Anesthesia and Genetics: Why Genetics Is Relevant to the OR Anesthesiologist

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Anesthesiologists have long recognized that response to drug administration or stress depends on the individual. In fact, a bell-shaped curve of responses to various environmental perturbations (drug administration, hemodynamic challenge, inflammatory response to stress of surgery) demonstrates that although most patients respond in predictable patterns, others respond either more or less vigorously (Fig. 1). In fact, much of the "art" of anesthesiology is the astute clinician prepared to deal with "outliers." Increasingly, clinicians are appreciating that an individual patient's response to stress may alter perioperative outcomes such as incidence of respiratory distress syndrome, perioperative myocardial infarction, survival, and response to pain management. But what are the mechanisms underlying variability to pharmacodynamic and physiologic stress? The answers to this complex question include understanding how the unique genetic background an individual brings to the operating room affects his/her surgical outcome. This lecture reviews basic genetic information and then explores how some genetic variants have been shown to alter specific patient diseases and therefore may be important to consider during the perioperative period.

Basic Genetic Variability

Genetics has revolutionized medicine. Sequencing 3 million nucleotides of human DNA as part of the human genome project has been hailed as one of the greatest achievements of our time. Most DNA is identical between individuals, as evidenced by the fact that humans are usually easily differentiated as Homo Sapiens rather than other mammalian species. However, variation in exact DNA sequence does exist between individuals, making each person unique in terms of hair and eye color, body habitus, fingerprint, mood, and approach to life. In the context of medicine, such genetic variability may have important implications (Fig. 2). For example, a single nucleotide change in DNA in the hemoglobin gene results in an altered amino acid in the encoded protein leading to enhanced hemoglobin sickling on exposure to hypoxia or acidosis; sickle-cell anemia is the resulting disease. Although most classically inherited genetic diseases tend to be rare, DNA variation may have more subtle effects in complex diseases where multiple genes are thought to interact to produce the final clinical outcome (Fig. 3). In such a situation (e.g., diabetes, hypertension, atherosclerosis), rather than directly causing the disease, genetic variability may contribute to disease onset or progression. Even in biologically important proteins, not all genetic variants result in alterations in function. To characterize the functional consequence(s) of altered DNA sequence, researchers often resort to examining intermediate biologic endpoints. For example, genetic variants of P450 metabolizing enzyme genes may result in altered enzyme activity and altered drug levels or in no change at all. Furthermore, specific variants may alter drug metabolism to differing degrees. Sometimes, the effects of genetic variability are not as easily quantitated, as they result in altered biological function only during stress (e.g., receptor variants with enhanced desensitization properties on agonist stimulation). Such genetic variability may have significant clinical implications during surgery or trauma that cannot be predicted at this point with anything other than identification of the DNA sequence variant and its association with perioperative outcome. Though more difficult to elucidate, such investigations (which require the combination of detailed genetic and clinical databases) may lead to some of the most important discoveries in clinical medicine over the next 5–10 yr. The broad field examining effects of genetic variability on protein function or clinical outcome defines the brave new world of pharmacogenetics and functional genomics.

Biologic Consequences of Genetic Variability: Mouse Models

One way scientists have evaluated biological consequences of genetic variability is to over express or eliminate genes using mouse models (transgenic and knockout mice, respectively) (Fig. 4). Many important discoveries and mechanisms have been elucidated using these approaches. For example, the fact that receptors exist in dynamic equilibrium between inactive (R)

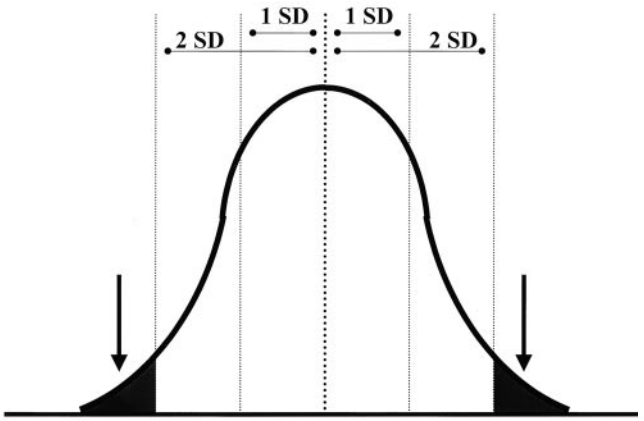

Figure 1. Normal curve of responses to various environmental perturbations (drug administration, hemodynamic challenge, inflammatory response to stress of surgery). Arrows demonstrate outliers.

