Nuts and Bolts of Genetic Studies: Does This Stuff Actually Relate to Anesthesiology?

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Genomics has revolutionized medicine. Words such as pharmacogenetics, transcriptomics, proteomics, and metabolomics have become common at international scientific and clinical meetings, universities advertise expertise in proteomics and genomics in airline magazines, and some genetic tests are now available for use in clinicians' offices. Whether predicting patient outcome or monitoring warfarin therapy, genetics is firmly established in medicine and will eventually become integrated into perioperative practice. Yet to many in our specialty, genomics seems to have left anesthesiology behind; such individuals see no evidence that the genomics revolution affects the process of rendering a patient unconscious for surgery. Fortunately many anesthesiologists have the understanding that anesthesiology involves far more than simply rendering patients unconscious—it represents caring for the whole person during the entire perioperative period, including the intensive care unit.

Background

In many parts of the world, genetic and genomic tests are performed daily as part of routine care for sick patients. Increasingly, DNA amplification technology is used to identify pathogens causing infections in the intensive care setting, as well as suggesting whether resistance to antibiotics has already occurred. In addition to antibody-based analyses, nucleic acid tests are increasingly used for diagnosing inborn metabolic derangements in newborns (1), a specific genetic variant of the β_2-adrenergic receptor (β_2AR; Arg16 homozygosity associated with impaired β_2AR desensitization) has recently been determined to protect against preterm labor (2), genomic analyses are being used to identify biomarkers that predict acute coronary syndromes (3), and variants in P450 metabolizing enzymes predict that a significant minority of the population is not capable of having pain relief with codeine because of their inability to metabolize this parent compound to the active ingredient, morphine (4,5). In addition, the activity of various drugs is also influenced by genetic variation present in metabolizing enzymes, drug receptors, and also receptor-activated signaling cascades.

With this in mind, a few definitions may be helpful. In simplistic terms, genetics refers to gene variants in DNA. Single nucleotide polymorphisms (SNPs) are DNA variants that alter a single nucleotide in the sequence of DNA. Often SNPs travel in groups together in genes, a concept called a haplotype block. Other DNA variants include insertions and/or deletions of "chunks" of DNA as well. DNA variants may be transcribed into altered RNA sequences and/or alter levels of otherwise "normal" RNA, findings that can be determined using traditional molecular biology approaches of measuring RNA levels and examining transcription rates, splice variant production, and RNA stability. Because altered RNA may be translated into altered proteins, either in level or function, biochemical approaches can be utilized to determine protein structure and function. Finally, because proteins work in concert to coordinate function of cells and organs, examination of resulting metabolites within the cell can be very informative.

What, then, is genomics and how does it differ from genetics? Genomics is the "ramping up" of genetics, in that it represents analysis of many genetic processes and pathways concurrently, not one-by-one. For example, genomic analysis of DNA variants would include examination of many SNPs across all chromosomes and mitochondria as well as analysis of many haplotypes; such studies might include whole genome-wide association approaches. Genomic analysis at the RNA level is provided by microarrays where thousands of RNA species are examined simultaneously, with changes in patterns of RNA expression compared over time or between conditions. Analysis of many proteins simultaneously is called proteomics, and simultaneous analysis of metabolic pathways is called metabolomics. The advantage of using genomic approaches is that patterns of genes, RNA, proteins, or metabolites can be identified that predict disease or response to drug therapy. Because genomic analysis does not presume the role of physiologic pathways already known to exist in medicine, it is thought to be a more unbiased way of analyzing the effect of drugs and/or disease. Instead, patterns of DNA, RNA, proteins, or metabolites are identified that better characterize physiologic states. The end

result of this era of medical research will be the subdividing of major diseases (e.g., diabetes) into many more sub-diseases, each characterized in more refined ways. Ultimately this should have positive benefits for patients because it will more accurately predict whether specific pharmacologic drugs work in some subtypes of disease versus others—bringing a greater likelihood that initial therapy will benefit a given patient. This represents a new way of thinking about personalized medicine.

Genetic Variability in Humans: The β_2AR

One example of genetic variability in humans is the β_2-adrenergic receptor (β_2AR). β_2AR genetic polymorphisms have been known to exist for over a decade and clinically relevant in diseases such as hypertension (6), asthma (7), and congestive heart failure (8). In the β_2AR gene, genetic alterations in the upstream leader sequence (an introductory regulatory sequence occurring immediately upstream from where the protein coding sequence begins) result in enhanced β_2AR expression (9); resultant increased airway β_2ARs have been shown to be protective against methylcholine-induced bronchoconstriction. Another β_2AR genetic variant (Gly16) enhances down-regulation, or dampening of receptor function (10). Because β_2ARs mediate vasodilation, it is not surprising that this dampened variant results in increased blood pressure. Finally a rare, but clinically important, β_2AR variant is the Thr164Ile; this variant appears to have no observed clinical cardiac effects until patients experience congestive heart failure (CHF), often later in life. Once CHF appears, patients with 164Ile are less responsive to βAR-agonist drugs and have a more rapid downhill course clinically (10). It is important to note that most often genetic variants alter understood physiologic pathways. Hence β_2AR variants make sense clinically. However, because we do not fully understand 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 genomic approaches to elucidate how genetic variants affect complex clinical outcomes in humans.

Genetic Variants Affecting Perioperative Pharmacology

In addition to β_2ARs, identification of variants in drug-metabolizing enzymes determines a population of patients in whom codeine is not effective pain relief because individuals are incapable of metabolizing codeine to the active metabolite morphine (5). In fact a variety of drugs used in the perioperative period are metabolized by P450 enzymes CYP2D6, CYP2D9, and CYP2D19, enzymes known to contain variants that affect their drug metabolizing function (4). Such drugs include those metabolized by CYP2D6 (metoprolol, alprenolol, class 1C antiarrhythmic propafenone, codeine, tramadol, many antidepressants, droperidol, ondansetron, and tropisetron) and CYP2D19 (diazepam, omeprazole, propranolol, amitriptyline) (for more detailed description, see Sweeney (11)). In addition, most inhalational anesthetics are metabolized by CYP2E1; therefore genetic variants of this enzyme may affect recovery from anesthesia including postoperative nausea and vomiting (11). In addition to single genetic variants in metabolizing enzymes, genomic studies have determined distinct cascades of genes are activated in ischemic versus anesthetic preconditioning (12). Other less well defined genetic effects also appear to modify response to anesthetic agents. For example, hair color (red) has been associated with 20% higher desflurane requirements, implying a genetic basis for anesthetic agent activity itself (13).

Genetics of Perioperative Outcomes

In the last 3 yr, significant advances have been made in terms of elucidating whether genetic variability might have a role in predicting adverse outcome after surgery. This emerging field is called "perioperative genomics" (14–16). In terms of postoperative outcomes, a general mechanistic theme is emerging. Although a certain degree of inflammation is required to heal, genetic variants predisposing patients to heightened inflammatory responses appear to place individuals at risk for a variety of postoperative adverse events including renal injury (17), stroke (18), sepsis (19), bleeding (15,20), and myocardial events (21–23). Animal studies demonstrating the presence of ischemia-independent up-regulation of proinflammatory genes during cardiopulmonary bypass support this mechanistic theme. A review of perioperative genomics and results from recent trials can be found in Podgoreanu et al. (14).

Conclusion

As genomic approaches facilitate better characterization of the human physiologic response to injury and trauma, new mechanisms are being revealed; such findings will likely lead to new perioperative drugs of the future. In summary, genomic medicine is not only here to stay, it increasingly influences daily anesthetic practice.

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