



Letter to the Editor

Estimating genotype and allele frequencies of the CYP2D6 gene



We wish to comment on the manuscript "Characterization of the CYP2D6 drug metabolizing phenotypes of the Chilean mestizo population through polymorphism analyses" [1]. This report has in our opinion serious conceptual shortcomings in basic genetics, population genetics and statistics. The authors tested for three alleles, *CYP2D6**2, *CYP2D6**3, *CYP2D6**4, they summarize their results in Table 3. They committed what we consider to be a very basic mistake here; they treated each allele as if it were part of a different bi-allelic gene. For each of the three alleles *2, *3 and *4, if they detected a heterozygote they recorded it as *1/*X, and if the allele did not stain they noted it as *1/*1. This is why there are no *2/*3, *2/*4 or *3/*4 genotypes noted in Table 3; they did not check the other stains for the same individual to see if she/he had one or both of these alleles. What Table 3 is actually showing is the frequencies of allele *X (X = 2, 3, 4) vs. alleles "Not *X", and note that "Not X" is different for the three alleles. Since they erroneously assumed that "Not *X" = *1, from their total values in Table 3 we could estimate the frequency of "allele *1" as 0.593, 0.989 and 0.882 for alleles *2, *3 and *4, respectively (<http://www.cypalleles.ki.se/cyp2d6.htm>). The lack of understanding of basic genetics by the authors is confirmed in Table 4, where they treated the heterozygotes *2/*3 and *2/*4 they observed as if they were tetraploids!

Another strange result reported in Table 3 is the low number of *2/*2 men, which is so much less than expected that (using the appropriate statistical tests, see below) both the frequency of genotype *2/*2 and the frequency of allele 2 are significantly lower in males than in females. The latter is indicated in Table 3, but is not mentioned in the manuscript. This may be a result of their sampling method, which is only described superficially; they indicate only that it comes from a mestizo population with 18% Amerindian-Caucasian mixture (we must assume that the 18% refers to the Amerindian component). There are a number of human population genetic studies of Chile published in several international journals which demonstrate that the percentage of Amerindian mixture is strongly correlated with socioeconomic stratum, the authors include one of these references in their manuscript [2]; there is much less mixture in the highest strata and much more in the lower strata. The differences reported between men and women suggest that they sampled asymmetrically men and women with different Amerindian components.

The authors indicate under section Statistical Analyses that they used Student's t and the chi squared test, however, they present no results using the latter. Below Table 3 they indicate that they used one-way ANOVA and Student's t, but no results of ANOVA are reported, and neither analysis is appropriate to compare genotype and allele frequencies.

The information provided in this paper is not reliable, for the reasons detailed above.

References

- [1] N. Varela, L. Quiñones, J. Stojanova, J. Garay, D. Cáceres, S. Cespedes, J. Sasso, C. Miranda, Characterization of the CYP2D6 drug metabolizing phenotypes of the Chilean mestizo population through polymorphism analyses, *Pharmacol. Res.* 101 (2015) 124–129, <http://dx.doi.org/10.1016/j.phrs.2015.07.020>.
- [2] C.Y. Valenzuela, M.P. Acuña, Z. Harb, Sociogenetic gradient in the Chilean population, *Rev. Med. Chil.* 115 (4) (1987) 295–299.

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