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BRIEF REPORT

Association of the *IFNL4*-ΔG Allele With Impaired Spontaneous Clearance of Hepatitis C Virus

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Interferon lambda 4 protein can be generated in *IFNL4*-ΔG carriers but not *IFNL4*-TT homozygotes. We studied 890 anti–hepatitis C virus (HCV)–positive participants in the Women's Interagency HIV Study. Among blacks (n = 555), HCV was more often cleared for those with genotype *IFNL4*-TT/TT (32.6%; odds ratio [OR], 3.59; $P = 3.3 \times 10^{-5}$) than *IFNL4*-TT/ΔG (11.3%; OR, 0.95; $P = .86$) or *IFNL4*-ΔG/ΔG (11.9%; referent). Pooling these data with published results in blacks (n = 1678), ORs were 3.84 ($P = 8.6 \times 10^{-14}$) for *IFNL4*-TT/TT and 1.44 ($P = .03$) *IFNL4*-TT/ΔG, and the area under the curve was 0.64 for *IFNL4*-ΔG genotype and 0.61 for rs12979860 (*IL28B*). *IFNL4*-ΔG is strongly associated with impaired spontaneous HCV clearance.

Keywords. genetic; HCV; *IFNL4*; *IL28B*; viral clearance.

About 70%–80% of individuals who become infected with hepatitis C virus (HCV) fail to clear the virus spontaneously [1]. Worldwide, approximately 185 million are infected with HCV [2], and in the United States, chronic hepatitis C is the leading cause of hepatocellular carcinoma, end-stage liver disease, and liver transplantation [1].

Genome-wide association studies identified variants located in the interferon lambda region that are strongly associated with spontaneous HCV clearance, as well as response to interferon alfa–based treatment of chronic hepatitis C [3]. Recently, we discovered interferon lambda 4 (*IFNL4*), a new gene that may account for those associations [4]. The interferon lambda 4 protein (IFN-λ4) can be generated by individuals who carry the ΔG allele of the ss469415590 variant (*IFNL4*-ΔG); IFN-λ4 is not produced by individuals who are homozygous for the *IFNL4*-TT allele because of a frameshift in exon 1 caused by the insertion variant. The rs12979860 variant, which was associated with spontaneous HCV clearance in earlier studies [5, 6] and is commonly referred to as *IL28B*, is actually located within intron 1 of *IFNL4*. Linkage disequilibrium is strong between the *IFNL4*-ΔG allele and the unfavorable rs12979860-T allele in individuals of European or Asian ancestry, whereas this linkage disequilibrium is moderate in individuals of African ancestry [4].

Previously, we examined the association between *IFNL4*-ΔG and spontaneous HCV clearance in 2 cohorts of injection drug users (IDUs)—the Urban Health Study (UHS), which enrolled a multiethnic group of IDUs in the San Francisco Bay area, and the AIDS Linked to the IntraVenous Experience (ALIVE) study, which enrolled a predominately black cohort of IDUs in Baltimore [4]. Among black participants, *IFNL4*-ΔG genotype was associated with spontaneous HCV clearance more strongly than rs12979860 genotype in UHS, whereas in ALIVE associations for the 2 variants were similar. To further examine the association between *IFNL4*-ΔG and spontaneous HCV clearance, we studied participants in the Women's Interagency HIV Study (WIHS) [7]. To increase statistical power and summarize all available data for the association of *IFNL4*-ΔG genotype with spontaneous HCV clearance among black individuals, we pooled data from WIHS, UHS, and ALIVE.

METHODS

Study Population

WIHS is a prospective cohort study of human immunodeficiency virus (HIV)–seropositive and at-risk HIV-seronegative women who were enrolled at 6 clinical sites [7]. Initial enrollment was conducted during 1994–1995, a second recruitment occurred during 2001–2002, and a third recruitment period

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occurred in 2011. Subjects are followed semiannually with physical exams, specimen collection including blood, and detailed questionnaires regarding health and behavior. The WIHS protocol was approved by each local institutional review board, and all participants included in this analysis provided written informed consent for genetic testing. This study focused on the 890 WIHS women who were successfully genotyped for both *IFNL4*-ΔG and rs12979860, were anti-HCV seropositive at the enrollment visit, and provided information on race/ethnicity (Supplementary Figure 1).

