Published in final edited form as:
Annu Rev Pharmacol Toxicol. 2009 ; 49: 97–121. doi:10.1146/annurev-pharmtox-061008-103222.

Progress in Genetic Studies of Pain and Analgesia

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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.

Keywords

pain; analgesia; genetics; linkage; association

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,

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

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 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.

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/4105/0602paingeneticsdatabase.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 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).

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.

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 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 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 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 un-like 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.

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 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 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). Potential reasons for the lack of replication include population stratification (175,176), under-powering (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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

LITERATURE CITED

1. IASP Subcommittee on Taxonomy. Pain terms: a list with definitions and notes on usage. Pain 1979;6:249–52. [PubMed: 460932]
2. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765–68. [PubMed: 10846153]
3. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84:95–103. [PubMed: 10601677]
4. Liebeskind JC. Pain can kill. Pain 1991;44:3–4. [PubMed: 2038486]
5. Macfarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population-based study. Br Med J 2001;323:662–64. [PubMed: 11566829]
6. Brune K. Next generation of everyday analgesics. Am J Ther 2002;9:215–23. [PubMed: 11941381]
7. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289–305. [PubMed: 16213659]
8. Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. Pain 2005;119:65–74. [PubMed: 16298065]
9. Lanier LH. Variability in the pain threshold. Science 1943;97:49–50. [PubMed: 17730829]
10. Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, et al. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain 2004;109:488–96. [PubMed: 15157710]
11. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288:1769–72. [PubMed: 10846154]
12. Chen ACN, Dworkin SF, Haug J, Gehrig J. Topographic brain measures of human pain and pain responsivity. Pain 1989;37:129–41. [PubMed: 2748188]
13. Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. J Neurophysiol 1998;80:1533–46. [PubMed: 9744957]
14. Zubieta J-K, Smith YR, Bueller JA, Xu Y, Kilbourn MR, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 2001;293:311–15. [PubMed: 11452128]
15. Coghill RC, McHaffie JG, Yen Y-F. Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci USA 2003;100:8538–42. [PubMed: 12824463]
16. Veldman PHJM, Reynen HM, Arntz IE, Goris JA. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–16. [PubMed: 8105263]
17. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central poststroke pain. Pain 1995;61:187–93. [PubMed: 7659428]
18. Cluff RS, Rowbotham MC. Pain caused by herpes zoster infection. Neurol Clin 1998;16:813–32. [PubMed: 9767064]

19. Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology 2005;65:437–43. [PubMed: 16087910]
20. Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. Anesthesiology 2003;98:1415–21. [PubMed: 12766651]
21. Lasagna L, Beecher HK. The optimal dose of morphine. J Am Med Assoc 1954;156:230–34. [PubMed: 13191954]
22. Wolff BB, Kantor TG, Jarvik ME, Laska E. Response of experimental pain to analgesic drugs. I Morphine, aspirin, and placebo. Clin Pharmacol Ther 1965;7:224–38. [PubMed: 5327178]
23. Levine JD, Gordon NC, Smith R, Fields HL. Analgesic responses to morphine and placebo in individuals with postoperative pain. Pain 1981;10:379–89. [PubMed: 7279424]
24. Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for nonspecific activation of endogenous opioids. Pain 2001;90:205–15. [PubMed: 11207392]
25. Day RO, Graham GG, Williams KM, Brooks PM. Variability in response to NSAIDs: fact or fiction? Drugs 1988;36:643–51. [PubMed: 3065056]
26. Walker JS, Sheather-Reid RB, Carmody JJ, Vial JH, Day RO. Nonsteroidal antiinflammatory drugs in rheumatoid arthritis and osteoarthritis. Arthritis Rheum 1997;40:1944–54. [PubMed: 9365082]
27. Turk DC, Flor H, Rudy TE. Pain and families. I Etiology, maintenance, and psychosocial impact. Pain 1987;30:3–27. [PubMed: 3614978]
28. Bruehl S, Chung OY. Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems. Pain 2006;124:287–94. [PubMed: 16725261]
29. Edwards CL, Fillingim RB, Keefe F. Race, ethnicity and pain. Pain 2001;94:133–37. [PubMed: 11690726]
30. Campbell CM, France CR, Robinson ME, Logan HL, Geffken GR, Fillingim RB. Ethnic differences in the nociceptive flexion reflex (NFR). Pain 2008;134:91–96. [PubMed: 17482362]
31. Rahim-Williams FB, Riley JL III, Herrera D, Campbell CM, Hastie BA, Fillingim RB. Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. Pain 2007;129:177–84. [PubMed: 17296267]
32. MacGregor, AJ. The heritability of pain in humans. In: Mogil, JS., editor. The Genetics of Pain, Progress in Pain Research and Management. Seattle: IASP Press; 2004. p. 151-70.
33. Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. Brain 2007;130:3041–49. [PubMed: 17932101]
34. Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain 2008;136:21–29. [PubMed: 17692462]
35. Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Heritability of low back pain and the role of disc degeneration. Pain 2007;131:272–80. [PubMed: 17335977]
36. Arquelles LM, Afari N, Buchwald DS, Clauw DJ, Furner S, Goldberg J. A twin study of posttraumatic stress disorder symptoms and chronic widespread pain. Pain 2006;124:150–57. [PubMed: 16701954]
37. Kato K, Sullivan PF, Evengard B, Pedersen NL. Importance of genetic influences on chronic widespread pain. Arthritis Rheum 2006;54:1682–86. [PubMed: 16646040]
38. Fejer R, Hartvigsen J, Kyvik KO. Heritability of neck pain: a population-based study of 33,794 Danish twins. Rheumatology 2006;45:589–94. [PubMed: 16332950]
39. Zondervan KT, Cardon LR, Kennedy SH, Martin NG, Treloar SA. Multivariate genetic analysis of chronic pelvic pain and associated phenotypes. Behav Genet 2005;35:177–88. [PubMed: 15685430]
40. Michalowicz BS, Pihlstrom BL, Hodges JS, Bouchard TJ Jr. No heritability of temporomandibular joint signs and symptoms. J Dent Res 2000;79:1573–78. [PubMed: 11023277]
41. MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis Rheum 2004;51:160–67. [PubMed: 15077255]
42. Mogil JS, Wilson SG, Bon K, Lee SE, Chung K, et al. Heritability of nociception. I Responses of eleven inbred mouse strains on twelve measures of nociception. Pain 1999;80:67–82. [PubMed: 10204719]

