Genetic Contributions to Opioid Side Effects

Helix Me, Helix Me Not

ALTHOUGH opioids represent a primary treatment for moderate to severe pain, their clinical benefits are offset by substantial side effects. Moreover, both analgesic and nonanalgesic responses to opioids vary widely across individuals, which further complicates the use of these medications in the clinical setting. Genetic factors have long been suspected in this robust interindividual variability in responses to opioids; however, clear evidence regarding the magnitude of the genetic contribution has been lacking. In this issue of ANESTHESIOLOGY, Angst *et al.*[1] report the results of a twin study, which enabled them to estimate the heritability of multiple side effects of the opioid alfentanil. One hundred fourteen twin pairs (81 monozygotic, 33 dizygotic) underwent a single laboratory session in which alfentanil and placebo were administered in counterbalanced order and opioid side effects were assessed. A computer-controlled infusion was used to achieve a targeted steady-state concentration of 100 ng/ml alfentanil. The findings revealed significant heritability for respiratory depression (respiratory rate 30%), nausea (average nausea 59%, maximum nausea 56%), and drug disliking (maximum rating 36%), whereas drug liking, sedation, and dizziness showed no heritability. The highest heritability estimates were noted for nausea, which is among the most common and bothersome averse side effects reported by patients. For the reader wondering about the heritability of opioid analgesia, the authors have also addressed this question, and these results will be presented in a separate manuscript. This is indeed an impressive, well-designed, and (no doubt) challenging study to carry out, and the findings warrant due consideration.

"[In this study of twins] the heritability estimates differed widely across different side effects [nausea, respiratory depression, drug disliking]."

Although it is not surprising that genetic factors contribute to opioid side effects, this study is noteworthy, as this is the first twin study to directly evaluate the heritability of responses to opioids. Indeed, numerous pharmacogenomics studies of opioids have been conducted based on the assumption that responses to opioids are subject to genetic influences,[2] and this important study by Angst *et al.* now provides empiric support for this assumption. Moreover, the pattern of results permits several other potentially important conclusions. First, the heritability estimates differed widely across different side effects. Although there may be statistical or methodologic explanations for this (*e.g.*, some measures may be more error-laden than others, sample size may have precluded detecting some heritable effects), it seems equally plausible to suggest that different effects of opioids are under different levels of genetic control. Thus, genetic testing for the purpose of tailoring opioid treatments may be fruitful in identifying persons at risk for some opioid side effects but not others.

Second, most opioid effects for which heritability was low showed significant familial aggregation, indicating significant shared environmental contributions to these phenotypes (*e.g.*, drug liking, pruritus, dizziness, sedation, transcutaneous carbon dioxide). This suggests that preexisting environmental influences may contribute importantly to opioid responses, raising the possibility that prediction models incorporating both genetic and environmental factors may account for a broader range of opioid effects, which would potentially strengthen personalized treatment efforts. In addition, although heritability for drug liking was low, familial effects accounted for 23–26% of the variance in this phenotype. Given that drug liking could be considered a risk indicator for nonmedical use of opioids, it is tempting to speculate that environmental influences may contribute

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more importantly than genetic factors to this component of addiction risk.

Third, the authors have also examined the association of several nongenetic variables with opioid side effects, including age, sex, race/ethnicity, and psychologic measures. Age and sex were the two covariates most consistently associated with opioid effects, consistent with previous clinical studies that have primarily examined opioid consumption or analgesia.[3,4] Specifically, greater age was associated with increased drug effects on respiratory depression and cognitive speed as well as with greater drug disliking. Women reported greater dizziness and pruritus than men; however, no sex differences in nausea were noted, which is surprising given previous findings.[5] Due to sample size constraints, it was not possible to examine interactions between genetic and nongenetic variables, and this will be an important issue to address in future studies.

The findings of this study raise several interesting questions and point toward important lines of future research. Perhaps the most obvious question is "what specific genes contribute to variability in responses to opioids?" Although twin studies such as this can estimate the proportion of phenotypic variance that can be attributed to genetic factors, they do not provide information regarding the specific genes or how many genes are involved. However, these findings do suggest which specific side effects are more likely to be strongly influenced by genetic factors, and these responses would be the highest priority phenotypes to pursue in future genetic association studies. In their discussion, the authors highlight several possible candidate genes that have been associated with opioid responses in previous research, including several genes associated with nausea/vomiting (*e.g.*, *UGT2B7, ABCB1*, *HTR3B, COMT,* and *OPRM1*). *OPRM1* was also noted for its association with opioid-induced respiratory depression. Interestingly, although *OPRM1* has been associated with opioid responses in some studies, a recent meta-analysis of the most commonly studied *OPRM1* single nucleotide polymorphism (A118G) found only weak evidence for associations with nausea and analgesic dosage requirements.[2] Thus, there remains considerable work to do to identify specific genetic determinants of opioid responsiveness.

Another interesting question is whether common or independent genetic factors contribute to variability in different side effects as well as analgesia. That is, are the same genes responsible for increased nausea and increased respiratory depression? Similarly, are nausea and analgesia influenced by the same genetic variants? Because these authors have reported their analgesic and side effect findings separately, they have not examined the associations between these two different classes of responses to opioids. This would be an interesting analysis for a future manuscript. In previous research, analgesic responses have not been not strongly associated with side effects.[5] Indeed, our own findings suggest that even analgesic scores across pain modalities are not highly intercorrelated.[6] Thus, future genetic studies of responses to opioids should collect phenotypic data on both side effects and analgesia to more directly address this question.

Perhaps the most important question is whether the current findings, based on acute opioid administration in the laboratory setting, provide information relevant to opioid responses among patients with clinical pain. In particular, might the presence of clinical pain alter the side effect profile and the genetic determinants thereof? In addition, it will be important to investigate genetic influences on responses to chronic opioid administration. These clinical questions are much more complex and less amenable to twin studies; therefore, other methodologic approaches to studying their genetic underpinnings will be required.

Like most first-of-its-kind studies, this research by Angst *et al.* not only provides important new information, but generates multiple important questions to be pursued in future research. Continued research to delineate the genetic and nongenetic determinants of individual differences in response to opioids is needed to ultimately achieve the goal of more effective patient care through personalized pain medicine.

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