

current findings from Valenti et al. neither demonstrate nor specifically suggest an opposite conclusion since their study patients were in fact quite hyperinsulinemic, and hyperinsulinemia significantly improved with iron depletion.

However, the fact that iron depletion has anti-inflammatory effects, per se, is, suggested by studies on other models of chronic liver disease, such as hepatitis C<sup>3</sup> and experimental alcoholic hepatitis.<sup>4</sup> As iron catalyzes oxidative stress it is possible that lowering of iron to low levels, has effects similar to iron chelation, e.g., it reduces overall oxidative stress no matter how originated.

Therefore, the current findings by Valenti et al. appear, rather than discordant, complementary to our findings,<sup>1</sup> and indicate that iron depletion improves necroinflammatory markers in NAFLD even in the absence of abnormal glucose metabolism, such as seen in impaired glucose tolerance and type 2 diabetes.

When all of the above findings are eventually integrated, one other conclusion seems apparent: how little pathogenetic relevance all such disease classifications have, if the final common pathway of liver damage is the same whether or not initiated via metabolic stress, HFE genes, chronic infection, or chronic exposure to toxins such as ethanol.

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## High Frequency of CCR5-Δ32 Homozygosity in HCV-Infected, HIV-1-Uninfected Hemophiliacs Results From Resistance to HIV-1

Dear Sir:

CCR5-Δ32 homozygotes are resistant to infection by human immunodeficiency virus type 1 (HIV-1)<sup>1–3</sup> because they do not express CCR5, which is a major HIV-1 coreceptor.<sup>4–7</sup> Woitas et al.<sup>8</sup> recently reported that the CCR5-Δ32 homozygous genotype was increased in 153 patients who were infected with hepatitis C virus (HCV) but not HIV-1. They also found that HCV-infected, HIV-1-uninfected subjects with the CCR5-Δ32 homozygous genotype had higher HCV levels than CCR5 wild-type patients.<sup>8</sup> Based on these findings, the authors concluded, “The CCR5-Δ32 mutation may be an adverse host factor in hepatitis C.” Because most HCV-infected patients in that study had hemophilia, we examined this hypothesis among subjects enrolled in a large international study of hemophiliacs who were at high risk of infection with HCV and HIV-1.

The Multicenter Hemophilia Cohort Study (MHCS) is a prospective cohort study of hemophilic patients enrolled in the United States and Europe. Hemophilic patients were at very high risk of infection with HIV-1 and HCV until the mid-1980s when use of virally inactivated plasma-derived clotting factor concentrates became the standard of care. The CCR5-Δ32 genotypes of 1419 Caucasian patients were determined by polymerase chain reaction (PCR) amplification of DNA, followed by single-stranded conformational polymorphism analysis as previously described.<sup>3</sup> Most subjects were male (98.5%) and the median age at enrollment was 29.4 years (interquartile range, 20.8–38.3 years). The vast majority was infected with HCV (1362/1419, 96.0%), and 72.1% (1023 of 1419) were infected with HIV-1. CCR5-Δ32 homozygotes comprised 1.1% of the total population and the overall genotypic distribution for the CCR5 allele was consistent with Hardy–Weinberg equilibrium (HWE) (Table 1). To determine whether CCR5-Δ32 homozygotes were more likely to be infected with HCV, we looked at genotypes among the 1362 patients who were infected with HCV. The distribution in this group was very similar to that of all hemophiliacs and of other large Caucasian populations<sup>3</sup>; 13 of 1362 (1.0%) were CCR5-Δ32 homozygotes, with no evidence of deviation from HWE (Table 1). These data provide no support for the hypothesis that CCR5-Δ32 homozygosity increases the risk of HCV infection.

Per Woitas et al.,<sup>8</sup> we also examined the distribution of genotypes among the 358 patients with hemophilia who were infected with HCV, but not HIV-1. Contrary to what we observed in all HCV-infected hemophiliacs, but very similar to what Woitas et al.<sup>8</sup> reported, 3.4% of the HCV-infected, HIV-uninfected hemophiliacs

**Table 1.** Distribution of Observed and Expected CCR5 Genotypes in Multicenter Hemophilia Cohort Study Subjects of European Descent, by HCV and HIV Infection Status

	Subjects		CCR5 Genotype			P value <sup>a</sup>
			WT/WT	WT/Δ32	Δ32/Δ32	
All hemophiliacs	1419	Observed	1201 (84.6%)	203 (14.3%)	15 (1.1%)	>0.05
		Expected	1195.6 (84.3%)	213.9 (15.1%)	9.6 (0.7%)	
HCV+ hemophiliacs	1362	Observed	1153 (84.7%)	196 (14.4%)	13 (1.0%)	>0.05
		Expected	149.0 (84.4%)	203.9 (15.0%)	9.0 (0.7%)	
HCV+/HIV– hemophiliacs	358	Observed	292 (81.6%)	54 (15.1%)	12 (3.4%)	

