Letters to the Editor

Linkage Disequilibrium across the UGT1A Locus Should Not Be Ignored in Association Studies of Cancer Susceptibility

The study by Wang et al. (1) reported an association between human UGT1A7 gene polymorphisms and hepatocellular carcinoma (HCC) in Japanese patients with hepatitis C virus infection. The authors observed a significantly higher frequency of UGT1A7*1/*3 and UGT1A7*2/*3 genotypes/diplotypes in hepatitis C virus–infected patients with HCC compared with those without HCC. This association seemed to be from the higher allele/haplotype frequencies of UGT1A7*2 and UGT1A7*3 in the former group than the latter. However, this correlation did not rule out the effect of other polymorphisms in linkage disequilibrium (LD) with UGT1A7.

UDP-glucuronosyltransferases play a major role in glucuronidation of xenobiotics and endobiotics. An extensive superfamily of UDP-glucuronosyltransferases has been revealed and the genes have been assigned to two families: UGT1A and UGT2B. The UGT1A locus represents a complex cluster of 13 genes spanning ~190 kb on human chromosome 2q37 (for recent review, see ref. 2). This consists of nine unique first exons (plus four pseudoexons), which are each spliced to the four 3′ common exons. The expression of these transcripts occurs in a tissue-specific manner. Recent studies have also discovered dozens of polymorphisms from each of the first exons and promoters among different populations, which accounts for most interindividual variability of glucuronidation. Given the important role of UGT1A genes in elimination of various environmental carcinogens, they hereby have been deemed as good candidates to cancer susceptibility. There has been significant interest in the association of UGT1A7 alleles with risk of a variety of cancers (2).

The association between UGT1A7 and HCC was first observed in a German population (3). In the report by Wang et al. (1), a weak correlation was also observed in a Japanese population, although they focused only on hepatitis C virus–infected patients. However, it is well known that UGT1A7 is not expressed in human liver tissues, it is expressed in the upper digestive tract, including oropharynx, esophagus, and stomach (2, 4–6). Although the authors speculated that the association might result from lower activity of UGT1A7 in the entry sites of mutagens, this seems unlikely. Alternatively, we think that it might be more important that the other polymorphic regions around UGT1A7, being in LD with UGT1A7 alleles, could play, at least cooperatively, critical role in HCC risk. Specifically, strong LD across UGT1A7, UGT1A6, and UGT1A1 was shown in both Caucasians and Egyptians. UGT1A7*3 was predominantly linked with UGT1A6*2 and UGT1A1*28 in a Caucasian population (7). Meanwhile, our recent studies also showed LD between UGT1A9 (upstream of UGT1A7) and UGT1A1 in both Caucasians and Asians, which accounts for a linkage spanning 89 kb. Furthermore, the cooperation among functional polymorphisms seems to differentially alter the glucuronidation of SN-38 in human liver tissue (8). The study by Wang et al. also suggested that UGT1A7*2/*3 alleles had a higher risk for HCC than did *2/*2 or *3/*3. This could be a strong indication that other polymorphisms in LD may interact with UGT1A7 alleles. A large case-control study suggested that the UGT1A1*28 allele may be associated with an increased risk for breast cancer among Chinese women under age 40 years (9). Therefore, we suggest that association between UGT1A7 and cancer risk should consider the possible effects from other UGT1A exons.

In conclusion, due to the unique genomic structure of UGT1A locus as well as the functional cooperation or interaction of these genes, association studies based on haplotype analysis would be much more helpful to understand the roles of these genes in cancer etiology. For such a purpose, it would be critical to determine the LD and haplotype map across the whole cluster in each relevant population. On the other hand, when single UGT1A isoforms are investigated in such association studies (like in the study of Wang et al.), careful evaluation of tissue expression of individual UGT1A4 genes is required. In the study of Wang et al., it is more likely that the typed UGT1A7 alleles are simply a marker of other causative variants of IA genes expressed in the liver, such as IAI and IA6 (and others), which are in LD with IA7.

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In Response: We thank Drs. Liu, Innocenti, and Ratain for their suggestions to our study. Our study revealed that the frequencies of the UGT1A7 lower detoxification activity genotypes in patients with hepatocellular carcinoma (HCC) were significantly higher than those in patients without HCC compared with the higher detoxification activity genotypes. Because polymorphisms in this gene were reported to be associated with HCC in German population (1), we wanted to assess it among Japanese. Moreover, we would like to find a patient group with higher susceptibility to HCC by combining single nucleotide polymorphisms in UGT1A7 and interleukin-1β genes (2, 3). Because certain single nucleotide polymorphisms are often only a marker of susceptibility to a certain disease without a causative role, we have little concern about whether UGT1A7 single nucleotide polymorphisms have causative role in HCC susceptibility (4, 5).

As we mentioned in the discussion of our article (2), it is possible that UGT1A7 polymorphisms are simply a marker of other causative variants. UGT1A genes, other than UGT1A7, expressed in the liver that are in strong linkage disequilibrium with UGT1A7 may be a candidate of causative variants. However, it is still possible that UGT1A7 polymorphisms are causative variants by the following reasons. (a) Lower detoxification ability genotypes of UGT1A7 polymorphisms are associated with HCC. (b) Because hepatocarcinogenesis is a complexed pathway and circumstances around hepatocyte are important factors for this pathway, it is not necessary that causative genes are expressed in hepatocyte. Interestingly, UGT1A7, which detoxifies or glucuronidates carcinogens, is expressed in the most proximal tissues, where primary contact to orally administered and inhaled carcinogens occurs. (c) Ehmer et al. and Vogel et al. studied polymorphisms in UGT1A3, UGT1A4, UGT1A8, UGT1A9, and UGT1A10 and found no association with HCC (1, 6).

As Dr. Liu et al. suggested, it is necessary to perform genome-wide polymorphism analysis around UGT1A genes to find the causative susceptibility locus. Further prospective study using larger size cohorts and various polymorphisms should be conducted to get the incontrovertible fact at last.

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