A Primer to Pharmacogenetics of Postoperative Pain Management

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There is substantial variability in patients' response to medications. The healthcare system is in the midst of a transformation to a targeted precision health approach in which disease treatment and prevention take into account individual genetic variability. This change is informed by studies, which show that genetic variations alter the structure and function of proteins such as drug transporters, drug-metabolizing enzymes, and receptors. Tailoring medication administration based on genetic makeup can minimize adverse effects and maximize efficacy. As a result, many healthcare centers have begun incorporating genomic information into healthcare decision making. Unfortunately, many anesthesia providers may be unfamiliar with the genetics concepts and principles underlying variability in patients' response to medication. This article reviews genetic diversity in humans and the various ways in which this genetic variability may influence pharmacokinetics and pharmacodynamics of drugs. This knowledge will ensure that anesthesia providers can effectively tailor anesthesia care and postoperative pain management to improve outcomes.

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Healthcare in the United States is in the middle of a transformation from 1-size-fits-all to a targeted precision medicine approach to delivering care. Precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[1] The new approach assumes that the underlying molecular causes of disease and response to medications are partly specific to each patient. In other words, each patient has a unique genetic makeup that plays a major role in his or her disease condition and response to treatment. Thus, identifying a patient's genetic makeup may help predict the therapy that is most effective, with minimal adverse effects. Rather than dosing medications based primarily on age and weight, the premise of pharmacogenomics is to administer the right drug, to the right patient, at the right frequency, via the right route, based on genetic predisposition.[2] Effectiveness and adverse effects of medications used in postoperative pain management are related to variability in various genes.[3] As a result, many direct-to-consumer genetic testing companies are encouraging patients to obtain their genetic information, and many healthcare institutions have begun incorporating pharmacogenomic information into healthcare decision making.

However, anesthesia providers may be unfamiliar with the concepts and principles underlying this rapidly evolving field.[4] For an anesthesia provider, crucial parts of perioperative patient care are building rapport, relieving anxiety, and providing effective pain management. If an anxious patient shares a printout of his or her genetic profiles showing that he or she is a poor metabolizer of opioids, will the anesthesia provider be ready to use that information to tailor the anesthesia and postoperative care to that patient's unique needs? Would the anesthesia provider be able to advise the patient and relieve that person's anxiety?

Given this knowledge gap, the purpose of this review is to provide anesthesia providers with a primer on the principles and molecular mechanisms underlying the pharmacogenomics of postoperative pain management. In the first section, this premise is explained within the context of genetic diversity in humans. This is followed by an overview of the genetic basis of variability in pharmacokinetics and pharmacodynamics.

Genetic Diversity in Humans

The correlation between human genomic DNA variations (genotype) and variable response to medications (phenotype) is the cornerstone of pharmacogenomics. The genetic sequence between any 2 randomly selected unrelated individuals in a population is about 99.5% identical. Therefore, the uniqueness of each person is explained by only a 0.5% genetic difference.[5] Given the diversity of humans, there is no "normal" human genome. Instead, specific locations in the human genome where differences occur are referred to as variations, and by convention, the most common sequence in a population is designated the common, major, or wild-type sequence. The other sequences are referred to as the minor, mutant, or variant sequence. Generally, we inherit 2 alleles (different versions of the same gene). Our 2 alleles may be

the same or may be different versions of the gene. The most common form is referred to as the major or wild-type allele, while the other forms are referred to as minor alleles. The frequency of the variant allele in the population is used as the basis for classifying variations as mutations and polymorphisms. By convention, any inherited genomic variant in a population with a frequency of greater than 1% is termed a polymorphism, and a variant with a population frequency of less than 1% is termed a mutation. The frequency at which the second most common (mutant) allele occurs in the given population is known as the minor allele frequency. Moreover, the allele frequency can vary from one subpopulation (eg, race or ethnicity) to the next.

