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Ethnicity Can Affect Anesthetic Requirement

LABORATORY investigations in model organisms show that changes in genes can influence inhaled anesthetic requirement. For example, in *Caenorhabditis elegans*, mutations in unc-1/stomatin[1] and syntaxin[2] affect anesthetic requirement; in *Drosophila*, alterations in genes coding for particular ABC transporters can affect responses to anesthetic[3]; in mice, mutations in glycine receptors,[4] two-pore domain potassium channels,[5] and stomatin[1] change minimum alveolar concentration (MAC). These genetic modifications are by and large engineered into animals to discover how anesthetics work, and have little immediate relevance to the conduct of clinical anesthesia in humans. But even in normal healthy populations, there is evidence of genetic influences on anesthetic requirement. Among inbred laboratory mice, MAC varies depending on the strain.[6] Red-headed human patients have a higher MAC than other patients,[7] probably either because variants of genes that govern hair color (*e.g.*, melanocortin[8]) affect MAC, or genes closely linked to those determining hair color affect MAC. In this issue of ANESTHESIOLOGY, Ezri *et al.*[9] build on this background and show that ethnicity can influence MAC.

These investigators determined sevoflurane MAC in three ethnic groups of Jewish patients undergoing surgery: European Jews, Oriental Jews, and Jews from the Caucasus Mountain region. The patients were demographically similar except for ethnicity. They found that MAC between groups varied by up to 24%, with European Jews having the lowest MAC, Caucasian Jews having the highest MAC, and Oriental Jews being in between.

What can account for this variability? In broad terms, the variability may be (1) technical, *e.g.*, from measurement error; (2) genetic, as discussed above; (3) nongenetic but biologic, a category that includes many well-known factors affecting MAC such as temperature, pregnancy, circadian rhythms, and age; (4) environmental factors such as drug use and diet; and (5) gene–environment interactions, which may be important to many disease and behavioral phenotypes. Ezri *et al.*[9] are circumspect in ascribing a biologic basis for their observations. But by performing a

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blinded study with the same investigators at a single hospital, they have greatly reduced the possibility of systematic technical errors. Similarly, by studying patients at the same time of day, excluding pregnant patients, and excluding patients with a history of chronic pain or analgesic or sedative drug use, they eliminated several potential confounders. In fact, by carefully limiting sources of variability, they make a reasonable case for a genetic basis for the described ethnic differences in MAC, although, as they note, this will require further study.

Let us suppose that different variants (alleles) of genes that are important to MAC are indeed present in the three ethnic groups studied and account at least in part for the difference in MAC that was found. Can the MAC differences in these populations be used to identify these genes? Using traditional approaches, probably not. These approaches use either linkage analysis or a candidate gene approach. Linkage analysis is used to identify alleles of genes associated with higher or lower values of phenotype such as MAC. This would require a pedigree of related individuals with different MACs, rather than groups of unrelated individuals, a pedigree that has never been identified. Candidate gene studies use a knowledge of biochemistry and physiology to identify genes that may plausibly affect phenotype. This technique is best pursued in animals rather than in humans, where genes can be manipulated and their effect can be measured directly. Indeed, this approach has been actively pursued in mice in studies of inhaled anesthetic mechanisms for approximately a decade, with mixed results.[10]

The study by Ezri *et al.*[9] nonetheless arrives at a propitious time. New techniques, based on recent advances in genomics, can now be applied to populations of unrelated individuals to identify the genetic basis for phenotypic (*e.g.*, MAC) differences. Two developments have enabled this to happen. The first is DNA array technology, permitting rapid, accurate identification of single nucleotide differences in DNA sequences (called *single nucleotide polymorphisms* [SNPs]). Current commercially available technology allows the genotyping of hundreds of thousands of SNPs per subject. The second is the work of the International HapMap project.[11] This consortium seeks to group adjoining SNPs that are inherited together into blocks called *haplotypes*. The theoretical reason for doing this is that cataloging haplotypes should ultimately permit patterns of inheritance of genetic variants that underlie drug and disease susceptibility to be identified. Practically, this knowledge reduces the amount of genotyping required in any gene association study: Because SNPs within a haplotype are inherited together, only one SNP need be genotyped for each haplotype. Of note to the study by Ezri *et al.*,[9] these haplotypes are identified by SNP genotyping of individuals from different ethnic groups.

These technologies enable a conceptually simple study design. First, measure MAC in a large number of subjects. Second, exhaustively genotype subjects at one SNP per haplotype block. Third, determine which haplotype blocks are associated with higher and lower MAC: Genes within those haplotype blocks should underlie the difference in MAC in the study population. A recent genome-wide association study of type 2 diabetes mellitus[12] provides a proof of principle for this type of investigation. In this study, almost 1,400 subjects (affected individuals plus controls) were studied. Subjects were genotyped at approximately 400,000 unique SNPs. The study confirmed an association with a previously identified zinc transporter. More importantly, it found associations with another zinc transporter expressed only in the secretory vesicles of insulin-producing β cells, and two haplotype blocks containing genes involved in pancreatic development. The finding of new genes whose variants affect the development of type 2 diabetes mellitus illustrates the power of genome-wide association studies. Although the logistic issues of performing such a study with inhaled anesthetics would be formidable, the identification of ethnic groups with differences in MAC opens the door to identifying genes determining anesthetic sensitivity *via* a genome-wide association study in humans.

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