Laboratory

At enrollment in WIHS, HCV antibody status was determined using a commercial second- or third-generation enzyme immunoassay. For participants who tested anti-HCV positive, the HCV RNA level in plasma was determined using either the COBAS Amplicor Monitor 2.0 (linear range, 600–5.0×10^5 IU/mL) or the COBAS Taqman assay (linear range, 10–2.0×10^8 IU/mL).

Genotyping for ss469415590 (*IFNL4*-ΔG) and rs12979860 was performed at the Laboratory of Translational Genomics, National Cancer Institute with custom TaqMan allelic discrimination genotyping assays, as previously described [4]. For quality control, blinded duplicate specimens were included in the panel; genotype concordance was 130 of 130 (100%) for *IFNL4*-ΔG and 129 of 130 (99.2%) for rs12979860.

Statistical Analysis

All analyses were stratified by (self-reported) race/ethnicity. Participants who were positive for anti-HCV and HCV RNA at enrollment were categorized as "chronic," and those who were anti-HCV positive but had a negative HCV RNA result were categorized as "cleared." For each *IFNL4*-ΔG and rs12979860 genotype, we determined the proportion of participants who had cleared HCV infection and determined unadjusted and adjusted odds ratios (ORs), 95% confidence intervals (CIs), and *P* values for HCV clearance. Adjusted analyses included age (quartiles), chronic hepatitis B virus (HBV) infection status, and HIV infection status as covariables. For sparse data (white subjects), we calculated the median unbiased estimate of the OR and the exact *P* value.

To increase statistical power, we pooled data from WIHS with published data from UHS and ALIVE [4] and calculated Mantel–Haenszel ORs and the corresponding 95% CIs and *P* values. As previously described [4], we compared the area under the receiver operating characteristics curve (AUROC) for the *IFNL4*-ΔG and rs12979860 genotypes based on a *z* test statistic where the variance of the difference of the AUROCs was computed using a parametric bootstrap.

Among WIHS participants categorized as chronic, we examined the relationship between the HCV RNA levels (log 10-transformed) at the enrollment visit and *IFNL4*-ΔG genotype using the Kruskal–Wallis test.

RESULTS

Demographic and Clinical Characteristics of the Study Population

Among the 555 black women included in this investigation, the median age was 41 years (Supplementary Table 1). Most of these women were recruited during 1994 or 1995 (88.8%), acknowledged a history of injection drug use (81.8%), and were infected with HIV (86.1%), whereas few (2.5%) were chronically infected with HBV. In addition, 185 Hispanic and 150 white women were included in this study (Supplementary Table 1). The women in these groups were somewhat younger (median age, approximately 37 years in each group) than the black participants and less often coinfected with HIV (white, 85.3%; Hispanic, 77.8%). The frequency of the *IFNL4*-ΔG allele was 61.7% among the black participants, 36.8% among Hispanic participants, and 32.7% among the white participants (Supplementary Table 1). Linkage disequilibrium (r^2) between *IFNL4*-ΔG and rs12979860 in WIHS participants was: 0.83 for blacks, 0.97 for Hispanics, and 0.99 for whites. In each population, the distribution of *IFNL4*-ΔG genotypes was consistent with expectations under Hardy–Weinberg equilibrium.