Human genomic variations can also be distinguished by the nature of the variant: quantitative (change of gene dose, defined below) and qualitative (affecting single nucleotides) variants. Regarding quantitative variants, humans inherit most genes as 23 pairs of chromosomes (46 total): 22 pairs of autosomes and 1 pair of sex chromosomes. The quantitative description of genetic material is referred to as the gene dose. Having the right number of genes is essential for normal function; lesser or greater than 46 chromosomes is associated with disease and disorders. For instance, about half of patients with Turner syndrome have only 1 sex chromosome (typically 1 X chromosome and no Y chromosome), which results in 45 total chromosomes. These patients have characteristic short webbed neck, kidney problems, and cardiac defects. On the other hand, most cases of Down syndrome result from having an extra copy of chromosome 21 (3 instead of 2 copies of chromosome 21, trisomy 21), which results in 47 total chromosomes. Similarly, lesser or greater dosages of standard gene copies are related to altered protein function. For instance, lack of a gene that codes for a drug-metabolizing enzyme may result in a decrease in the rate of metabolism of that drug, whereas having multiple copies of that gene may increase the rate of metabolism of that drug. On the other hand, in qualitative variations, individuals have the "normal" quantity of genetic material, but variations in the content of the genes result in differences in the structure and function of proteins (quality of the proteins). A single nucleotide variation such as substitution of one nucleotide for another on a gene is an example of a qualitative variation.

• ***Single Nucleotide Variations.*** Single nucleotide variations that occur in more than 1% of the population are referred to as single nucleotide polymorphisms (SNPs, pronounced "snips"). SNPs are the most common type of genetic variations among humans. The human genome contains approximately 3 billion base pairs (nucleotide pairs), and each SNP represents a difference in a single nucleotide. For instance, a SNP may be the substitution of the nucleotide adenine (A) for thymine (T) on the DNA sequence. About 10 million such differences (SNPs) have been identified in the human genomes. Most SNPs have no clinical relevance because the difference in nucleotide does not result in a change in the amino acid sequence of the protein, or it occurs in regions that do not code for or regulate protein synthesis. A SNP that does not result in a change in the amino acid sequence is known as a synonymous polymorphism, whereas one that results in a change in the amino acid sequence is known as a nonsynonymous polymorphism.

Nonsynonymous SNPs change the amino acid sequence of proteins and may alter the structure and function of those proteins. For instance, substitution of guanine with adenine on the catechol-O-methyl transferase (*COMT*) gene results in the amino acid change from valine to methionine at codon 158 (Val158Met).[6] This nonsynonymous change alters the structure and function of the COMT enzyme, which breaks down catecholamines such as dopamine in the brain. In this example, the wild-type allele, guanine (G), codes for the amino acid valine, whereas the minor allele (variant), adenine (A), codes for the amino acid methionine. In the postoperative period, having the minor allele (A) has been associated with decreased enzyme activity and decreased morphine consumption.[6] This type of SNP that substitutes one amino acid for another is known as a missense mutation. A mutation resulting in the premature termination of the amino acid sequence (a shortened protein) is referred to as a nonsense mutation. Clinically significant SNPs affect the quality of the gene and resultant protein.

• ***Structural Variations.*** Unlike SNPs that primarily affect gene quality, deletions, insertions, copy number variation, and tandem repeats affect the quantity of the gene. Deletion results in the removal of a segment of the DNA. The segment of the DNA deleted can vary from a few nucleotide pairs within a gene to entire genes or several genes on a chromosome. The absence of the deleted segment on the DNA alters the structure and function of the resultant protein or proteins. Just as deletion can result in loss of functions, insertion of extra copies of genetic material can alter the function of the protein. The genetic material inserted can include nucleotides, gene segments, genes, or chromosome segments. Insertions and deletions are collectively referred to as "indels" because the genetic material deleted from one segment may insert into another segment of a homologous chromosome. In some instances, indels cause genes to be copied an abnormal number of times, resulting in gene duplication or copy number variation. Duplication of the normal gene may result in increased activity of the resultant protein. For instance, individuals classified as ultrarapid metabolizers inherit more than 2 copies of the normal *CYP*2D6 gene. This gene codes for the enzyme that converts codeine into morphine. Duplication of the gene results in increased enzymatic activity and rapid

conversion of codeine into morphine, increasing the risk of morphine toxicity.[3]

