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An observational study of the impact of genetic testing for pain perception in the clinical management of chronic non-cancer pain

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ABSTRACT

Objective: Pain levels are a key metric in clinical care. However, the assessment of pain is limited to basic questionnaires and physician interpretation, which yield subjective data. Genetic markers of pain sensitivity, such as single nucleotide polymorphisms in the catechol-O-methyltransferase gene, have been shown to be associated with pain perception and have been used to provide objective information about a patient's pain. The goal of this study was to determine if physician treatment adjustments based on genetic tests of pain perception resulted in improved outcomes for patients.

Material and methods: A prospective, longitudinal study was conducted with 134 chronic non-cancer pain patients genotyped for pain perception-related catechol-O-methyltransferase haplotypes. Physicians were provided with patients' results and asked to document 1) their assessment of benefit of the genetic test; 2) treatment changes made based on the genetic test; and 3) patient clinical responses to changes implemented.

Results: Based on genetic testing results, physicians adjusted treatment plans for 40% of patients. When medication changes were made based on genetic testing results, 72% of patients showed improvement in clinical status. When non-pharmacological actions were performed, 69% of physicians felt their patients' clinical status improved. Moreover, physicians believed the genetic test results were consistent with patient pain levels in 85% of cases.

Conclusions: These results demonstrate that providing personalized medicine with genetic information related to pain perception affected physician clinical decision-making for a substantial proportion of patients in this study, and that the availability and utilization of this information was a contributing factor in clinical improvement.

1. Introduction

The perception of pain is a complex neuropsychosocial phenomenon that is notoriously difficult to measure objectively. An interplay of various factors – genetic, physiological, socioeconomic, geographic, stress, gender – contribute to the manner in which an individual both perceives and tolerates different types of pain. The subjective nature of pain perception is commonly measured in clinical care: patients are asked to rate their pain using a pain rating scale (e.g. Numeric Rating Scale or Visual Analog Scale), or questionnaire, such as the Brief Pain Inventory (Keller et al., 2004) or the McGill Pain Questionnaire (Grieve et al., 2016; Thimineur et al., 2004). These scales and questionnaires yield important but subjective data, and their validity is contingent upon accuracy of the patient's answers. Because a patient's perception of pain is a critical factor for clinicians to consider when prescribing treatments, the addition of objective information is essential to guide clinical decisions and may ultimately lead to better outcomes.

The evaluation of genetic variation is one such objective measurement that has been shown to play a part in pain perception (Belfer et al., 2015; Diatchenko et al., 2013, 2006, 2005; Slade et al., 2015; Tan et al., 2015; Wang et al., 2015). For example, a single

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nucleotide polymorphism (SNP) of catechol-O-methyltransferase (COMT), an enzyme that degrades catecholamines such as epinephrine, norepinephrine, and dopamine, was shown to modulate pain perception (Zubieta et al., 2003) by leading to a 3- to 4-fold reduction of COMT activity (Lachman et al., 1996; Lotta et al., 1995; Weinshilboum, 2006). Later, Diatchenko et al. (2005). identified 3 common COMT haplotypes composed of several SNPs in this gene that are associated with up to a 20-fold difference in COMT activity. Lower COMT enzymatic activity is correlated with higher sensitivity to painful stimuli and vice versa (Diatchenko et al., 2006).

COMT SNP variants have been examined in dozens of independent association studies of human pain (Andersen and Skorpen, 2009) and have been shown to be associated with several different pain conditions including musculoskeletal, orofacial, and post-surgical pain. Specifically, COMT variants are associated with altered cortical pain processing (Vossen et al., 2010), increased pain intensity (Jacobsen et al., 2012), and less favorable treatment outcomes (Dai et al., 2010; Jacobsen et al., 2010; Omair et al., 2012) in lower back pain; and interaction with orthodontic treatment (Slade et al., 2008), reduced efficacy of propranolol treatment (Tchivileva et al., 2010), and experimental pain sensitivity in temporomandibular joint dysfunction (Diatchenko et al., 2005). Several findings have also been reported for COMT variant associations with fibromyalgia: namely, increased pain level during elevated pain attention (Finan et al., 2011), thermal and pressure pain sensitivity (Martínez-Jauand et al., 2013), increased number of tender points (Cohen et al., 2009), and pain and positive affect interaction (Finan et al., 2010), fatigue, sleep disturbance, morning stiffness, and disability (Barbosa et al., 2012; Vargas-Alarcón et al., 2007).

