Can Heterogeneity of Chronic Sickle Cell Disease Pain Be Explained by Genomics?

A Literature Review

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Abstract

Aim: This literature review explores the potential of genomics to explain, or at least contribute to the discussion about, heterogeneity in chronic pain in sickle cell disease (SCD).

Background: Adults with SCD, a single-gene disorder, are living longer than in years past, yet report being burdened by chronic pain. With only a few studies on chronic pain in this population, the epidemiology is unclear. However, research in the area of pain genetics continues to advance since the conclusion of the Human Genome Project. Two pain susceptibility genes, catechol-O-methyltransferase (*COMT*) and cytochrome P450, have, to date, been discovered that can increase individual susceptibility to the development of chronic pain.

Method: A search was conducted in PubMed, CINAHL and EBSCO using the terms “sickle cell,” “chronic pain,” “polymorphism,” “genetics,” “pain genetics,” “human,” “adult,” “association studies,” and “pain susceptibility genes” to search for articles published between 1970 and 2008.

Findings: Chronic pain generally is more prevalent and severe than previously reported, and individuals with SCD report daily pain. The genomic era has made it possible for scientists to identify pain susceptibility genes that contribute to variability in the interindividual experience of chronic pain.

Conclusion: Nurses are well positioned to generate and translate genomic research, thus improving care delivery. Such research may lead to the identification of polymorphisms associated with pain sensitivity in individuals with SCD.

Key words: genomics, sickle cell, pain, chronic, literature review, nurses, genetics

Findings emerging from genomic studies suggest that it may be possible to forecast in some patients potential phenotypic complications such as chronic pain. Such a capability could revolutionize healthcare delivery for adults with many diseases, including sickle cell disease (SCD). SCD, an inherited disorder, is characterized by genetic abnormalities affecting beta hemoglobin and resulting in polymerization and sickling of the red blood cells (Steinberg & Brugnara, 2003). The sickled cells are unable to deliver adequate oxygen to the tissues, resulting in tissue damage and pain (Elander, Lusher, Bevan, & Telfer, 2003). The pain is unpredictable and varied and may occur as acute or chronic or as both acute and chronic. Currently, there are no means available to adequately manage the pain.

Though there have been many studies on acute pain related to crisis events in SCD, few studies have addressed chronic pain in adults with SCD (Dunlop & Bennett, 2006). Most of the adult patients with SCD are ambulatory and most often enter the acute inpatient system for catastrophic events such as crises or acute pain. This situation may explain why chronic pain in persons with SCD has rarely been investigated.

In this literature review, I explore what is known about chronic pain and pain and genetics, looking at evolving genomic information that might guide further study of chronic pain in SCD based on the concept of pain-susceptibility genes. I conducted a search through PubMed, EBSCO's CINAHL Plus with full text, PsycINFO and Medline databases to locate literature published from 1970 to 2008, using the search terms "sickle cell," "chronic pain," "polymorphism," "genetics," "pain genetics," "human," "adult," "association studies," and "pain susceptibility genes." For the purpose of this review, genetics (the study of single genes and their effects) and genomics (the study, not only of single genes, but also of the function and interactions of all the genes in the genome; Guttmacher & Collins, 2004) are used interchangeably.

History and Pathophysiology of Sickle Cell Disease

SCD was one of the first diseases identified and discussed as having a genetic basis. In SCD, a monogenic hemoglobinopathy, the primary dysfunction is the formation of abnormal beta chains in the hemoglobin molecule. With this abnormality of the red blood cells, hemoglobin S (HbS) is produced by a single base substitution in the gene encoding the human β -globin subunit, with the resulting replacement of $\beta 6$ glutamic acid by valine (Bunn, 1997). HbS, when deoxygenated, forms polymers causing red cell sickling and damage to the membrane. Some sickle cells adhere to endothelial cells leading to vaso-occlusion (Bunn, 1997; Steinberg, 1999) with resulting “crippling pain” (Schubert, 2005 p. 23) and organ damage.

Almost a century has elapsed since Herrick first described the appearance of sickle-shaped cells in the blood smear of a student who presented with pulmonary symptoms (Herrick, 1910). Modern tools of molecular and cell biology have redefined our understanding of the pathophysiology of SCD and will yet enable advances in the field (Frenette & Atweh, 2007). However, no definitive cure has been established, and many perplexing questions remain unanswered about SCD pathology. Additionally, chronic pain management in SCD remains inadequate and elusive (Kutlar, 2005; Platt et al., 1994; Reed & Vichinsky, 1998).

In 1973, the average life span of a patient with SCD was 14 years. Now, with the development of comprehensive care models, day hospitals, and ongoing clinical research, life expectancy of persons with SCD has increased to more than 42 years, with females with hemoglobin C living up to 68 years (Ashley-Koch, Yang, & Olney, 2000; Claster & Vichinsky, 2003; Platt et al., 1994) and beyond. Advances in the management of SCD

have dramatically changed the outlook for patients. However, despite increased life span, individuals experience pain, decreased quality of life (QOL), depression, and increased mortality at young ages (i.e., not living the expected number of years). Interestingly, patients with SCD are not homogenous with respect to disease severity even within the same genotypic subset (Houston-Yu, Rana, Beyer, & Castro, 2003).

Pain and Pain Management in SCD

Crippling pain is the most frequent symptom associated with SCD (Edwards, C. L., et al., 2005). It can be unrelenting, unpredictable, and chronic and is the leading cause of emergency department visits and hospitalizations among adults with SCD. Nevertheless, there is little epidemiological research on the prevalence of chronic pain generally (McHugh & Thoms, 2001) and even less on chronic pain in SCD. The pain, which is complex and poorly understood, becomes the major focus of these individuals' attention throughout their lives (Newcombe, 2002). Thus, past, present, and anticipated pain experiences influence the individual's response to life and pain events. (Edwards, C. L. et al., 2005; Lenoci, Telfair, Cecil, & Edwards, 2002; Max et al., 2006).