43. Wilson SG, Smith SB, Chesler EJ, Melton KA, Haas JJ, et al. The heritability of antinociception: common pharmacogenetic mediation of five neurochemically distinct analgesics. J Pharmacol Exp Ther 2003;304:547–59. [PubMed: 12538806]
44. Wilson SG, Bryant CD, Lariviere WR, Olsen MS, Giles BE, et al. The heritability of antinociception II: pharmacogenetic mediation of three over-the-counter analgesics in mice. J Pharmacol Exp Ther 2003;305:755–64. [PubMed: 12606637]
45. Chesler EJ, Ritchie J, Kokayeff A, Lariviere WR, Wilson SG, Mogil JS. Genotype-dependence of gabapentin and pregabalin sensitivity: the pharmacogenetic mediation of analgesia is specific to the type of pain being inhibited. Pain 2003;106:325–35. [PubMed: 14659515]
46. Elmer GI, Pieper JO, Negus SS, Woods JH. Genetic variance in nociception and its relationship to the potency of morphine-induced analgesia in thermal and chemical tests. Pain 1998;75:129–40. [PubMed: 9539682]
47. Mogil JS, Kest B, Sadowski B, Belknap JK. Differential genetic mediation of sensitivity to morphine in genetic models of opiate antinociception: influence of nociceptive assay. J Pharmacol Exp Ther 1996;276:532–44. [PubMed: 8632319]
48. Terner JM, Lomas LM, Smith ES, Barrett AC, Picker MJ. Pharmacogenetic analysis of sex differences in opioid antinociception in rats. Pain 2003;106:381–91. [PubMed: 14659521]
49. Rode F, Thomsen M, Brolos T, Jensen DG, Blackburn-Munro G, Bjerrum OJ. The importance of genetic background on pain behaviours and pharmacological sensitivity in the rat spared nerve injury model of peripheral neuropathic pain. Eur J Pharmacol 2007;564:103–11. [PubMed: 17383631]
50. Evans WE, Johnson JA. Pharmacogenomics: the inherited basis for interindividual differences in drug response. Annu Rev Genomics Hum Genet 2001;2:9–39. [PubMed: 11701642]
51. Roses AD. Pharmacogenetics and the practice of medicine. Nature 2000;405:857–65. [PubMed: 10866212]
52. Wilson SG, Mogil JS. Measuring pain in the (knockout) mouse: big challenges in a small mammal. Behav Brain Res 2001;125:65–73. [PubMed: 11682095]
53. Capecchi MR. Altering the genome by homologous recombination. Science 1989;244:1288–92. [PubMed: 2660260]
54. Beck JA, Lloyd S, Hafezparast M, Lennon-Pierce M, Eppig JT, et al. Genealogies of mouse inbred strains. Nat Genet 2000;24:23–25. [PubMed: 10615122]
55. Yang H, Bell TA, Churchill GA, Pardo-Manuel de Villena F. On the subspecific origin of the laboratory mouse. Nature Genet 2007;39:1100–7. [PubMed: 17660819]
56. Frazer KA, Eskin E, Kang HM, Bogue MA, Hinds DA, et al. A sequence-based variation map of 8.27 million SNPs in inbred mouse strains. Nature 2007;448:1050–55. [PubMed: 17660834]
57. Panocka I, Marek P, Sadowski B. Inheritance of stress-induced analgesia in mice. Selective breeding study. Brain Res 1986;397:152–55. [PubMed: 3801859]
58. Belknap JK, Haltli NR, Goebel DM, Lamé M. Selective breeding for high and low levels of opiate-induced analgesia in mice. Behav Genet 1983;13:383–96. [PubMed: 6639563]
59. Devor M, Raber P. Heritability of symptoms in an experimental model of neuropathic pain. Pain 1990;42:51–67. [PubMed: 2234999]
60. Mogil JS, Sternberg WF, Marek P, Sadowski B, Belknap JK, Liebeskind JC. The genetics of pain and pain inhibition. Proc Natl Acad Sci USA 1996;93:3048–55. [PubMed: 8610166]
61. Shuster, L. A pharmacogenetic approach to the brain. In: Lieblich, I., editor. Genetics of the Brain. Amsterdam: Elsevier; 1982. p. 157-73.
62. Ikeda K, Kobayashi T, Kumanishi T, Niki H, Yano R. Involvement of G-protein-activated inwardly rectifying K^+ (GIRK) channels in opioid-induced analgesia. Neurosci Res 2000;38:113–16. [PubMed: 10997585]
63. Mogil JS, Ritchie J, Smith SB, Strasburg K, Kaplan L, et al. Melanocortin-1 receptor gene variants affect pain and m-opioid analgesia in mice and humans. J Med Genet 2005;42:583–87. [PubMed: 15994880]
64. Martinez-Cue C, Baamonde C, Lumbreras MA, Vallina IF, Dierssen M, Florez J. A murine model for Down syndrome shows reduced responsiveness to pain. Neuroreport 1999;10:1119–22. [PubMed: 10321494]

