Almost 50 years elapsed between the discovery of the structure of DNA and the sequencing of the human genome. Now, genetic research in pain is just beginning. Sensory input is processed through an individual’s genetic composition, prior experience, physiological status, idiosyncratic appraisals, expectations, mood, and sociocultural environment, leading to variability in pain perception and tolerance (Figure 1). Some day, it may be possible to determine treatments based on each individual’s genetic profile. This issue of Pain: Clinical Updates presents concepts related to genetic influences on clinical pain and analgesia that may help clinicians reach that goal.

Figure 1. Variability of genes at multiple sites contributes to individual differences in nociceptive processing.
A role for genetics in pain is suggested by the genetic factors inherent in gender, and more controversially, ethnicity, that give rise to differences in pain sensitivity in humans and animals.

Is Pain Genetically Influenced?

Genetic factors explain a significant amount of the variance in abnormal human behavior, psychosocial interactions, cognition, and psychophysiological processes. Dissection of genetic influences on pain sensitivity has been challenging because these influences most likely reflect the interactions of many genes, each with a small effect, and environmental factors, rather than coming from a few genes with major effects.

A role for genetics in pain is suggested by the genetic factors inherent in gender, and more controversially, ethnicity, that give rise to differences in pain sensitivity in humans and animals.

Heritability is essentially the proportion of variance due to all genetic factors. The value of estimating heritability is to establish the likely success of strategies to detect the action of individual genes in pain. A wide range of heritability estimates have been obtained for different types of clinical pain. In one carefully controlled animal study, 24% of heat pain sensitivity could be attributed to heritability.

Correlations between siblings can define the portion of trait variance attributable to genetic variation; they range from 0.11 to 0.23 for experimental cold and thermal pain sensitivity. Twin studies provide a more direct method for separating genetic from environmental influences, although significant epigenetic differences may arise during the lifetime of monozygotic (i.e., genetically identical) twins that blur this distinction.

In contrast to experimental pain models, pain in many diseases in which it is a predominant feature is strongly heritable.

In contrast to experimental pain models, pain in many diseases in which it is a predominant feature is strongly heritable. Heritability accounts for approximately 50% of migraine pain, 55% of menstrual pain, 35–68% of low back and neck pain, 50% of shoulder and elbow pain, and 40% of the pain experienced in carpal tunnel syndrome. The remainder of the variance is most likely explained by genetic-environmental interactions and by environmental factors.

Pain Mechanism Genes Versus Pain Susceptibility Genes

Using molecular biological techniques, we have started to define (a) genes involved in the mediation of pain (pain mechanism genes) and (b) polymorphic genes that contribute to variation in responses to experimental painful stimuli and pathological conditions (pain susceptibility genes). With rare exceptions, the principal pain genes and their molecular products are conservative. Knockout of a gene is very rare in nature. Most genetic variations identified in pain mechanism genes usually do not alter the sequence of amino acids in peptides or proteins encoded by these genes. The few polymorphisms that do result in amino acid replacement do not as a rule affect the function of the encoded protein. Nociception is essential for survival, and if a variation in a pain mechanism gene alters the function of a nociception-related molecule, the survival rate would probably be low.

Knockout of a pain gene is very rare in nature. Because pain mechanism genes are too well conserved to explain individual variation, research attention has shifted to pain susceptibility genes.

Mutations leading to decreased pain sensitivity occur in well under 1% of the population and lead to frequent injuries and inadvertent self-mutilation, which are incompatible with longevity or transmission to offspring. A single critical change causing a major impairment in nociception, as in hereditary sensory and autonomic neuropathy (HSAN), is rare. Most variations in pain perception appear to be due to summation of many changes causing small differences in multiple genes, which have been difficult to isolate from among the roughly 22,000 protein-encoding human genes identified so far (www.ensembl.org/Homo_sapiens).

Because pain mechanism genes are too well conserved to explain individual variation, research attention has shifted to pain susceptibility genes. Several candidate pain susceptibility genes have been described in mice. For example, the melanocortin-1 receptor gene (Mc1r) affects the magnitude of kappa-opioid analgesia in experimental models of heat pain and ischemic pain, in addition to that gene’s widely known influence upon skin and hair color.

