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(Accepted for publication September 24, 2012.)

Monozygotic Twins: Identical in Name Only

To the Editor:

We found the study of clinical responses to opioids by Angst *et al.*[1] to be an excellent first-of-its-kind study for distinguishing the contribution of heredity *versus* environment. Much work has been done using twins to separate heredity from environment and this addition to our literature is timely.

Although the use of twins to separate nature from nurture is a long-established model, we would have appreciated more detailed analysis of the monozygotic twins. Genetically, dizygotic twins are no different from other nontwin siblings (assuming the same parents). Contrary to what was stated by the authors, monozygotic twins do not share 100% of their DNA. Copy number variants and single-nucleotide polymorphisms have been discovered, which distinguish one monozygotic twin from the other.[2,3] Moreover, there are differences in regulation and expression of the shared monozygotic genes. These very small and seemingly inconsequential differences probably account for the differences in disease susceptibility between monozygotic twins[4–9] and may be significant in their reaction to opioids.

Twins raised together do not share 100% of the same environment. Very small differences in environment such as those that occurred in the womb or even in the seemingly identical home and school environments may result in the methylation of a gene in one twin but not in the other.[9–11] Epigenetic variability has also been found to increase with age, which may lead to increasing differences as monozygotic twins move from infancy to adulthood.[5] We look forward to further investigation from the authors, which will address these additional factors.

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(Accepted for publication October 10, 2012.)

In Reply:

We thank Drs. Greek and Rice for their interest in our pharmacogenomic twin study reporting heritability estimates for aversive and reinforcing opioid effects.[1] Studies on monozygotic and dizygotic twins are almost uniquely positioned to examine to what extent genetic variations contribute to disease susceptibility and pharmacologic variance.[2] The classical twin study paradigm compares phenotypical resemblance of monozygotic and dizygotic twins and infers heritability if monozygotic twins resemble each other more than dizygotic twins do. Inherent to the analysis of such data is the assumption that monozygotic twins are genetically identical, whereas dizygotic twins share 50% of their genome on average. The twin study paradigm also allows examining the relative importance of the shared familial environment by assuming that monozygotic and dizygotic twins share the same environment. Twin studies have significantly advanced our understanding of the genetic and familial contributions to disease burden by indicating that outlined assumptions, although not entirely correct, are very reasonable.[3–5]

Monozygotic twins share the overwhelming portion of their DNA. However, small portions may indeed vary. Studies examining phenotypical dissimilarities rather than similarities in monozygotic twin pairs (discordant twins)

exploit this very fact and have received significant recent attention as the odds of correctly attributing phenotypical differences to structural differences in DNA are favorable.[6] Although appealing in concept, the overall utility of discordant twin studies for identifying mechanisms underlying complex traits or pharmacologic responses has not yet been established.

The primary aim of our study was to examine the overall genetic contribution to interindividual differences in analgesic, aversive and reinforcing opioid effects.[1,7] Our results suggest that genetics clearly matter, thereby justifying future and more detailed studies examining molecular mechanisms underlying observed differences. We agree with Drs. Greek and Rice that studying discordant monocytic twin pairs is a plausible approach to unravel some of these mechanisms.

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(Accepted for publication October 10, 2012.)