65. Yamazaki K, Nakazawa T, Matsunaga M, Kumazawa A, Kaneko T, Wakabayashi T. Behavioral study on the gracile axonal dystrophy (GAD) mutant mouse. Exp Anim 1992;41:523–27.
66. Ogasawara M, Kurihara T, Hu Q, Tanabe T. Characterization of acute somatosensory pain transmission in P/Q-type Ca^{2+} channel mutant mice, leaner. FEBS Lett 2001;508:181–86. [PubMed: 11718712]
67. Vermeirsch H, Meert TF. Morphine-induced analgesia in the hot-plate test: comparison between $NMRI^{nu/nu}$ and NMRI mice. Pharmacol Toxicol 2004;94:59–64.
68. Ikeda K, Ide S, Han W, Hayashida M, Uhl GR, Sora I. How individual sensitivity to opiates can be predicted by gene analyses. Trends Pharmacol Sci 2005;26:311–17. [PubMed: 15925706]
69. Mogil JS, Yu L, Basbaum AI. Pain genes? : natural variation and transgenic mutants. Annu Rev Neurosci 2000;23:777–811. [PubMed: 10845081]
70. Mogil JS, Grisel JE. Transgenic studies of pain. Pain 1998;77:107–28. [PubMed: 9766829]
71. Kieffer BL. Opioids: first lessons from knockout mice. Trends Pharmacol Sci 1999;20:19–26. [PubMed: 10101958]
72. Malmberg, AB.; Zeitz, KP. Studies of pain mechanisms in genetically manipulated mice. In: Mogil, JS., editor. The Genetics of Pain, Progress in Pain Research and Treatment. Seattle: IASP Press; 2004. p. 21-48.
73. LaCroix-Fralish ML, Ledoux JB, Mogil JS. The *Pain Genes Database*: an interactive web browser of pain-related transgenic knockout studies. Pain 2007;131:3.e1–3.e4. [PubMed: 17574758]
74. Lariviere WR, Chesler EJ, Mogil JS. Transgenic studies of pain and analgesia: mutation or background phenotype? J Pharmacol Exp Ther 2001;297:467–73. [PubMed: 11303031]
75. Mogil JS, Wilson SG. Nociceptive and morphine antinociceptive sensitivity of 129 and C57BL/6 inbred mouse strains: implications for transgenic knock-out studies. Eur J Pain 1997;1:293–97. [PubMed: 15102394]
76. Mogil JS, McCarson KE. Finding pain genes: bottom-up and top-down approaches. J Pain 2000;1 (Suppl 1):66–80. [PubMed: 14622845]
77. Nolan PM, Peters J, Strivens M, Rogers D, Hagan J, et al. A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse. Nature 2000;25:440–43.
78. Hrabe de Angelis M, Flaswinkel H, Fuchs H, Rathkolb B, Soewarto D, et al. Genome-wide, large-scale production of mutant mice by ENU mutagenesis. Nature 2000;25:444–47.
79. Cook MN, Dunning JP, Wiley RG, Chesler EJ, Johnson DK, et al. Neurobehavioral mutants identified in an ENU-mutagenesis project. Mamm Genome 2007;18:559–72. [PubMed: 17629744]
80. Sayah DM, Khan AH, Gasperoni TL, Smith SJ. A genetic screen for novel behavioral mutations in mice. Mol Psychiat 2000;5:369–77.
81. Ogawa S, Pfaff DW. Application of antisense DNA method for the study of molecular bases of brain function and behavior. Behav Genet 1996;26:279–92. [PubMed: 8754251]
82. Kim DH, Rossi JJ. Strategies for silencing human disease using RNA interference. Nature Rev Genet 2007;8:173–84. [PubMed: 17304245]
83. Rohl T, Kurreck J. RNA interference in pain research. J Neurochem 2006;99:371–80. [PubMed: 17029593]
84. Pasternak GW, Standifer KM. Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology. Trends Pharmacol Sci 1995;16:344–50. [PubMed: 7491712]
85. Anseloni VCZ, He F, Novikova SI, Turnbach Robbins M, Lidow IA, et al. Alterations in stress-associated behaviors and neurochemical markers in adult rats after neonatal short-lasting local inflammatory insult. Neuroscience 2005;131:635–45. [PubMed: 15730869]
86. Yang H-YT, Mitchell K, Keller JM, Iadarola MJ. Peripheral inflammation increases Scya2 expression in sensory ganglia and cytokine and endothelial related gene expression in inflamed tissue. J Neurochem 2007;103:1628–43. [PubMed: 17883394]
87. Rabert D, Xiao Y, Yiangou Y, Kreder D, Sangameswaran L, et al. Plasticity of gene expression in injured human dorsal root ganglia revealed by GeneChip oligonucleotide microarrays. J Clin Neurosci 2004;11:289–99. [PubMed: 14975420]

