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EDITORIAL

Do genes matter?

Do genes matter? Well, *of course they do*, but how much do they matter to obstetric anesthesiologists? In this issue of the *International Journal of Obstetric Anesthesia (IJOA)*, Tan et al. report an investigation of the effect of genetic variants within three genes involved in the renin-angiotensin-aldosterone system on maternal hypotension during spinal anesthesia for cesarean delivery.¹ They demonstrate an increase in the incidence of hypotension in patients carrying a specific allele of one of the three genes studied - the gene coding for the angiotensin receptor. So, does this mean that genes do matter with regard to spinal hypotension or potentially with regard to other issues in obstetric anesthesia?

At the White House in Washington, DC, USA, on June 26, 2000, the United States President Clinton and the United Kingdom Prime Minister Blair announced the “completion” of the Human Genome Project; many genetic variants, especially single-nucleotide polymorphisms (SNPs) were identified. Faster, more powerful techniques for genetic sequencing, including whole exome and genome analysis, rapidly followed. Enthusiasm and expectations were high that an understanding of the human genome, and its variation, would allow for ‘precision’ or ‘personalized’ medicine, with treatments tailored to the specific genetic makeup and related physiology of each patient. This expectation was, and is, reflected on the National Institute of Health website (National Center for Biotechnology Information) which states:

“Wouldn’t it be wonderful if you knew exactly what measures you could take to stave off, or even prevent, the onset of disease? Wouldn’t it be a relief to know that you are not allergic to the drugs your doctor just prescribed? Wouldn’t it be a comfort to know that the treatment regimen you are undergoing has a good chance of success because it was designed just for you? With the availability of millions of SNPs, biomedical researchers now believe that such exciting medical advances are not that far away.”²

Over the ensuing two decades, has this promise been fulfilled for anesthesiology or obstetric anesthesia? There have been some clinically relevant genetic findings that impact on clinical care relevant to anesthesiologists, although some of these, such as variation in drug metabolism due to cytochrome genetic variability, were known well before the Human Genome Project was completed. Areas in which genetics does seem to have

some clinically relevant implications include the genetic influence causing people with red hair to require higher anesthetic doses due to the specific genotype of the melanocortin-1 receptor gene,^{3,4} genetic influence of metabolizing enzyme genes on propofol metabolism and anesthetic emergence,⁵ genetic effects on vasopressor action,⁶ and of course, further investigations into one of the earliest anesthesia/genetic issues, malignant hyperthermia.⁷

In the field of obstetric anesthesia, the main areas of investigation regarding genetic effects on clinical treatment and outcome to date have included preterm labor and delivery,^{8–10} response to systemic or neuraxial opioids after cesarean delivery^{11–14} or in labor,^{15,16} and the focus of the current study: hypotension and response to vasopressors during spinal anesthesia for cesarean delivery.^{17–23} Tan et al. have re-analyzed data from four of their own studies.^{17,20,21,24} All four studies followed similar protocols evaluating automated systems to prevent and treat hypotension during spinal anesthesia for elective cesarean delivery.^{17,20,21,24} In the current study, they examined whether genetic variation influenced either the incidence of hypotension (defined as a 20% decrease in systolic blood pressure [SBP]) or the dose of vasopressor (predominantly phenylephrine) required to treat hypotension. The three genes examined were SNP in the genes for the angiotensin type-1 receptor AT1R (A1166C) and for aldosterone synthase/CYP11B2 (C344T), and an insertion/deletion variant in the gene coding for the angiotensin converting enzyme (ACE). The rationale for examining these variants is that the A1166C variant increases gene expression of AT1R, the CC genotype of CYP11B2 has been associated with hypertension, and the deletion variant of ACE doubles ACE activity. Among the 577 subjects in the four studies, 556 had sufficient data and DNA samples. The authors reported a difference in the incidence of hypotension between the genetic variants of AT1R, with an odds ratio of 2.7 (95% CI 1.38 to 5.28) for AC/CC versus AA individuals not possessing a C allele, but no difference in the amount of vasopressor required among the genetic variants. In terms relevant to the clinician, this means that 12% of the population possessed the AC or CC genotype of AT1R and these subjects had an 83% incidence of hypotension. Eighty-eight percent of subjects possessed the AA genotype; this larger group had a 66% incidence of hypotension. So

most subjects did become hypotensive and required treatment, with a somewhat higher percentage occurring in the AC/CC genotype groups.

