Progress in Genetic Studies of Pain and Analgesia

Michael L. LaCroix-Fralish and Jeffrey S. Mogil

Department of Psychology and Center for Research on Pain, McGill University, Montréal, Quebec, H3A1B1 Canada; email: jeffrey.mogil@mcgill.ca

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Abstract

Interindividual variability in pain sensitivity and the response to analgesic manipulations remains a considerable clinical challenge as well as an area of intense scientific investigation. Techniques in this field have matured rapidly so that much relevant data have emerged only in the past few years. Our increasing understanding of the genetic mediation of these biological phenomena have nonetheless revealed their surprising complexity. This review provides a comprehensive picture and critical analysis of the field and its prospects.

INTRODUCTION

Pain is a fundamental experience characterized by an unpleasant physical perception and corresponding emotional state (1). Pain is biologically adaptive in that it signals actual or potential tissue damage, which evokes withdrawal and/or recuperative behaviors. In some instances and in some people, however, pain becomes chronic and exquisitely maladaptive, through pathophysiological processes that remain the subject of intense investigation (2). Chronic pain conditions are highly prevalent, and represent a huge economic burden on society [the direct costs of back pain alone are on par with heart disease and Alzheimer's (3)] and in addition to causing unimaginable suffering, chronic pain also contributes to mortality (4, 5).

The control of pain has been a major goal of pharmacotherapy from the earliest times. Several plant-derived products (the opiates, derived from *Papaver somniferum*, and the salicylates, derived from the *Salix* family, being the most notable) have been used to relieve pain for thousands of years (6). Today, analgesic development is a multi-billion dollar effort, reflecting both the importance of pain control to patients and health-care practitioners, and the fact that the effective management of both acute and chronic pain remains suboptimal. The situation is particularly challenging for chronic neuropathic pain sufferers, where current frontline therapies have low efficacy, with none featuring a number-needed-to-treat (NNT) of less than 2 (7).

INDIVIDUAL DIFFERENCES IN PAIN AND PAIN INHIBITION

One of the major reasons why pain relief remains such a challenge is the robust interindividual variability that exists in sensitivity to pain, the propensity to develop chronic pain conditions, and the response to analgesic manipulations. Laboratory studies have documented impressive individual differences in thresholds, tolerance and psychophysical (pain scale) ratings of standardized noxious stimuli (8–10), and in pain proxies such as activation of the cortical pain matrix (11) revealed by functional magnetic resonance imaging (fMRI) (12, 13). The possibility that individual differences in ratings are mere artifacts of scale usage is rendered unlikely by the demonstration of impressive correlations between pain ratings and simultaneously obtained measures of cortical activation using fMRI or positron emission tomography (PET) (14, 15). Epidemiological studies of chronic pain syndromes known to develop after specific traumatic or infectious insults (e.g., central pain after stroke, postherpetic neuralgia after herpes zoster, and complex regional pain syndrome after fracture) consistently reveal that only a small fraction of patients go on to develop chronic pain (16–18). Clearly, these insults are not themselves sufficient to produce chronic pain; some factor intrinsic to the receiver of the injury is also to blame. The fundamental explanation is very likely to be a classic example of genetic-environmental interaction; that is, both the injury and the innate propensity are necessary. A surprising but potentially useful fact is that individual differences in laboratory pain sensitivity are predictive of clinical pain severity and response to treatment (19).

Impressive interindividual variability has been documented in experimental and clinical responses to analgesic manipulations as well, including to opioids (20–23), placebo (22–24), and nonsteroidal anti-inflammatory drugs (22, 25, 26). It remains unclear (at least in humans) whether this variability is related or unrelated to the variability underlying the pain inhibited by these analgesics. Given the considerable evidence for the former possibility, no consideration of the pharmacogenetics of analgesia can be considered comprehensive without a simultaneous review of the neurogenetics of pain.

Heritability of Pain and Analgesia

Trait (phenotypic) variability is a result of variation in either the genetic (genotype) or environmental milieu, as well as the complex interaction of the two, which includes the increasingly

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appreciated role of epigenetic factors. The relative weightings of nature and nurture in the mediation of this variability continues to fascinate. Familial aggregation of both rare and common pain syndromes have been noted repeatedly, although this may be the result of either genetic inheritance of pain susceptibility and/or familial modeling of pain behavior (27). One intriguing new hypothesis suggests that what is actually being inherited in chronic pain patients with a family history of chronic pain is endogenous opioid analgesic dysfunction (28). Recent years have seen a resurgence of interest in differences in pain and analgesic sensitivity among ethnic groups (29–31), although again these effects may be genetic and/or cultural.

Twin studies. Unlike family history designs and ethnic comparisons, the twin study methodology (albeit with some caveats) is able to estimate heritability (h^2) of a trait, that is, the proportion of trait variance due to inherited genetic factors. Any number of experimental and clinical pain traits have been so studied (32–39), with widely varying estimates of heritability ranging from essentially zero (40) to 68% (41). The heritabilities of various modalities of experimental pain in the most modern studies (33, 34) are quite comparable to those obtained in systematic studies in mouse models (42). In many of the clinical studies, it is difficult to know whether what is being estimated is the heritability of developing the painful pathology, or the heritability of the pathology being painful. It is, of course, quite likely that different sets of genes underlie each.