Pain caused by SCD can be classified as acute, chronic and mixed (Okpala et al., 2002). This pain is primarily due to tissue ischemia and vaso-occlusion of the microcirculation by sickled cells (Ballas, 1998). Acute pain acts as a protective agent in response to tissue injury, giving the body warning of potentially harmful agents (Ballas, & Lusardi, 2005; Bergman, 2005; Okpala et al., 2002), and disappears when the injury heals. The resolution of acute pain usually occurs in a few days to several weeks (Todd, 2005). Acute pain that exacerbates and is prolonged to a chronic state is called mixed pain.

In SCD, acute pain has been described as a “crisis,” and it heralds tissue infarction (Okpala et al., 2002). In the past, healthcare providers assumed that pain episodes of patients with SCD correlated with healthcare utilization. That is, they assumed that visits to emergency and outpatient departments were good indications of frequency of pain in this population. New data, however, reveal that using *crisis* and *pain* interchangeably in the case of SCD is incorrect. Smith and colleagues (2008) determined in their important study that the prevalence and severity of pain in SCD are much higher than previously estimated. The study was conducted to validate a biopsychosocial model for management of adults with SCD pain and their healthcare use. The 232 participating SCD patients were asked to complete daily diaries reporting, among other things, the previous 24 hours’ activities. They also recorded their worst sickle cell pain intensity on a scale from 0 (none) to 9 (unbearable) and whether they were in a sickle cell crisis, had taken any medication or had made an unscheduled medical or emergency room visit or were hospitalized. The researchers concluded that “Pain in SCD is a daily phenomenon and that patients are at home mostly struggling with their pain rather than coming to the hospital or ER” (p. 98). On more than half of the study days, 56% of the patients had pain, while 29% had pain every day. Only 15% stated that they rarely suffered pain. Of the entire group, patients sought treatment on only 4% of the days during the study period. Those who utilized the healthcare system during the study period also experienced more intense pain and used more opiates than persons who reported no utilization. Pain days not associated with crisis events occurred 10 times more often than pain days associated with healthcare utilization. This study accurately portrayed for the first time the prevalence and severity of chronic pain in SCD. Importantly, the study also distinguished pain events, which patients often

manage at home without utilization of the healthcare system, from crises, in which the intensity of the pain event increases and the patient seeks help from a healthcare practitioner or hospital.

Thus, many individuals with SCD who have pain are not having a crisis (Smith et al., 2005; Smith et al., 2008). Instead, they may be experiencing mixed or chronic pain. Patients with SCD have frequent pain episodes but manage much of the pain in the community, usually only seeking hospital services or utilizing other healthcare options (emergency visits, hospitalizations) when the severity of the pain episodes increase (Anie, Steptoe, & Bevan, 2002; Anie & Steptoe, 2003; Smith, Penberthy, Bovbjerg, McClish, Roberts, Dahman, 2008). A more accurate clinical use of the term *crisis*, then, is to describe pain that precipitates healthcare utilization. Likewise, in research studies of SCD, painful crises have been described as “visit[s] to medical facilit[ies] that lasted more than 4 hours for acute-sickling related pain” (Charache et al., 1995) and as recent painful events that warranted utilization of the healthcare system (Montañez & Berland, 2002).

Chronic pain persists longer than acute pain, usually more than 3-6 months, and thus longer than would be expected for tissue healing (Todd, 2005; Todd, Green, Bonham, Haywood, & Ivy, 2006; Vukmir, 2004). It may thus reflect ongoing damage to tissue and bone (Bergman, 2005; Dunlop & Bennett, 2006). As opposed to acute pain, chronic pain serves no adaptive purpose (Todd, 2005). It results in distress, discomfort and disparate care (McHugh & Thoms, 2001) for individual sufferers and places financial and economic burdens on society (Nietert, Silverstein, & Abboud, 2002). Vukmir (2004), while discussing the unclear pathophysiology of chronic SCD pain, states that, unlike with other

chronic diseases, “pain defines the condition” in SCD (p. 557). Individuals with SCD have, in various studies, described chronic pain as persistent and “always there,” consistent and recurring (Westerdale & Jegede, 2004), and have said that it “does not go away” (Ballas, 2005; Ballas & Lusardi, 2005; Ballas et al., 2006). Chronic pain can lead to psychologic changes such as sleep disturbances (Geller & O'Connor, 2008; Todd et al., 2006) and psychopathology such as depression, anxiety and personality disorders (Dersh, Polatin, & Gatchel, 2002).

When chronic pain is accompanied by physiologic and psychopathologic symptoms it is called chronic pain syndrome (von Knorring, 1989). In the Smith and colleagues (2008) study discussed above, descriptions that participants provided in their diaries fit the definition of a chronic pain syndrome. While Smith and colleagues provided no detailed qualitative reports in their study and “did not distinguish chronic pain syndrome from pain that may be from other complications such as avascular necrosis” (p. 100), in an earlier qualitative study, Strickland, Jackson, Gilead, McGuire, and Quarles (2001) utilized focus groups to obtain information regarding the characteristics of the pain in adults with SCD and to identify pain influences on quality of life and coping strategies in these patients. Several of the participants expressed difficulty in dealing with recurring painful episodes associated with SCD and attributed their chronic pain to long-term damage to body organs. Those with recurrent pain reported feelings of fatalism, despair and hopelessness.

