	SVR %	OR (95% CI)	Adjusted OR** (95% CI)
GCC/GCC	147	23.1%	23	16%	1	
ACC/GCC	179	28.1%	27	15%	0.96 (0.52, 1.75)	0.98 (0.51, 1.88))
ACC/ACC	37	5.8%	12	32%	2.59 (1.14, 5.87)	3.24 (1.33, 7.87)
ACC/ATA	89	14.0%	13	15%	0.92 (0.44, 1.93)	1.07 (0.48, 2.37)
ATA/ATA	38	6.0%	3	8%	0.46 (0.13, 1.63)	0.55 (0.14, 2.13)
GCC/ATA	147	3.1%	22	15%	0.95 (0.50, 1.79)	1.02 (0.51, 2.03)

** Adjusted for pre-treatment HCV RNA level, presence of cirrhosis, AST/ALT ratio, baseline viral load, HFE H63D genotype, and prior treatment with ribavirin.