Heritability of analgesia. Likewise, for practical reasons, it is extremely difficult to establish the heritability of analgesic response. We are aware of only one attempt, a study of the inhibition of cold pressor test pain by 10 mg/70 kg morphine sulfate in 10 monozygotic twins (with, unfortunately, no dizygotic twins for comparison). Variance within twin pairs was lower than within pairs of unrelated individuals, although not significantly so because of the small sample size. Data from mice and rats (43–49) has established that drug analgesia is indeed heritable at least in these species, albeit with heritabilities somewhat lower than for pain per se.

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Scope of the Review

Regardless of the precise weightings of each of these factors, the value in understanding the what and the how of these determinants of variability lies in the promise of personalized pharmacotherapy (i.e., individualized medicine) (50, 51), a promise that remains largely elusive despite some recent progress. In this review, we summarize the current methodologies available to identify genes (and polymorphisms within those genes) relevant to pain and analgesia, as well as present a critical evaluation of progress to date. We consider only acute analgesia, not analgesic tolerance or dependence/withdrawal. Developments in gene therapy, the attempt to influence expression levels of genes already known to be relevant, are also outside the scope of this review.

UNCOVERING THE GENETIC DETERMINANTS OF PAIN AND ANALGESIA USING LABORATORY RODENTS

Basic pain researchers have extensively utilized the domesticated Norway rat (*Rattus norvegicus*) as a mammalian model system for several decades. Recently, the mouse (*Mus musculus*) has gained popularity in pain studies (52) for largely one reason: the increased interest in genetics. The mouse enjoys considerable advantages over the rat when it comes to genetic investigations. The first has to do with the advent of embryonic stem cell–derived transgenesis techniques such as knockouts (null mutants) (53). To date, only mouse transgenic knockouts can easily be constructed. The second advantage is the large number of inbred strains that have been produced

and maintained over the last century (54). For a mouse to be considered inbred, it must be mated brother-by-sister for at least 20 generations, resulting in almost complete homozygosity at all loci. Therefore, all mice within a particular inbred strain are isogenic to (i.e., clones of) one another, whereas different inbred strains represent different mosaics of the original founder populations (*M. m. domesticus*, *M. m. musculus*, and *M. m. castaneus*) (55). The genomes of a large number of mouse strains have now been sequenced (56), further facilitating genetic studies in this species.

The heritability of pain and analgesia in rodents was first demonstrated in selective breeding projects (57–59); findings from these interesting studies have been reviewed previously (60). Given the enduring challenges of identifying genes whose allelic frequencies have been altered by selection, however, most current research in pain and analgesia genetics is focused on mutants and inbred strains, as described below.

Mutant mice, in which one gene has been altered—often catastrophically, so that it ceases to function—are attractive as a research model because of their relative simplicity. The state-of-the-art has progressed from finding and studying chance spontaneous mutants to the engineering of gene ablations and single-nucleotide changes.

Spontaneous mutants. A small number of spontaneously arising mutants, usually with visible coat color changes or neurological abnormalities, are known to have altered pain or analgesic sensitivity (61–68). Now that mutations can be produced experimentally (see below), there remains little interest in screening existing mutants for pain-related traits.

Transgenic knockouts. Transgenic knockout mice have been widely employed in pain research, and previously reviewed in depth (69–72). We have recently compiled an interactive online database of published investigations featuring the testing of knockout mice on assays of pain and analgesia (73) (**http://paingeneticslab.ca/4105/06_02_pain_genetics_database.asp**). We conceive of this database as a useful alternative to print literature reviews, and thus we refrain from detailed comment on any individual findings. As of this writing, there are reports of changes in either nociceptive or analgesic sensitivity from null mutants of 245 different genes, described in 533 manuscripts. In some cases, the association is tenuous and the route from gene to pain might be very indirect, but the large number of genes that have been implicated in such a short period of time suggests that there are likely far more genes associated with pain and pain modulation than was previously thought. This fact has serious implications for analgesic drug development, with the focus switching from identifying potential drug targets to prioritizing among them.

It should be noted that, issues of compensation and other noted confounds (74, 75) aside, the valuable role of the transgenic knockout approach is to implicate particular genes (and, therefore, their protein products) in pain processing generally. It does not follow that the demonstration of a knockout phenotype necessarily implicates the gene in the mediation of the individual differences described above, since true human knockouts are likely very rare. To find such pain variability genes, other techniques are required (76).

Chemical mutagenesis. Whereas the transgenic knockout technique aims to produce a null mutation of a known gene and then test the mutants on a phenotype of interest, the complementary chemical mutagenesis strategy aims to produce random mutations (using the potent mutagen, *N*-ethyl-*N*-nitrosourea) and test the resultant mutants on a phenotype of interest to identify the relevant (mutated) genes. A number of large mutagenesis programs were conducted with a pain

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test as part of the phenotyping battery (77–80), but to our knowledge only a single pain-relevant mutant has been produced (79), and the underlying gene in that case remains unknown.

Gene Knockdown Studies of Pain and Analgesia

Among the conceptual disadvantages of transgenic knockout mice is the fact that expression of the targeted gene is reduced to zero from the moment of conception to that of testing. Compensatory responses are guaranteed, and one never knows for sure whether the mutant's phenotype is due to the targeted gene or one of the compensatory changes. A more subtle approach would be a knockdown, a transitory reduction of gene expression in adulthood, with some degree of temporal control. This can be achieved using injections (or viral vector delivery) of antisense oligodeoxynucleotides (81), or small-interfering RNA molecules (also known as RNA interference), which reduce gene expression with much higher efficiency (82). A MEDLINE search revealed the existence of at least 102 genes whose knockdown altered pain or analgesic sensitivity; these are provided in **Supplementary Table 1** (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**). The use of RNA interference in pain research has thus far been limited to a handful of published papers (83), but is increasing (see **Supplementary Table 1**). Many pain research laboratories are now routinely using knockdown strategies to complement or replace pharmacological approaches. The antisense mapping technique, where individual exons of alternatively spliced genes (notably including the μ-opioid receptor gene, *Oprm*) are knocked down to reveal the differential function of alternatively spliced forms, has been particularly valuable (84).