The American Pain Society has published the “*Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease*,” which is a helpful directive for clinicians who care for patients with this unique pain syndrome (Benjamin et al., 1999). Chronic pain in general is widely viewed as a multifaceted, biopsychosocial phenomenon that, as

mentioned above, can be associated with psychopathology (Nadel & Portadin, 1977). It is best managed using a holistic, multidisciplinary approach (Montañez & Berland, 2002; Okpala et al., 2002; Thomas, Dixon, & Milligan, 1999; Thomas, 2000; Vukmir, 2004). Likewise, chronic SCD pain should be handled using a multidisciplinary approach (Ballas, 2005; Ballas, 2002; Bodhise et al., 2004; Mogil, 2004) to manage and prevent chronic pain syndromes. The multidisciplinary focus of a biopsychosocial model of management is thus ideal for individuals with chronic pain (Dersh et al., 2002; Gatchel, 2004).

Treatment of Chronic Pain

Patients with chronic pain should be cared for in the acute care environment (Geller & O'Connor, 2008) and referred to a comprehensive multidisciplinary team for further management. In addition to outpatient and inpatient team management, patients with chronic pain may benefit from early intervention pain management with home infusion therapy (Schubert, 2005). Holistic treatment of chronic pain syndrome includes use of opioids (Geller & O'Connor, 2008; Jacob, 2001; Mogil, 2004), non-opioids, and adjuvants including cognitive behavioral therapy, psychotherapy, acupuncture and imagery (Anie, 2005; Anie & Green, 2006; Comer, 1999; Comer, 2004; Comer, Meier, & Galinsky, 2004; Thomas & Barton, 2005; Thomas & Taylor, 2002).

Based on the principle of beneficence, healthcare clinicians have the ethical obligation to help relieve pain and suffering in all patients whenever possible (Rosenblatt & Mekhail, 2005; Somerville, 2004; Woods et al., 1997). Studies have shown, however, that all individuals with chronic pain are not treated equally by healthcare providers, with some of the differences in treatment associated with ethnicity, age or socioeconomic status of the patient (Haque & Telfair, 2000; van Ryn & Fu, 2003). Additional studies

have found that physicians and nurses sometimes lack the proper understanding of patients' reports of chronic pain (McHugh & Thoms, 2001; Pack-Mabien, Labbe, Herbert & Haynes, 2001; Shapiro, Benjamin, Payne, & Heidrich, 1997) or doubt these reports and, thus, do not provide adequate care for these patients (Benjamin et al., 1999; Elander et al., 2003; Midence & Elander, 1996). In some instances, disbelief in patients' reports of pain (Tait & Chibnall, 1997) and the resulting lack of adequate care result in pseudoaddiction (Weissman & Haddox, 1989) and a risk of increased pain.

Pseudoaddiction, as described by Weissman and Haddox, is an iatrogenic syndrome of abnormal behavior developed as a direct consequence of inadequate pain management. The patient develops feelings of anger and isolation that lead to acting-out behavior. The healthcare provider then perceives the patient as having a behavioral problem and, while initially frustrated at not being able to control the patient's complaint of pain, becomes fearful of inducing drug tolerance or dependence. Over time, the healthcare provider avoids contact with the patient as a means to reduce conflict. In response, the patient begins to distrust the provider. The resulting vicious cycle culminates in pseudoaddiction syndrome in which pain medication may be withheld from chronic pain sufferers because clinical staff is unable to distinguish between responses to real pain and drug-seeking behaviors (Todd, 2005; Todd et al., 2006).

To avoid these pitfalls in treatment, it is essential for clinicians to adequately assess pain history and individual patients' needs. One of the challenges for healthcare providers in treating pain in SCD, however, is that there is no objective method for assessing underlying vaso-occlusive pathophysiologic alterations directly (Todd et al., 2006). Pain history is determined by self report and there are usually no obvious biophysical signs.

Previous authors have proposed guidance and strategies for chronic pain management designed to maintain consistent and competent care for patients with chronic pain (Baker, 2005; Jacob, 2001; Rosenblatt & Mekhail, 2005; Todd, 2005; Todd et al., 2006).

Generally, healthcare providers should be adequately versed in pain management principles, which will enable them to deliver compassionate, skilled care void of biases that may compromise professional objectivity.

Ethnicity, Gender and Pain

Multiple factors may contribute to differences in clinical pain reports. Among these factors are ethnicity and gender, which represent individual characteristics that can be affected by social and environmental influences that, in turn, affect pain responses (Fillingim, 2004). Studies on pain reports have differed widely in sample size, confounding variables, contributing psychosocial factors, biological factors, gender of researcher (Weisse, Foster, & Fisher, 2005), gender and ethnicity of subjects, methodology, social context, and results (Bernardes, Keogh, & Lima, 2008). There are conflicting and inconsistent findings on gender and pain, which have been attributed to physiologic differences such as hormonal changes (Craft, 2008; Greenspan et al., 2007; Schneider, Randoll, & Buchner, 2006). In some studies, there has been lack of stratification, hence researchers have not been able to generalize findings.

Ethnicity and pain

Most studies on chronic pain have either been conducted primarily with Caucasians or have not reported results by racial or ethnic groups (McClish et al., 2006). Those studies that have examined ethnicity and pain have had inconsistent results. There is evidence to suggest that African Americans experience more pain, symptom stress and disability than

do Caucasians with otherwise similar illnesses (Ruehlman, Karoly, & Newton, 2005; Vallerand, Hasenau, Templin, & Collins-Bohler, 2005; Weisse et al., 2005). Researchers have found that African Americans with chronic pain have higher levels of pain incidence and severity, depression and disability compared to Caucasians with chronic pain (Green, Ndao-Brumblay, Nagrant, Baker, & Rothman, 2004) and demonstrate greater sensitivity to noxious stimuli compared to Caucasians (Campbell et al., 2008; Kim et al., 2004). However, in another study, Caucasians required more morphine for analgesic coverage than did Asians and Africans (Dahmani, Dupont, Mantz, Desmonts, & Keita, 2001). Age of the individual and duration of pain also impacted the severity of pain in at least one of the above-mentioned studies. African Americans who were younger and had experienced 30 months of more of pain had more chronic pain disability than their older African American counterparts (Green et al., 2004).

