Genetic basis of pain variability: recent advances

Erin E Young,1 William R Lariviere,1,2 Inna Belfer1,3

ABSTRACT
An estimated 15–50% of the population experiences pain at any given time, at great personal and societal cost. Pain is the most common reason patients seek medical attention, and there is a high degree of individual variability in reporting the incidence and severity of symptoms. Research suggests that pain sensitivity and risk for chronic pain are complex heritable traits of polygenic origin. Animal studies and candidate gene testing in humans have provided some progress in understanding the heritability of pain, but the application of the genome-wide association methodology offers a new tool for further elucidating the genetic contributions to normal pain responding and pain in clinical populations. Although the determination of the genetics of pain is still in its infancy, it is clear that a number of genes play a critical role in determining pain sensitivity or susceptibility to chronic pain. This review presents an update of the most recent findings that associate genetic variation with variability in pain and an overview of the candidate genes with the highest translational potential.

INTRODUCTION
Pain—the “unpleasant sensory and emotional experience associated with actual or potential tissue damage…” (International Association for the Study of Pain taxonomy; http://www.iasp-pain.org)—is a necessary and informative sensory experience which encourages avoidance of danger and recuperative behaviours that promote healing and protection of an injured or diseased area of the body.1 In pathological conditions, the pain may no longer be useful and may produce more harm than good. Estimates suggest that 15–50% of the population is experiencing pain at any given time.2–4 This prevalence is associated with substantial cost, both societal in the form of lost productivity and increased healthcare utilization,4 5 as well as personal in the form of increased risk for psychological disorders6 and reduced relationship satisfaction and greater distress.7 Because pain is the most commonly reported symptom in clinical settings,4 8 individual differences in pain reporting could contribute to delayed or ineffective treatment of underlying disease in those with low sensitivity,8 while hypersensitivity could increase an individual’s reporting of pain leading to significant inordinate healthcare utilisation and unnecessary personal suffering, and may increase risk for a number of chronic pain conditions.9–11

Though pain is often a normal part of human condition (with rare exceptions), there is a high degree of inter-individual difference in pain responses and in reporting of pain in the clinical setting.12 This variability is likely due to the complex interaction of environmental and innate factors. For example, socioeconomic status and prior history of trauma/stress exposure have both been shown to modulate pain reporting and responding.13–17 Heritability estimates based on inbred strains of laboratory mice studies suggest that up to 30–76% of the variance in pain responding is explained by genetic factors.18–20 Race and ethnicity have also been shown to explain differences in reports of pain, with African American and non-Caucasian Hispanics typically reporting more pain than Caucasians within the same clinical populations.21–24 In addition, gender has been shown to affect pain thresholds as well as pain reporting in a clinical setting, with women typically reporting greater pain than men.25–27 Even when the variability explained by each of these factors is accounted for, individual differences remain and genetic variation has been shown to explain a significant portion of this remaining variability. While understanding the phenomenon has basic intellectual value, the influence of genetic variation on pain variability is also highly clinically relevant as it may lead to more individualised care for patients and the identification of novel therapeutic targets.

Early research using twin and family studies has established the heritable nature of both experimental and clinical pain.28 29 These studies were instrumental in identifying familial trends for pain conditions and rare disorders in which pain responding is significantly altered.29–33 Linkage and association studies have pinpointed a number of genes responsible for heritable conditions involving alterations in pain. The hereditary sensory and autonomic neuropathies (HSAN I–V) are a family of such syndromes in which pain perception and responses are significantly reduced or absent due to mutations in single genes (table 1).

Individuals diagnosed with HSAN often exhibit progressive injuries to the areas of the body affected (ie, ulcerations, joint deformities, etc) but do not report discomfort as a result. Other Mendelian heritable conditions are associated with increased pain including erythromalgia, familial hemiplegic migraine, and paroxysmal extreme pain (table 1).45–46 54 While these types of pathological conditions add to our overall knowledge regarding pain processing, they do not necessarily give insight into variations within the general population. There is growing evidence that in order to understand the genetics of pain, pain must be considered a complex phenotype or trait resulting from complex polygenic and environmental contributions. Now, more than ever, researchers are focusing on the genetic contribution to normal variation in pain reporting and responding, as this may facilitate translation of...
basic science findings into pain treatment protocols individually tailored to a patient’s risk or resilience.