Microarray Studies of Pain and Analgesia

Microarray-based gene expression profiling is a potentially powerful way to identify genes related to pain, especially in chronic pain states featuring large-scale changes in gene regulation owing to the injury and its varied consequences. Features of the 26 directly relevant microarray studies identified at the time of writing are presented in **Supplementary Table 2** because we are unaware of any previous review of this emerging literature.

Gene expression changes after a variety of injuries, both neuropathic (axotomy, partial peripheral nerve injuries, and spinal cord injury) and inflammatory (carrageenan, complete Freund's adjuvant, and formalin), have been assessed using a variety of commercially available oligonucleotide or cDNA-based systems. The vast majority of animal studies have used as their tissue source dorsal root ganglia or dorsal spinal cord, which reflects their status as the locus of the nociceptors and central transmission neurons in the pain pathway. There has been far less investigation into changes in peripheral tissues or the brain (85, 86), where critical neural processing of pain signals and much of the pain modulation produced by analgesic manipulations occurs. Thus, the spatially distributed physiology of pain will continue to impose practical hurdles on mRNA-based genetic techniques. This problem is particularly relevant to human microarray studies, where other than the rare opportunity to study surgically removed neural tissue (87), pain researchers have access only to biopsied peripheral tissues (88, 89) or blood (90, 91). This situation is contrasted with that of cancer biologists [where the microarray technique has been immensely successful (92)], who have ready access to surgically removed tumor tissue. However, in at least one case, a gene identified in a rat microarray study, *Gch1*, led directly to a successful human association study implicating the human analogue, *GCH1*, in both experimental and clinical pain states (93).

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To our knowledge, only three published microarray studies of analgesia exist, all examining acupuncture (90, 94, 95). Given the fact that many analgesic drugs begin exerting clinically relevant effects within minutes, it is rather unlikely that acute administration of drugs would regulate the expression of many genes. This approach may prove useful, however, in the study of the chronic effects of analgesic use, and indeed such studies are being undertaken by those with an interest in addiction (96).

Strain Surveys of Pain-Related Traits

The standard approach to the identification of pain variability genes underlying individual differences is to perform genome-wide linkage mapping, or quantitative trait locus (QTL) mapping (97, 98). Like microarray profiling, it has great heuristic utility, representing a blind, systematic search of the entire genome. Unlike microarray profiling, however, QTL mapping searches for DNA variants associated with trait variability, not mRNA expression levels. This difference is important because a difference in gene expression can be either causal to or the result (direct or indirect) of a phenotypic change, but DNA variants must be causal.

To implement this strategy one first selects a panel of inbred strains and measures their sensitivity on relevant phenotypes: a phenomics project (99). Invariably, one sees a distribution of phenotypic values in which the within-strain differences are due to environmental variability and the between-strain differences are, by definition, genetically mediated. We and others have tested panels of mouse and rat strains using a variety of experimentally delivered mechanical, thermal, and chemical nociceptive stimuli, both in naïve animals and those given inflammatory or neuropathic injuries, and have tested the analgesic effects of a variety of pharmacological agents on these algesiometric tests. The results of these investigations have been reviewed previously, in depth (60, 100–102). Suffice it to say that robust quantitative strain differences and moderate-to-high heritabilities have been observed across the board. In one case, for example, two mouse strains were identified whose ED_{50}s for the analgesic effect of epibatidine, a nicotinic receptor agonist, were higher than their LD_{50}s to the same drug (43).

In addition to quantitative strain differences, which are fully expected, the literature reports a large number of intriguing qualitative differences between strains, which are suggestive of the existence of multiple mechanistic pathways. For example, analgesic states can be reversed or blocked by opioid receptor or *N*-methyl-D-aspartate receptor antagonists in some mouse strains but not others (103, 104). Heroin analgesia can be blocked using different opioid receptor type-specific (μ, δ, κ) antagonists in different mouse strains (105). The mechanical hypersensitivity produced by neuropathic injury is sensitive to α-adrenergic blockade in some rat strains but not others (106). Even the neuroanatomy of pain modulation is genotype-dependent, with observed rat substrain differences in the course and termination of descending noradrenergic circuitry (107).

Genetic Correlations Among Pain-Related Traits

Even prior to the determination of the responsible genes, much has been learned about the organization of pain and analgesic processing by the study of genetic correlations among pain-related traits. Essentially, this approach can be employed in much the same way fMRI studies often are, to establish whether phenomenon A is similarly or differently mediated than phenomenon B. Correlation or dissociation of the underlying variability genes, or cortical activation patterns, implies (although does not prove) similar or differing underlying physiology, respectively. Using this approach, we and others have established the following general principles, which have proven heuristic.

