Pain can be highly variable and unpredictable. Genetics may be key to identifying pain mechanisms that control the intensity, duration, and physiologic response in individuals with chronic pain. Pharmacogenomics and precision medicine are permitting advances in pain control with analgesic drugs that have increased effectiveness and lead to decreased side effects. Knowledge of genetic variations related to how and why patients experience pain will aid in identifying those at risk, provide a better understanding of the phenomenon of pain, and possibly lead to innovative therapies to control pain.

AT A GLANCE

- Pain variability is influenced by heritability, environmental factors, and genetic polymorphisms in nociceptive and neurotransmitter genes.
- Genes controlling voltage-gated channels of neurons and genes regulating catecholamines, as well as cell membrane receptors, contribute to pain sensation and transmission.
- Healthcare providers should incorporate family pain history into the patient's overall assessment to identify potential genetic risk that could aid in providing personalized pain management strategies.

KEYWORDS
pain; genetics; pain assessment; pain management; precision medicine; pharmacogenomics

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Cancer-Related Pain

Understanding genetic influences and determining implications for practice

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In cancer care, nurses are familiar with pain management, yet many aspects about pain remain puzzling. For example, the ways in which individuals experience pain and the susceptibility of individuals to pain—and whether genetics play a role—are questions still under consideration. This article reviews findings related to the genetics of human pain that affect sensitivity and the nervous system's transmission of pain, as well as nursing implications concerning pain management therapies in clinical practice.

Pain Variability

Variability in the pain experience has long been attributed to a number of external factors. Pain variability may also be linked to behaviors attributed to certain personality types and is indirectly related to risk-taking behaviors (Devor, 2014). For example, men in many cultures are taught to be stoic and not express feelings of pain, even if pain is present (Devor, 2014).

Mogil (2012) reviewed the interactions between environmental causes and genetics that play a role in pain susceptibility, intensity, and variability. Heritability studies of pain have been conducted with human and animal models to examine the degree to which heritability is responsible for chronic pain. Heritability is the percentage of variation in a population's trait that can be attributed to inherited genetic factors; it is an estimate of what portion of a particular trait can be explained by a person's genetic variation (National Cancer Institute, n.d.). These estimates are not indicators of disease risk, but they may indicate if a trait is highly heritable. In chronic pain disorders, pain sensitivity heritability estimates range from 9%–60% and increase with pain severity (Denk & McMahon, 2016).

Genetic Pain Studies

By studying chronic pain, researchers have been able to identify genes that could be responsible for pain conditions. Two groups of genes have emerged: ion channel subunits and nerve growth factor (NGF)-related genes (Denk & McMahon, 2016). The beta subunit of an NGF gene (*NGFB*) and a receptor gene (*NTRK1*) play a significant role in hereditary sensory automatic neuropathies (HSANs), specifically types 4 and 5, and cause insensitivity to pain (National Center for Advancing Translational Sciences, 2016).

Neurotransmitter-related genes also contribute to pain perception (James, 2013). Catecholamines (i.e., norepinephrine, epinephrine, and dopamine) affect pain sensitivity and perception through complex mechanisms in the central nervous system. Genes controlling the metabolism, function, and breakdown of catecholamines have been studied in several chronic pain conditions. For example, catechol-O-methyltransferase codes for enzymes that break down catecholamines, affecting pain sensitivity in fibromyalgia.

Altered ion channels and receptors can influence the excitability of pain-signaling neurons (Devor, 2014). More than 400

channel genes have been identified in the human genome (James, 2013). Ion channels facilitate communication between the cells and involve the transportation of ions into and out of the cell (James, 2013). There are two types of ion channels: ligand-gated and voltage-gated. Ligand-gated channels open when a neurotransmitter attaches to a receptor protein (a lock-and-key effect), whereas voltage-gated channels respond to changes in voltage between the ions (Copstead & Banasik, 2013).