Study findings regarding pain and ethnic differences in cancer patients have, likewise, been inconsistent. In Schneider and colleagues' (2006) study, African American cancer patients reported less pain than Whites and Hispanics. The authors, however, caution about generalizability of their findings since participants were recruited by convenience sampling. In fact, though one of the stated aims of the study was to achieve a gender-balanced sample, of the 276 participants, 79% were women, and the authors failed to clearly outline what adjustments were made as a result of this imbalance. In another study relying on a convenience sample, Im, Wonshik, and colleagues (2007) investigated ethnic differences in reported pain among Hispanic, non-Hispanic White, and non-Hispanic Black patients with cancer. The authors concluded that there were ethnic differences in types of pain and symptoms that patients reported, with non-Hispanic Blacks

reporting lower cancer pain scores than Whites or Hispanics. Ethnicity, however, was not a predictor of symptom scores. In a study of 480 multiethnic cancer patients, Im, Chee, and colleagues (2007) concluded that non-Hispanic Asians reported the lowest pain compared to other ethnic groups, women reported more pain than men, African Americans had lower symptom scores than members of other ethnic groups, and Hispanics had the highest functional status scores of the ethnic groups involved. The researchers concluded that there are differences in pain perception among ethnic groups (Im, Chee, et al., 2007; Im, Wonshik, et al., 2007). Conversely, Edwards and colleagues (2005) reported no significant ethnic differences in pain or pain-related disability in cancer patients. They did find, however, that coping measures for chronic pain differed among groups, with African Americans reporting significantly greater use of prayer than Caucasians.

Gender and pain

Though findings regarding differences in pain based on gender have been inconsistent, a number of studies have found gender to account for individual differences in pain symptoms (Foulkes & Wood, 2008). Women are also more likely than men to suffer from a variety of chronic pain disorders including fibromyalgia, trigeminal neuralgia and rheumatoid arthritis (Greenspan et al., 2007). Nevertheless, gender is not always included as a variable in pain studies, and more such studies have been conducted with male subjects than with females (Greenspan et al., 2007).

A number of studies have found that women experience more pain than men in similar situations or with similar conditions. For example, despite being healthier overall and practicing healthier lifestyle behaviors (such as increased activity and decreased tobacco consumption), women reported more back pain than men in a study by Schneider

and colleagues (2006) involving 5,315 subjects, 18-79 years of age, and designed to investigate gender-specific prevalence of low back pain among Germans. The authors reported 7-day back pain prevalence of 32% for men and 40% for women, though factoring in gender-specific somatization tendencies reduces the odds ratio of women vs. men from 1.42 to 1.23. In another study, females had more persistent pain than male counterparts when 33 women were matched with 33 men with fibromyalgia pretreatment after participants had undergone multidisciplinary pain rehabilitation (Hooten, Townsend, & Decker, 2007). Finally, Sarlani, Garrett, Grace, and Greenspan (2007) found that female patients with temporomandibular disorders (TMD) experienced more pain than did their male counterparts.

In contrast, McClish and colleagues (2006) reported that men and women with SCD generally reported similar pain experiences. Their study involved 226 adults with SCD who completed daily pain diaries for at least 30 days. They found no significant differences between men and women in the percentage of days individuals experienced SCD pain (men 58.5% vs. women 56.5%) or in the mean number of SCD pain episodes per 6-month period (2.5 for men vs. 2.2 for women).

Multiple factors may contribute to gender differences in pain. Fillingim and colleagues (2005) reported significant interaction between gender and genotype in pain reports, finding higher pain ratings among women with the rare allele genotype A118G than among men with the same genotype.

Genomics and Pain

In addition to ethnic and gender variations in pain and pain responses, researchers have begun to identify genetic differences as well. Uhl, Sora, and Wang (1999)

summarized analyses of human and murine studies, demonstrating that genetics accounts for a major proportion of variability in pain sensation and response to opiates. Stamer and colleagues (2003) analyzed data from 271 patients who had abdominal surgery and consumed analgesics postoperatively to determine whether there was a difference in response to postoperative analgesia between individuals classified as extensive metabolizers (EMs) and poor metabolizers (PMs) defined by cytochrome P450D6 (*CYP2D6*) polymorphisms. This question is particularly significant in the United States where, because of large ethnic and ancestral diversity, there are differing incidences of *CYP2D6* polymorphisms among groups. Caucasians with the *CYP2D6* PM phenotype had a significantly decreased response rate to analgesic treatment and required higher consumption and more rescue medications than did Caucasians with the EM phenotype (Stamer, et al., 2003). The *CYP2D6* gene locus appears to be more complex in African Americans than in Caucasians (Gaedigk, Bradford, Marcucci, & Leeder, 2002). African American carriers of *CYP2D6* reflect phenotype-to-genotype discordance not found in studies with Caucasians (Gaedigk, Bradford, Marcucci, & Leeder, 2002 ; Gaedigk et al., 2005). Hence it is more difficult to predict pain and drug responses among African Americans using the poor metabolizer and extensive metabolizer categorizations that have been used in Caucasian populations. Cai and colleagues (2006) noted that there is limited available information on the frequency of the many allelic *CYP2D6* variants found in African Americans and advised that further evaluation is necessary to identify these variants and help direct care.

Genetics and Pain Research

With the conclusion of the Human Genome Project in 2003, researchers have gained insights into the pathophysiology underlying SCD and into previously unknown associated genetic polymorphisms. The discovery of single nucleotide polymorphisms (“many forms”; SNPs), which are the most prevalent markers of human genetic diversity, has greatly increased the extent to which particular genes and their individual copies can be recognized (Mogil, 2004; Nussbaum, McInnes, & Willard, 2001). SNPs are varying alleles or alternate forms of a gene at any specific locus on the genome that might alter protein expression. This variance occurs when there are at least two relatively common alleles at the locus in the population and represents physical variation in the DNA molecule (Hartl & Jones, 2005; Micklos & Freyer, 2003; Nussbaum et al., 2001). The allele or SNP may be in a coding sequence or a gene but it differs at the nucleotide site “often” (Hartl & Jones, 2005, p. 70).