88. Wang X-M, Wu T-X, Hamza M, Ramsay ES, Wahl SM, Dionne RA. Rofecoxib modulates multiple gene expression pathways in a clinical model of acute inflammatory pain. Pain 2007;128:136–47. [PubMed: 17070997]
89. Wang X-M, Wu T-X, Lee Y-S, Dionne RA. Rofecoxib regulates the expression of genes related to the matrix metalloproteinase pathway in humans: implication for the adverse effects of cyclooxygenase-2 inhibitors. Clin Pharmacol Ther 2006;79:303–15. [PubMed: 16580899]
90. Chae Y, Park H-J, Hahm D-H, Yi S-H, Lee H. Individual differences of acupuncture analgesia in humans using cDNA microarray. J Physiol Sci 2006;56:425–31. [PubMed: 17083754]
91. Sjostrand C, Duvefelt K, Steinberg A, Remahl IN, Waldenlind E, Hillert J. Gene expression profiling in cluster headache: a pilot microarray study. Headache 2006;46:1518–34. [PubMed: 17115985]
92. Garcia-Escudero R, Paramio JM. Gene expression profiling as a tool for basic analysis and clinical application of human cancer. Mol Carcinog 2008;47:573–79. [PubMed: 18324660]
93. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nature Med 2006;12:1269–77. [PubMed: 17057711]
94. Ko J, Na DS, Lee YH, Shin SY, Kim JH, et al. cDNA microarray analysis of the differential gene expression in the neuropathic pain and electroacupuncture treatment models. J Biochem Mol Biol 2002;35:420–27. [PubMed: 12297003]
95. Gao YZ, Guo SY, Yin QZ, Hisamitsu T, Jiang XH. An individual variation study of electroacupuncture analgesia in rats using microarray. Am J Chin Med 2007;35:767–78. [PubMed: 17963317]
96. McClung CA. The molecular mechanisms of morphine addiction. Rev Neurosci 2006;17:393–402. [PubMed: 17139840]
97. Lander ES, Schork NJ. Genetic dissection of complex traits. Science 1994;265:2037–48. [PubMed: 8091226]
98. Belknap, JK.; Dubay, C.; Crabbe, JC.; Buck, KJ. Mapping quantitative trait loci for behavioral traits in the mouse. In: Blum, K.; Noble, EP., editors. Handbook of Psychiatric Genetics. New York: CRC Press; 1996. p. 435-53.
99. Paigen K, Eppig JT. A mouse phenome project. Mamm Genome 2000;11:715–17. [PubMed: 10967127]
100. Mogil, JS. Complex trait genetics of pain in the laboratory mouse. In: Mogil, JS., editor. The Genetics of Pain, Progress in Pain Research and Management. Seattle: IASP Press; 2004. p. 123-49.
101. Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. Proc Natl Acad Sci USA 1999;96:7744–51. [PubMed: 10393892]
102. Xu, X-J.; Wiesenfeld-Hallin, Z. Individual differences in pain: rat models. In: Mogil, JS., editor. The Genetics of Pain, Progress in Pain Research and Management. Seattle: IASP Press; 2004. p. 107-21.
103. Mogil JS, Belknap JK. Sex and genotype determine the selective activation of neurochemically-distinct mechanisms of swim stress-induced analgesia. Pharmacol Biochem Behav 1997;56:61–66. [PubMed: 8981610]
104. Urca G, Segev S, Sarne Y. Footshock-induced analgesia: its opioid nature depends on the strain of rat. Brain Res 1985;329:109–16. [PubMed: 3978436]
105. Rady JJ, Elmer GI, Fujimoto JM. Opioid receptor selectivity of heroin given intracerebroventricularly differs in six strains of inbred mice. J Pharmacol Exp Ther 1999;288:438–45. [PubMed: 9918543]
106. Lee DH, Chung K, Chung JM. Strain differences in adrenergic sensitivity of neuropathic pain behaviors in an experimental rat model. Neuroreport 1997;8:3453–56. [PubMed: 9427306]
107. Clark FM, Proudfit HK. Anatomical evidence for genetic differences in the innervation of the rat spinal cord by noradrenergic locus coeruleus neurons. Brain Res 1992;591:44–53. [PubMed: 1446232]
108. Edwards RR, Haythornthwaite JA, Tella P, Max MB, Raja S. Basal heat pain thresholds predict opioid analgesia in patients with postherapetic neuralgia. Anesthesiology 2006;104:1243–48. [PubMed: 16732096]

109. Mogil JS, Wilson SG, Bon K, Lee SE, Chung K, et al. Heritability of nociception. II "Types" of nociception revealed by genetic correlation analysis. Pain 1999;80:83–93. [PubMed: 10204720]
110. Lariviere WR, Wilson SG, Laughlin TM, Kokayeff A, West EE, et al. Heritability of nociception. III Genetic relationships among commonly used assays of nociception and hypersensitivity. Pain 2002;97:75–86. [PubMed: 12031781]
111. Shir Y, Zeltser R, Vatine J-J, Carmi G, Belfer I, et al. Correlation of intact sensibility and neuropathic pain-related behaviors in eight inbred and outbred rat strains and selection lines. Pain 2001;90:75–82. [PubMed: 11166972]
112. Yoon YW, Lee DH, Lee BH, Chung K, Chung JM. Different strains and substrains of rats show different levels of neuropathic pain behaviors. Exp Brain Res 1999;129:167–71. [PubMed: 10591890]
113. Mogil JS, Meirmeister F, Seifert F, Strasburg K, Zimmermann K, et al. Variable sensitivity to noxious heat is mediated by differential expression of the CGRP gene. Proc Natl Acad Sci USA 2005;102:12938–43. [PubMed: 16118273]
114. Deleted in proof
115. Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135–43. [PubMed: 15537663]
116. Lotsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. Clin Pharmacokinet 2004;43:983–1013. [PubMed: 15530129]
117. Hamabe W, Maeda T, Kiguchi N, Yamamoto C, Tokuyama S, Kishioka S. Negative relationship between morphine analgesia and P-glycoprotein expression levels in brain. J Pharmacol Sci 2007;105:353–60. [PubMed: 18071274]
118. Coulbault L, Beaussier M, Verstuyft C, Weickmans H, Dubert L, et al. Environmental and genetic factors associated with morphine response in the postoperative period. Clin Pharmacol Ther 2006;79:316–24. [PubMed: 16580900]
119. Liang D-Y, Liao G, Lighthall GK, Peltz G, Clark DJ. Genetic variants of the P-glycoprotein gene *Abcb1b* modulate opioid-induced hyperalgesia, tolerance and dependence. Pharmacogenet Genomics 2006;16:825–35. [PubMed: 17047491]
120. Kieffer BL, Gaveriaux-Ruff C. Exploring the opioid system by gene knockout. Prog Neurobiol 2002;66:285–306. [PubMed: 12015197]
121. Belknap JK, Mogil JS, Helms ML, Richards SP, O'Toole LA, et al. Localization to chromosome 10 of a locus influencing morphine analgesia in crosses derived from C57BL/6 and DBA/2 mouse strains. Life Sci 1995;57:PL117–24. [PubMed: 7643715]
122. Bergeson SE, Helms ML, O'Toole LA, Jarvis MW, Hain HS, et al. Quantitative trait loci influencing morphine antinociception in four mapping populations. Mamm Genome 2001;12:546–53. [PubMed: 11420618]
123. Smith SB, Marker CL, Perry C, Liao G, Sotocinal SG, et al. Quantitative trait locus and computational mapping identifies *Kcnj9* (GIRK3) as a candidate gene affecting analgesia from multiple drug classes. Pharmacogenet Genomics 2008;18:231–41. [PubMed: 18300945]
124. Grupe A, Germer S, Usuka J, Aud D, Belknap JK, et al. In silico mapping of complex disease-related traits in mice. Science 2001;292:1915–18. [PubMed: 11397946]
125. Chesler EJ, Rodriguez-Zas SL, Mogil JS. In silico mapping of mouse quantitative trait loci. Science 2001;294:2423. [PubMed: 11752534]
126. Darvasi A. In silico mapping of mouse quantitative trait loci. Science 2001;294:2423. [PubMed: 11865449]
127. Wang J, Liao G, Usuka J, Peltz G. Computational genetics: from mouse to human. Trends Genet 2005;21:526–32. [PubMed: 16009447]
128. Kest B, Wilson SG, Mogil JS. Sex differences in supraspinal morphine analgesia are dependent on genotype. J Pharmacol Exp Ther 1999;289:1370–75. [PubMed: 10336528]
129. Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KVS, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci USA 2003;100:4867–72. [PubMed: 12663858]