Research into the genetics of pain in humans utilises a number of methodologies to identify genetic correlates of behaviour. Identifying mutations may explain rarer inherited pain syndromes, but the application of these findings to variations in the general population has been less fruitful. Twin studies offer an opportunity to evaluate polygenic inheritance. Twin studies and other studies suggest that 30–60% of the variation in chronic pain syndromes may be due to heritable factors. This review will primarily focus on findings from human genetic association studies, including hypothesis driven candidate gene studies and genome-wide association studies (GWAS). Recently developed genome-wide arrays allow for the objective unbiased evaluation of the association of human pain phenotypes with single nucleotide polymorphisms (SNPs) across the entire genome, including variations in the number of copies of a gene that an individual has (copy number variation (CNV)). The current review will highlight the most recently identified genetic factors (2008 to present) that confer protection or susceptibility to pain in general and clinic based populations and which do not show a Mendelian pattern of inheritance.

**GENETIC CORRELATES OF PAIN: RECENT PROGRESS**

Significant individual variability is observed in both pain threshold and in susceptibility to chronic pain conditions, and a portion of this variation can be explained by variation within specific genes. Single functional SNPs or combinations of SNP alleles that tend to be inherited together (haplotypes) can contribute to increased or decreased susceptibility to pain. One of the most extensively studied pain candidate genes is *catechol-O-methyltransferase (COMT)*, which is known to be involved in the inactivation of dopamine, epinephrine, and norepinephrine neurotransmission and associated with variations in experimental and clinical pain behaviour. Four SNPs have been identified that may contribute to a haplotype characterised by differences in COMT metabolic enzyme activity that is inversely correlated with alterations in pain perception. Additionally, a single protective haplotype has been related to increased enzymatic activity, decreased pain sensitivity, and reduced risk for temporomandibular joint disorder, a common musculoskeletal pain syndrome. While genomic variation in *COMT* affects RNA stability and protein translation and affects pain through variations in neurotransmitter metabolism, SNPs in the *μ*-opioid receptor gene (*OPRM1*) alter pain sensitivity through variations in receptor function. Relationships between *OPRM1* and pain sensitivity and efficacy of opioid analgesics have been shown in a number of experimental and clinical populations. Furthermore, recent data show that genetic mutations in *COMT* and *OPRM1* may interact and act synergistically to affect morphine analgesia and side effect burden. Additional evidence comes from the identification of SNPs within the *melanocortin 1 receptor (MC1R)* gene that are associated with pain sensitivity and *μ*-opioid analgesia in certain populations.

