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Genetic Factors Explain the Association Between Pain Catastrophizing and Chronic Widespread Pain

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Abstract: **This study aimed to clarify whether there are shared genetic and/or environmental factors explaining the strong link between pain catastrophizing (PC) and chronic widespread pain (CWP). Data were available for N = 1,109 female twins from TwinsUK. Information on self-reported CWP and PC was subject to variance component twin analysis. Heritabilities were 40% for PC and 77% for CWP. The genetic correlation between PC and CWP was .40%, whereas no evidence of an environmental correlation could be detected (.0). According to the best-fitting additive genetic, non-shared environmental (AE) Cholesky model, an additive genetic factor loading on PC as well as CWP, as well as an additive genetic factor loading on CWP alone was found. In terms of environmental influences, 2 individual environmental factors could be identified, loading separately on PC and CWP. Overall, the results add to the knowledge on the nature of CWP and the basis of its close relationship with PC by suggesting a shared genetic etiological structure. The findings highlight a potential avenue for future research and may provide useful insight for the clinical management of pain and pain coping.**

Perspective: ***Results suggest a shared genetic etiological structure between CWP and PC with no shared influence of environmental factors. Clinicians should be aware of this biological link within the context of clinical management of pain and pain coping.***

Key words: *Pain catastrophizing, chronic widespread pain, twins, genetics, etiology.*

The tridimensional concept of pain catastrophizing (PC) consists of helplessness, magnification, and rumination and, as a whole, describes a set of negative emotional and cognitive responses to actual or anticipated pain.[26] Research findings on the origins of PC point toward a multifactorial etiology in which psychological factors (eg, neuroticism, negative affectivity, specific sickness belief about the origins of pain), genetic factors (eg, heritability of 37% for PC), as well as cognitive-behavioral frameworks (eg, operant learning and social learning models) give rise to the tendency to catastrophize pain sensations.[7,12,15,23,26-28]

PC is thought to result in a set of negative cognitive-affective schemata, which leaves patients exaggerating the seriousness of pain sensations by making them unable to divert attention away from pain.[3,24] PC has now been established as a robust predictor for a range of adverse pain outcomes, including heightened pain intensity and higher levels of psychological distress and depressive symptoms across a variety of pain conditions (including, eg, chronic widespread pain [CWP]) but also in pain-free individuals.[6,11,13,26,28] Chronic widespread musculoskeletal pain is the cardinal symptom of fibromyalgia, which, according to the definition of the

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American College of Rheumatology describes the presence of pain in the upper and lower quadrants and the right and left sides of the body, as well as axial pain as a constant feature.[31] With a population prevalence of 10 to 15% and high frequency of comorbid conditions such as depression and anxiety, CWP not only leads to profound individual suffering but is also associated with high health care utilization and costs.[4] Recent research attempts to disentangle the pathoetiology have provided consistent evidence for a genetic influence on CWP, with heritability estimates of up to 58%.[2,10] In addition, numerous recent studies have shown strong correlations between PC and CWP/fibromyalgia, albeit the source of the covariation remains unknown.[6,8] By examining the genetic and environmental influences on the shared association between PC and CWP, multivariate genetic analyses using twins can help to clarify some of the mechanisms that underpin the relationship. One possibility is that PC and CWP share similar genetic factors that account for their co-occurrence. We have previously shown that CWP shares a high genetic correlation with depression and a range of other psychoaffective correlates including anxiety sensitivity.[2] Apart from showing a strong correlation with anxiety sensitivity, PC is also associated with a range of other traits and behaviors, such as neuroticism or fear of pain.[7,9] Thus, the genetic influence on PC may be distinct from the influence on CWP and instead, environmental influences such as social learning or life events, may explain the relationship between PC and CWP.

The aim of the current study, therefore, was to determine the genetic and environmental influence on the observed association between PC and CWP. Using a large sample of female twins, we investigated the phenotypic correlation between PC and CWP and then explored whether and to what extent genetic and environmental factors underlie these phenotypes.

Methods

Participants

Subjects in this study were monozygotic (MZ) and dizygotic (DZ) female twins enlisted in the TwinsUK registry.[17] Twins in the registry have been recruited through national media campaigns and from other twin registers since 1992. The twins have undergone extensive clinical investigations and have been shown to be comparable with age-matched singletons in terms of lifestyle characteristics and disease prevalence, including CWP.[1,2] Zygosity was established by using standardized questions about physical similarity that have >95% accuracy when judged against genotyping and was further confirmed by multiplex DNA genotyping and more recently by genetic association markers on DNA obtained from venous blood samples. Data collection using self-reported questionnaire was performed in 2 waves. Information on CWP was collected in 2013 and self-reported PC was assessed in 2016. Excluded from the study were twins having conditions with known causes of somatic pain such as fracture, cancer, rheumatoid arthritis, and defined causes of neuropathic pain. Furthermore, only female twins aged older than 18 years, of Caucasian ethnicity, and for which zygosity had previously been established, were included in the sample. A total of N = 1,109 participants had matching CWP and PC data were subsequently included in this study, consisting of 195 full MZ pairs, 121 full DZ pairs, and 477 individuals whose cotwin did not participate. Twin pairs in which 1 twin had data but the cotwin did not have data (treated as missing values) were also included in the study. Previous simulation studies have shown that this full information approach in which all the available data are used is more powerful than the usual twin pair approach.[5] The study was approved by the St. Thomas' Hospital research ethics committee and all twins provided written informed consent.

Materials

Similar to numerous previous studies and in accordance with the American College of Rheumatology definition, information on CWP was assessed using the musculoskeletal pain questions (not including the fatigue ones) from the London Fibromyalgia Epidemiology Symptom Screening Questionnaire (LFESSQ).[9,19,30] This 6-item self-report questionnaire consists of 4 items relating to widespread pain (and 2 items relating to fatigue). According to the 4 pain items, pain left and right of the body and above and below the diaphragm lasting at least 7 days in the previous 3 months were considered positive for CWP status. To be classified as having CWP, participants had to respond "yes" to all 4 pain items with either a right- as well as left-side positive response or a positive response for pain at both sides.

The "Pain Catastrophizing Scale" (PCS) is regarded as the gold standard in assessing PC.[18,25] The 13-item questionnaire asks participants to reflect on past painful experiences and to indicate the degree to which they experienced thoughts or feelings when experiencing pain. Response options are on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (all the time). The scale consists of 3 subscales—rumination, magnification, and helplessness—for each of which a score may be calculated by summing the relevant items, in addition to a total PCS score. The PCS has shown solid psychometric properties and adequate internal consistency (coefficient αs: total PCS = .87, rumination = .87, magnification = .66, and helplessness = .78).[18,25,29] Cronbach α in our study was .94 for total PCS, .89 for helplessness, .74 for magnification, and .92 for rumination.

Statistical Analysis and Twin Modeling

Data handling and all statistical analyses were carried out using Stata software (StataCorp, 2007). Genetic analyses were conducted using the R package "OpenMx" (https://CRAN.R-project.org/package=OpenMx). PC was treated as a continuous trait whereas CWP was coded as a dichotomous variable (0 = no/1 = yes) according to the previously defined LFESSQ score. To check for systematic differences across the study variables in MZ and DZ