Voltage-gated sodium (Na_v) and calcium channels have been identified as subtypes of voltage-gated channels that contribute to pain; they are located on the sensory nerves (James, 2013). For example, the Na_v 1.3, Na_v 1.7, Na_v 1.8, and Na_v 1.9 channels may be subject to mutations and single nucleotide polymorphisms (SNPs), which could affect pain sensitivity (Devor, 2014; James, 2013).

SNPs are variations in the DNA nucleotides (i.e., adenine, thymine, cytosine, and guanine) that are altered and found in at least 1% of the population (James, 2013). SNPs occur in large numbers in DNA and may or may not influence pain; whether they do so is dependent on if the portion of the DNA that produces biochemicals used in pain is affected.

Changes in Na_v channels may cause either hyperexcitability or hypoexcitability in neurological fibers, depending on whether those fibers have been damaged (James, 2013). These changes are often referred to as gain-of-function or loss-of-function mutations. For example, a gain-of-function mutation in the Na_v 1.8 channel is believed to cause increased pain in peripheral neuropathy by increasing the excitability of neurons and peripheral nerve axons (Faber et al., 2012). A loss-of-function mutation response has been identified when an SNP affecting the *SCN9A* gene decreased pain sensitivity in postoperative patients (James, 2013).

An SNP in the *SCN9A* gene, affecting the Na_v channels, increases pain sensitivity in conditions including sciatica, osteoarthritis, and phantom limb pain (James, 2013). Other significant ion-channel genes include the following:

- *KCNS1*, encoded for a potassium channel, increases the risk for pain.
- *CACNA2D3*, encoded for a calcium channel, is known to decrease the risk for chronic back pain following surgery.
- *CACNG2*, encoded for a calcium channel, increases the risk for developing chronic postsurgical pain after a partial or full mastectomy.

> "More studies on pain sensitivity are needed to increase understanding of the genetic basis of human pain."

In addition to changes in DNA caused by mutations or SNPs, environmental factors also contribute to pain variation. Epigenetics is a mechanism that changes the expression of genes, not the genes themselves (James, 2013; Starkweather & Pair, 2013). Factors such as diet, environmental exposures, or social pressures may turn off genes through DNA methylation or histone modification (Denk & McMahon, 2016). In addition, researchers have found evidence that cells often carry a memory of these epigenetic effects from generation to generation (James, 2013). Epigenetic changes have been found to silence nociceptive genes that influence pain perception by either lessening or increasing pain sensation. The transition from acute to chronic pain and the existence of some postsurgical neurologic pain can be attributed to epigenetics. Many challenges remain in conducting research, such as homogeneity of patients with identical pathology, confounding environmental influences, and SNP identification of epigenetic influences on nociceptive pathways in acute and chronic pain.

Monogenic, or single-gene, disorders are rare but follow an identifiable Mendelian pattern of inheritance; they are either autosomal recessive or autosomal dominant. The study of genes associated with these monogenic conditions has yielded insights into nociceptive neuron function (Sexton, Cox, Zhao, & Wood, 2018). For example, an autosomal recessive mutation in the *WNK1* gene causes HSAN type 2, resulting in the loss of pain, temperature, and touch sensations. Familial hemiplegic migraine (FHM) is an autosomal dominant condition in which only one copy of the gene is needed to cause the condition. Of the four genes associated with FHM, three affect neurotransmission of the neurons (ion channel genes), and the fourth gene (*PRRT2*) produces a protein thought to influence neurotransmission, but its exact function is unknown (Genetics Home Reference, 2018). Many other inherited pain conditions and syndromes have been identified. Knowledge about genetics and neuron functionality is being applied to the development of therapies to target pain (Sexton et al., 2018).

Genome-wide association studies may be used to identify genetic mutations or SNPs that affect chronic pain conditions (Zorina-Lichtenwalter, Meloto, Khoury, & Diatchenko, 2016). These are large typically multicenter studies that require the involvement of multiple generations of families with a pathologic area of interest matched against a healthy population. However, genome-wide association studies of chronic pain have been limited. Online databases are available and share results obtained through such studies (www.ncbi.nlm.nih.gov/gap) and information about genetic mutations and SNPs associated with pain (http://hpgl.ca/hpgdb).