**Table 1** Mendelian heritable pain conditions

<table>
<thead>
<tr>
<th>Pain syndrome</th>
<th>Gene affected</th>
<th>Transmission</th>
<th>Gene product effect</th>
<th>Phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSAN-I*</td>
<td>A: SPTLC1</td>
<td>Dominant</td>
<td>Disrupted sphingolipid synthesis</td>
<td>Pain and heat loss</td>
<td>34 35</td>
</tr>
<tr>
<td></td>
<td>B: SPTLC2</td>
<td>Dominant</td>
<td>Disrupted sphingolipid synthesis</td>
<td>Sensory loss</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>C: ATL1</td>
<td>Dominant</td>
<td>Reduced GTPase activity; disrupted sensory neuron function</td>
<td>Sensory loss</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>E: DNMT1</td>
<td>Dominant</td>
<td>Disrupted DNA methylation resulting in neurodegeneration</td>
<td>Sensory loss; hearing loss; early onset dementia</td>
<td>37</td>
</tr>
<tr>
<td>HSAN-II (Morvan’s disease)</td>
<td>HSN2</td>
<td>Recessive</td>
<td>Disrupted transmission of sensory signals</td>
<td>Loss of sensation</td>
<td>38</td>
</tr>
<tr>
<td>HSAN-III (familial dysautonomia or Riley–Day syndrome)</td>
<td>IKBKAP</td>
<td>Recessive</td>
<td>Reduced transcription of IKAP</td>
<td>No pain sensation</td>
<td>40</td>
</tr>
<tr>
<td>HSAN-IV (CIPA)</td>
<td>NTRK1</td>
<td>Recessive</td>
<td>Reduced NTR activity/impaired neuronal differentiation</td>
<td>Congenital insensitivity to pain with anhydrosis</td>
<td>41</td>
</tr>
<tr>
<td>HSAN-V (CIPA)</td>
<td>NGFB</td>
<td>Recessive</td>
<td>Loss of functional TrKA receptor</td>
<td>Congenital insensitivity to pain with partial anhidrosis</td>
<td>42 43</td>
</tr>
<tr>
<td>Channelopathy-associated insensitivity to pain</td>
<td>SCN9A</td>
<td>Recessive</td>
<td>Loss of function in Na(<em>{+})(</em>{+}) channel</td>
<td>Congenital insensitivity to pain without anhidrosis</td>
<td>44</td>
</tr>
<tr>
<td>Erythermalgia</td>
<td>SCN9A</td>
<td>Dominant</td>
<td>Decreased threshold in Na(<em>{+})(</em>{+}) channel</td>
<td>Chronic inflammation/burning pain</td>
<td>45</td>
</tr>
<tr>
<td>PEPD</td>
<td>SCN9A</td>
<td>Dominant</td>
<td>Impaired Na(<em>{+})(</em>{+}) channel inactivation</td>
<td>Mandibular, ocular, and rectal pain</td>
<td>46 47</td>
</tr>
<tr>
<td>FHM-I</td>
<td>CACNA1A</td>
<td>Dominant</td>
<td>Increased Ca(^{2+}) channel activation at negative potentials</td>
<td>Migraine (with or without aura/hemiparesis) and cerebellar degeneration</td>
<td>48–50</td>
</tr>
<tr>
<td>FHM-II</td>
<td>ATP1A2</td>
<td>Dominant</td>
<td>Loss of function/reduced Na(^{+}/K(^{+})(_{+}) ATPase activity</td>
<td>Migraine (with or without aura/hemiparesis)</td>
<td>51 52</td>
</tr>
<tr>
<td>FHM-III</td>
<td>SCN1A</td>
<td>Dominant</td>
<td>Loss of Na(_{+}) channel subunit; neuronal hyperexcitability</td>
<td>Migraine (with or without aura/hemiparesis)</td>
<td>53</td>
</tr>
</tbody>
</table>

*Also referred to as hereditary sensory radicular neuropathy, ulcerocutaneous neuropathy, Thevenard syndrome, familial trophoneurosis, mal perforant du pied, familial syringomyelia, and Charcot–Marie–Tooth type 2B syndrome (subtype 1C only).
CIPA, congenital insensitivity to pain with anhydrosis; FHM, familial hemiplegic migraine (types I–III); HSAN, hereditary sensory and autonomic neuropathy (types I–V); PEPD, paroxysmal extreme pain disorder.
with reduced sensitivity to both clinical and experimental pain measures. GTP cyclohydrolase 1 is the rate limiting enzyme in tetrahydrobiopterin (BH4) formation, a necessary step in the biosynthesis of serotonin, dopamine, norepinephrine, epinephrine, and nitric oxide, all of which have been shown to have a significant role in pain processing. As with COMT, it is unclear which of the target neurotransmitters is critically affected and by what mechanism the genetic differences result in an alteration in pain phenotype. A GCH1 haplotype based on 15 SNPs was shown to contribute to reduced experimental pain sensitivity and to decreased pain persistence after lumbar discectomy in a population of lower back pain patients.11 Moreover, protection from pain following surgery has been linked with one SNP within GCH1 and a common haplotype confirming previous findings.71 A protective haplotype characterised by reduced GCH1 activity and reduced BH4 synthesis has also been associated with decreased pain reporting and decreased need for specialised pain therapy following cancer diagnosis.72 73 However, it is important to note that it is not clear whether GCH1 plays a role in modulating all pain phenotypes. In two separate studies, recurrent acute and chronic pancreatitis and chronic widespread pain (CWP) symptoms showed no relationship with variations in GCH1.74 80 Whether the inconsistencies are reflective of a specific role for GCH1 in certain pain types remains to be fully elucidated. However, other genetic loci that contribute to catecholamine synthesis and transmission have been implicated in a number of pain phenotypes. Most recently, an association has been revealed between polymorphisms of the serotonin transporter gene (SLC6A4) and experimental thermal pain thresholds76 as well as the conditioned81 and emotional82 modulation of experimental pain. Moreover, carriers of the s-allele in the serotonin transporter linked promoter region (5-HTTLPR) within SLC6A4 show decreased 5-HTT function83 and an increased risk for the CWP condition fibromyalgia.84

