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## Notes

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# Re: CYP2D6 Genotype and Tamoxifen Response in Postmenopausal Women With Endocrine-Responsive Breast Cancer: The Breast International Group 1-98 Trial

Two recent articles by Regan et al. (1) and Rae et al. (2), accompanied by an editorial (3), purport to settle the controversy of whether *CYP2D6* genotype is associated with the pharmacodynamics of tamoxifen. There have been many previous studies, which vary in source of DNA (tumor, blood), phenotype (efficacy, toxicity, pharmacokinetics), general design (prospective, retrospective), concomitant medications (other anticancer medications, CYP2D6 inhibitors), and statistical approaches (4). A key issue in all genetic studies is the quality of the primary genetic data, as no inferences can be drawn from genotype data of low quality. In regard to the latter, a critical and fundamental first step in assessing the quality of genotypes is a test for deviation of the genotype distribution from Hardy–Weinberg equilibrium (HWE) (5), which should be considered of particular importance when DNA for genotyping has been extracted from tumor, rather than germline tissue.

Thus, it is of grave concern that one of the recent studies (1) shows clear evidence of massive departures from HWE; insufficient information was provided in the second study (2) to assess the quality of the genotype data. Using the data in Table 2 of the Regan et al. study (1), the two most important variants, rs3892097 and rs28371725, fail quality control, with unacceptable $P$ values (from $\chi^2$ tests for consistency with HWE) of approximately $10^{-91}$ and $10^{-173}$, respectively.

For both variants, there is an excess of homozygotes, consistent with the hypothesis that hemizygous deletions of *CYP2D6* in tumors from which DNA samples were obtained may account for these flawed results. The estimated excess of homozygotes is approximately 5% for each genotype, consistent with approximately 33% of tumor samples having *CYP2D6* deletions. Because *CYP2D6* is located on chromosome 22q13 where frequent losses of heterozygosity in breast cancer cells have been reported (6), it would not be surprising if *CYP2D6* were deleted in breast cancer. In addition, 22q13 deletions have been associated with a worse prognosis, as exemplified by a large single-institution Japanese study in which 32% of tumors had 22q13 deletions (7). Thus, if a tumor from a patient who is a germline heterozygote loses one of the alleles, this causes misclassification of that patient's tamoxifen metabolism phenotype. An alternative explanation, given the incomplete genotyping in these DNA samples, is that samples from heterozygotes are disproportionately not called (ie, the missing data are not missing at random). Genotyping of additional markers on chromosome 22q13 could distinguish these hypotheses. In any case, the genotype data from this study fail the most rudimentary quality tests, and therefore, we question its validity. Given the importance of the question being studied, we urge the retraction of the Regan et al. study (1).

We also urge reanalysis of other studies that have utilized tumor DNA for genotyping, given the potential for hemizygous deletion of *CYP2D6* in breast cancer. Hopefully, this will be another important "lesson learned" for investigators in breast cancer genomics (3). The goal of personalized medicine is to provide an appropriate dose of the optimal drug to each individual patient, but it is critical that quality data from rigorous studies be used to inform these decisions.

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