Indels can result in a special kind of duplication in which a short DNA sequence that involves a repetitive unit of 2 to 6 base pairs is repeated a variable number of times end-to-end at a defined locus. Such repetitive DNA sequences, also called satellite DNA, are grouped into 2 main categories: microsatellites and minisatellites. Microsatellites, also known as short tandem repeats (STR), are tandem repeats of 2, 3, or 4 nucleotide repeat units that occur in 5 to 25 copies. In STR, different alleles are the result of differing numbers of repeated nucleotide units. Minisatellites, on the other hand, are an array of 100 to more than 1,000 copies, in tandem, of 10 to 100 nucleotide repeats. Minisatellites, also known as variable number tandem repeats (VNTR), usually have many alleles due to the variation in the number of copies of tandem repeats. Tandem repeat polymorphisms are usually groups of indels because of their variation between individuals. These DNA segments are used by the Federal Bureau of Investigation for identifying individuals as suspects at a crime scene. Hence, they are referred to as DNA "fingerprints." A typical DNA fingerprint includes more than a dozen VNTR.

Overview of Pharmacogenetics

The terms *pharmacogenetics* and *pharmacogenomics* are often used interchangeably. However, there is a subtle difference. Although pharmacogenetics refers to the effect of single genes on drug response, pharmacogenomics encompasses the relationship between the genomic variations and drug response. Pharmacogenomics uses a genomewide approach to investigate genomic relationships with drug response, with no a priori knowledge of the role of the genes. Rather, the entire genome is queried for association with a specific drug response. Pharmacogenetics, on the other hand, uses a candidate gene approach in which genes with known effects are investigated for association with drug response based on a hypothesis.

Pharmacogenomics and pharmacogenetics play 2 important roles in precision medicine. First, they guide the pharmaceutical industry in drug discovery and development. Second, they guide healthcare providers in selecting the right drug for the right patient, at the right dose, and right frequency based on the patient's genetic makeup, to maximize efficacy and minimize adverse effects. Genetic variability may affect pharmacokinetics (drug transport proteins, and drug-metabolizing enzymes), pharmacodynamics (drug-receptor proteins), and associated downstream responses, which ultimately produce a therapeutic effect or adverse reaction. It is important to remember that nongenetic factors such as age, disease, environment (smoking, diet, alcohol), and drug interactions may also influence a patient's response to medication.

Pharmacokinetic Variability

Pharmacokinetics refers to the absorption, transport, metabolism, and excretion of drugs. Drug transporters regulate the movement of drugs across basal epithelial cells and cell membranes to reach their target receptors. They are localized in organs such as the small intestine, the liver, and the kidney, which are critical for absorption and elimination of drugs. In addition, they are found in specialized barriers such as the blood-brain barrier, where they regulate the concentration of drugs in the central nervous system. Besides drug transporters, metabolism also affects the concentration of drugs at the receptor site. Drug metabolism is frequently divided into phase 1 and phase 2 metabolism, which converts lipophilic (fat-soluble) drugs into hydrophilic (water-soluble) molecules for elimination. Phase 1 metabolism is characterized by oxidation, hydrolysis, and reduction processes, which start the detoxification of active drugs or conversion of prodrugs into active drugs. On the other hand, phase 2 metabolism is characterized by glucuronidation, acetylation, and sulfation reactions (catalyzed mainly by transferases). Collectively, genetic variations that affect the structure and functions of drug transporters and drug-metabolizing enzymes may affect pharmacokinetics and effects of the drug. The next sections will discuss the genetic bases of variability in drug transport proteins and drug-metabolizing enzymes.