Recent data suggest an association between genes encoding for two neurotransmitter receptors, one for serotonin and one for epinephrine, and an increased risk for developing CWP in which pain is the primary symptom of concern (table 2). Hocking et al77 conducted a prospective study in a community sample to evaluate the risk for CWP. Two SNPs (rs12654778 and rs1042713) within ADRB2, which encodes for the β2 adrenergic receptor, were associated with risk of CWP. Common functional haplotypes for ADRB2 were also associated with self-reports of the extent and duration of pain in that population. This confirms an association previously shown between ADRB2 haplotypes, functional imbalance of β adrenergic signalling and an increased risk for temporomandibular pain.85 Recently, the presence of a T allele at a single SNP within HTR2A, the gene encoding the serotonin receptor 2A, was also associated with an increased risk of CWP diagnosis79 and post-surgical pain burden.79 Taken together with previous data, these findings suggest that genotype differences can result in alterations in neurotransmission, which can in turn contribute to variations in pain reports within normal and clinical populations.

### Genetic determinants of ion channel function contribute to pain susceptibility

While alterations in neurotransmission directly affect the messages sent and received by neurons, alterations in ion channels can alter the transmission of messages received by augmenting or decreasing neuronal excitability. Sodium, potassium, and calcium channels are known to play a vital role in initiation and propagation of intracellular signals in neurons, including primary nociceptors that innervate peripheral tissues and are activated by noxious stimulation to propagate nerve impulses towards the spinal cord.86 Emerging data offer convergent evidence for the importance of ion channels in both pain sensitivity in normal populations and pathological pain states (table 3). Recent findings suggest an SNP within the SCN9A gene that encodes the α subunit of the voltage gated sodium channel NaV1.7 may play a role in determining risk for chronic pain conditions as well as variation in pain responding within normal populations.81 In a mixed cohort of sciatica, osteoarthritis, pancreatitis, lumbar discectomy, and phantom limb pain

### Table 2 Pain related genes associated with neurotransmitter systems

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Neurotransmitter system affected</th>
<th>Phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCH1</td>
<td>Serotonin, dopamine, norepinephrine, epinephrine, nitric oxide (all via BH4)</td>
<td>↓ Sensitivity to experimental pain ↓ Post-surgical pain (lumbar discectomy)</td>
<td>11 71–74</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Serotonin</td>
<td>↑ Risk for CWP ↑ Facilitation of experimental pain</td>
<td>75 76</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Epinephrine</td>
<td>↑ Risk for CWP</td>
<td>77</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Serotonin</td>
<td>↑ Risk for CWP ↑ Post-surgical pain</td>
<td>78 79</td>
</tr>
</tbody>
</table>

CWP, chronic widespread pain.