IFNL4-ΔG Genotype and HCV Clearance in WIHS

Overall, 20.8% of the women had cleared HCV infection; however, this proportion varied markedly by race/ethnicity (black, 15.0%; Hispanic, 35.7%; white, 24.0%). The proportion of women with cleared HCV infection also varied by *IFNL4*-ΔG genotype (Table 1). Among black women, this proportion was similar for those with the *IFNL4*-ΔG/ΔG genotype (11.9%) or the *IFNL4*-TT/ΔG genotype (11.3%) but was much higher among those with the *IFNL4*-TT/TT genotype (32.6%; OR, 3.59 [compared with *IFNL4*-ΔG /ΔG]; $P = 3.3 \times 10^{-5}$). These associations remained the same in an adjusted analysis (Table 1). For rs12979860 genotype, the corresponding proportions of black women with cleared HCV infection were 11.4% for rs12979860-TT, 12.7% for rs12979860-CT (OR, 1.14 [compared with rs12979860-TT]; $P = .67$), and 26.1% for rs12979860-CC (OR, 2.75; $P = 9.4 \times 10^{-4}$).

Among Hispanic participants, 16.0% of those with the *IFNL4*-ΔG/ΔG genotype had cleared HCV, compared with 24.4% with *IFNL4*-TT/ΔG (OR, 1.70; $P = .38$) and 55.4% with *IFNL4*-TT/TT (OR, 6.52; $P = 1.6 \times 10^{-3}$). Among the white participants, none of the 15 individuals with the *IFNL4*-ΔG/ΔG genotype cleared HCV infection, compared with 16.2% of those with *IFNL4*-TT/ΔG ($P = .20$) and 37.3% with *IFNL4*-TT/TT genotype ($P = 3.8 \times 10^{-3}$). Sparse data for the *IFNL4*-ΔG/ΔG genotype in white participants precluded a meaningful calculation of adjusted ORs.

IFNL4-ΔG Genotype and HCV Clearance in Blacks: Pooled Analysis

In addition to WIHS, data on *IFNL4*-ΔG genotype and spontaneous HCV clearance among black individuals is available

Table 1. Numbers and Proportions of Anti–Hepatitis C Virus (HCV)–Positive Women Who Had Cleared HCV RNA, by Race/Ethnicity and *IFNL4*-ΔG Genotype, Women's Interagency HIV Study

Genotype	Number	Cleared, %	OR	95% CI	*P* Value	OR_a^a	95% CI	*P* Value
Black								
All	555	15.0						
ΔG /ΔG	219	11.9	Referent			Referent		
TT/ΔG	247	11.3	0.95	.54–1.67	.86	0.96	.54–1.72	.90
TT/TT	89	32.6	3.59	1.96–6.56	3.3×10^{-5}	3.58	1.93–6.62	5.0×10^{-5}
Hispanic								
All	185	35.7						
ΔG /ΔG	25	16.0	Referent			Referent		
TT/ΔG	86	24.4	1.70	.52–5.50	.38	1.69	.51–5.58	.39
TT/TT	74	55.4	6.52	2.04–20.88	1.6×10^{-3}	7.02	2.14–23.03	1.3×10^{-3}
White								
All	150	24.0						
ΔG /ΔG	15	0.0	Referent					
TT/ΔG	68	16.2	3.88[b]	.58–∞	.19[c]			
TT/TT	67	37.3	12.06[b]	1.90–∞	.004[c]			

Sparse data for the *IFNL4*-ΔG/ΔG genotype in white participants precluded a meaningful calculation of adjusted odds ratios for this group. Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for age, hepatitis B virus infection status, and human immunodeficiency virus infection status as covariables.

[b] Median unbiased estimate of the odds ratio.

[c] Exact *P* value.

Table 2. Numbers of Black Participants from Women's Interagency HIV Study, Urban Health Study, and AIDS Linked to the IntraVenous Experience (ALIVE) Study With Chronic or Cleared Hepatitis C Virus Infection, Genotype Proportions for *IFNL4*-ΔG (ss469415590) and rs12979860 Variants, and Corresponding Mantel–Haenszel Odds Ratios, 95% Confidence Intervals, and *P* Values for Each Association