Interestingly, COMT genetic changes have also been associated with pain catastrophizing (Finan et al., 2011) and psychological distress (Desmeules et al., 2012). Psychological traits that influence the perception of pain may predispose some individuals to exhibit pain disorders more severely than others, despite having similar prognoses or other physical similarities (Fernández-de-las-Peñas et al., 2013). Evidence that COMT-dependent pain is mediated by β-adrenergic receptors (Kline et al., 2015) has indicated therapies designed to target cognitive-affective behaviors – such as Cognitive Behavioral Therapy (CBT) (Carroll et al., 2015) – can be effective in modulating biological and learning processes relevant to symptom relief (Lonsdorf et al., 2010). Moreover, COMT-dependent pain disorders have shown promising response to β-adrenergic receptor antagonists, such as propranolol (Tchivileva et al., 2010), in peripheral, musculoskeletal pain. COMT modulation of catecholamines may also explain the analgesic effects of antidepressants versus opioids in pain management (Segall et al., 2012).

Despite the increasing evidence that the genetic component of pain is substantial (Nielsen et al., 2008; Norbury et al., 2007), genetic testing is not routine in clinical care. Therefore, this study was conducted in collaboration with physicians that currently use genetic testing to guide clinical decisions. The primary goals of this study were to evaluate how physicians use objective, genetic information related to pain perception in the clinical setting, and to evaluate patients' responses to treatment modifications when they occur. A secondary goal was to determine whether genetic predictions of pain perception were consistent with patients' self-reported pain.

2. Material and methods

The data was collected in a prospective, longitudinal study that took place from April 30, 2015 until November 17, 2015. The study protocols 1JAN15-14CR and 1JAN15-20CR were reviewed, approved, and overseen by Solutions IRB, an institutional review board licensed by the U.S. Department of Health and Human Services, Office for Human Research Protections. the investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.1. Study population

Subjects enrolled in the study were pain patients ≥18 years of age that were seen by a physician at clinical research sites across the United States and received the Pain Perception genetic profile. Written consent was obtained from all subjects. Although many subjects in this prospective study received multiple genetic tests, only those subjects that received the Pain Perception genetic profile exclusively (n = 155) – a panel test evaluating the genetic component of pain perception based on COMT haplotypes – were included in this analysis to ensure that patient outcomes and clinician actions were solely due to the Pain Perception genetic test. Of the 155 subjects who received the genetic test, 134 had reportable results. The remaining 21 were excluded from this study due to insufficient DNA samples or due to the presence of rare COMT haplotypes that have thus far not been associated with a particular pain phenotype.

Per protocol, exclusion criteria were significant diminished mental capacity, recent febrile illness that precludes or delays participation by more than 1 month, pregnancy or lactation, incomplete gene report, invalid Pain Perception test result, participation in a clinical study that may interfere with participation in this study, and anything that would place the individual at increased risk or preclude full compliance.

2.2. Data collection

Each subject's medical history was reviewed to determine eligibility based on inclusion and exclusion criteria. After enrollment, demographic information was obtained from patient questionnaires and medical records. Buccal swabs were performed in order to obtain genetic samples. Once genotyping results were available, physicians reviewed the results and completed an evaluation form (Fig. 1). The evaluation form was used to document the physician's assessment of the validity and utility of the genetic tests, and also track any changes made to a patient's treatment.

An electronic questionnaire was also employed in February 2016 to subsequently survey a larger group of physicians (n = 95) on a national scale regarding their use and relative efficacy of implementing non-pharmacological treatments based on genetic testing results during the period of October 1 – December 31, 2015. These physicians evaluated 4,541 patients in total during this time period.

2.3. Genotyping

Two buccal swab specimens were obtained from each subject and transported to Proove Medical Laboratories, Irvine, CA, USA. Genomic DNA was isolated from one swab using a proprietary DNA isolation technique and DNA isolation kit (Macherey Nagel GmbH & Co, KG, Germany), according to the manufacturer's instructions. COMT SNPs rs6269, rs4633, rs4818, and rs4680 were genotyped using Taqman® SNP Genotyping Assays (Thermo Fisher Scientific, Carlsbad, CA, USA). For each patient, pain perception haplotypes were calculated and classified accordingly to Diatchenko et al. (2006). The following are the three major COMT haplotypes constructed from SNPs rs6269, rs4633, rs4818, and rs4680: low pain perception – G_C_G_G, moderate pain perception – A_T_C_A, and high pain perception – A_C_C_G. A proprietary algorithm was used to score diplotypes in combination of all represented COMT haplotypes in patients. The resulting scores ranged from 1 to 5, where a