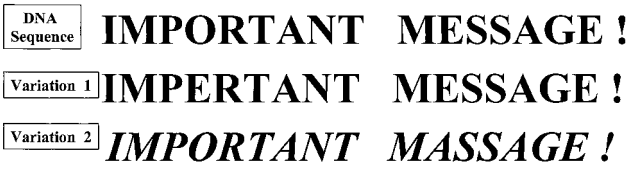

Figure 2. Illustration of importance of implications of genetic variability. The meaning in variation 1 is clear—it is a spelling error. However, variation 2 gives an entirely different meaning.

and active (R*) forms was first discovered in transgenic mice over expressing β_2-adrenergic receptors (β_2ARs). If 1% of receptors are in the active (R*) state in normal mice, then it will take agonist isoproterenol (ISO) to activate the receptor. However when the receptor is over expressed dramatically, 1% becomes a very large number, leading to maximal activity in the absence of agonist (Fig. 4A). The discovery of an elevated baseline in the absence of agonist was a surprising discovery that led theoreticians back to the concept that agonists stabilize R* rather than causing the shift from R to R* (Fig. 4B). Despite these elegant mechanistic discoveries, lingering questions remain regarding the ultimate usefulness of murine (mouse) models because not all signaling molecules are the same in mice and men. Hence, the rest of this review will focus on genetic variability in humans.

Genetic Variability in Humans

Some genetic variability in humans can be considered "background," leading to distinctive personal traits, but having no biologic consequence (see Fig. 1, variation 1). Other genetic variants, however, are important clinically because they may be linked to patient outcome. Indeed, β_2AR genetic polymorphisms have been shown to be clinically relevant in diseases such as hypertension, asthma, and congestive heart failure (CHF) (Fig. 5). In the β_2AR gene, genetic alterations in

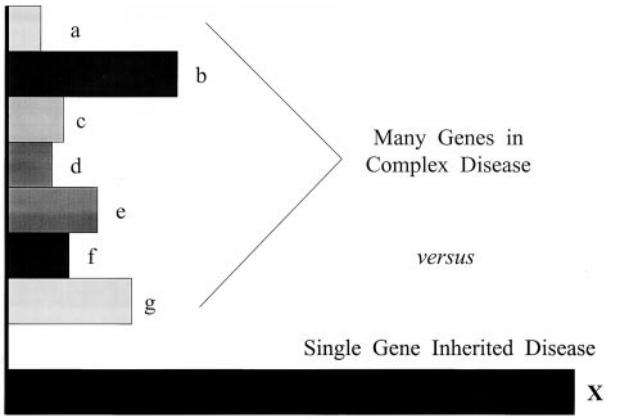

Figure 3. DNA variation may have subtle effects in complex diseases where multiple genes are thought to interact to produce the final clinical outcome.

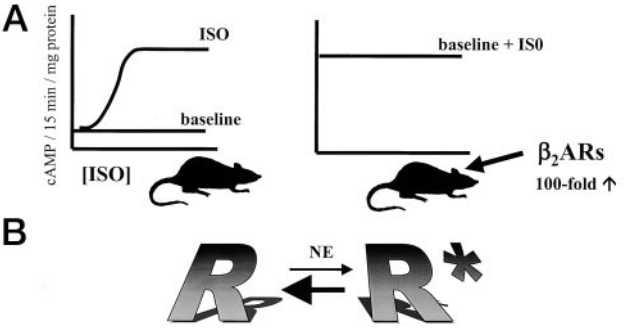

Figure 4. Mouse models have led to new understanding of receptor activation. See text for details.