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Genetic correlation of pain and analgesia. Many studies have reported a strong negative correlation between nociceptive sensitivity and analgesic sensitivity. For example, the more sensitive a given mouse strain is to a particular nociceptive stimulus, the less sensitive that strain is to inhibition of that stimulus by analgesics (43, 45–47). The demonstration of this correlation in animal models inspired human studies that also observed the relationship (19, 108). Elmer and colleagues (46) have hypothesized that the correlation can be explained in terms of genetic differences in effective stimulus intensity affecting fractional receptor occupancy of the analgesic. That is, strains that are more sensitive to the noxious stimulus require more analgesic to inhibit the pain. Edwards and colleagues (19) suggest instead that genetic differences in the efficacy of endogenous analgesic mechanisms might simultaneously affect pain sensitivity and the response to exogenous analgesics.

Genetic dissociation of different pain modalities. It has been shown in both rats and mice that strains are not universally sensitive or resistant across a variety of nociceptive assays, supporting the notion that pain is not a unitary construct with a single underlying physiology. Multivariate analyses performed using 12 inbred mouse strains and over 20 nociceptive assays have revealed genetically defined clusters of assays, within which essentially the same strains are sensitive and the same strains resistant (42, 109, 110). These clusters are rather obviously defined by their stimulus modality (thermal, chemical, and mechanical), and not by any number of dimensions that may have been equally likely a priori (e.g., stimulus duration, stimulus location, and injury type). Although the general principle of genetic dissociation of different assays is true among rat strains as well, the clusters are not the same (111, 112). These findings predict that when pain variability genes are identified in rodents, their effects will be rather specific, and this indeed is the case so far (113). The genetic dissociation of different pain modalities in rodents also suggests that the same is likely to be true in humans. This is currently a rather contentious issue because a number of existing genetic association studies in humans (see below) have employed aggregate pain scores summing over many tests of different modalities (93, 115). The existing evidence from human twin studies is mixed, but the only study to examine the issue directly concluded that assay-specific (cold-pressor test versus heat pain) genetic and environmental variance greatly outweighed the assay-common variance (34).

Stimulus-dependent genetic correlation of analgesic response. The seemingly obvious genetic candidates for the mediation of variability in drug response would be those genes coding for the molecular binding sites of the drug in question, or those related to its transport and metabolism. Although plenty of evidence exists linking genes related to P-glycoprotein and both phase I (cytochrome P450) and phase II (UDP-glucuronosyl transferase) enzymes to variable drug pharmacokinetics (116–119), the genetics of analgesic pharmacodynamics appears somewhat paradoxical. We and others (43, 45–47) have found that strain sensitivity to drug analgesia is not related to the drug itself, but rather to the nature of the pain being inhibited by the drug. For example, the C57BL/6 strain was simultaneously a low responder to morphine's inhibition of thermal pain, but a high responder to morphine's inhibition of chemical/inflammatory pain (46). It is exceedingly difficult to reconcile this fact with a presumption that variants affecting the *Oprm* gene coding for the μ-opioid receptor, the major binding site of morphine (120), are primarily responsible for its analgesic variability. Any genetically mediated change in the density or activity of the μ-opioid receptor would be expected to affect morphine's potency and/or efficacy regardless of the nature of the noxious stimulus. As this is clearly not the case, our thinking is obviously too simplistic. In fact, the mouse *Oprm* gene is likely responsible for variability in morphine's inhibition of thermal nociception (especially in males) (121, 122), but no linkage can be found when considering instead

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morphine's inhibition of inflammatory nociception (H. S. Hain, J. S. Mogil and J. K. Belknap, unpublished data).

Additionally, we have observed that within a noxious stimulus modality, drugs from very different neurochemical classes (e.g., μ-opioid, κ-opioid, cannabinoid, nicotinic, and α_2-adrenergic) share surprisingly high genetic correlations (43). That is, in terms of their inhibition of thermal pain on the 49°C tail-withdrawal test, the same mouse strains are sensitive and the same strains resistant, regardless of what drug is used. This finding clearly predicts that genes will be discovered with effects on analgesic sensitivity generalizable across drug class. To this end, we recently identified one such gene, *Kcnj9* (123), although many more remain to be discovered.

QTL Mapping Studies of Pain and Analgesia

Historically, QTL mapping has been performed using genetically segregating populations (e.g., F_2 intercross, backcross, recombinant inbred strains, and congenics), and has involved correlating the phenotype of the segregating unit (either an individual or a strain) with its genotype at polymorphic genetic markers spanning the genome (restriction fragment length polymorphisms, then microsatellites, and now SNPs) (97). Because the technique has limited spatial resolution, additional steps are required before the responsible gene can be identified: either a series of positional refinement steps (positional cloning), and/or the testing of candidate gene hypotheses. Often this hypothesis testing makes use of other genetic techniques we have already discussed, such as transgenesis, gene knockdown, and/or microarray profiling.

QTL mapping can now be attempted *in silico* (124) [although with some caveats; (125, 126)] via what is known as haplotype mapping (126, 127). As noted above, the genome of an inbred mouse is a unique mosaic of three founder populations (55); because of this mosaic structure many individual SNPs are not inherited independently of each other, but rather exist in a state of linkage disequilibrium in the same haplotype block. The genome can thus be fully covered by a manageable number of these blocks, and haplotypes inferred by genotyping only a few SNPs within each block. This has been accomplished for a large number of mouse strains (see **http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=snps/door**), such that QTL mapping can often be performed simply by correlating the phenotypes of a panel of inbred strains to their haplotypes across the genome.

Using the older or newer (or both) approaches, our laboratory and others have identified a small number of QTLs associated with pain and analgesic variability. These are listed in **Table 1**. Note that a number of the existing linkages are sex-specific, which would be predicted by the repeatedly observed sex-genotype interactions in both the mouse and rat literature (48, 128). In many cases, evidence supporting a particular candidate gene has also been provided. In one case, the female-specific linkage of *Mc1r* (melanocortin-1 receptor) with κ-opioid analgesia in mice perfectly predicted the results of a subsequent *MC1R* association study in humans (129).

