Original Article

Pain, Genes, and Function in the Post–Hip Fracture Period

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Abstract:

Post–hip fracture generalized pain can lead to a progressive decline in function and greater disability. The purpose of this study was to explore the factors that influence pain among older adults post–hip fracture, including genetic variability, and evaluate whether pain directly or indirectly influenced upper and lower extremity function. This was a secondary data analysis using data from the first 200 participants in a Baltimore Hip Study (BHS), BHS-7. Assessments were done at 2 months post–hip fracture and included age, sex, marital status, education, cognitive status, comorbidities, body mass index (BMI), upper and lower extremity function, single nucleotide polymorphisms (SNPs) from 10 candidate genes, and total areas of pain and pain intensity. Model testing was done using the AMOS statistical program. The full sample included 172 participants with an average age of 81. Fifty percent were female and the majority was Caucasian (93%). Model testing was done on 144 individuals who completed 2 month surveys. Across all models, age, cognition, and BMI were significantly associated with total areas of pain. Thirty SNPs from five genes (*BDNF, FKBP5, NTRK2, NTRK3,* and *OXTR*) were associated with areas of pain and/or pain intensity. Together, age, cognition, BMI, and the SNP from one of the five genes explained 25% of total areas of pain and 15% of pain intensity. Only age and cognition were significantly associated with lower extremity function, and only cognition was significantly associated with upper extremity function. The full model was partially supported in this study. Our genetic findings related to pain expand prior reports related to *BDNF* and *NTRK2*.

BACKGROUND

Hip fractures commonly occur among older adults, with more than 1.5 million occurring each year worldwide (Cheng et al., 2011). Fewer than half of

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individuals who experience a hip fracture return to prefracture physical function (Magaziner et al., 2003). The return to prefracture physical function is influenced by many factors, including cognitive status, type of surgical interventions, age, other comorbid conditions, and course following surgery (Ariza-Vega, Jiménez-Moleón, & Tange Kristensen, 2014; Beaupre, Jones, Johnston, Wilson, & Majumdar, 2012). In addition, pain has been associated with physical disability (Eggermont et al., 2014) and sedentary behavior (Stubbs et al., 2013). In the post–hip fracture period, the presence of generalized pain can lead to a progressive decline in function and greater disability (Jensen, Moore, Bockow, Ehde, & Engel, 2011). The relationship between pain and function also is influenced by the anatomical location of the pain, the intensity of the pain, and whether there are multiple sources or sites of pain (Eggermont et al., 2014; Yagci, Duymaz, & Cavlak, 2014). It has been noted repeatedly that chronic pain in multiple musculoskeletal locations increases the risk of future decline in mobility and function (Eggermont et al., 2014; Fowler-Brown, Wee, Marcantonio, Ngo, & Leveille, 2013).

Age-related changes in the structure, function, and chemistry of the nervous system may alter the perception of pain. These changes include a reduction of myelinated and unmyelinated fibers and a slowing of nerve conduction (Verdú, Ceballos, Vilches, & Navarro, 2000), a reduction in the functional integrity of sensory neurons that impact pain (Khalil, Ralevic, Bassirat, Dusting, & Helme, 1994), changes in brain volume in the prefrontal cortex and hippocampus that further influence pain perception (Farrell, 2012), and reduced functioning of endogenous pain modulatory mechanisms with regard to dopaminergic neurons in the basal ganglia (Cole, Farrell, Gibson, & Egan, 2010). Generally the cumulative effect of these changes and clinical findings suggests that with age there is an increased threshold and decreased tolerance for pain (Gibson & Farrell, 2004).

There is evidence to suggest that single nucleotide polymorphisms (SNPs) in multiple genes influence pain perception and interpretation (Table 1). SNPs are variations in a single DNA building block (A, T, C, G), called a nucleotide. Genetic influences on pain contribute to the modulation of pain in both the central nervous system (CNS) and in the periphery; SNPs in genes that participate in synaptic plasticity or the activation of spinal microglia have been associated with pain. Genetic variation also can influence nerve conduction and synaptic transmission, which could lead to altered pain sensation. To date, candidate gene analyses in pain research have focused mainly on 10 genes that were identified either in animal models or humans as associated with pain (Belfer et al., 2013; Di Lorenzo et al., 2014; Renn, Leitch, & Dorsey, 2009). These genes include *BDNF, FKBP5, NTRK2, NTRK3, OXTR, NTRK1, DRD4, SLC6A4, COMT* and *MAOA*. Table 1 provides a detailed description of these genes and their mechanisms of action. The candidate genes are believed to influence pain on the basis of their encoded proteins being involved in pathways that are logically expected to affect pain. Details of how specific SNPs from these genes influence pain are not yet established. Replication of the associations tested between the genes, associated SNPs, and pain has not been consistent across studies and patient populations. Moreover, there have been no prior studies examining genetic factors that are associated with pain and subsequent function among older adults post–hip fracture.

The purpose of this study was to explore the factors that influence pain among older adults post–hip fracture and whether pain directly or indirectly influenced upper and lower extremity function. As shown in Figure 1, it was hypothesized that relevant demographic and descriptive factors (i.e., those that were significantly correlated based on bivariate correlations with total areas of pain, total pain intensity, or upper or lower extremity function) and genetic variability would be associated with total areas of pain and total pain intensity and all of these variables would directly and indirectly be associated with upper and lower extremity function at 2 months post–hip fracture.

METHODS

Design and Sample

This was a secondary data analysis using data from the first 200 participants in a Baltimore Hip Study (BHS), BHS-7. The primary focus of the parent study, BHS-7, was to compare men and women, frequency matched (1:1) on calendar time of fracture and hospital, regarding consequences, recovery trajectories, and their predictors post–hip fracture. Individuals were eligible if they were living in the community prior to fracture, aged 65 years or older, and admitted for surgical repair of a hip fracture to one of the eight study hospitals. Individuals were excluded if they had a pathologic fracture, were not ambulating unaided by another person prior to the fracture, did not speak English, resided more than 70 miles from the hospital, weighed more than 300 pounds or had hardware in the contralateral hip. To obtain the sample of 200 participants, 911 hip fracture patients were screened, 517 (57%) were eligible (222 men and 295 women), and 105 men and 107 women consented to participate. Twenty-three participants were withdrawn (eight participants failed to provide baseline or 2-month data; six