the upstream leader sequence (an introductory regulatory sequence occurring immediately upstream from where the protein coding sequence begins) result in enhanced β_2AR expression. Resultant increased airway β_2ARs have been shown to be protective against methylcholine-induced bronchoconstriction. Another β_2AR genetic variant (Arg16) enhances down-regulation, or dampening of receptor function. Because β_2ARs mediate vasodilation, it is not surprising that this dampened variant results in increased blood pressure. Finally, a very rare, but clinically important β_2AR variant is the Thr164Ile; this variant appears to have no clinical cardiac effects until patients experience CHF, often later in life. Once CHF occurs, patients with 164Ile have a more rapid downhill course clinically. It is important to note that most often genetic variants alter understood physiologic pathways. Therefore, β_2AR variants make sense clinically. However, because we do not understand fully all of the pathways necessary for normal cell function, naturally occurring genetic variants often give surprising insights. This suggests that until all human biochemical pathways are understood in detail, it will be important to continue to use a combination of genome-wide

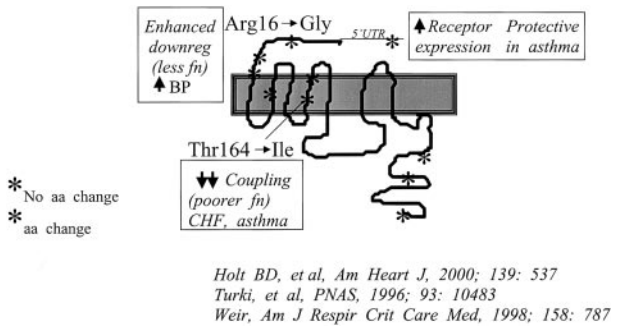

Figure 5. β_2AR genetic polymorphisms have been shown to be clinically relevant in diseases such as hypertension, asthma, and congestive heart failure.

scans, targeted candidate gene studies, and intensive resequencing of genes already known to be important in given diseases to elucidate how genetic variants affect complex clinical outcomes in humans.

Genetic Haplotypes

Up until this point, we have described mutations that are causative. That is, the genetic variant described is responsible for disease mechanistically. However, in clinical medicine, it may not be necessary to identify precisely the genetic mutant involved/associated with a disease. Because genetic variability is most often the result of chromosomal crossovers over generations, this means that regions of each chromosome travel together. The ability to categorize human chromosomes by "chunks" of chromosomes, or haplotypes, is convenient (Fig. 6). This fact suggests that clinical outcomes may be able to be predicted simply from the presence of a known genetic marker, as it should predict presence/absence of a disease-altering genetic variant downstream on the chromosome. From a practical laboratory perspective, one genetic variant is often easier to discern than another given its chemical properties. Therefore, clinical tests may be able to be designed more easily for a marker downstream than for the causative variant. It is the ability to know which genes travel together that enables genetic markers to be valuable in identifying individuals at risk for a given disease. This is particularly relevant as this fact enables us to design predictive clinical tests for disease now while scientists work out the details of precisely which genetic variant actually mechanistically causes disease or alters its progression.

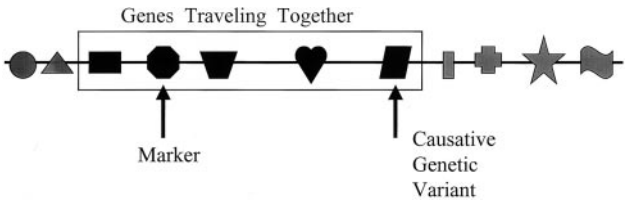

Figure 6. We can categorize human chromosomes by "chunks" of chromosomes, or haplotypes.

Perioperative Genetic Predictions

Perioperative pharmacologists currently incorporate genetic tools into their studies to identify factors that influence perioperative outcome. In the future, rather than simply tabulating patient risk factors (e.g., age, race, sex, history of hypertension, CHF, chronic obstructive pulmonary disease), a more detailed genetic history will need to be taken into account. It is not hard to imagine use in the near future of a preoperative "gene chip" designed to highlight the most notable genetic variants thought important in bleeding, inflammatory, and neurologic responses to perioperative stress. At that point in medical history, we as perioperative physicians will have far more robust information for use in designing the most appropriate and safest anesthetic plan for a given patient. Thus "designer anesthesia" is not far away in this new pharmacogenomic era.

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