Although progress has been slow, owing to the labor- and time-intensive requirement of creating congenic and subcongenic strains, the ability to map *in silico* and the increasing ease of entertaining candidate gene hypotheses in both animals and human subjects suggests that this effort will greatly accelerate in the coming years. It remains to be seen, however, whether identifying pain-relevant genes by QTL mapping in animal models will be rendered moot by human genome-wide association studies.

Limitations of Animal Models

Animal genetic models are thought to be useful because of the short generation times involved, and the high degree of control experimenters have over both genetic background and environmental

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Table 1 Statistically significant QTLs of relevance to pain and analgesia in laboratory rodents

Phenotype	Chromosome	LOD[a]	Location[b]	Candidate gene(s)	Evidence[c]	Reference
Acute/tonic pain						
Capsaicin	2	5.9	30			(185)
	7	4.8	10			(185)
	7	5.8	50			(185)
	8	4.4	30			(185)
Formalin	10	4.3	70			(186)
Hargreaves	7	6.3	50	*Calca* (54 cM)	Pharm., siRNA, gene expr.	(113)
Hot-plate	4	3.8 (♂ only)	71	*Oprd1* (65 cM)	Pharm.	(187)
Tail withdrawal	4	3.6 (♂ only)	56	*Oprd1* (65 cM)	Position	(123)
	7	12.6	33	*Trpv1* (44 cM)	Position	(123)
	11	7.8	46			(123)
Chronic pain						
Autotomy	15	3.9	44			(188)
	15	3.0	44			(189)
	15	3.3 (♀ only)	32			(190)
	2 (rat)	3.6	20			(191)
Analgesia						
Clonidine	1	4.7	100	*Kcnj9* (94 cM)	Mutant, gene expr.	(123)
Morphine	1	4.7 (♀ only)	10	*Oprk1* (6 cM)	Position	(122)
	1	3.2	91			(123)
	9	5.2 (♀ only)	20			(122)
	9	4.5	42	*Htr1b* (46 cM)	Pharm.	(192)
	10	7.5	9	*Oprm1* (8 cM)	Receptor binding	(121)
Stress-induced	8	6.1 (♀ only)	56	*Mc1r* (68 cm)	Position	(193)
U50,488	8	2.7 (♀ only)	67	*Mc1r* (68 cM)	Pharm., mutant	(129)
WIN55,212–2	1	4.4	100	*Kcnj9* (94 cM)	Mutant, gene expr.	(123)
	7	4.8	40	*Trpv1* (44 cM)	Position	(123)
Opioid hyperalgesia						
Chronic morphine	5	$p = 0.000083$*	1	*Abcb1b* (1 cM)	Pharm., mutant	(119)
	18	$p = 0.00037$*	34	*Adrb2* (34 cM)	Pharm., mutant	(194)

[a]LOD: logarithm of the odds.

[b]Location of peak LOD score in centiMorgans (cM), a unit of genetic distance. Note that confidence intervals in QTL mapping projects are generally very large.

[c]Gene expr.: strain-dependent expression of the candidate gene; Mutant: null mutation of the candidate gene shown to affect phenotype; Pharm.: strain-dependent effects of pharmacological manipulation of the candidate gene product; Position: inference based on genomic position of candidate gene; Receptor binding: demonstrated correlation of phenotype to strain-dependent density of candidate gene product; siRNA: rescue of strain difference using siRNA knockdown of candidate gene mRNA.

*Study used haplotype mapping; *p*-values represent uncorrected correlation between phenotypic and haplotype block distributions of a set of inbred mouse strains.

factors. The true degree of environmental standardization in mouse studies is probably exaggerated, however (130), and environmental factors (and gene-environment interaction) account for a majority of the trait variance (131, 132).

The usefulness and predictive power of genetic animal models of pain and analgesia are limited by the extent to which they accurately model the depth and breadth of human clinical pain. As

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mentioned, there are at least two high-profile examples of direct translation of genetic findings from rodent models to humans (93, 129). However, major criticism of animal models of pain more generally stems from the promising targets identified in animals that failed to demonstrate clinical efficacy in human trials. It is unclear, however, whether the blame is properly placed on the animal research, on the trials themselves, or on the bad luck of unanticipated toxicity.

There is continual need for basic scientists to reevaluate and modify their pain models to better reflect clinical symptomology and disease etiology. For example, the vast majority of currently employed pain assays measure reflexive responses to evoked pain, whereas the chief (and most prevalent) clinical complaint is of spontaneous pain (133), with an important cognitive and emotional overlay (134). In the end, it is certainly true that no animal model will ever be able to fully reproduce human clinical pain conditions in all of their complexity. (The same, by the way, can be said about experimental pain models in human subjects.) In fact, some genetic techniques are as easily employed with human subjects as with animals (given the fact that genomic DNA is readily available from blood draws and buccal swabs), and human pain and analgesia genetics studies are rapidly gaining popularity.

