CYP3A4 is a member of the cytochrome P450 supergene family that mediates the metabolism of numerous compounds involved in human carcinogenesis, including steroid hormones such as testosterone. Recently, a variant in the 5'- regulatory region of CYP3A4 (CYP3A4-V) was reported to confer higher stage prostate tumors compared with homozygous wild-type CYP3A4 (CYP3A4-W) in both Caucasians and African-Americans (1,2). To date, these associations have not been supported by data that address the functional significance of this polymorphism.

Westlind et al. (3) recently reported that CYP3A4-V had no effect on testosterone 6β-hydroxylation (T6βH). However, this inference was made without any formal statistical analysis. By using the raw data provided in that paper, genotype-specific mean values of T6βH were computed. The mean T6βH in CYP3A4-W homozygotes (n = 36) was 1660.6 pmol/mg per minute, whereas the mean T6βH in carriers of a CYP3A4-V allele (n = 3) was 4850.0 pmol/mg per minute. This difference was highly statistically significant by analysis of variance with F1,35 = 13.85 (P = .0007) and by Kruskal–Wallis analysis of variance by ranks with χ2 = 5.63 (P = .02). Thus, despite the small sample size, these data support the inference that CYP3A4-V is associated with altered testosterone metabolism.

The 2.9-fold higher T6βH activity in CYP3A4-V relative to CYP3A4-W (Table 1) suggests that the downstream effect of CYP3A4-V on testosterone metabolism pathways may be physiologically relevant. However, the study of CYP3A4 expression in humans is complicated by common exposure to many inducers and inhibitors of the enzyme. For example, extremely high T6βH was observed in one CYP3A4-V carrier in the study by Westlind et al. (3) who had exposure to barbiturates, which are known CYP3A4 inducers. Furthermore, studies of nifedipine metabolism (Table 1) do not indicate an association of metabolic rate with CYP3A4 genotype (5,6). Thus, additional research will be required to better define the functional significance of CYP3A4-V and to clarify the mechanism that explains the epidemiologic associations of CYP3A4-V with prostate cancer.

Estimates of the ethnic distribution of CYP3A4-V have also been reported recently that mirror the rates of prostate cancer in each ethnic group. CYP3A4-V frequencies were 0% in U.S. Japanese (2), U.S. Chinese (2,6), Taiwanese (7), and Japanese (5,6); 4%-9% in U.S. and Swedish Caucasians (2,3,6,7); 9%-10% in U.S. Hispanics (2,6); and 53%-55% in African-Americans (2,6,7). Westlind et al. (3) suggested that the higher allele frequency estimate of 9% in one Caucasian sample (7) was due to genotyping errors. Genotyping is unlikely because all variants (and a subset of nonvariants) in that study were confirmed by direct sequence analysis. Given that substantial variability in allele frequency is common across ethnic groups, it is more likely that the differences in the reported frequencies of CYP3A4-V are due to ethnic or geographic differences, rather than to technical problems in mutation detection. It is noteworthy that the frequencies of CYP3A4-V are highest among African-Americans, intermediate in Caucasians, and lowest in Asians, reflecting rates of prostate cancer in each of these populations. Although far from conclusive, the initial reports of T6βH and of CYP3A4-V frequency by ethnicity support the previously reported epidemiologic associations of CYP3A4 and prostate cancer.

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REFERENCES


Note

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