Genetic Influence on Pain Sensitivity in Humans

Given the relative genetic uniformity and psychosocial simplicity of inbred animal strains, along with species differences between animals and humans, genetic influences on pain observed in animals may not readily translate to humans. Inbreeding or knockout technology has helped elucidate the genetics of pain in animals, but is not feasible in humans. One promising approach is to explore associations with pain sensitivity for common genetic variations in humans. This approach is possible because there are 7 million common single-nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of at least 5% across the entire human population; an additional 4 million SNPs exist with an MAF between 1 and 5%. Due to their fairly high frequency and wide distribution, SNPs may serve as genetic markers for assembly of a high-resolution map that can assist in the identification of phenotype-related loci.

In the clinical setting, patient populations may be difficult to assemble into coherent groups of subjects for phenotypic characterization because of variability in the etiology of their pain, their diverse clinical presentations, and inadequacies in objective methods for pain assessment. Experimental pain stimuli that involve distinct mechanisms have been suggested as a means to screen for pain-sensitive or pain-insensitive phenotypes.
Association studies between genetic markers such as SNPs and nociceptive processing are the most frequent genetic studies in humans. Polymorphisms in genes that mediate nociceptive transduction (transient receptor potential subtype 1, TRPV1) or modulate pain processing (OPRD1) predict variations in heat and cold pain sensitivity and also appear to differ in their association with both pain tolerance and pain perception, depending on gender and on the type of applied stimuli. These findings are consistent with evidence suggesting a sex-specific quantitative trait locus on murine chromosome 4 that contains Oprd1, which affects baseline thermal sensitivity and mediates acute, thermal nociception measured using hot-plate testing.

Congenital insensitivity to pain with anhidrosis, now termed hereditary sensory and autonomic neuropathy (HSAN) type IV, is an example of mutational change resulting in a group of peripheral neuropathies characterized by loss of nociception, along with other sensory and autonomic abnormalities. At the molecular-genetic level, three causative SNPs have been identified in NTRK1 for HSAN type IV: a single base deletion causing a frameshift, an A-C transversion causing an RNA splicing error, and a G-C transversion causing a glycine-to-arginine substitution in the third exon. Through linkage analysis of family data, a novel gene causing HSAN type II was recently identified.

Genetic Influence on Painful Clinical Conditions

In the field of migraine genetics, missense mutations in the ATP1A2 gene, encoding an Na+, K+–ATPase, have been identified in a rare form of familial hemiplegic migraine. ATP1A2 maps in chromosome 1q23 and is expressed in the brain, similar to the voltage-gated calcium channel gene, CACNA1A, previously identified as the first recognized hemiplegic migraine gene (FHMI). The hemiplegic migraine phenotype seen with mutations in ATP1A2 and CACNA1A suggests that both genes regulate ion homeostasis, mediating susceptibility migraine’s initiation and pain phases. For the more common and complex forms of migraine, loci on 4q24, 6p12.2-21.1, 11q24, and 14q21.2-22.3 have been identified recently, although no specific candidate genes have yet been reported. In addition, a recent large case-control association study has linked SNPs in the insulin receptor (INSR) gene with migraine. How-
Optimal pain control may be achievable through understanding of molecular-genetic mechanisms, yielding individualized analgesic medications and dose regimens based upon each person’s genetic endowment.

Summary

Pain has diverse etiologies, mechanisms, and temporal characteristics. Investigations of genetic influences upon nociception and pain have revealed genetic polymorphisms underlying specific pain phenotypes. These phenotypes range from subjective responses to experimental pain, to the severity of pain experienced in painful clinical conditions. Research on genes that mediate and control pain may lead to understanding of how to better modulate the function of specific pain pathways. Other DNA sequences located between genes that comprise a large percentage of the human genome may be converted into small RNAs that regulate the expression of pain genes. Optimal pain control may be achievable through understanding of molecular-genetic mechanisms, yielding individualized analgesic medications and dose regimens based upon each person’s genetic endowment.

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Hyungsuk Kim, DDS, PhD
Raymond A. Dionne, DDS, PhD
Pain and Neurosensory Mechanisms Branch
National Institute of Dental and Craniofacial Research
National Institutes of Health
Building 10, Room 1N103
10 Center Drive
Bethesda, MD 20892-1197, USA
Tel: 301-496-0294
Fax: 301-496-1005
Email: rdionne@dir.nidcr.nih.gov

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Tel: 206-547-6409; Fax: 206-547-1703; email: iaspdesk@iasp-pain.org; Internet: www.iasp-pain.org and www.painbooks.org
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