### Table 3 Pain related genes associated with ion channel function

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Channel type affected</th>
<th>Phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN9A</td>
<td>Voltage gated Na⁺ channels</td>
<td>↑ Chronic pain in mixed cohort (sciatica, osteoarthritis, pancreatitis, lumbar discectomy, and phantom limb)</td>
<td>87</td>
</tr>
<tr>
<td>KCNS1</td>
<td>Voltage gated K⁺ channels</td>
<td>↑ Sensitivity for experimental pain</td>
<td>88</td>
</tr>
<tr>
<td>CACNA2D3</td>
<td>Voltage gated Ca²⁺ channels</td>
<td>↑ Sensitivity for experimental pain</td>
<td>89</td>
</tr>
<tr>
<td>CACNG2</td>
<td>Voltage gated Ca²⁺ channels</td>
<td>↓ Chronic post-surgical pain (discogenic disease)</td>
<td>90</td>
</tr>
</tbody>
</table>
patients, increased pain was associated with the presence of an A allele at SNP rs6746030 within SCN9A (chromosome 2q24), resulting in an amino acid change from arginine to tryptophan at position 1150 of the Na\textsubscript{v}1.7 voltage gated sodium channel. This same SNP was associated with decreased thresholds for a composite measure of experimental pain (combined thermal, mechanical, ischaemic, and temporal summation of thermal stimuli).\textsuperscript{57} The subunit encoded by this gene is widely expressed in nociceptors and loss of function alleles have been implicated in congenital autonomic recessive channelopathies characterised by an inability to feel pain (channelopathy associated insensitivity to pain) (table 1).\textsuperscript{44 53} Further implicating SCN9A in modulation of pain, primary erythromalgia and paroxysmal extreme pain disorder—both disorders characterised by an increase in pain sensitivity—are the result of autosomal dominant mutations shown to facilitate activation of Nav\textsubscript{v}1.7.\textsuperscript{87 92}

Intracellular communication within the nervous system depends on the movement of sodium and potassium ions, and both populations of ion channels have recently been linked with alterations in pain sensitivity. While SCN9A has been associated with variations in pain sensitivity, Costigan et al\textsuperscript{55} identified one SNP within KCNS1, the gene encoding a voltage gated potassium channel (subfamily S, member 1), which may play a role in the risk for chronic pain. In this study, five cohorts of lumbar pain, amputation, sciatica, and phantom limb pain patients, and of healthy adults tested for experimental pain, respectively, showed a significant increase in self reported pain associated with the SNP rs754784, a missense A to G exonic substitution of KCNS1 (chromosome 20q12) resulting in a valine in place of isoleucine at residue 488. Two genes related to calcium channel function have been recently identified for their association with altered pain sensitivity. Individuals homozygous for two minor allele variants within CACNA2D3 (C/C at SNP 6777055 and A/A at SNP rs1851048), encoding for the alpha 2 delta 3 subunit of voltage dependent calcium channels, exhibit reduced sensitivity to acute noxious heat as well as with lower risk for chronic back pain following surgical intervention for discogenic disease.\textsuperscript{59} Providing further evidence for the importance of calcium channel function in determining pain sensitivity, Nissenbaum et al\textsuperscript{90} reported an association between increased susceptibility for pain following full or partial mastectomy and a given haplotype defined by a homozygous A-C-C haplotype at three SNPs (rs4820242, rs2284015, and rs2284017) within the CACNG2 gene that encodes for the gamma 2 subunit (also known as stargazin).\textsuperscript{93-95} This gene product is also intimately involved in the trafficking and function of AMPA receptors and associated ion channels.\textsuperscript{94-99} In the mouse, the genomic region containing Cacng2 was linked to self injury of the hindlimb (autotomy behaviour), a measure of neuropathic pain, and the gene was downregulated in mice in a nerve injury model of sciatic and saphenous nerve transaction in mice.\textsuperscript{90} Moreover, knockout mice that do not express Cacng2 exhibited greater autotomy after injury than wild type mice.\textsuperscript{90} The precise role that variations in Cacng2/CACNG2 play in the manifestation of these pain behaviours in mice and chronic pain risk in humans remains to be fully defined, but these findings suggest a place for genetic testing in determining treatment plans with a known potential for inducing chronic pain (eg, surgical procedures, other standard treatments, etc).