Pain genetics research is an evolving field that can help researchers to explore pain mechanisms in chronic states (Belfer et al., 2004; Mogil, 2004). In genetics research, regions of the genome can be mapped using linkage methods and association studies with distinct phenotypic and genotypic features of a particular disease. Through these types of studies, researchers have found that genomic variation influences interindividual sensitivity to pain and susceptibility to chronic pain disorders (Mogil, 2004; Mogil & Devor, 2004; Stamer & Stuber, 2007). Recent human genetic studies suggest that SNPs of specific genes contribute significantly to this variability in pain (Diatchenko et al., 2005; Edwards, 2005; Šerý, Hrazdilová, Matalová, & Ševčík, 2005). These SNPs of pain

susceptibility genes are probably not from one gene but rather from many polymorphic genes with multiple allelic qualities.

Pain susceptibility genes can make individuals such as those with SCD more susceptible to pain that damages nerves and other tissues, hence leading to secondary development of pain (Mogil, 2004). One area ripe for further study, then, is to look at vaso-occlusive complications such as chronic pain and seek associations with polymorphisms in candidate genes, thus evaluating interactions among many SNPs and the risk for SCD complications such as chronic pain. The identification of genetic variables that are associated with chronic pain should be helpful for clarifying pathophysiologic mechanisms of, identifying patients at risk for, and assisting in the treatment plan of individuals with chronic pain. The ultimate promise of this type of research is the development of personalized approaches to pain treatment based on an individual's genomic structure (Oertel & Lötsch, 2008).

Emerging research has identified allelic variants in the opioid receptor gene *OPRM1* and in genes involving nonopioid systems such as catechol-O-methyltransferase (COMT) that play a significant role in the epidemiology of pain and heritability. Genomic studies of pain can test for hypoexpression or hyperexpression of molecular activity that affects human pain phenotypes (Max & Stewart, 2008). Studies on pain and genomics are summarized in Table 1.

<Table 1 near here.>

COMT, an enzyme involved in the degradation of neurotransmitters such as dopamine, norepinephrine and epinephrine, is highly associated with human pain perception (Diatchenko et al., 2005) and pain regulation in the central nervous system

(Zubieta et al., 2003). The enzymatic activity is influenced by genetic polymorphisms located on chromosome 22. Coding that substitutes methionine for valine at amino acid position 158 reduces COMT activity and increases pain sensitivity. Zubieta et al. (2003) recognized that *COMT* polymorphisms influence human pain and hypothesized that they may underlie interindividual differences in pain responses. In their study, individuals with homozygous Met158 genotype reported greater sensory and affective pain compared with heterozygotes. In another study, Diatchenko et al. (2005) studied 202 healthy female volunteers to identify risk factors for temporomandibular disorders (TMD). They limited their subjects to females because they exhibit a higher prevalence of TMD relative to men. With genotyping, six SNPs were chosen that display higher polymorphism frequency in human populations (> 40% prevalence). The researchers concluded that COMT activity inversely influences pain sensitivity, with low COMT activity leading to elevated levels of norepinephrine and epinephrine and resulting in exaggerated pain sensitivity states. Thus, the gene that encodes for COMT is associated with pain perception and pain may be related to an SNP in the *COMT* gene. In a 3-year prospective cohort study among healthy female volunteers, Slade et al. (2007) likewise concluded that *COMT* haplotypes influence the risk of clinical pain. Rakvag et al. (2005) investigated the impact of the *COMT* Val158Met polymorphism on 201 Caucasian cancer patients who were taking oral morphine. Those homozygous for the 158 Val allele consumed more morphine than heterozygous patients and homozygotes for the 158 Met allele (Met/Met). Darbari, Minniti, Rana, & van den Anker (2008) recently concluded that genetic variability in *COMT*, though not directly involved in morphine metabolism, can influence the efficacy of morphine.

There is some evidence that individual differences in basal pain response are predictive of the development of chronic pain in initially pain-free subjects (Diatchenko et al., 2005; Edwards, C. L., et al., 2005; Edwards, R. R., et al., 2005; Edwards, 2005; Slade et al., 2007; Somogyi, Barratt, & Collier, 2007) and that molecular epidemiologic mechanisms can explain the phenotype of pain. With pain no longer attributed solely to neurophysiologic changes, it is clear that the study of pain must include genomic inquiry (Max & Stewart, 2008).

Pharmacogenetics

Beyond the genetic contributions to pain, itself, researchers are also looking into how genetic factors play a role in determining the efficacy and toxicity of analgesic drugs (Mogil & Devor, 2004). Pharmacogenetics helps to clarify the inherited basis of interindividual differences, or variants, in drug effects, metabolism and disposition. Pharmacogenomics refers to the study of the entire relay of genes that determines the pharmacokinetics (how much of a drug reaches its targets and for how long) and pharmacodynamics (what the drug does when it gets to the target) of a drug. Pharmacogenomics, then, provides a scientific basis for optimal drug therapy and individual dosing based on genetic variations and their consequences (Desmeules, Piguet, Ehret, & Dayer, 2004; Skorpen & Laugsand, 2008).

Cytochrome P450 2D6 (CYP2D6) belongs to a group of more than 80 enzymes that metabolize numerous drugs and convert the prodrug into an active metabolite. In humans, *CYP* gene families are the original implicators of cytochrome P450 isozymes, which are suggestive of inactivation of drugs and endogenous substrates (Desmeules et al., 2004; Somogyi et al., 2007). These gene families have varying allelic presentations

in different ethnic populations. Some individuals who inherit mutant *CYP2D6* gene alleles manifest a wide, unpredictable range of pain relief in response to opioids.

