On the Role of Genetic Testing for Personalized Drug Overdose Management

Alex Manini • Michelle Jacobs • David Vlahov • Yasmin Hurd

Published online: 17 July 2013
© American College of Medical Toxicology 2013

Author Reply:

We thank our colleagues for their interest in our study entitled “Opioid Receptor Polymorphism A118G Associated with Clinical Severity in a Drug Overdose Population.” Our results add to the growing literature over the past decade that implicate a handful of promising single nucleotide polymorphisms (SNPs) of the mu opioid receptor gene (*OPRM1*) as candidates for clinically relevant variability in baseline mesolimbic reward neurobiology (dopamine–opioid interaction), opioid sensitivity, and addiction [1]. Our findings warrant further research to understand the mechanisms underlying specific at-risk overdose populations. We completely concur that results of our pilot study, as with all such investigations, will require validation in larger populations, an effort which is currently being addressed at our institution. Confirming our results would have significant impact in the field of addiction to pave the way for personalized prescription practices not only for opioids, but for those at risk for drug overdose.

Our data which demonstrated higher overdose severity in G allele subjects, not limited to opioid drugs, is likely due to dopamine–opioid interactions in the mesolimbic/striatal pathways relevant to reward and habit formation. Indeed, several lines of evidence have established significant disturbances of the opioid system in association with various drugs of abuse [2, 3]. We therefore chose not to limit the analysis to only opioids given the biologic plausibility of enhanced abuse and addiction behaviors which apply for all drugs, not limited to opioids. To address our colleagues’ suggestion to eliminate sympathomimetics, such as cocaine, from the analysis, we would argue that it is equally plausible that *OPRM1* variants

affect the same reward pathways for sympathomimetics, and thus arbitrary removal of these exposures would actually introduce, not eliminate, bias.

A question was also raised as to whether the 118G allele confers resistance rather than increased susceptibility as suggested by the findings of our study. Consistent with the results of our study, multiple investigations have reported an association of the 118G allele with opioid abuse [4–6]. However, the mu opioid receptor is involved in multiple physiological functions, thus the 118G allele could be beneficial for some processes, but adverse for others.

Our colleagues also question whether race/ethnicity may have introduced confounding into our analysis. To truly control for the effect of racial bias, it would be necessary to not only gather self-reported data, which is difficult to gather on critically ill patients with altered mental status due to overdose, but also it would be necessary to perform additional analyses such as ancestral informative markers (AIMs), which we did not have available at the time. The poor specificity of racial/ethnic variables in addiction research is often compounded by failure to measure social and environmental exposures that track with self-identified race in the USA, thereby masking important gene–environment effects. Missing these effects means missing an opportunity to disentangle the complex social, environmental, behavioral, and genetic factors that interact to create disease and determine treatment outcomes [7]. To account for this, future studies of *OPRM1* variants in overdose populations should gather social and environmental variables as well as perform AIMs analysis.

A. Manini (✉) • M. Jacobs • Y. Hurd
The Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: manini.alex@gmail.com

D. Vlahov
University of California, San Francisco, CA, USA

References

1. Kasai S, Ikeda K (2011) Pharmacogenomics of the human mu-opioid receptor. *Pharmacogenomics* 12(9):1305–1320
2. Hurd YL, Herkenham M (1993) Molecular alterations in the neostriatum of human cocaine addicts. *Synapse* 13:357–369

3. LaForge KS, Yuferov V, Kreek MJ (2000) Opioid receptor and peptide gene polymorphisms: potential implications for addictions. *Eur J Pharmacol* 410:249–268
4. Bart G, Kreek MJ, Ott J, LaForge KS, Proudnikov D, Pollak L, Heilig M (2005) Increased attributable risk related to a functional mu-opioid receptor gene polymorphism in association with alcohol dependence in central Sweden. *Neuropsychopharmacology* 30:417–422
5. Drakenberg K, Nikoshkov A, Horvath MC, Fagergren P, Gharibyan A, Saarelainen K, Rahman S, Nylander I, Bakalkin G, Rajs J, Keller E, Hurd YL (2006) Mu Opioid receptor A118G polymorphism in association with striatal opioid neuropeptide gene expression in heroin abusers. *Proc Natl Acad Sci U S A* 103:7883–7888
6. Haerian BS, Haerian MS (2013) OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis. *Pharmacogenomics* 14:813–824
7. Unger JB, Schwartz SJ (2012) Conceptual considerations in studies of cultural influences on health behaviors. *Prev Med* 55:353–355