Drug Transport Proteins

Drug transport genes encode the production of membrane proteins that regulate the movement of drugs into or out of cells or specialized junctions such as the blood-brain barrier. The most common transporters belong to 2 superfamilies, ABC (ATP-binding cassette) and SLC (solute-linked carrier). Although SLC transporter is a gradient facilitator, ABC uses energy to transport drugs against a concentration gradient. Studies have shown that the ABC transporters control the efflux of drugs such as morphine across the blood-brain barrier, thereby affecting their pharmacokinetic properties.[7] As a result, the ABC superfamily of drug transporters is a major target for variability in response to pain medications.

The *ABC* gene encodes the ABC drug transporters. This superfamily of transporters includes the ABC subfamily B member 1 (*ABCB1*), which has become one of the most widely studied and best-characterized members of the ABC superfamily. The *ABCB1* gene, also known as the multidrug-resistant protein 1 (*MDR1*) gene, encodes the P-glycoprotein 1 (P-gp) that pumps foreign substances out of cells (cellular efflux transporter) against its concentration gradient.[8] The *ABCB1* gene is expressed in various tissues, including the liver, kidneys, intestine, lungs, placenta, and brain.[9] Some studies have reported associations of polymorphisms of the *ABCB1* gene with variability in response to opioids in the postoperative setting.[7,8,10-14]

Drug-Metabolizing Enzymes

The cytochrome P450 (CYP) and UDP glucuronosyltransferase (UGT) superfamilies of enzymes metabolize most drugs. CYP enzymes catalyze the phase 1 metabolism of most analgesic medications, while UGT enzymes catalyze the phase 2 metabolism. It has been estimated that polymorphisms in drug-metabolizing enzymes account for 10-fold to 10,000-fold variations in drug activity.[9] The variations can be divided into those CYP and UGT polymorphisms.

• ***Cytochrome p450.*** The CYP superfamily comprises about 57 enzymes, which are divided into families, subfamilies, isoenzymes, and alleles according to their share sequence homology. Enzymes in families 1, 2, and 3 are polymorphic and are responsible for 70% to 80% of phase 1 metabolism of clinically useful drugs.[2] Polymorphisms in *CYP* genes can produce enzymes with abolished, reduced, normal, or increased enzyme activity. Results of genetic testing of CYP enzymes are frequently reported as star (*) alleles, and nomenclature of the CYP star alleles has previously been explained.[15] Briefly, enzymes in the same family (CYP2) share 40% amino acid variants, whereas those in a subfamily (eg, CYP2B, CYP2D,) share 55% amino acid variants. The number after the letter identifies the specific isoenzyme (eg, CYP2D6, CYP2C9, CYP2B6), and the *number is used to designate specific allele variants (eg, CYP2D6*1, CYP2D6*3).[15]

• CYP2D6. Variations in CYP enzyme activity was first reported for *CYP2D6* gene, which is a highly polymorphic gene located on chromosome 22q13.1.[16] Despite the fact that it accounts for only about 2% to 4% of hepatic metabolism, CYP2D6 is the most studied CYP enzyme consisting of more than 100 alleles.[17] Given that CYP2D6 is subject to deletions and gene duplications and multiplications, functional polymorphisms in the *CYP2D6* alleles are frequently classified by enzyme activity: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM).[3,18-20] The Table summarizes phenotypic classification, some functional alleles, incidence in the population, impact on CYP2D6 enzyme function and clinical considerations. Suffice to mention that while PMs have no functional alleles, UMs have duplicate or multiduplicate copies of the normal *CYP2D6* alleles. Unlike most *CYP* genes that are inherited as diplotypes, UMs can inherit 3 or more copies of the *CYP2D6* gene. In fact, carriers of up to 13 copies of the functional allele have been identified.[21] Many studies have explored the impact of *CYP2D6* polymorphism on postoperative pain management. The Clinical Pharmacogenetics Implementation Consortium has published guidelines for genotype-guided clinical use of codeine.[3]

