Letters to the Editor

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The −75A→C Substitution in the 5′ UTR of the Wilson Disease Gene Is a Sequence Polymorphism in the Mediterranean Population

To the Editor:

In their haplotype and mutation analysis of Wilson disease (WD) in Japanese patients, Nanji et al. (1997) report an A→C substitution at position −75 in the 5′ UTR of the WD gene, found in 1/42 WD chromosomes investigated. The authors considered this substitution to be a disease-causing mutation, and they postulated that the mutation adversely affects WD-gene expression, either by abolishing ribosome binding or by interfering negatively with transcriptional factor(s)–DNA binding. However, Nanji et al. (1997) did not report screening for the presence of the A→C mutation in normal chromosomes, to exclude the possibility that this mutation is a simple polymorphism.

Of 228 WD chromosomes analyzed in our study of WD in Mediterranean populations, we found the −75A→C substitution in 23 WD chromosomes that carry an unquestionable disease-causing mutation, as well as in 16 WD chromosomes in which the mutation has not yet been defined. The A→C substitution at position −75 was also detected in 15 (28%) of 54 normal chromosomes from the same Mediterranean population.

These data clearly indicate that −75A→C is a sequence polymorphism that most likely does not affect the function of the WD gene. We previously reported the same A→C substitution in the 5′ UTR (Figus et al. 1995); however, because of erroneous numbering of the nucleotide sequence in the sequence ladder, we incorrectly indicated its position as −74 instead of −75.

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Reply to Loudianos et al.

To the Editor:

We appreciate receiving additional information on the A→C substitution at position −75 in the 5′ UTR of the Wilson disease gene. When we reported this substitution (Nanji et al. 1997), we were careful to indicate that it was in the "putative promoter" region and that it *might* be associated with the disease. We pointed out that direct testing of the effect of the mutation on expression would be required to confirm the nature of the mutation. We described the results of the analysis of 21 normal chromosomes from a Japanese group, which is the same ethnic group as that of the patient. These normal-chromosome results were obtained from the analysis of the normal chromosomes in the heterozygous parents of the patients. None of the putative promoter mutations were identified in the normal sample. We did report, in table 3 of our previous study (Nanji et al. 1997), some alterations that we felt were definitely polymorphisms. Ap-