Individuals with deficient alleles may not be able to convert codeine to morphine. A detailed list of known cytochrome alleles and current information on varying *CYP2D6* alleles can be acquired from the Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee web site at <http://www.imm.ki.se/CYPalleles>.

CYP2D6 polymorphisms can be classified according to four levels of activity: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM) and ultrarapid metabolizers (UM). The majority of people express the EM phenotype, which is considered to be the norm. Those with PM polymorphisms inherit two deficient *CYP2D6* alleles and thus metabolize drugs at a slower rate, leading to higher accumulation of unmetabolized drugs, possible adverse events and lower drug efficacy. As poor metabolizers, such individuals usually continue to experience pain despite analgesic coverage. The UM phenotype results from an overexpression of metabolic enzymes and is usually caused by gene duplication resulting in increased activity. Individuals with the UM phenotype rapidly metabolize and eliminate drugs, leading to the potential for dangerous opioidergic effects and potentially lower drug efficacy. The IM phenotype covers a wide range of metabolic activity, from PM to EM (Bernard, Neville, Nguyen, & Flockhart, 2006).

Pain-related mutation in the *CYP2D6* gene has been implicated in pharmacogenetic studies that explain some of the interindividual variation in response to pain medication (Brousseau, McCarver, Drendel, Divakaran, & Panepinto, 2007; Stamer et al., 2003). Skorpen and Laugsand (2008) found that genetic markers may be used to

predict opioid efficacy. Thus, genotyping individuals for allelic variants can be helpful in clinical pain management. Brousseau et al. (2007), for example, concluded that of the 73 children with SCD in their study, 42 (58%) had a reduced-functioning allele. Further, it may be that some individuals who come to the emergency room with SCD pain have a reduced-functioning *CYP2D6* allele and are, thus, unresponsive to their opioid treatment. This genetic variance may explain the frequent healthcare utilization in some with SCD (Brousseau et al., 2007). The Brousseau study, to my knowledge, has been the only human study to investigate genetically determined lack of response to opioid pain medication for those with SCD.

In individuals without SCD, researchers have found evidence of allelic variants in genes involved in morphine pharmacogenetics and pharmacodynamics that may modulate the response to opioid analgesics (Lötsch & Geisslinger, 2005; Lötsch & Geisslinger, 2006; Lötsch, Skarke, Grosch, et al., 2002).

Genetic Variants That Influence Pain or Response to Opioids

In addition to altered protein function and the presence of inflammatory mediators such as interleukin, cytokines, and neutrophils (Okpala et al., 2002; Steinberg & Brugnara, 2003), the presence of pain-relevant proteins contributes to chronic pain. It is unlikely, however, that variation in pain sensitivity is caused by a single gene; rather evidence suggests that it is related to the interaction of many genes (Šerý et al., 2005). Case-control association studies may thus prove helpful in the development of treatments for individuals with chronic pain.

Association studies, using a case-control design, are statistical statements about the co-occurrence of alleles or phenotypes with candidate genes (Nussbaum et al., 2001).

In these studies allele frequencies in patients with chronic pain (or any disease of interest) are compared to those in a disease-free comparison group (Christensen & Murray, 2007; Pearson, 2008). This means that polygenic characteristics of the study are based on comparison between the frequencies of a given allele and a disease phenotype in nonrelated cases and controls, with the null hypothesis being that there is no difference between the groups (Belfer et al., 2004).

Challenges that researchers face when conducting case-control studies include finding appropriate cases and controls because the sets must be identical in respect to demographics such as age and gender and at the same time be homogenous with respect to the phenotype of interest, for example, pain perception (Christensen & Murray, 2007; Foulkes & Wood, 2008; Makis, Hatzimichael, & Stebbing, 2006). Selection bias is a problem in studies if the subjects exhibiting the phenotypes of interest are acquired from specialty or primary care clinics, for such individuals may not represent the general population (Max, Stewart, 2008). Another challenge in these studies is stratification by ethnicity. However, even given these limitations, researchers have made important strides in using association studies to identify pain-relevant SNPs.

Morphine, M-6-G, and M-3-G

In order to understand the mechanisms by which particular SNPs alter pain perception or response to opioids, it is important to understand the mechanism of action of one of the most frequently used opioids, morphine. Morphine is a frequently used opioid due to its availability and clinical efficacy (Darbari et al., 2008). Primarily morphine metabolism involves conjugation with glucuronic acid by the UDP-glucuronosyltransferase 2B7 enzyme (UGT2B7), resulting in the formation of two major

metabolites: morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) (Coffman, Rios, King, & Tephly, 1997). After the glucuronide formation process, morphine and its metabolites are eliminated via glomerular filtration (Darbari et al., 2008). M6G, an active metabolite, contributes to analgesia by binding to μ -opioid receptors (Andersen, Sjøgren, Hansen, Jensen, & Christrup, 2004; Klepstead, 2004; Osborne, Joel, Trew, & Slevin, 1990; Osborne et al., 1992; Stain-Textier, Boschi, Sandouk, & Scherrmann, 1999) and may actually be a more potent analgesic than morphine.

Andersen and colleagues (2004) analyzed blood samples for morphine, M3G, and M6G in 42 cancer patients who were treated with oral sustained-release (SR) morphine. In addition to finding that M6G had analgesic properties, the researchers found that M3G showed a low affinity for opioid receptors and had no analgesic activity but was able to elicit side effects. Animal studies have shown that M3G may actually antagonize the analgesic effect of morphine and M6G, but there have been no human studies to validate this (Andersen, Christrup, & Sjøgren, 2003). Other researchers have also suggested that certain adverse effects of morphine in humans are due to M3G formation (Coffman et al., 1997; Skorpen & Laugsand, 2008).