• CYP2C9. In the human liver, CYP2C9 is one of the most abundant enzymes, accounting for about 20% of the total hepatic CYP content. It is located on chromosome 10q24 and metabolizes several clinically relevant drugs, including warfarin, antibiotics, antihypertensive agents (β-blockers), cannabinol, and nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, indomethacin, meloxicam, and diclofenac).[22] To date, about 60 alleles have been identified in the human *CYP2C9* gene,[23] with *CYP2C9*2* (R144C) and *CYP2C9*3* (I359L) classified as variants with low enzyme activity (poor metabolizers).[22] Several studies have reported that adverse effects of NSAIDs are associated with the presence of CYP2C9*2 and *3 alleles.[24-27]

• CYP2B6. CYP2B6 has been mapped to chromosome 19q13.2 and is expressed in the liver, skin, brain, kidney, lung, and right heart ventricle.[28] CYP2B6 is one of the most polymorphic genes containing over 100 SNPs, many haplotypes, a variety of ethnic variabilities[29] and controversy regarding differences in liver expression related to gender.[30] The enzymes oxidize steroids, fatty acids, and xenobiotics,[28] such as the substrates including antidepressants (bupropion),[31] anesthetics (propofol and ketamine), and synthetic opioids (methadone).[15,32,33] To date, 37-star alleles of the *CYP2B6* isoenzyme with distinct amino acid sequences have been identified. These include *CYP2B6 *6A, *16*, and *26*, which have decreased activity,[34] and *CYP2B6*4A*, which has increased enzyme activity.[31]

• CYP3A4. The *CYP3A4* gene is part of the *CYP450* genes found on chromosome 7q21.1, and CYP3A4 enzymes metabolize approximately 50% of medications on the market today.[35] Inhibition and ease of induction of CYP3A4 and CYP3A5 are quite common and may contribute to adverse effects of the medications that use these pathways, such as ketamine. Some inhibitions, as with grapefruit, may be related to the presence of intestinal CYP3A4. Studies have indicated that CYP3A4 substrates are metabolized more quickly in females compared with males.[36] Many potent inhibitors that have been identified include clarithromycin, erythromycin, verapamil, and grapefruit.[37,38] Some inducers of the CYP3A4/3A5 enzymes include medications such as phenobarbital, phenytoin, and glucocorticoids.[39,40]

• ***Glucuronosyltransferase.*** The uridine-diphosphate glucuronosyltransferases (UGT) catalyze the addition of glucuronic acid to lipophilic medications or their metabolites to form hydrophilic metabolites. The UGT superfamily of enzymes contains 2 families, UGT1 and UGT2, according to their primary amino acid sequence homology. The UGT1 enzymes catalyze the glucuronidation of endogenous compounds (eg, bilirubin) and drugs.[15] The isoenzyme UGT1A3 contributes to the glucuronidation of many drugs, including hydromorphone. Variants of the *UGT1A3* SNPs show variable enzyme activity. UGT2B7 catalyzes the glucuronidation of corticosteroids and important drugs such as codeine, hydromorphone, morphine, oxycodone, and oxymorphone. The UGT2B7

Phenotype	Rate of metabolism	Genotype (CYP2D6)[a]	Incidence (%)	Clinical effect	Clinical recommendation
Poor metabolizers (PM)	None	*3, *4, *5, *6, *7, *8, *11, *12, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56, *62	Whites: 5-10 Africans: 2-4 Asians: 1-2 Hispanics: 2-6	Unable to convert prodrug into active drug, resulting in lack of efficacy Lack of metabolism of active drug with resultant accumulation and toxicity	Avoid prodrugs due to lack of response (eg, no conversion of codeine to morphine; thus, no analgesia) Avoid or reduce dose of active drug (eg, tramadol) to reduce risk of toxicity
Intermediate metabolizers (IM)	Reduced	*9 *10 *17 *29 *41	Asians: 51 Whites: 1-2	Convert prodrug into active drug at a very slow rate, resulting in reduced efficacy Metabolize active drug at a very slow rate with higher risk of side effects	For prodrugs (eg, codeine) use recommended dose, but be ready to switch to an alternate if no response For active drug (eg, tramadol) monitor closely for side effects
Extensive metabolizers (EM)	Normal	*1 *2 *39	Whites: 71 Asians: 50 Africans: 54 African Americans: 50	Convert prodrug to active drug at normal rate Metabolize drugs administered in active form at normal rate	Administer the recommended dose Administer the recommended dose
Ultrarapid metabolizers (UM)	Rapid	*1 x N *2 x N	Whites: < 2-4 Africans: 28-56 Asians: 20 Hispanics: < 2	Convert prodrug into active drug at a faster rate resulting in risk of toxicity	Avoid prodrug due to high risk of toxicity (eg, rapid conversion of codeine to morphine, may result in morphine toxicity)

