Letter to the Editor

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“To characterize the P450 phenotype, one should take into account the drug–gene interactions over more than one drug and one gene.”

Letter regarding: Ekhardt C, Matic M, Kant A, van Puijenbroek E, Schaik RV. CYP450 genotype and aggressive behavior on selective serotonin reuptake inhibitors. *Pharmacogenomics* 18(7), 613–620 (2017) [1].

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With great interest, we read the paper by Ekhardt *et al.* on the relationship between CYP450 genotype, selective serotonin reuptake inhibitors (SSRIs) and aggressive behavior [1]. They reported that Lareb, The Netherlands Pharmacovigilance Centre, received 50 reports of aggression while on SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline or venlafaxine) between 2010 and 2014. Genetic profiles were generated for two of the CYP450 genes that are known to be involved in the metabolism of SSRIs: CYP2D6 and CYP2C19. The allelic and predicted phenotypic frequencies for these genes were compared to a healthy blood donor control group of 99 individuals and literature data in Caucasians, but no significant differences between the aggression cases and the controls were found. Based on these data, the authors concluded: "We found no supporting evidence for a significant relationship between CYP2C19 and CYP2D6 genetic polymorphisms and aggression in patients using SSRIs." We believe this paper has multiple, serious methodological problems, which call the authors' conclusion into question.

Our first comment involves their sample size for cases involving aggression (in other words, 18 cases). The authors base their conclusions on a very selected, small group of patients and then stretch those conclusions to the general population. This is an example of inappropriate generalization or proof by example. That the authors did not see differences between cases and controls for frequencies of functionally compromised P450 alleles may well have been a result of their small sample size. This is in addition to the well-known fact that statistics, performed using small sample sizes, may lack sufficient statistical power to reject a null hypothesis and detect a true effect. We note that the study by Lucire and Crotty [2], which did detect increased frequency of variant CYP450 alleles in cases (akathisia) versus controls, had sample sizes of 85 (cases) and 150 (controls).

The authors go on to state that they did not find a single case of a poor metabolizer (PM) for either CYP2D6 or CYP2C19 among their 18 cases, and subsequently state that, with respect to CYP2D6, this absence fails to substantiate the hypothesis that it plays a role in the risk of aggressive behavior. A PM for either enzyme would be a likely candidate for increased adverse events based on decreased metabolism. We believe, however, that there may be other reasons for this finding. Individuals, who are receiving psychotropic drugs and are PMs, are the first to feel the adverse effects of medication, and it is certainly possible and may be likely that they stop the medication when they feel increasingly worse instead of better. This is supported by the fact that, in clinical trials on psychotropic medication, the number of dropouts is usually around half of the participants. If that is the case here, it is not surprising that PMs do not make it to the stage where they report aggression as a side effect. It is also possible that, among the 32 who did not agree to participate or who did not submit DNA, there were people with such bad experiences on SSRIs that they did not wish to be involved. The PMs (0–2) that the authors expected out of their

18 cases could be in the group of nonparticipants. We believe that the authors' method of selecting participants creates a bias in favor of the lack of an association. Finally, with such a small sample size, it is possible that PMs were simply missed due to random chance. Given the expected frequency of PMs given in the paper (5–10%), the binomial probability of seeing zero PMs among 18 cases ranges from 0.15 to 0.40.

We also disagree with the authors' decision to limit their study to just *CYP2C19* and *CYP2D6*. Considering patient M053720, this subject was prescribed citalopram, and is characterized as an intermediate metabolizer for both *CYP2C19* and *CYP2D6*. According to the paper, citalopram is metabolized by *CYP2C19* (~40%), *CYP2D6* (~30%) and *CYP3A4* (~30%). To us, it seems unlikely that the authors could completely understand the relationship between a drug and P450 genotypes without having information on all of the P450 enzymes that metabolize the drug. The authors do not explain why *CYP3A4* was not investigated, when it is as involved in the metabolism of citalopram as the other two enzymes. To characterize the P450 phenotype, one should take into account the drug–gene interactions over more than one drug and one gene. Citalopram is known to inhibit both *CYP2D6* and *CYP2C19*. For this patient, *CYP2D6**4 is a loss of function allele and *CYP2C19**2 exhibits decreased activity. The patient is on medication that will further reduce the metabolic capabilities of both P450s. This patient might well be considered a PM due to phenoconversion [3]. The same applies to patient M053719, who is using paroxetine, a paninhibitor. This patient's *CYP2D6**5 is a loss of function allele, *CYP2C19**2 exhibits decreased activity, and the patient is on medication that inhibits both enzymes as well as most other P450 enzymes (including *CYP3A4*) that might be recruited if the titer of the medication in the blood starts increasing. This patient is also an excellent candidate for phenoconversion to a PM. The *CYP3A4* gene is the work horse of the CYP450 system and could assist in metabolizing both citalopram and paroxetine, but the status of that enzyme is unknown in all the patients included in this study.

Finally, the last four cases (out of 18) reported in Table 1 do not include any information on the medication that these patients were taking. Without this information, we do not believe these four cases can contribute anything to the understanding of the relationship between *CYP450* genotype and aggressive behavior, since the authors do not, in fact, know which P450 enzymes are specifically involved. Elimination of these four cases would bring their sample size down to 14 and increase our concern regarding all matters relating to small sample size.

We believe that the issues mentioned here should have been addressed by the authors. While the study of the relationship between P450 genetic polymorphisms and the occurrence of aggressive behavior in patients using SSRIs is critically important in our present-day health care system, the methodological problems inherent in this study significantly limits its contribution to increasing our understanding of this relationship. Furthermore, the use of this study to support particular points of view on this topic for criminal cases in front of court systems or for decisions by governmental organizations regarding future research is, in our opinion, not scientifically warranted.

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