One strength of this analysis is that a single well-established and respected research group performed all four studies that contributed data. However, the studies were not identically conducted, with slightly different methods of measuring blood pressure used in each. The treatment protocols involved automated intermittent bolus injections of phenylephrine or ephedrine to maintain blood pressure >90% baseline pressure. There is evidence and some consensus that continuous infusion, often given prophylactically to maintain baseline SBP, may be a more effective treatment and prevention strategy.²⁵ This may have contributed to the relatively high incidence (68%) of hypotension (defined as <80% of baseline SBP). If there had been a lower overall incidence of hypotension, it is reasonable to expect an even smaller difference between the two groups. In addition, this report is a secondary analysis of pre-existing data, so is more prone to a type-2 error. When assessing genetic association studies, it is important to acknowledge that, while reports correlating a single polymorphism to a clinical outcome are common, many of these findings cannot be replicated, sometimes due to small sample size. The failure to replicate is often attributed to differences in the physiological or phenotypic effect of a given genetic variation in different populations or ethnicities, a limitation acknowledged by the authors of this study; frequently the failure to replicate is unexplained. In the study of Tan et al., the actual effect on incidence of hypotension is rather small, with no measurable effect on the administered vasopressor dose.

It would be difficult to justify any clinical recommendation or strategy based on knowing that the incidence of hypotension is 66% versus 83% in two genetically determined groups, since it would make sense to try to prevent hypotension in both groups, especially since the best way to do that, a titrated prophylactic phenylephrine infusion, is relatively benign. The authors suggest that this genetic association should be investigated in “high-risk parturients.”¹ It seems hard to argue that studies should *not* be done in higher-risk patients, by which most investigators mean women with pre-eclampsia or gestational hypertension. However, prior work on hypotension during cesarean delivery in pre-eclampsia tends to demonstrate less hypotension than in normotensive women. In addition, studies comparing phenylephrine and ephedrine requirements in these women have tended to show no differential effects in women with pre-eclampsia compared with lower-risk subjects, for whom phenylephrine has often been shown to be superior.²⁶ So it is not at all clear that increased differential genetic effects on hypotension would be expected in these ‘high-risk’ parturients. Genetic association

studies have been conducted, some of them by our group, examining the role of polymorphisms of the beta-₂ adrenergic receptor on the incidence of hypotension during cesarean delivery,^{18,19,22,23} with conflicting and mostly minor effects reported, which is similar to the present work.

So where does this leave us with regard to genetics and obstetric anesthesia? Given the small and often contradictory effects reported with regard to hypotension during cesarean delivery, it seems unlikely that any genetic variation examined to date will lead to clinically important or actionable effects on hypotension, especially given the efficacy of titrated infusions of alpha-agonists in preventing or treating hypotension. It is possible, although of course not certain, that most candidate gene variants with important effects on blood pressure have been examined. In fact, studies based on phenotypic (clinical) characteristics of individuals have shown somewhat better ability to predict hypotension. Characteristics that have been correlated with the risk of hypotension include such simple measurements as baseline SBP, in the current study¹ and a recent publication by our group,¹⁹ and several studies of heart rate variability and other computerized analysis techniques.^{27,28}

Similarly, the results with regard to the effect of the common A118G variant of the μ -opioid receptor on systemic morphine requirements after cesarean delivery do not appear to be of sufficient magnitude to alter normal clinical practice.¹² With postoperative intravenous analgesia or intra-operative hypotension prevention or treatment, the need to alter therapy because of genetic variation is less critical as therapy can be titrated to effect. One area of obstetric anesthesia where therapy cannot easily be titrated is the administration of single-dose spinal or epidural opioids for labor or post-cesarean analgesia. Here, studies have not shown a large or consistent effect of genetic variation on post-cesarean analgesia from neuraxial morphine.²⁹ In contrast, two studies of neuraxial opioids for labor analgesia did show significant effects of μ -opioid receptor genetics on intrathecal fentanyl¹⁶ or epidural sufentanil¹⁵ analgesia. These studies, however, have not been replicated since their publication a decade or so ago.

So, what is the role for genetic association studies in obstetric anesthesia 20 years on? In my opinion, the current direction appears very limited; there do not appear to be any areas where there is a strong suggestion of clinically important genetic variation that might affect clinical practice. There is always the potential for small clinical effects detected in genetic studies to uncover or suggest novel pharmacologic, physiologic, or pathophysiologic pathways that can lead to new therapies and clinical strategies, or to new physiologic pathways for study. Very rare genetic variants may explain unusual or ‘idiosyncratic’ responses during obstetric

anesthesia care, but the idea that we will be able to design obstetric anesthetic or analgesic drugs specifically to manage patients based on genotype appears to be a promise of 2000 that will not be kept.

Declaration of interests

The author is a member of the editorial board of *IJOA*. The author's spouse owns stock in two pharmaceutical corporations, Abbvie and Amgen, neither of which to my knowledge manufactures or sells products discussed in this article.

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