Table. Genotype and Description of CYP2D6 Alleles

[a]N signifies more than 2 copies of the genotype.

enzyme is polymorphic, and variants of the UGT2B7 show variable enzyme activity.[41] For instance, patients, who are homozygous for UGT2B7 802C needed less morphine in the postoperative period for pain relief in one report.[42]

Pharmacodynamic Variability

Pharmacodynamic variability refers to the variations in the interaction of drugs with receptors or intracellular signal transduction. Genetic variations of the drug-receptor proteins may affect the affinity of the drug for its receptor, with a resultant alteration in drug efficacy and drug toxicity. Drug-receptor genes of relevance to postoperative pain management include μ-opioid receptor (OPRM), COMT, and cyclooxygenase (COX) genes.

• ***Mu-Opioid Receptor Gene.*** The opioid receptor μ 1 (OPRM1) gene encodes the μ-opioid receptor, which is the primary site of action for endogenous and exogenous opioids such as β-endorphin and encephalin. The *OPRM1* gene has more than 100 SNPs, with the most well-characterized variants being the A118G, which is located on chromosome 6q25.2. Several studies have shown that carriers of the minor allele (G) reported higher pain and required higher doses of opioids to achieve adequate pain management relief in the postoperative period.[43-46] However, other studies have found that carriers of the A alleles reported lower pain scores and required less opioid for pain relief.[47,48] A study of 196 women did not find any association between *OPRM1* genetic variants and postoperative fentanyl requirements.[13] Thus, even though the *OPRM1* A118G variant appears to influence opioid analgesia, its role in postoperative pain management remains inconclusive.

• ***Catechol-O-Methyl Transferase Gene.*** The *COMT* gene encodes the COMT enzyme, which is one of the several enzymes that metabolize catecholamines such as dopamine, epinephrine, and norepinephrine. These neurotransmitters play an important role in modulating response to pain. SNPs in the *COMT* gene account for about 10% of the variability in sensitivity to pain.[49] The most frequently investigated SNP in the *COMT* gene is the G→A (G>A) substitution, which results in an amino acid change from valine to methionine at codon 158 (Val158Met) on chromosome 22q11. In the postoperative period, carriers of the homozygous *COMT Val158Val* genotype required higher doses of opioid compared with Val158Met and Met158Met genotypes.[6] The occurrence of GCGG haplotype was

associated with more fentanyl consumption 24 hours after radical gastrectomy.[50]

• ***Cyclooxygenase Gene.*** The COX 1 and 2 receptors are encoded by the prostaglandin-endoperoxide synthase 1 (*PTGS1*) and prostaglandin-endoperoxide synthase 2 (*PTGS2*) genes, respectively. Genetic polymorphism in these genes would be expected to be associated with variability in response to NSAIDs. However, the functional effects of the SNPs in the *PTGS1* and *PTGS2* genes remain unknown.[51]

Conclusion

Implementation of pharmacogenomics into clinical practice is rapidly progressing in many institutions across the United States. The FDA has approved genetic insert for more than 100 drugs that are currently in clinical use. These include frequently used medications such as codeine, tramadol, amitriptyline, lidocaine, and prilocaine. Genetic polymorphisms alter the efficacy and toxicity of these medications. As the cost of pharmacogenomic testing decreases and as direct-to-consumer testing increases, correct interpretation and utilization of actionable genetic information may become a standard of care.

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