130. Crabbe JC, Wahlsten D, Dudek BC. Genetics of mouse behavior: interactions with laboratory environment. Science 1999;284:1670–72. [PubMed: 10356397]
131. Chesler EJ, Wilson SG, Lariviere WR, Rodriguez-Zas SL, Mogil JS. Influences of laboratory environment on behavior. Nature Neurosci 2002;5:1101–2. [PubMed: 12403996]
132. Chesler EJ, Wilson SG, Lariviere WR, Rodriguez-Zas SL, Mogil JS. Identification and ranking of genetic and laboratory environment factors influencing a behavioral trait, thermal nociception, via computational analysis of a large data archive. Neurosci Biobehav Rev 2002;26:907–23. [PubMed: 12667496]
133. Mogil JS, Crager SE. What should we be measuring in behavioral studies of chronic pain in animals? Pain 2004;112:12–15. [PubMed: 15494180]
134. Vierck CJ, Hansson PT, Yezierski RP. Clinical and preclinical pain assessment: are we measuring the same thing? Pain 2008;135:7–10. [PubMed: 18215466]
135. Mogil, JS.; Max, MB. The genetics of pain. In: Koltzenburg, M.; McMahon, SB., editors. Wall and Melzack's Textbook of Pain. Vol. 5. London: Elsevier Churchill Livingstone; 2005. p. 159-74.
136. Diatchenko L, Nackley AG, Tchivileva IE, Shabalina SA, Maixner W. Genetic architecture of human pain perception. Trends Genet 2007;23:605–13. [PubMed: 18023497]
137. Lotsch J, Geisslinger G. Current evidence for a modulation of nociception by human genetic polymorphisms. Pain 2007;132:18–22. [PubMed: 17706868]
138. Limer KL, Nicholl BI, Thomson W, McBeth J. Exploring the genetic susceptibility of chronic widespread pain: the tender points in genetic association studies. Rheumatology 2008;47:572–77. [PubMed: 18321946]
139. Montagna P. Recent advances in the pharmacogenomics of pain and headache. Neurol Sci 2007;28 (Suppl 2):208–12.
140. Johnson MP, Fernandez F, Colson NJ, Griffiths LR. A pharmacogenomic evaluation of migraine therapy. Expert Opin Pharmacother 2007;8:1821–35. [PubMed: 17696786]
141. Lotsch J, Geisslinger G. Current evidence for a genetic modulation of the response to analgesics. Pain 2006;121:1–5. [PubMed: 16472919]
142. Stamer UM, Stuber F. Genetic factors in pain and its treatment. Curr Opin Anaesthesiol 2007;20:478–84. [PubMed: 17873601]
143. Caraco Y, Maroz Y, Davidson E. Variability in alfentanil analgesia may be attributed to polymorphism in the mu opioid receptor. Clin Pharmacol Ther 2001;69:P63.
144. Rakvag TT, Klepstad P, Baar C, Kvam T-M, Dale O, et al. The Val158Met polymorphism of the human catechol-*O*-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005;116:73–78. [PubMed: 15927391]
145. Lee Y-S, Kim H, Wu T-X, Wang X-M, Dionne RA. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 2006;79:407–18. [PubMed: 16678543]
146. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, et al. An *SCN9A* channelopathy causes congenital inability to experience pain. Nature 2006;444:894–98. [PubMed: 17167479]
147. Goldberg YP, MacFarlane J, MacDonald ML, Thopmson J, Dube M-P, et al. Loss-of-function mutations in the $Na_v1.7$ gene underlie congenital indifference to pain in multiple human populations. Clin Genet 2007;71:311–19. [PubMed: 17470132]
148. Yang Y, Wang Y, Li S, Xu Z, Li H, et al. Mutations in *SCN9A*, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet 2004;41:171–74. [PubMed: 14985375]
149. Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, et al. *SCN9A* mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron 2006;52:767–74. [PubMed: 17145499]
150. Liveing, E. On Megrim, Sick-Headache, and Some Allied Disorders; a Contribution to the Pathology of Nerve-Storms. London: Churchill Press; 1873. p. 512
151. Peroutka SJ, Wilhoit TL, Boatwright M, Derksen M, Jones KW. Polymorphisms within the CACNL1A4 gene are not associated with migraine wihout aura or migraine with aura. Headache 1997;37:326–27.