ASSESSING GENETIC FACTORS IN HUMAN PAIN AND ANALGESIC VARIABILITY

Only recently have the experimental tools been available to get past the nature/nurture question in human genetics research and actively attempt to identify genes responsible for trait variability and disease susceptibility in our species. Two major approaches have been employed. A number of monogenic diseases, featuring either insensitivity to pain or pathological pain, have been studied using human genetic linkage mapping. Although these disorders are exceedingly rare, a working assumption is that the genetic pathologies may illuminate the pathophysiology of more common conditions. Others have chosen to study the more common disorders, or experimental pain sensitivity, using the genetic association study approach. Recent years have seen the publication of a large number of reviews of the current findings of these efforts (135–140). Because of this, we make no attempt herein to discuss the specifics of the published research, although a summary is provided in **Tables 2** and **3**.

With respect to analgesia, much work is still focused on genes related to the pharmacokinetics of opioids (e.g., *ABCB1* and *CYP2D6*) (141, 142), although some findings are being published regarding the genetic control of the pharmacodynamics of analgesic drugs (63, 129, 143–145).

Are Genes Underlying Monogenic Pain-Related Pathologies Broadly Relevant?

As of this writing, the genes responsible for all known subtypes of hereditary sensory neuropathy (HSN Types I-V) had been elucidated, as have genes for three subtypes of familial hemiplegic migraine (FHM Types I-III) and two disorders of severe, unexplained pain (see **Table 2**). The proteins involved span a wide range of biological functions, including synthesis enzymes, transcription factors, ion channels, and neurotrophins. Currently engendering great excitement is the demonstration that loss-of-function (nonsense) mutations of *SCN9A* (encoding the α subunit of the voltage-gated $Na_v1.7$ sodium channel) cause HSN Type V (146, 147) whereas gain-of-function mutations of the same gene are responsible for primary erythromelalgia (148) and paroxysmal extreme pain disorder (149). Much of the perceived importance derives from the fact that quite unlike the mouse *Scn9a* knockout, which dies shortly after birth, humans with nonfunctional $Na_v1.7$ channels reportedly have normal life spans and no clinical phenotype other than their complete insensitivity to pain (146). These facts would suggest the safety of $Na_v1.7$-blocking therapeutics, which are currently under development.

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Table 2 Human genes responsible for monogenic disorders featuring pathological pain or insensitivity to pain

Disorder[a]	OMIM[b]	Linkage	Gene	Protein	Reference
Pathological pain					
FHM type I	141500	19p13	*CACNA1A*	Cav2.1 calcium channel	(195)
FHM type II	602481	1q21	*ATP1A2*	α_2 subunit, Na^+,K^+-ATPase	(196)
FHM type III	609634	2q24	*SCN1A*	Nav1.1 sodium channel	(197)
FMF	249100	16p13	*MEFV*	Pyrin	(198)
HNA	162100	17q25	*SEPT9*	Septin 9	(199)
PE	133020	2q24	*SCN9A*	Nav1.7 sodium channel	(148)
PEPD	167400	2q24	*SCN9A*	Nav1.7 sodium channel	(149)
Congenital insensitivity to pain					
CIDP	243000	2q24	*SCN9A*	Nav1.7 sodium channel	(146)
HSAN type I	162400	9q22	*SPTLC1*	Serine palmitoyltransferase, long chain 1	(200, 201)
HSAN type II	201300	12p13	*HSN2*	Unknown	(202)
HSAN type III	223900	9p31	*IKBKAP*	IKK-complex associated protein	(203, 204)
HSAN type IV	256800	1q21	*NTRK1*	Neurotrophic tyrosine kinase receptor	(205)
HSAN type V	608654	1p13	*NGFB*	Nerve growth factor, β	(206)

[a]CIDP: congenital indifference to pain (autosomal recessive); FHM: familial hemiplegic migraine; FMF: familial Mediterranean fever; HNA: hereditary neuralgic amyotrophy; HSAN: hereditary sensory and autonomic neuropathy; PE: primary erythromelalgia (primary erythermalgia); PEPD: paroxysmal extreme pain disorder (familial rectal pain).
[b]Online Mendelian Inheritance in Man entry number (**http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim**).

Although the elucidation of these genes is undoubtedly welcome news for the sufferers of these extraordinarily rare syndromes, we are unaware of any replicated association study (or other evidence) implicating any of the genes in **Table 2** in mediating susceptibility to or severity of more common disorders. Notably, it is not the case that the development of idiopathic (common) migraine with aura, which runs in families (150), is affected by any common polymorphism within the *CACNA1A* gene (151, 152). It is perfectly conceivable, of course, that such evidence will be provided in time, or that the failure to have provided evidence so far is the fault of association study methodology (see below). It is also possible that genes producing rare disorders are not the same genes on which common variants arise to produce the subtle but aggregate and interacting alterations that may underlie common diseases (153), including common pain disorders (154).

Genetic Association Studies of Pain and Analgesia in Humans

We are aware of at least 23 genes associated with experimental pain, clinical pain, or analgesia (excluding headache/migraine genes; see **Table 3**). Although the list seems impressive at first glance, it should be treated with great caution. In only a handful of cases has the association been independently replicated in another laboratory. The involvement of *CYP2D6* variants in determining the efficacy of certain opioids (via biotransformation to active molecules) has been clearly established (141, 142). Both Offenbaecher et al. (155) and Cohen et al. (156) report a higher frequency of so–called short alleles of the *SLC6A4* gene (encoding the serotonin transporter) in patients with fibromyalgia, and Kim and colleagues (157) observed an association of *SLC6A4* with pain following third molar removal. Both Jeremias et al. (158) and Foster et al. (159) observed a frequency of the allele 2 genotype in a variable number tandem repeat polymorphism in the second intron of the *ILRN* gene, coding for the endogenous interleukin-1 receptor antagonist. In all other cases the findings either remain unreplicated (at least for now) or contradictory evidence

Table 3 Genes (excluding *HLA*) associated with clinical and experimental pain states[a] and analgesia in humans. Only positive findings are referenced.