Disease related genes play a role in pain responding

Susceptibility to a disease and the pain associated with that disease may have overlapping genetic contributions. On face value alone, it stands to reason that when variation in a gene is associated with an increase in disease severity, one might expect higher pain reporting. However, it is not always the case that disease severity and disease induced pain go hand-in-hand. In fact, there is often pronounced variability of pain reports even within a seemingly homogenous population.\textsuperscript{59 65} Two recently identified candidate genes known to be involved in chronic disease processes have specifically been associated with pain as well. One such gene, CASP-9, which encodes for caspase-9 known to be involved in programmed cell death, was previously shown to play a role in determining the severity of lumbar discogenic disease.\textsuperscript{100} More recently, an SNP within the promoter region of this gene and known to increase transcriptional activity of the gene has also been shown to increase self reporting of pain without effects on disease process per se.\textsuperscript{100} In a population of females diagnosed with endometriosis, a recent study found an increased representation of the C allele at rs4778889 within the IL16 gene for interleukin 16 compared with normal healthy females (ie, more C/C homozygotes and T/C heterozygotes than T/T homozygotes were found in this population).\textsuperscript{101} This polymorphism shows a further increase in prevalence in the subset of those diagnosed with endometriosis and reporting disease associated pain compared with those diagnosed but not reporting pain.\textsuperscript{101} While the specific role played by these factors in normal variability in pain remains to be determined, the implication is that these genes may contribute independently to augmentation of pain processing and the progression of disease. Moreover, previously identified ‘pain genes’ may affect pain without altering disease process, but this does not detract from their inherent importance for clinical practice. In short, though pain and disease may be somewhat related in nature, it is important to address each effectively, and genetics may offer a tool for maximising quality of life by decreasing pain as a separate focus during treatment.

PAIN GWAS: PROGRESS AND PITFALLS

Our understanding of the genetics of human pain is rapidly growing and several recent GWAS have offered a glimpse of what is to come in terms of pinpointing distinct genetic contributions to risk and severity of pain syndromes. One such study revealed a strong relationship between genotype for an SNP in linkage disequilibrium with SNPs for ZNF429 on chromosome 19 and analgesic use following oral surgery.\textsuperscript{102} Two other SNPs were tentatively associated with pain ratings following surgery, but these associations did not reach statistical significance. In this study the sample size was small (60 females and 52 males), resulting in a lack of statistical power to evaluate adequately multiple genetic associations within the same population.

Oedegaard et al\textsuperscript{103} used a much larger sample of approximately 1000 cases to evaluate genetic associations for migraine pain in populations with a diagnosis of bipolar disorder or attention deficit hyperactivity disorder. In these two populations, an SNP within the previously uncharacterised KIAA0564 gene region on chromosome 13 was associated with an increased diagnosis of migraine. Comorbid diagnoses are common in GWAS designs, but it should be noted that these comorbidities could contribute to reduced power to detect significant associations or idiosyncratic findings that do not generalise to the overall population. Anttila et al\textsuperscript{104} report a link between the minor allele of rs1835740 on chromosome 8q22.1 and the risk for migraine pain. This study may mark a transition in the human genetics of pain literature in that it is the first to use a powerful design with...
for these studies. There is substantial population variability between studies, defined by differences in demographics as well as differences in diagnoses and pain status. For example, it remains to be seen whether genetic associations that exist for one type of chronic pain (eg, chronic post-mastectomy pain) are also true for other types of chronic pain (eg, lower back pain, cancer pain, phantom limb pain). This may be, at least in part, due to the relatively small number of studies published using genetic association methods to assess human pain that are available for comparisons and hypothesis generation. Moreover, the lack of consistent replication across human studies may be due to inadequate power, population heterogeneity in a single study (ie, based on differential disease diagnosis, ethnicity, gender, etc) or differences in the method of measurement and reporting of pain across studies.68 108

