The Pain Protective Haplotype: Introducing the Modern Genetic Test

Chronic pain is a major health problem, affecting 2%–46.5% of adult populations (1, 2). In the United States, common pain conditions account for approximately $61.2 billion in lost workplace time (3). The human sensation of pain is affected by an individual’s past experiences, health status, psychological state, cultural and ethnic backgrounds, pain-coping skills, age, sex, and even pending litigation (4, 5). Emotional variables profoundly influence the perception of painful stimuli (6). In addition, genetic contributions to the experience of pain have increasingly been recognized (7). However, the complexity of pain processing, the multiplicity of influences on it, and the sensation’s inherent subjectivity and protean manifestations make the elucidation of relevant heritable factors extremely challenging.

Neuropathic pain is caused by injury to, or dysfunction of, the peripheral or central nervous system (8). It is particularly troublesome because of its prevalence, severity, chronicity, and resistance to therapy (9). Patients with conditions as diverse as diabetes mellitus, alcoholism, HIV, multiple sclerosis, postherpetic neuralgia, and spinal radiculopathies may suffer from chronic neuropathic pain. Radiculopathic pain is among the most frequently encountered neuropathic pain syndromes (8, 9).

Sciatica associated with intervertebral disc herniation is the most common type of radicular leg pain in adult working populations (10). Although many patients with herniated discs have favorable outcomes with medical therapy, individuals who have ongoing or severe pain often undergo lumbar discectomy. Recently, Tegeder et al. (11) described a putative association between an apparently common haplotype (15.4% of alleles in the study population) of the GTP cyclohydrolase gene (dopa-responsive dystonia, GCH1) and lower degrees of persistent pain after back surgery.

GTP cyclohydrolase is the rate-limiting enzyme in tetrahydrobiopterin (BH4) synthesis. BH4 serves as an essential cofactor in the production of catecholamines, serotonin, and nitric oxide, as well as in phenylalanine metabolism. Inactivating mutations in GCH1 have been shown to cause dopa-responsive dystonia, and an atypical hyperphenylalaninemia characterized by mental retardation, seizures, hyperthermia, and abnormalities of muscle tone (12). Tegeder et al. (11) postulate a relationship between the pain protective haplotype and reduction in the upregulation of GCH1 that normally occurs in response to pain-inducing stimuli. According to this hypothesis, patients carrying the haplotype have lower than expected BH4 synthesis and diminished catecholamine and nitric oxide production.

In this issue of Clinical Chemistry, Lotsch et al. (13) describe the development of sequence-based single nucleotide polymorphism (SNP) identification assays for the detection of the pain-protective haplotype. The authors performed discriminant analysis, together with in silico haplotyping using the Bayesian algorithm PHASE, to decrease the number of SNPs needed to identify the haplotype from 15 to ≤3. This work greatly facilitates its laboratory detection.

A simple, inexpensive assay to detect the pain-protective haplotype, whether using Pyrosequencing or another SNP detection method, has obvious utility in research settings. At some point, such an assay may form the basis of a useful clinical diagnostic test. This latter prospect captures the central dilemma presented by the recent flurry of literature reporting on possible genotype-phenotype associations with yet undetermined medical relevance. Tools and techniques that allow for the quick and easy design, validation, and implementation of DNA-based tests are now available. However, the acquisition of knowledge about the clinical significance and utility of genetic information is laborious, and is proceeding far more slowly than are technical advances in molecular diagnostics.

The report of the discovery of a pain-protective haplotype is fascinating and potentially groundbreaking, but questions about the underlying research remain. The pain-protective haplotype was identified by haplotyping enrollees in the Maine Lumbar Spine Study (MLSS) (14, 15). This outcomes study compared medical and surgical treatment for sciatica associated with low back pain. It was organized to address geographically related variations in the rate of back surgery, a likely reflection of professional uncertainty about the relative benefits of surgical and nonsurgical treatment. The MLSS was nonrandomized and observational. Its enrollment percentage was low. Consequently, potential biases in patient recruitment are of concern. In addition, enrollment was based on sciatica symptoms without other neurologic confirmation of nerve injury, and follow-up information was obtained by mailed survey rather than during face-to-face interviews by trained professionals (14, 15).

Low back pain is caused by a combination of neuropathic, skeletal, and myofacial mechanisms. No generally accepted diagnostic criteria exist to isolate its neuropathic components. Outcomes of patients with low back pain and sciatica secondary to disc herniation vary, and knowledge of causative factors is incomplete. In the MLSS, as in other studies, surgical patients tended to display more severe symptoms than those receiving only medical treatment. At 10 years, increased numbers of operative patients reported complete pain relief and greater satisfaction, but surgical treatment did not independently predict improvement in patients’ predominant symptom, whether back pain or sciatica. Other variables such as receipt of workers’ compensation and better physical and mental health status were associated with worse and better outcomes, respectively.

Given the controversy over appropriate management of low back pain/sciatica and the lack of correlation of symptom severity with objective findings, the strong statistical relationship between the haplotype and persis-
tent pain is surprising. This is especially true because the majority of haplotype-positive patients (42 of 46) were heterozygotes, in whom one might expect limited effects. Given the apparent strength of association of the haplotype with pain predisposition, the large number of haplotype-positive patients who underwent an elective surgical procedure for symptomatic relief (46 of 162) is troublesome and unexplained. Moreover, only 4 of the limited number of study participants were homozygotes. Finally, the authors provided insufficient clinical information about the enrollees to allow us to assess potentially confounding variables. This research now awaits confirmation by other investigators.

How do we decide whether and when to transfer the pain-protective haplotype test, and others similar to it, into clinical use? At what point do we have enough data? While achieving a consensus may be difficult, the number of reported genotype-phenotype correlations ensures that we will encounter such conundrums with increasing frequency. Comprehensive data collection often takes years. In the meantime, our clinical colleagues are eager to make use of information that may help them better care for their patients.

The issues that must be addressed before the introduction of DNA-based assays do not necessarily differ in principle from those associated with other diagnostic testing. However, it is the volume of novel findings arising from the abundance of genomic research, coupled with widely varying and often indistinct phenotypes, that mandates special attention to the area.

Standard concepts of analytical and clinical sensitivity and specificity, positive and negative predictive values, and test utility are as applicable to assays that detect phenotypically relevant SNPs as they are to routine clinical chemistry tests. In today’s world, analytical sensitivity and specificity of DNA-based testing usually approach 100%. Clinical sensitivity and specificity are much harder to assess, particularly when considering amorphous phenotypes affected by many associated variables. Therefore, we must first establish through rigorously performed prospective validation studies that reported associations are indeed real.

Even if a proposed correlation has been confirmed, we must ask ourselves whether an assay provides sufficient information to improve the care of our patients. Will it help direct the workup or management of a clinical problem? Does it aid in identifying candidates for specific medications. Yet, there remains a paucity of specific data that instructs us on how to actually apply this knowledge in clinical practice. Moreover, there is little demonstration that acquisition of such information positively impacts patient outcomes.

Confirmation of the existence of the pain-protective haplotype by other investigators, assuming it will occur, will be insufficient to inform us of ways to properly use the resulting information. The era in which we can rapidly design and analytically validate SNP detection assays is here. The responsibility will increasingly be on us to ensure that the clinical utility of these tests, and guidelines for their appropriate use, are established before their unrestricted introduction into clinical practice.

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References