152. Lea RA, Curtain RP, Hutchins C, Brimage PJ, Griffiths LR. Investigation of the CACNA1A gene as a candidate for typical migraine susceptibility. Am J Med Genet 2001;105:707–12. [PubMed: 11803518]
153. Risch NJ. Searching for genetic determinants in the new millennium. Nature 2000;405:847–56. [PubMed: 10866211]
154. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders—pathways of vulnerability. Pain 2006;123:226–30. [PubMed: 16777329]
155. Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Kruger M, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum 1999;42:2482–88. [PubMed: 10555044]
156. Cohen H, Buskila D, Neumann L, Ebstein RP. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis Rheum 2002;46:845–47. [PubMed: 11920428]
157. Kim H, Lee H, Rowan J, Brahim J, Dionne RA. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute postsurgical pain in humans. Mol Pain 2006;2:24. [PubMed: 16848906]
158. Jeremias J, Ledger WJ, Witkin SS. Interleukin 1 receptor antagonist gene polymorphism in women with vulvar vestibulitis. Am J Obstet Gynecol 2000;182:283–85. [PubMed: 10694325]
159. Foster DC, Sazenski TM, Stodgell CJ. Impact of genetic variation in interleukin-1 receptor antagonist and melanocortin-1 receptor genes on vulvar vestibulitis syndrome. J Reprod Med 2004;49:503–9. [PubMed: 15305821]
160. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. Anesthesiology 2005;102:509–14. [PubMed: 15731586]
161. Valverde P, Healy E, Jackson I, Rees JL, Thody AJ. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. Nature Genet 1995;11:328–30. [PubMed: 7581459]
162. Zubieta J-K, Heitzeg MM, Smith YR, Bueller JA, Xu K, et al. COMT $val^{158}met$ genotype affects μ-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240–43. [PubMed: 12595695]
163. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, et al. Catechol-*O*-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain 2006;125:216–24. [PubMed: 16837133]
164. Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskyi O, et al. Human catechol-*O*-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science 2006;314:1930–33. [PubMed: 17185601]
165. Birklein F, Depmeier C, Rolke R, Hansen C, Rautenstrauss B, et al. A family-based investigation of cold pain tolerance. Pain 2008;138:111–18. [PubMed: 18194840]
166. Kim H, Dionne RA. Comment on Diatchenko et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain 2007;129:365–66. [PubMed: 17407801]
167. Gursoy S, Erdal E, Herken H, Madenci E, Alasehirli B, Erdal N. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. Rheumatol Int 2003;23:104–7. [PubMed: 12739038]
168. Armero P, Muriel C, Santos J, Sanchez-Montero FJ, Rodriguez RE, Gonzalez-Sarmiento R. COMT (Val158Met) polymorphism is not associated to neuropathic pain in a Spanish population. Eur J Pain 2005;9:229–32. [PubMed: 15862471]
169. Reyes-Gibby CC, Shete S, Rakvag T, Bhat SV, Skorpen F, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: *OPRM1* and *COMT* gene. Pain 2007;130:25–30. [PubMed: 17156920]
170. Tegeder I, Adolph J, Schmidt H, Woolf CJ, Geisslinger G, Lotsch J. Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. Eur J Pain 2008;12:1069–77. [PubMed: 18374612]

171. Kim H, Dionne RA. Lack of influence of GTP cyclohydrolase gene (*GCH1*) variations on pain sensitivity in humans. Mol Pain 2007;3:6. [PubMed: 17343757]

172. Smith BH, Macfarlane GJ, Torrance N. Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? Pain 2007;127:5–10. [PubMed: 17140732]

173. Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, et al. NCI-NHGRI Working Group on Replication in Association Studies. Replicating genotype-phenotype associations. Nature 2007;447:655–60. [PubMed: 17554299]

174. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. Genet Med 2002;4:45–61. [PubMed: 11882781]

175. Campbell CD, Ogburn EL, Lunetta KL, Lyon HN, Freedman ML, et al. Demonstrating stratification in a European American population. Nat Genet 2005;37:868–72. [PubMed: 16041375]

176. Freedman ML, Reich D, Penney KL, McDonald GJ, Mignault AA, et al. Assessing the impact of population stratification on genetic association studies. Nat Genet 2004;36:388–93. [PubMed: 15052270]

177. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nature Genet 2003;33:177–82. [PubMed: 12524541]

178. Schulze TG, McMahon FJ. Defining the phenotype in human genetic studies: forward genetics and reverse phenotyping. Hum Hered 2004;58:131–38. [PubMed: 15812169]

179. Ioannidis JP. Why most published research findings are false. PLOS Med 2005;2:e124. [PubMed: 16060722]

180. International HapMap Consortium. The International HapMap Project. Nature 2003;426:789–96. [PubMed: 14685227]

181. Carlson CS, Eberle MA, Kruglyak L, Nickerson DA. Mapping complex disease loci in whole-genome association studies. Nature 2004;429:446–52. [PubMed: 15164069]

182. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nature Rev Genet 2008;9:356–69. [PubMed: 18398418]