Phenotype	Gene	Protein	Reference
Angina			
	ADRA2C	Adrenergic receptor, α2C	(207)
	ADRB2	Adrenergic receptor, β2	(207)
	NOS3	Nitric oxide synthase, endothelial	(208)
Arthritis pain			
	ESR1	Estrogen receptor, alpha	(209)
	IL6	Interleukin-6	(210)
Back pain			
	GCH1	GTP cyclohydrolase 1	(93)
	IL1A/B	Interleukin-1 (α and β)	(211)
	IL1RN	Interleukin-1 receptor antagonist	(211)
	IL6	Interleukin-6	(212)
Burning mouth syndrome			
	IL1B	Interleukin-1β	(213)
Experimental pain			
	COMT	Catechol-O-methyltransferase	(115, 162–163)
	FAAH	Fatty acid amide hydrolase	(214)
	GCH1	GTP cyclohydrolase 1	(93, 170)
	MC1R	Melanocortin-1 receptor	(63)
	OPRD1	Opioid receptor, delta 1	(105, 214)
	OPRM1	Opioid receptor, mu 1	(215, 216)
	TRPA1	Transient receptor potential, A1	(214)
	TRPV1	Transient receptor potential, V1	(10, 214)
Fibromyalgia			
	COMT	Catechol-O-methyltransferase	(167)
	HTR2A	Serotonin receptor, 2A	(217)
	SLC6A4	Serotonin transporter	(155)
Headache/migraine			
	Many (see references for reviews)		(140, 218)
Irritable bowel syndrome			
	IL10	Interleukin-10	(219)
	HTR2A	Serotonin receptor, 2A	(220)
	SLC6A4	Serotonin transporter	(221)
	TNFA	Tumor necrosis factor, α	(222)
Non-steroidal anti-inflammatory drug analgesia			
	PTGS2	Cyclooxygenase-2	(145)
Opioid analgesia			
	COMT	Catechol-O-methyltransferase	(144, 169)
	CYP2D6	Cytochrome P450 2D6	(223, 224, 225)
	MC1R	Melanocortin-1 receptor	(63, 129)
	OPRM1	Opioid receptor, mu 1	(143, 169, 226–230)

(*Continued*)

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Table 3 (*Continued*)

Phenotype	Gene	Protein	Reference
Pelvic pain			
	IL10	Interleukin-10	(231)
Postoperative pain			
	MAOB	Monoamine oxidase B	(232)
Temporomandibular disorder			
	ADRB2	β_2-adrenergic receptor	(233)
	COMT	Catechol-O-methyltransferase	(115)
	SLC6A4	Serotonin transporter	(156, 234)
Vulvar vestibulitis			
	IL1B	Interleukin-1β	(235)
	IL1RN	Interleukin-1 receptor antagonist	(159)
	MC1R	Melanocortin-1 receptor	(159)

[a]Some disorders on this list are painful by definition. In other cases (e.g., arthritis), studies are included only when pain within the disorder was a specific dependent measure.

exists. A discussion of three high-profile cases involving contradictory evidence (*MC1R*, *COMT*, and *GCH1*) follows.

MC1R. We reported in 2005 that people inheriting two or more inactivating variants of the *MC1R* gene displayed reduced sensitivity to electrical pain (63). However, in the same year, Liem and colleagues (160) observed that redheaded women displayed increased sensitivity to thermal pain. Two obvious differences between these studies were the different pain modalities tested and the fact that we grouped subjects based on *MC1R* genotype whereas Liem et al. grouped subjects based on phenotype (hair color). Neither of these facts obviously clarify the situation, however. Although we tested humans for sensitivity to electric shock only, mouse recessive yellow mutants (C57BL/6-*Mc1r*$^{e/e}$) also with nonfunctional melanocortin-1 receptors were less sensitive to pain of multiple modalities, including thermal. Also, although up to 20% of redheads are not, in fact, melanocortin-1 receptor deficient (161), the potential miscoding of a few subjects in Liem et al.'s (160) study is not a likely explanation of their directionally opposite conclusions.

COMT. In 2003, Zubieta and colleagues (162) reported that the well-studied *val*^{158}*met* variant (due to a SNP called rs4680) of the *COMT* (catechol-*O*-methyltransferase) gene was associated with variable pain sensitivity (and μ-opioid receptor binding in vivo) to injection of hypertonic saline into the masseter muscle. This was partially replicated two years later when Diatchenko and colleagues (115) reported association of the *COMT* gene with experimental pain (across a number of modalities) and the prospective risk of developing temporomandibular disorder (TMD). Importantly, however, the association in this latter study was with a haplotype of four SNPs within the *COMT* gene including rs4680. A follow-up effort by the Diatchenko/Maixner lab revealed that these inherited *COMT* diplotypes were associated with thermal pain sensitivity and temporal summation of thermal pain (163). They went on to show, impressively, how the various haplotypes could alter mRNA secondary (local stem-loop) structure leading to differences in enzymatic activity of the protein (164). Nonetheless, the rs4680 SNP alone showed no significant association with pain, thus this cannot really be considered a replication. More worrisome, however, are studies by Kim and colleagues (10, 157), much more highly powered than their predecessors, which failed to see an association of either rs4680 or the high pain sensitivity *COMT* haplotype with either

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experimental pain or postsurgical pain in the third molar model. Further, using a family-based design, Birklein and colleagues (165) did not see an association of rs4680 to cold-pressor pain. In addressing the contradictory literature, Kim & Dionne (166) point to very small sample sizes [$n = 3$ in the *val/val* homozygote group in Zubieta et al. (162); $n \approx 10$/haplotype in the TMD patients of Diatchenko et al. (115)], possible ethnic stratification, and the dangers of combining measures of pain threshold and pain tolerance into a single score.