In the case of SCD, patients have additional disease-related pathology such as hepatic and renal complications that may also affect morphine variability (Darbari et al., 2008). For example, in renal failure there is accumulation of M6G, which results in prolonged narcosis (Gerber & Apseloff, 1993; Osborne et al., 1992). In severe liver disease it may be that glucuronidation plays a role, but Andersen (2002) found that in mild liver disease cancer patients did not manifest abnormality of morphine metabolism.

Human opioid receptor A118G polymorphism (OPRM1)

The human μ -opioid receptor (MOR), which is coded by the *OPRM1* gene, is the major site of action for most opioid analgesics, including morphine (Beyer, Koch, Schröder, Schulz, & Höllt, 2004; Lotsch & Geisslinger, 2006). It is central to both pain responses and opioid addiction (Compton, Geschwind, & Alacron, 2003). *OPRM1* is among the first of the neurobiology-related genes that have been examined for polymorphisms in various populations (Uhl et al., 1999). Researchers have found that there are varying clinical individual responses to morphine based on polymorphisms in *OPRM1*, which might influence expression and functioning of the binding sites (Chou, Wang et al., 2006; Chou, Yang et al., 2006; Klepstad et al., 2004; Lötsch & Geisslinger, 2006; Lötsch & Geisslinger, 2005; Manton, Goumon, Esch, & Stefano, 2005; Stamer & Stuber, 2007).

Two SNPs of *OPRM1* are A118G and C17T. Both of these SNPs have been investigated in substance abuse (Bond et al., 1998). The A118G mutation, in which A to G substitution in exon 1 occurs and results in amino acid exchange at position 40, is the most commonly identified SNP in *OPRM1*. The amino acid exchange is from asparagine to aspartate (N40D) (Bond et al., 1998). The functional properties of the A118G mutation reveal increased receptor binding affinity for B-endorphin and decreased potency of M6G (Bond et al., 1998; Lötsch, Skarke, Schmidt, Liefhold, & Geisslinger, 2002).

OPRM1 118 > G heterozygosity varies across populations, from 1–2% frequencies of the minor (118G) allele in African Americans (Bond et al., 1998) to approximately 16% of the same allele in Caucasians (Skorpen & Laugsand, 2008; Lötsch

& Geisslinger, 2006). Table 2 highlights polymorphisms and population frequencies for genes thought to be related to pain.

<Table 2 near here>

Chou, Wang, Liu, et al. (2006) studied 80 female patients who had elective total hysterectomies. Patients who were homozygous for the 118 allele needed more morphine to achieve adequate postoperative pain control. In another study of 140 Taiwanese patients undergoing total knee arthroplasty, Chou, Yang, Lu, et al. (2006) found that the group homozygous for G118 (GG) consumed 60% more morphine than did the group homozygous for A118 (AA) or the heterozygous (AG) group in the first 48 hr. They found no difference in consumption between the AA and AG groups. The researchers concluded that genotype may influence the postoperative response to morphine and cause differences in postoperative analgesic use.

Klepstad and colleagues (2004) analyzed data from 99 Caucasian patients (from an original sample of 207) with cancer using morphine who were genotyped for polymorphisms in the *OPRM1* gene. They found that pain intensity differed between groups, with patients who were homozygous for the 118A>G polymorphism having more pain and needed more morphine to achieve pain control. All homozygous (GG) patients were male.

Filligim and colleagues (2005) examined the sensory effects of analgesic medications among healthy nonsmokers who were free of clinical pain. Subjects with one or more rare A118G alleles exhibited lower sensitivity to pressure pain compared to subjects with wild type. The rare allele genotype was associated with lower pain ratings among men and higher pain ratings among women as compared to the wild type in men

and women. Women reported lower heat pain tolerance, higher pain ratings and lower pressure pain threshold compared to men.

Janicki et al. (2006) studied 121 patients with chronic pain and 101 surgical patients undergoing elective laparoscopic abdominal surgery to determine if A118G polymorphism in *OPRM1* could explain interindividual differences in opioid analgesic requirements. The researchers found that the frequency for the A118G SNP of *OPRM1* was significantly less in the group of patients with chronic pain being treated with opioids when compared to the group of patients being treated for acute postoperative pain. Patients with chronic pain who were homozygote carriers of the major allele needed higher opioid doses than did carriers of the minor allele.

C17T

In the C17T SNP of *OPRM1*, the amino acid alanine is exchanged for valine; thus the SNP is also referred to as Ala6Val or A6V. C17T has a higher frequency among drug-dependent individuals than does A118G (Bond et al., 1998), but the majority of studies have reported no correlation between C17T and substance abuse. For example, Crowley and colleagues (2003) investigated the association between *OPRM1* gene polymorphism and opioid dependence. Their sample included 213 drug-dependent African American and European Americans and 196 drug-free controls from both ethnic groups. The researchers found there was no association but that allelic frequency differed between African Americans and European Americans for five polymorphisms. Compton and colleagues (2003) explored the role of genotypic differences in *OPRM1* in human pain tolerance and opioid addiction. The researchers investigated 50 individuals of different ethnicities (38% Caucasians) in treatment for opioid addiction and 59 healthy

individuals (81% Caucasians). They found no differences in *OPRM1* allele frequencies between addicts and controls.

Potential of Genomics for Clinical Researchers

Unrelieved pain has major effects on the lives of individuals and results in pecuniary, social and psychological losses (Thomas, Gruen, & Shu, 2001). Recent advances in genetics and genomics have increased the potential for the development of more effective analgesics and other therapeutic interventions that will impact outcome of care (Nebert & Menon, 2001; Thomas et al., 2001). The greatest potential, however, for the utilization of genomic research in clinical care is the possibility that clinicians will be able to predict outcomes and personalize care.