<sup>a</sup>χ<sup>2</sup> test of Hardy-Weinberg equilibrium.

were *CCR5-Δ32* homozygotes, which is 3-fold higher than expected under HWE ( $P < 0.0001$ ; Table 1). *CCR5-Δ32* homozygosity was increased among HCV-infected, HIV-uninfected hemophiliacs because only 1 of 13 (7.7%) *CCR5-Δ32* homozygotes were infected with HIV-1, compared with 861 of 1153 (74.7%) wild-type patients and 142 of 196 (72.4%) *CCR5-Δ32* heterozygotes. Therefore, the increased frequency of the *CCR5-Δ32/Δ32* genotype among HCV-infected, HIV-uninfected hemophiliacs resulted from resistance to infection with HIV-1, not increased susceptibility to HCV.

Woitas et al.<sup>8</sup> also reported that HCV blood levels were higher in *CCR5-Δ32* homozygotes (median,  $32.3 \times 10^6$  copies/mL) than *CCR5* wild-type patients ( $5.7 \times 10^6$  copies/mL;  $P = 0.045$ ).<sup>8</sup> In contrast, among HCV-infected, HIV-uninfected hemophiliacs enrolled in MHCS, the median HCV bDNA level was slightly lower among *CCR5-Δ32* homozygous patients ( $2.0 \times 10^6$  equivalents/mL) than wild-type patients ( $3.1 \times 10^6$  equivalents/mL;  $P > 0.05$  Wilcoxon rank sum test). The difference in HCV viral levels between *CCR5-Δ32* homozygotes and wild-type patients in the study by Woitas et al. could be a chance finding, or it could reflect differences between the 2 genotype groups in the distribution of other factors (e.g., age, duration of infection) that affect HCV levels.

Our findings do not support the hypothesis that the *CCR5-Δ32* homozygous genotype increases the risk of HCV infection. Rather, we have shown that the increased frequency of *CCR5-Δ32* homozygosity in HCV-infected, HIV-1-uninfected hemophiliacs is due to the protective role of this genotype against HIV-1 infection. Because HIV-1 was readily transmitted through contaminated blood products, the proportion of *CCR5-Δ32* homozygotes among HIV-1-uninfected hemophiliacs is heavily enriched.

Host genetics play an important role in HIV-1 infection and other human infections. As our knowledge of the human genome expands, additional links between human genetics and infectious agents will no doubt be identified. Epidemiologic studies of the potential role of host genetics and infectious diseases should be carefully designed to avoid biases that can yield spurious associations.

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## HCV Chronic Infection and *CCR5-Δ32/Δ32*

Dear Sir:

In the June 2002 issue of *GASTROENTEROLOGY*, Woitas et al.<sup>1</sup> document an increased prevalence of *CCR5-Δ32* homozygosity in patients with chronic hepatitis C and suggest that the *CCR5-Δ32* mutation may be an adverse host factor in HCV hepatitis. The findings are in agreement with the 6.7% frequency of *CCR5-Δ32* homozygous patients with HCV infection, reported by Nguyen et al.<sup>2</sup> The author of the accompanying editorial<sup>3</sup> supports the conclusions of these studies on the association between a homozygous mutation in the chemokine receptor CCR gene and increased prevalence of HCV infection. It is somewhat intriguing that mutant alleles of the *CCR5* chemokine receptor gene seem to confer resistance to HIV infection,<sup>4</sup> while favoring susceptibility to the HCV infection.<sup>1,2</sup>

These researches give us an opportunity to share our experience on the evaluation of the *CCR5* genotype in 235 chronic carriers of HCV infection and in 96 healthy controls<sup>5</sup>: the homozygous *CCR5-Δ32* mutation was found in only 1 patient (0.4%), whereas the heterozygous mutation was present in 18 patients (7.7%) and in 9 controls (9.4%). The frequency of the *CCR5-Δ32* allele was 4.7% in the anti-HCV positive patients and 4.7% in the controls ( $P = \text{NS}$ ). These rates are in keeping with the  $\Delta32$  allele frequency of 4.7%, reported by Zamarchi et al. among 371 healthy Italian blood donors.<sup>6</sup>

These conflicting observations may be explained by a different population of HCV-infected patients under investigation in these studies. Hemophilia was the major risk factor for infection in the 2 positive studies, Woitas et al.<sup>1</sup> study and in the Nguyen et al.<sup>2</sup> study, whereas no hemophiliac patient was included in our series. Moreover, acquisition of the infection through the intravenous route was ascertained in a minority of our patients: (14.7%) whereas it was recalled by most patients in the other studies.<sup>1,2</sup>

The logical conclusion that hemophiliacs rather than HCV-infected patients have an increased prevalence of *CCR5-Δ32* mutations is challenged by the Woitas et al. observation that hemophiliacs