Adding to the uncertainty regarding *COMT*'s true role in pain are the published findings that *COMT* may be associated with fibromyalgia (167), but appears not to be associated with neuropathic pain in patients with multiple etiologies (168). Finally, it was shown that the rs4680 SNP may influence morphine requirements in cancer pain patients (although in this study no genotypic differences in predrug pain intensity were noted) (144). This finding was not replicated by Reyes-Gibby and colleagues (169), who instead reported a significant association with morphine dose of the joint inheritance of the *met/met* genotype of *COMT* and the well-known 118A/A genotype of *OPRM*, the μ-opioid receptor gene. In summary, while it is likely that *COMT* does indeed play some role in pain variability, it may take time to fully delineate that role.

GCH1. The latest controversy in this field concerns the association of *GCH1*, coding for GTP cyclohydrolase, the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, in experimental and clinical pain states. In a particularly comprehensive series of studies, the gene, identified via a microarray study of neuropathic pain in rats, was shown to have broad relevance to both neuropathic and inflammatory pain processing in animal studies, and a 15-SNP haplotype of *CGH1* was found to be significantly associated with mechanical pain in two separate cohorts of humans with chronic lumbar root pain (93). In a follow-up study with slightly higher power ($n = 6$ homozygotes), no significant effects of haplotype were observed in the basal state (a nonreplication of the prior study by the same group), but significant effects were obtained after sensitization of the tested tissues using freeze lesions or capsaicin (170). Kim and Dionne (171), again investigating postsurgical pain in a large cohort of patients with impacted third molars, observed no association. Tegeder and colleagues (170) point to differences in the haploblock architecture between the two study populations as a possible reason for the contradictory findings.

Do Genetic Association Studies Replicate?

The reporting of genetic associations with pain and analgesia has led to great excitement in the pain field, as it promises a revolution in our understanding of the risk factors for chronic pain development (172). This excitement is tempered by the reality of slow progress toward replication, contradictory data upon replication, and the modest percentage of the trait variance accounted for by the associated genes. One complicating factor is that so far in this field, no true attempt at replication has occurred; every study differs from the other enough so that by diminishing the scope of the claimed association (electrical but not thermal pain, TMD but not postsurgical pain), all findings remain uncontradicted. Perhaps pain genetics is indeed extraordinarily heterogeneous with respect to study population and pain modality (as the animal research would predict), in which case we have much, much more work to do. Alternatively, the field of pain genetics may be riddled with false-positive and/or false-negative findings.

The current controversies in the human pain genetics field are not hugely surprising given the prior experiences of other fields in which many genetic association studies have been performed. In fact, this technique is widely known to be problematic (173). In a comprehensive review of over 600 reported genetic associations of common variants and disease, the authors found that of the 166 putative associations studied three or more times, only six were consistently replicated (174).

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Potential reasons for the lack of replication include population stratification (175, 176), underpowering (the "winners curse") (177), too-broad (and thus ill-defined and possibly misattributed) phenotypes (178), and various types of bias (179). Solutions have been proposed for many of these problems, but have not yet been thoroughly implemented in the pain field.

Prospects for Genome-Wide Association Studies of Pain and Analgesia

The increasing sophistication and decreasing cost of high-throughput methodologies for SNP genotyping and the completion of the HapMap project (180) have made it possible to scan the entire human genome with sufficient density to perform association studies without a priori gene candidates (181). Combining the advantages of linkage mapping (full coverage) and association (high spatial resolution), a number of large-scale, high-density genome-wide association studies (GWASs) have now been performed for common and high-profile diseases such as diabetes, cancer, heart disease, and asthma (**http://www.genome.gov/26525384**). In a GWAS, phenotypic data from many hundreds (at least) of subjects are correlated with commercial gene chip-based sets of hundreds of thousands of SNP and copy number variant markers, and association is established by linkage disequilibrium. Their success so far has been mixed; some have found multiple loci, others very few (182).

The systematic nature of the GWAS approach might be particularly advantageous for human pain genetics, as a large number of high-priority candidate genes for neuropathic pain (183) have been studied without success (M.B. Max, personal communication). In addition, GWAS studies are considerably more heuristic than the candidate gene studies currently dominating human pain genetics. However, although the cost of genotyping has come down considerably, the power requirements of a GWAS (135) render the phenotyping side of the enterprise very expensive nonetheless. As a result, no GWAS has yet been performed on a pain trait. The true power of the GWAS, and perhaps the first real dividends from the Human Genome Project, come from the meta-analysis of multiple projects, as has been recently achieved for type 2 diabetes (with over 10000 cases and controls) (184).

The rewards of such an effort aimed at pain and analgesia would likely be immense, and eventually lead to new treatments both for pain and true individualized medicine. In the best of all possible worlds, researchers would proceed by identifying relevant genes/proteins in humans (thereby proving their relevance), studying the roles played by these molecules in animal models, and then using this information to provide better treatments for those in pain. We believe that this new paradigm for pain research is inevitable, but not yet imminent.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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Errata

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