Study	Variant Genotype	*IFNL4*-ΔG (ss469415590)			rs12979860		
		ΔG/ΔG	TT/ΔG	TT/TT	TT	CT	CC
WIHS	Chronic, % (n = 472)	40.9	46.4	12.7	36.2	46.4	17.4
	Cleared, % (n = 83)	31.3	33.7	34.9	26.5	38.6	34.9
	Odds ratio	Referent	0.95	3.59	Referent	1.14	2.75
	95% CI		.54–1.67	1.96–6.56		.64–2.03	1.49–5.08
	P value		.86	3.3×10^{-5}		.67	1.2×10^{-3}
UHS	Chronic, % (n = 350)	39.1	48.0	12.9	34.0	52.3	13.7
	Cleared, % (n = 109)	23.9	48.6	27.5	23.9	49.5	26.6
	Odds ratio	Referent	1.66	3.51	Referent	1.35	2.77
	95% CI		.99–2.80	1.88–6.56		.80–2.28	1.48–5.17
	P value		.056	7.9×10^{-5}		.26	1.5×10^{-3}
ALIVE	Chronic, % (n = 586)	43.5	45.2	11.3	38.9	46.9	14.2
	Cleared, % (n = 78)	24.4	46.2	29.5	19.2	47.4	33.3
	Odds ratio	Referent	1.82	4.68	Referent	2.05	4.76
	95% CI		1.02–3.26	2.40–9.10		1.09–3.82	2.40–9.43
	P value		.043	5.5×10^{-6}		.025	7.6×10^{-6}
Total	Chronic, % (n = 1408)	41.5	46.3	12.1	36.8	48.1	15.1
	Cleared, % (n = 270)	26.3	43.3	30.4	23.3	45.6	31.1
	Mantel–Haenszel odds ratio	Referent	1.44	3.84	Referent	1.44	3.23
	95% CI		1.05–1.97	2.67–5.52		1.04–2.00	2.23–4.66
	P value		.031	8.6×10^{-14}		.034	2.0×10^{-10}

Data for Urban Health Study and ALIVE were published previously [4]. Abbreviations: ALIVE, AIDS Linked to the IntraVenous Experience; CI, confidence interval; UHS, Urban Health Study; WHIS, Women's Interagency HIV Study.

from UHS and ALIVE [4](Table 2). Compared with individuals with the *IFNL4*-ΔG/ΔG genotype, we found pooled ORs of 1.44 ($P = .03$) for *IFNL4*-TT/ΔG and 3.84 for *IFNL4*-TT/TT ($P = 8.6 \times 10^{-14}$). We also pooled the data for rs12979860 in these studies (Table 2) and compared the association for rs12979860 genotype with that for *IFNL4*-ΔG genotype. The AUROC was 0.64 for *IFNL4*-ΔG genotype and 0.61 for rs12979860 genotype ($P = .09$, difference in AUROC values).

IFNL4-ΔG Genotype and HCV RNA Levels

HCV RNA levels ($\log_{10}$IU/mL) measured at study entry were available for 705 WIHS participants with chronic hepatitis C (Supplementary Table 2). Among the 472 black women, those with the *IFNL4*-ΔG/ΔG genotype had the lowest median HCV RNA level (6.16), those with the heterozygous *IFNL4*-TT/ΔG genotype had an intermediate level (6.31; $P = .02$ compared with *IFNL4*-ΔG/ΔG) and those with the *IFNL4*-TT/TT genotype, the most favorable genotype for spontaneous clearance and treatment response, had the highest HCV RNA level (6.48; $P = .008$ compared with *IFNL4*-ΔG/ΔG). A similar trend for median HCV RNA levels was observed among the 119 Hispanics: 5.99 for *IFNL4*-ΔG/ΔG, 6.26 ($P = .02$) for *IFNL4*-TT/ΔG, and 6.59 ($P = .0009$) for *IFNL4*-TT/TT. This trend was not seen among the 114 white participants with an HCV RNA measurement (*IFNL4*-ΔG/ΔG, 6.25; *IFNL4*-TT/ΔG, 6.12; IFNL4-TT/TT, 6.32); none of the differences among white individuals was statistically significant (Supplementary Table 2).

