Correspondence

Single Nucleotide Polymorphisms in Human Genes and Increased Susceptibility to West Nile Virus Disease

To the Editor—Yakub et al. have reported that single nucleotide polymorphisms (SNPs) in human genes are associated with susceptibility to West Nile virus (WNV) disease [1]. The most prominent association was observed with the transition from T to C in SNP rs3213545, which is located in exon 2 of the OASL gene (a member of the 2′-5′-oligoadenylate synthetase [OAS] family). Surprisingly, the nucleotide change was synonymous. Their analysis predicted that the nucleotide change T210C resulted in a new exon splice enhancer (ESE) sequence (a binding site for the SF2/ASF splicing factor protein) that could abolish activation of RNase L and, consequently, reduce degradation of viral RNA. The examination of human genes was stimulated by the finding that, in most inbred laboratory mouse strains, susceptibility to WNV disease is associated with a non-synonymous mutation, C820T, in exon 4 of the gene for Oasl1 [2, 3].

A number of issues should be clarified. Because the severity of WNV infection increases with age and because the 2′-5′-OAS family exerts pleiotropic effects, the observation of an increased frequency of a homozygous C at nt 210 might simply reflect increased longevity. A table stratifying age and allele frequency in case patients and control subjects would be of interest.

Symptoms develop in ~1 in 150 persons infected with WNV, yet 48% of the control subjects in Yakub et al.’s study were homozygous at the incriminated allele. Accordingly, additional factors must be involved in virulence. As mentioned by the authors, other loci in the 2′-5′-OAS family should be considered. They observed in case patients 8 “novel SNPs” that had not previously been found in data from the International Haplotype Mapping consortium. This observation suggests that the novel changes are rare and, consequently, could be associated with increased susceptibility to WNV disease. The 6 instances in which the novel SNPs were not found in their control subjects are of particular interest. The novel SNP 7 was associated with a nonsynonymous mutation, A727S, in exon 10 of OAS3 at a frequency significantly different from that in the control subjects. With the other novel SNPs having synonymous mutations, an analysis of possible ESEs should be made. Severity of disease may also be associated with genotype. Tabulation of genotype (including the novel SNPs) and disease manifestation (meningitis, encephalitis, and fever) might be informative.

Yakub et al. consider that both the C820T mutation in mice and the nucleotide change involving rs3213545 in humans result in dominant-negative mutants. Although overexpression of normal Oasl1 in Oasl1-820T-motorneurons decreases WNV replication [4], mating experiments in mice indicate that F1 hybrids of WNV-susceptible mice and wild-type resistant mice are not killed by WNV [3], a finding consistent with a recessive susceptibility gene. With respect to the change in the human SNP rs3213545, the finding of increased susceptibility to WNV disease only for the homozygous state is also consistent with a recessive inheritance pattern.

Another issue is the need for comment on the fact that the frequency of the nonsynonymous G15A change in SNP rs3741981 was statistically different between those control subjects whose OAS and RNASEL genes were completely sequenced and the remaining control subjects who were evaluated by an allele-specific mutation assay. In addition, it is unclear why the appearance of a new ESE should result in “full-length” OASL1. A truncated protein might have been anticipated.

Although flavivirus-resistant mouse strains have unaltered susceptibility to infection with other viruses (reviewed in [5]), a role for the OAS-RNase system in host defenses has been found with encephalomyocarditis and with reovirus, vaccinia virus, and coxsackievirus infections [6, 7]. Accordingly, implications of the observations of Yakub et al. may extend beyond the flaviviruses. Within the flaviviruses themselves, a number of possibilities should be explored. Yellow fever virus kills 30%–50% of infected individuals, a case fatality rate comparable with the homozygous occurrence of C at nt 210 in Yakub et al.’s control subjects. The rare occurrence of severe reactions in recipients of live yellow fever vaccine may be a consequence of some of the rarer nucleotide changes observed in the case patients in Yakub et al.’s study. Although Gould and I are concerned about the potential safety risks of live flavivirus vaccines [8], others have been impressed with the overall safety record of existing live yellow fever vaccines and of candidate flavivirus vaccines [9]. The genetics of vaccine recipients could be relevant. Rare genetic defects in the OAS-RNase system might allow replication of large quantities of vaccine virus, thereby facilitating reversion to virulence.

The article by Yakub et al. opens the door to a novel field: investigation of human innate viral immune defenses mediated by the OAS-RNase family. Additional studies are awaited with interest.
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References


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Reply to Seligman

To the Editor—We thank Seligman [1] for his discussion of the data we have presented [2]. We agree that the observed positive association between single nucleotide polymorphisms (SNPs) and susceptibility to West Nile virus disease comes with several caveats, and we took pains to explain these in our article. Given the similarity between the mean ages of the case patients and control subjects, it is not clear that a table stratifying age and allele frequency in these 2 groups would yield much useful information. Similarly, because the number of patients we studied was not large, we hesitated, as part of our analysis, to tabulate genotype and disease manifestations. Also, although a number of the novel SNPs appear to affect exon splice enhancers, they were observed at very low frequencies and lacked statistical significance. As a result, we did not draw any conclusions from these observations.

We agree that the door to a novel field has been opened, but we defer to the previously cited publications on flavivirus susceptibility in the mouse for its true origins [3, 4]. Additional work should target these variants in other diseases and conduct complete sequencing where possible, as a prelude to the protein and other functional studies that are recommended.

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The Male:Female Ratio Does Not Explain a Higher Risk of Vertically Acquired Hepatitis C Virus Infection in Girls

To the Editor—Our work on risk factors for mother-to-child transmission of hepatitis C virus (HCV) was published in the December issue of the Journal of Infectious Diseases [1] with an accompanying editorial commentary by R. Palmer Beasley [2]. We showed that girls were twice as likely as boys to be HCV infected (adjusted odds ratio, 2.07 [95% confidence interval, 1.23–3.48]; P = .006) [1]. We would like to point out that the editorial contains a mistake: when discussing the possibility that this association could be due to excess male mortality in utero, Beasley erroneously calculates the male:female sex ratio from our data as 668:802, or 0.833. However, as shown in table 1 of our article, there were 802 boys and 668 girls, so the male:female sex ratio at birth would therefore be 802:668, or 1.20. This error explains why Beasley was unable to interpret our statement in the Discussion, “Because the male:female ratio in our study population was higher than that observed in the general population, this finding is unlikely to be due to excessive deaths of infected males in utero” (p. 1877).

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