183. Belfer I, Wu T, Kingman A, Krishnaraju RK, Goldman D, Max MB. Candidate gene studies of human pain mechanisms: a method for optimizing choice of polymorphisms and sample size. Anesthesiology 2004;100:1562–72. [PubMed: 15166579]

184. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, et al. Meta-analysis of genome-wide association data and large-scale replication identifies several additional susceptibility loci for type 2 diabetes. Nature Genet 2008;40:638–45. [PubMed: 18372903]

185. Furuse T, Miura Y, Yagasaki K, Shiroishi T, Koide T. Identification of QTLs for differential capsaicin sensitivity between mouse strains KJR and C57BL/6. Pain 2003;105:169–75. [PubMed: 14499433]

186. Wilson SG, Chesler EJ, Hain HS, Rankin AL, Schwarz JZ, et al. Identification of quantitative trait loci for chemical/inflammatory nociception in mice. Pain 2002;96:385–91. [PubMed: 11973013]

187. Mogil JS, Richards SP, O'Toole LA, Helms ML, Mitchell SR, Belknap JK. Genetic sensitivity to hot-plate nociception in DBA/2J and C57BL/6J inbred mouse strains: possible sex-specific mediation by d_2-opioid receptors. Pain 1997;70:267–77. [PubMed: 9150302]

188. Seltzer Z, Wu T, Max MB, Diehl SR. Mapping a gene for neuropathic pain-related behavior following peripheral neurectomy in the mouse. Pain 2001;93:101–6. [PubMed: 11427320]

189. Devor M, Gilad A, Arbilly M, Yakir B, Raber P, et al. Pain1: a neuropathic pain QTL on mouse chromosome 15 in a C3HxC58 backcross. Pain 2005;116:289–93. [PubMed: 15979798]

190. Devor M, Gilad A, Arbilly M, Nissenbaum J, Yakir B, et al. Sex-specific variability and a 'cage effect' independently mask a neuropathic pain quantitative trait locus detected in a whole genome scan. Eur J Neurosci 2007;26:681–88. [PubMed: 17686043]

191. Nissenbaum J, Shpigler H, Pisante A, delCanho S, Minert A, et al. Pain 2: a neuropathic pain QTL identified on rat chromosome 2. Pain 2008;135:92–97. [PubMed: 17560719]

192. Hain HS, Belknap JK, Mogil JS. Pharmacogenetic evidence for the involvement of 5-hydroxytryptamine (serotonin)-1B receptors in the mediation of morphine antinociceptive sensitivity. J Pharmacol Exp Ther 1999;291:444–49. [PubMed: 10525057]

193. Mogil JS, Richards SP, O'Toole LA, Helms ML, Mitchell SR, et al. Identification of a sex-specific quantitative trait locus mediating nonopioid stress-induced analgesia in female mice. J Neurosci 1997;17:7995–8002. [PubMed: 9315917]

194. Liang D-Y, Liao G, Wang J, Usuka J, Guo Y, et al. A genetic analysis of opioid-induced hyperalgesia in mice. Anesthesiology 2006;104:1054–62. [PubMed: 16645459]

195. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4. Cell 1996;87:543–52. [PubMed: 8898206]

196. DeFusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, et al. Haploinsufficiency of *ATP1A2* encoding the Na^{+}/K^{+} pump a2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 2003;33:192–96. [PubMed: 12539047]

197. Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 2005;366:371–77. [PubMed: 16054936]

198. Booth DR, Gillmore JD, Lachmann HJ, Booth SE, Bybee A, et al. The genetic basis of autosomal dominant familial Mediterranean fever. Quart J Med 2000;93:217–21.

199. Kuhlenbaumer G, Hannibal MC, Nelis E, Schirmacher A, Verpoorten N, et al. Mutations in SEPT9 cause hereditary neuralgic amyotrophy. Nature Genet 2000;37:1044–46. [PubMed: 16186812]

200. Bejaoui K, Wu C, Scheffler MD, Haan G, Ashby P, et al. SPTLC1 is mutated in hereditary sensory neuropathy, type 1. Nat Genet 2001;27:261–62. [PubMed: 11242106]

201. Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach MN, Nicholson GA. Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. Nat Genet 2001;27:309–12. [PubMed: 11242114]

202. Lafreniere RG, MacDonald MLE, Dube M-P, MacFarlane J, O'Driscoll M, et al. Identification of a novel gene (*HSN2*) causing hereditary sensory and autonomic neuropathy Type II through the study of Canadian genetic isolates. Am J Hum Genet 2004;74:1064–73. [PubMed: 15060842]

203. Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, et al. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 2001;68:598–605. [PubMed: 11179008]

204. Anderson SL, Coli R, Daly IW, Kichula EA, Rork MJ, et al. Familial dysautonomia is caused by mutations of the IKAP gene. Am J Hum Genet 2001;68:753–78. [PubMed: 11179021]

205. Indo Y, Tsurata Y, Karim MA, Ohta K, Kawano T, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nature Genet 1996;13:485–88. [PubMed: 8696348]

206. Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, et al. A mutation in the nerve growth factor beta gene (*NGFB*) causes loss of pain perception. Hum Mol Genet 2004;13:799–805. [PubMed: 14976160]

207. Park JS, Zhang SY, Jo SH, Seo JB, Li L, et al. Common adrenergic receptor polymorphisms as novel risk factors for vasospastic angina. Am Heart J 2006;151:864–69. [PubMed: 16569551]

208. Ogimoto A, Shigematsu Y, Nakura J, Hara Y, Ohtsuka T, et al. Endothelial nitric oxide synthase gene polymorphism (Glu298Asp) in patients with coexistent hypertrophic cardiomyopathy and coronary spastic angina. J Mol Med 2005;83:619–25. [PubMed: 15778808]

