CORRESPONDENCE

RE: Loss of Heterozygosity at the CYP2D6 Locus in Breast Cancer: Implications for Germline Pharmacogenetic Studies

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Recently, Goetz et al. examined loss of heterozygosity (LOH) at the CYP2D6 locus in primary breast cancers in an attempt to determine its impact on germline CYP2D6 genotyping from DNA derived from tumors (1). They conclude that “Tumor DNA should not be used to determine germline patient CYP2D6 genotype without sensitive techniques to detect low frequency alleles…” Recently, we demonstrated that CYP2D6 genotypes from formalin-fixed, paraffin-embedded (FFPE) breast cancers are highly concordant with those from blood in 122 patient-matched samples and concluded that results from tumor DNA can be used for prospective-retrospective studies testing for association between CYP2D6 and tamoxifen response (2).

Over the preceding decade, 100% concordance has been consistently demonstrated between CYP2D6 genotypes derived from tumor vs blood (3-6). Indeed, in the first paper reported by Rae et al., 100% concordance in CYP2D6 genotypes was observed in a small sample set (n = 10)(3). In a subsequent study, conducted in collaboration with Goetz et al., DNA was extracted from 15 matched samples from patients who participated in NCCTG 89-30-52 at the Mayo Clinic and sent to the University of Michigan, where we performed CYP2D6 genotyping without knowledge of the individual patient or matched samples. These genotype results were returned to Dr. Goetz, who established concordance was 100%, as stated in our publication (4). Subsequently, Ahern et al. examined 105 matched FFPE tumor and FFPE normal tissue samples for CYP2D6 and, likewise, found 100% concordance (5). Furthermore, Thompson et al. compared CYP2D6 genotypes from leucocyte/germline DNA with frozen breast cancer tissue collected from 133 patients. Comprehensive genotyping with the AmpliChip CYP450 Test (Roche Molecular System, Inc, Pleasanton, CA), which queried 29 CYP2D6 polymorphisms to identify 33 different alleles, found complete concordance between the 133 lymphocyte/tumor pairs (6).

Thus, five separate previous studies conducted by three separate groups, who used different genotyping methods and compared tumor with normal tissue in 385 patients, have shown excellent concordance between CYP2D6 genotypes, confirming that tumor DNA is appropriate for germline CYP2D6 genotype determinations. Therefore, the recently reported 19.4% discordance in 31 matched samples by Goetz et al. suggests that methodological issues, and not tumor LOH, may be at play in their study. For example, extensive precautions are required during sample preparation to minimize sample-tracking errors and to prevent cross-contamination between different patients when using highly sensitive allele determination methodologies (3,6).

Overall, there is clear analytical validity of CYP2D6 genotyping from frozen or FFPE tumor DNA. Despite the established concordance, the large number of clinical studies using both normal and tumor DNA for CYP2D6 testing has not shown a clear association between CYP2D6 genotype and clinical outcomes for patients treated with adjuvant tamoxifen (7). Associating a biomarker with a clinically relevant endpoint is critical to establishing clinical utility. Therefore, the current data do not support changing clinical practice to include CYP2D6 genotype to guide tamoxifen therapy in breast cancer patients. Future studies are needed to aid in tailoring endocrine therapy based on patient germline genotype.

Editor’s Note

The authors of the original study have chosen not to respond to this correspondence and refer the reader to the editorial concerning their article (Johnson JA, Hamadeh IS, Langaeey TY. Loss of Heterozygosity at the CYP2D6 Locus in Breast Cancer: Implications for Tamoxifen Pharmacogenetic Studies. J Natl Cancer Inst. 2015;107(2):dju437 doi:10.1093/jnci/dju437).

References