Significance to Clinical Practice

Stigma can be associated with individuals who experience severe or chronic pain (Devor, 2014). Healthcare providers caring for patients with pain expect the severity and duration of pain to follow a patterned trajectory. When the pain experience deviates from the norm, a person may be branded as a complainer or as someone who wants more pain medications than are usually prescribed (McCaffery, Grimm, Pasero, Ferrell, & Uman, 2005). Patients often notice when a nurse is suspicious of their need for pain analgesia, which may also add to their distress and have negative effects on recovery (Newton, Southall, Raphael, Ashford, & LeMarchand, 2013). Nurses should be aware that genetic differences can contribute to their patients' pain sensitivity.

Pharmacogenomics and precision medicine have led to advances in pain control, particularly in terms of analgesic drugs designed for increased effectiveness and decreased side effects (Kapur, Lala, & Shaw, 2014). Patients' responses to analgesic medications may vary; such variance has been linked to genes that metabolize and eliminate these drugs. Genetic variation can cause alterations in drug serum concentrations with standard drug doses. The cytochrome P450 (CYP) enzymes play a significant role in drug metabolism and are estimated to be responsible for about 80% of all phase I drug metabolism, which is often an oxidation reaction.

Opioids, such as codeine and morphine, are metabolized by the CYP2D6 enzyme; when a genetic variation exists, this enzyme can either reduce drug effectiveness or cause respiratory depression or sedation and possible overdose (Kapur et al., 2014). Genetic variants in *CYP* genes are also responsible for the metabolism of nonsteroidal anti-inflammatory drugs that can influence the effectiveness of pain reduction. Difficulties can arise when the medication is metabolized too slowly, resulting in high serum concentrations of the drug that can cause adverse reactions, such as gastrointestinal bleeding. Many other genes influence drug effectiveness; they encode for proteins that transport drugs to the tissues, affect the receptors on the cell wall, and activate or inactivate catecholamines, resulting in variation in analgesic effects.

Knowing an individual's genetic pain profile (genotype) may aid diagnosis, prognosis, and guidance when caring for patients with pain. For example, Devor (2014) compared SNPs in the *CACNG2* gene in women who had undergone partial or complete mastectomy because of breast cancer; women who had a similar SNP trio in *CACNG2* had developed persistent neuropathic chronic pain in their chest wall. In this case, awareness of an individual's genotype could predict development of chronic chest discomfort and possibly influence surgical procedure choices to minimize nerve damage (Devor, 2014).

Clinical nurses should incorporate personal and family histories into their assessment; this should include details about past pain experiences related to surgeries, injuries, or illnesses and feature the pain type (e.g., stinging, burning, aching, stabbing), severity, and duration. Educating patients that pain is highly individualized and that studies are ongoing to identify the genetic mechanisms involved in pain, which may lead to more effective treatment, is important. Nurses should advocate for and facilitate enrollment in such studies by providing patients with information about the study and contact information for researchers, when applicable. In addition, nurses should offer patients credible information about the effects of genes on pain sensitivity and drug response. See Figure 1 for a list of resources pertaining to pain, pharmacogenetics, and studies and findings that may be useful to nurses and patients.

FIGURE 1.
PAIN AND GENETICS RESOURCES FOR NURSES AND PATIENTS

AMERICAN CHRONIC PAIN ASSOCIATION
- www.theacpa.org/pain-management-tools/resources

NATIONAL CANCER INSTITUTE
- www.cancer.gov/about-cancer/treatment/side-effects/pain/pain-hp-pdq

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
- www.genome.gov/health

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
- www.ninds.nih.gov/disorders/all-disorders/chronic-pain-information-page

PHARMGKB
- www.pharmgkb.org

Conclusion

Pain remains prevalent for patients with cancer during and following treatment. Some variance in the pain experience can be attributed to heritability, but more studies on pain sensitivity are needed to increase understanding of the genetic basis of human pain. Genetic profiles may guide future therapies to alleviate pain as precision medicine becomes more mainstream and further integrated into the care of patients with acute and chronic pain.

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