209. Kang S-C, Lee D-G, Choi J-H, Kim ST, Kim Y-K, Ahn H-J. Association between estrogen receptor polymorphism and pain susceptibility in female temporomandibular joint osteoarthritis patients. Int J Oral Maxillofac Surg 2007;36:391–94. [PubMed: 17391927]

210. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, et al. Cytokine genotypes correlate with pain and radiologically defined joint damage in patients with juvenile rheumatoid arthritis. Rheumatology 2005;44:1115–21. [PubMed: 15901906]

211. Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimaki H. Possible association of interleukin 1 gene locus polymorphisms with low back pain. Pain 2004;109:8–19. [PubMed: 15082121]

212. Noponen-Hietala N, Virtanen I, Karttunen R, Schwenke S, Jakkula E, et al. Genetic variations in *IL6* associate with intervertebral disc disease characterized by sciatica. Pain 2005;114:186–94. [PubMed: 15733644]
213. Guimaraes AL, de Sa AR, Victoria JM, de Fatima Correia-Silva J, Gomez MV, Gomez RS. Interleukin-1b and serotonin transporter gene polymorphisms in burning mouth syndrome patients. J Pain 2006;7:654–58. [PubMed: 16942951]
214. Kim H, Mittal DP, Iadarola MJ, Dionne RA. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. J Med Genet 2006;43:e40. [PubMed: 16882734]
215. Fillingim RB, Ness TJ, Glover TL, Campbell CM, Hastie BA, et al. Morphine responses and experimental pain: sex differences in side effects and cardiovascular responses but not analgesia. J Pain 2005;6:116–24. [PubMed: 15694878]
216. Lotsch J, Stuck B, Hummel T. The human mu-opioid receptor gene polymorphism 118A>G decreases cortical activation in response to specific nociceptive stimulation. Behav Neurosci 2006;120:1218–24. [PubMed: 17201465]
217. Bondy B, Spaeth M, Offenbaecher M, Glatzeder K, Stratz T, et al. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. Neurobiol Dis 1999;6:433–39. [PubMed: 10527809]
218. Pinessi L, Rainero I, Rivoiro C, Rubino E, Gallone S. Genetics of cluster headache: an update. J Headache Pain 2005;6:234–36. [PubMed: 16362673]
219. Gonsalkorale WM, Perrey C, Pravica V, Whorwell PJ, Hutchinson IV. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gut 2003;52:91–93. [PubMed: 12477767]
220. Pata C, Erdal E, Yazici K, Camdeviren H, Ozkaya M, Ulu O. Association of the -1438 G/A and 102 T/C polymorphism of the 5-Ht2A receptor gene with irritable bowel syndrome 5-Ht2A gene polymorphism in irritable bowel syndrome. J Clin Gastroenterol 2004;38:561–66. [PubMed: 15232358]
221. Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. Gastroenterology 2002;123:425–32. [PubMed: 12145795]
222. van der Veek PP, van den Berg M, de Kroon YE, Verspaget HW, Masclee AA. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. Am J Gastroenterol 2005;100:2510–16. [PubMed: 16279907]
223. Stamer UM, Lehnen K, Hothker F, Bayerer B, Wolf S, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003;105:231–38. [PubMed: 14499440]
224. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827–31. [PubMed: 15625333]
225. Dalen P, Frengell C, Dahl ML, Sjoqvist F. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. Ther Drug Monit 1997;19:543–44. [PubMed: 9357099]
226. Romberg RR, Olofsen E, Bijl H, Taschner PE, Teppema LJ, et al. Polymorphism of mu-opioid receptor gene (OPRM1:c.118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology 2005;102:522–30. [PubMed: 15731588]
227. Oertel BG, Schmidt R, Schneider A, Geisslinger G, Lötsch J. The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenet Genom 2006;16:625–36.
228. Skarke C, Darimont J, Schmidt H, Geisslinger G, Lotsch J. Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. Clin Pharmacol Ther 2003;73:107–21. [PubMed: 12545149]
229. Lötsch J, Skarke C, Grösch S, Darimont J, Schmidt H, Geisslinger G. The polymorphism A118G of the human mu-opioid receptor gene decreases the clinical activity of morphine-6-glucuronide but not that of morphine. Pharmacogenetics 2002;12:3–9. [PubMed: 11773859]
230. Janicki PK, Schuler G, Francis D, Bohr A, Gordin V, et al. A genetic association study of the functional A118G polymorphism of the human μ-opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006;103:1011–17. [PubMed: 17000822]

231. Shoskes DA, Albakri Q, Thomas K, Cook D. Cytokine polymorphisms in men with chronic prostatitis/chronic pelvic pain syndrome: association with diagnosis and treatment response. J Urol 2002;168:331–35. [PubMed: 12050565]

232. Sery O, Hrazdilova O, Didden W, Klenerova V, Staif R, et al. The association of monoamine oxidase B functional polymorphism with postoperative pain intensity. Neuroendocrinol Lett 2006;27:333–37. [PubMed: 16807522]

233. Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, et al. Three major haplotypes of the β_2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet 2006;141B:449–62. [PubMed: 16741943]

234. Herken H, Erdal E, Mutlu N, Barlas O, Cataloluk O, et al. Possible association of temporomandibular joint pain and dysfunction with a polymorphism in the serotonin transporter gene. Am J Orthod Dentofacial Orthop 2001;120:308–13. [PubMed: 11552131]

235. Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS. Interleukin-1b gene polymorphism in women with vulvar vestibulitis syndrome. Eur J Obstet Gynecol Reprod Biol 2003;107:74–77. [PubMed: 12593899]

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.

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).

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)

Phenotype	Gene	Protein	Reference
	OPRM1	Opioid receptor, mu 1	(143,169,226–230)
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 specific dependent measure.