DISCUSSION

These results provide further evidence that the *IFNL4*-ΔG variant and, by extension, the presence of IFN-λ4 protein that it generates are strongly associated with impaired clearance of HCV. Among black WIHS participants, the proportion of women with cleared HCV infection was >3-fold higher in those who do not produce IFN-λ4 (ie, *IFNL4*-TT/TT genotype) than in those with a genotype that generates IFN-λ4 (ie, *IFNL4*-TT/ΔG or -ΔG/ΔG genotype). To increase statistical power and summarize all available evidence in black individuals, we combined data from WIHS with that from 2 other studies of HCV clearance. In this pooled analysis of 1678 individuals, genotype for the *IFNL4*-ΔG allele yielded a higher AUROC than the rs12979860 genotype. In addition, participants with the *IFNL4*-TT/ΔG genotype cleared HCV significantly more often than those with the *IFNL4*-ΔG/ΔG genotype, which suggests that this relationship does not fit a dominant genetic model. Those patterns are consistent with our previous observations for the association between *IFNL4*-ΔG genotype and viral clearance in response to pegylated interferon alfa/ribavirin treatment for chronic hepatitis C [4]. Taken together, these data suggest that HCV viral clearance (spontaneous and treatment induced) may be inversely related to the number of *IFNL4*-ΔG alleles an individual carries.

With only 150 white WIHS participants and an r^2 of 0.99 between *IFNL4*-ΔG and rs12979860 in these subjects, we could not compare spontaneous clearance associations for the 2 variants in this group. Previously, we reported that the associations with spontaneous clearance were similar for these variants among 557 white participants in UHS [4], and among 633 patients in the Swiss HCV Cohort [8] the association (OR per allele) with spontaneous clearance was similar for *IFNL4*-ΔG (3.3-fold) and rs12979860 (3.2-fold) genotypes. There was low statistical power to detect differences between *IFNL4*-ΔG and rs12979860 in each of these analyses. The Swiss investigators did, however, find *IFNL4*-ΔG genotype to be a significantly better predictor of treatment response than rs12979860 genotype [8].

Our study did not address the mechanism by which *IFNL4*-ΔG and IFN-λ4 might cause impaired HCV clearance. Previously we showed that IFN-λ4 protein is differentially expressed according to *IFNL4*-ΔG genotype and that IFN-λ4 may preactivate the JAK-STAT pathway and limit further activation by type 1 and type 3 interferons [4]. In this study, HCV RNA levels (among black and Hispanic participants) were inversely related to the number of *IFNL4*-ΔG alleles, which is broadly consistent with results from earlier studies based on genome-wide association study markers for *IFNL4*-ΔG [9, 10]. Together, these findings suggest IFN-λ4 may exert modest ongoing viral control in HCV-infected individuals yet impair the fully effective immunological response needed for complete viral clearance. Bibert et al have attributed the effect of *IFNL4*-ΔG to decreased induction of *IFNL3* and *CXCL10* (IP-10) [8], but it is unclear how that might explain the association of *IFNL4*-ΔG with lower HCV RNA levels in untreated patients.

This study had limited statistical power for some comparisons of interest. Relatively small numbers of Hispanic and white WIHS participants restricted some comparisons in those groups, including the analysis of HCV RNA levels among white women (Supplementary Table 2). Although we examined data for >500 black WIHS participants, statistical power was low for some comparisons in that group, but we were able to address that issue by pooling data from WIHS with published results from similar cohorts. This pooled analysis of black individuals provides the most precise estimates available for the association of *IFNL4*-ΔG genotype with spontaneous clearance of HCV.

In conclusion, the recently discovered *IFNL4*-ΔG variant is an important determinant of spontaneous HCV clearance and is associated with modest ongoing viral control in HCV-infected individuals. Elucidation of the mechanism by which IFN-λ4 might affect viral clearance could lead to new insights into the pathogenesis of HCV infection.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. L. P.-O. and T. R. O. are inventors on patent applications filed by the National Cancer Institute for the *IFNL4*-ΔG (ss469415590) genotype-based test and for the IFNL4 protein.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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