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Polymorphisms In Melanoma Differentiation-Associated Gene 5 Are Not Associated With Clearance Of Hepatitis C Virus In A European American Population

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To the Editor

In a recent article in HEPATOLOGY (1), Hoffman *et al* used two different European-ancestry cohorts to identify a haplotype in the melanoma differentiation-associated gene 5 (*mda5*) that is associated with a 16-fold increased likelihood for spontaneous hepatitis C virus (HCV) clearance. In this haplotype, H843/T946, the SNP rs3747517 encoding the H843 variant was also associated with spontaneous HCV clearance whereas the SNP (rs1990760) encoding T946 was not. As discussed in an accompanying Editorial (2), if this finding is true, it broadens knowledge regarding the known innate immune response to HCV.

Given these results and the potential implications, we used existing genotype data from our genome-wide association study of 1708 European Americans previously-characterized for HCV clearance (N=689) and persistence (N=1019) to interrogate the same variants (3). Unfortunately, our results demonstrated no association of either variant (rs3747517, allelic OR=1.01, p value=0.87; rs1990760, allelic OR =1.05) with HCV clearance. Furthermore, the implicated H843/T946 haplotype was absent in our population.

The differences in these two studies may be reflective of the population compositions. The frequency of SNP rs3747517 varies widely across populations. Using 1000 genomes data (4) the minor allele frequency (T) ranges from 25% in Europeans, to 69% in Asians and 42% in Africans. In our study of individuals of European ancestry, the allele frequencies were consistent with the Europeans in 1000 genomes (26%) in both the HCV spontaneous clearance and persistent individuals, but differ from those reported by Hoffmann and colleagues (34%). Although their cohort is primarily German, 14% of the study population was from Ireland, Russia and Southern and Eastern Europe; thus population substructure may affect these association results and no correction was employed. Moreover, the haplotype frequency (TT) was reported at 5%, and yet this haplotype is completely absent from European populations in 1000 genomes, reflective of the strong LD ($D'=1.0$) between these two SNPs. Further studies are needed to explain the differences observed among populations and make the results applicable to other European cohorts.

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