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REPLY:

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We appreciate the attention that Weller et al. have given to our report and findings. Weller et al. used an *in vitro* system based on Huh-7.5 cells silenced for endogenous apolipoprotein E (apoE) protein expression to investigate if genetic variants of the *APOE* gene (ϵ2, ϵ3, and ϵ4), when ectopically expressed, influence the production of intracellular hepatitis E virus (HEV) RNA and the expression of HEV open reading frame 2 (ORF2) protein after the cells were transfected with an HEV genotype 3 replicon. Finding that HEV RNA and ORF2 protein production were not affected regardless of which isoforms were expressed, they concluded that *APOE* polymorphisms do not affect HEV RNA replication and virus production.

HEV RNA quantification was applied by Weller et al. as an index of viral replication, and ORF2 protein quantification was used as a marker of the extent of viral particle assembly. However, HEV RNA measurement shows replication of the viral genome, not productive viral replication. Furthermore, measurement of the ORF2 protein, *per se*, is inadequate to indicate virion assembly; and other means of verifying if assembly has taken place are needed.(1)

We also note that although the data depicted in Fig. 1C,D show a trend in the reduction in production levels of HEV RNA and ORF2, respectively, when HuH-7.5 cells were incubated in the presence of ribavirin, no formal statistics were applied to analyze the trend. The ranges for the ribavirin-associated data points were wide. In addition, genotypes 1 and 3 were reported by HEV surveillance as principal infecting genotypes in the United States(2); Weller et al. only used genotype 3 in their experiments.

Weller et al. also concluded that their data do not support the findings of our study,(3) suggesting that *APOE* ϵ*3* and *APOE* ϵ*4* were associated with protection against HEV infection in non-Hispanic blacks but not in non-Hispanic whites or Mexican Americans. What we conducted was a population-based genetic epidemiologic association study

Potential conflict of interest: Nothing to report.

following up on previously reported epidemiologic data showing the anti-HEV seropositivity rate among non-Hispanic blacks to be lower than that among the other two racial/ethnic groups.[4] We identified the host genetic factor associated with the lower seropositivity to be *APOE* or genes that are in linkage disequilibrium with *APOE*.

Assuming that *APOE* is a gene that confers protection against HEV infection, we proffered various mechanisms by which the apoE protein can exert such protection: (1) HEV using the same hepatocyte entry mediators as those of apoE, (2) the incorporation of apoE in the HEV envelope, and (3) apoE modulating the immune response against HEV. The role of apoE as having the capability to affect HEV replication was not considered, as Weller et al. had.

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