Importantly, one notable factor that has been somewhat overlooked is the potential for independent genetic associations with specific pain behaviours or pain states. Findings from animal studies18 20 would suggest that some specificity of genetic associations with modality or type of pain is expected and human studies have shown non-overlapping genetic associations with different pain modalities.29 As seen in figure 1, there is a lack of evidence for specificity of genetic associations with specific types of pain in humans. Experimental pain studies suggest that pain specific genetic associations are likely, but the translation of these findings to clinical pain has not yet been achieved. For instance, studies combining several cohorts (defined by diagnosis and/or pain outcome) may shed light on common mechanisms involved in multiple pain states, but may also fail to show significant genetic associations that are specific to only one of the cohorts in question. This circumstance could result in an artificial narrowing of the candidate gene list for subsequent hypothesis testing, and could lead to over-generalisation and false assumptions in future studies. The challenge at hand, therefore, is how to efficiently increase power in human pain studies to test specificity hypotheses in cohorts that represent different pain populations.

TRANSLATIONAL POTENTIAL OF GENETIC ASSOCIATION STUDIES

The ultimate value in understanding the genetic determinants of pain is to be able to reduce suffering in human populations. While the flow of information from basic and clinical science studies is beginning to increase, there has not been a boon of genetic testing for use in risk assessment and diagnosis of pain in typical healthcare settings. There are, however, a number of genes that seem to have the most translational potential and may represent key tools in diagnosis and treatment of pain in the future. These can be roughly divided into three categories of translational application based on the association between the gene and pain phenotype: pain facilitating alleles, pain protective alleles, and alleles related to analgesia.

A number of recent associations suggest that certain polymorphisms act to facilitate or increase pain; the most recent genes of interest within this group include KCNS1, SCN9A, ADRB2, HTRA1, CACNG2, and IL16 (for details, see above). Genetic association studies indicate that these genes contribute to an increase in pain sensitivity and, in many cases, an increased risk for developing chronic pain conditions. As a result, the combined genotype for an individual at these multiple loci could give insight into risk for pain following treatment in the clinical setting. For example, if a patient was considering the benefits and costs of an elective surgical procedure, his or her genetic
predisposition (or lack thereof) for developing neuropathic pain afterwards could be used as a factor in the decision.

Another family of alleles has been identified as conferring pain protection or a decrease in pain; the most recent candidates in this category include COMT, OPRM1, TRPV1, MC1R, GCH1, and CACNA2D3. These loci are associated with reductions in pain and/or resiliency to develop chronic pain. Thus, they could be of significant clinical importance to guide physicians and patients in determining who might be suitable for more aggressive treatment plans.

Finally, it is important to note that there are several alleles that have been shown to modulate the efficacy of analgesic agents in the treatment of pain. Polymorphisms in COMT, MC1R, and OPRM1 have been associated with resistance to the effects of analgesics. Polymorphisms within COMT, OPRM1, and TRPV1 result in decreased morphine efficacy, while mutations of MC1R are associated with a reduction in the analgesic effects of lidocaine administration. Interestingly, other polymorphisms within OPRM1 are associated with decreased morphine side effect sensitivity—that is, decreased pupil constriction and decreased respiratory depression. Conversely, polymorphisms within two other genes, CYP2D6 (encoding for cytochrome P450 enzyme involved in metabolism of opioids) and ABCB1 (encoding for the P-glycoprotein transporter), have been associated with increased side effects following opioid administration. COMT haplotype has recently been associated with the efficacy of the β-adrenergic antagonist propranolol for pain reduction in patients with temporomandibular disorder.

Interestingly, those with increased risk for chronic pain as a result of s-allele carrier status in the 5-HTTLPR of SLC6A4 exhibited better analgesic effects following opioid administration. While a risk assessment based on an individual’s pain related genotype is a long term translational goal, it may be more practical in the short term to identify those with a genotype suggestive of increased analgesic resistance and/or increased risk of negative side effects when designing pharmacological pain management plans, since these comprise much of the currently available arsenal used to fight pain.

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