Knowledge of the genetic structure of the targeted population will enable genetic testing in order to personalize care and drug development to an individual's genetic makeup (Brousseau et al., 2007; Desmeules et al., 2004; Lötsch & Geisslinger, 2005) and allow for a better decision making process and prediction of outcome (Meghani & Gallagher, 2008). Clinical researchers, when designing pharmacogenetic studies, should consider ethnic groups as potentially heterogenous regarding diversity of alleles (Nebert & Menon, 2001), plan studies accordingly, and thereby potentially reduce morbidity and mortality related to interindividual variability in drug response. Clinical studies should address the need to identify patient populations who will benefit from pharmacogenetically directed pain therapy and genotyping in pain therapy (Lötsch & Geisslinger, 2005). By far the greatest benefit to clinicians of integrating genetics and genomics into their studies will be the ability to personalize pain therapy after evaluating an individual's genetic capacity to metabolize pharmacologic agents (Uhl et al., 1999).

Implications for Nursing

Because of our numbers, access to healthcare consumers, and holistic, multidisciplinary focus, nurses are poised to carry the torch in the genomic era. We should act as agents of change, leading the way for the translation of genomic research into safe, evidence-based clinical practice. Nurses have strategic roles to play as research scientists, educators and practitioners in the generation and translation of genomic-based research for the benefit of healthcare consumers.

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Table 1. Summary of studies involving genomics and pain

Gene	No. of Subjects	Ethnicity/Nationality of Subjects	Clinical Type	Findings	Reference
<i>OPRM1</i>	12	not stated	Healthy volunteers	A118G reduces potency of M6G No significant difference in allele frequencies between opioid-dependent & nondependent participants	Lötsch, Skarke, Grosch, et al., 2002
<i>OPRM1</i> C17T SNP	113 + 39 control	AA, Cau, His	Former addicts + controls with no drug/alcohol dependence	No association between MOR polymorphism and drug addiction	Bond et al., 1998
	213 + 196 control	AA, EA	Drug dependent + drug free	Subjects homozygous for G118 allele require higher doses of morphine postsurgery (30% more) than those homozygous for 118A allele, evident at 24 hr	Crowley et al., 2003
<i>OPRM1</i> A118 SNP	80	Taiw	Post-op total abdominal hysterectomy patients	Homozygous (GG) patients consumed higher morphine doses postsurgery (~ 60%) than patients with 118AG or AA	Chou, Wang, et al., 2006
	120	Taiw	Post-op total knee arthroplasty patients	Individuals with one or more rare alleles exhibited lower sensitivity to pressure pain. Significant gender & genotype findings, with rare allele genotype associated with higher pain among women	Chou, Yang, et al., 2006
	167	Not stated	Healthy nonsmoking volunteers	A118G SNP frequency was significantly less in subjects with chronic, as	Fillingim et al., 2005
	121/101	Cau = 119, AA = 2, His = 0/Cau = 95, AA = 2, His = 4,	Chronic pain patients, opioid users/noncancer postsurgical patients, opioid		Janicki et al., 2006

Gene	No. of Subjects	Ethnicity/Nationality of Subjects	Clinical Type	Findings	Reference
<i>COMT</i>	99	Cau	Cancer patients	naïve compared to subjects with acute, pain, suggesting G118 MOR has a protective effect against and may alter response to chronic pain Homozygous (GG) allele patients consumed higher doses of morphine to achieve analgesia than heterozygous and AA homozygous patients <i>COMT</i> is highly associated with human pain perception and risk for chronic pain (TMD) <i>COMT</i> haplotypes increase risk of clinical TMD	Klepstad et al., 2004
	202	Not stated	Healthy female volunteers	Individuals homozygous for 158Met (met/met) allele had higher sensory and affective pain ratings	Diatchenko et al., 2005
	171	Not stated	Healthy females	<i>COMT</i> Val158Met polymorphism contributes to interindividual variation in morphine requirements for patients with cancer pain	Slade et al., 2007
	18	Not stated	Healthy volunteers		Zubieta et al., 2003
	207	Cau	Cancer		Rakvag et al., 2005

Note. AA = African Americans; Cau = Caucasians; His = Hispanics; EA = European Americans; MOR = human μ -opioid receptor; SNP = single nucleotide polymorphism; Taiw = Taiwanese; TMD = temporomandibular disorders.

Table 2. Single nucleotide polymorphisms (SNP) and population frequencies for genes thought to be related to pain.

Gene	SNP	Chromosome Region	Amino Acid Change	Population Frequency	Reference
<i>OPRM1</i>	A118	6q24-25	Asn40Asp	AA 1-2%	Bond et al., 1998
				His 14%	Bond et al., 1998
				Jap 50%	Bond et al., 1998
				Cau 10-12%	Bond et al., 1998
				Cau 16%	Lötsch & Geissler, 2006
<i>CYP2D6</i>	C17T	22q13.1	Ala6Val	AA 15%	Bond et al., 1998
				Cau 1%	dbSNP
				Opiate dependent 22%	Bond et al., 1998
				<u>PM</u>	
				As 1-2%	Gaedigk et al., 2002
<i>COMT</i>	A472G	22q11.21	Val158Met	AA 3.5-8%	Gaedigk et al., 2002
				Some functional variability due to gene duplication events.	
				<u>UM</u>	
				EI 30%	Cai et al., 2006
				AA 4.5-4.9%	Cai et al., 2006 p.23

Note. PM = poor metabolizers (all known variants); UM = ultra rapid metabolizers (all known variants, AA = African Americans, As = Asians, Cau = Caucasians, Ch = Chinese, EI = East Indians, His = Hispanics, Jap = Japanese.

dbSNP = Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda: National Center for Biotechnology Information, National Library of Medicine. Retrieved April 1, 2009, from <http://www.ncbi.nlm.nih.gov/SNP/>

Studies included examined acute pain response as well as chronic pain.