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Genetic factors explain the association between pain catastrophizing and chronic widespread pain

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Title Page

**Genetic factors explain the association between pain catastrophizing and chronic
widespread pain**

Running Title: Catastrophizing and chronic widespread pain

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Disclosures

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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 $r_G = 0.40$, while no evidence of an environmental correlation could be detected ($r_E = 0.0$). According to the best-fitting AE Cholesky model, an additive genetic factor (A1) loading on both PC and CWP, as well as an additive genetic factor (A2) loading on CWP alone was found. In terms of environmental influences, two 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 aetiological 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 aetiological structure between chronic widespread pain and pain catastrophizing 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, aetiology

Introduction

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 towards a multifactorial aetiology in which psychological factors (e.g., neuroticism, negative affectivity, specific sickness belief about the origins of pain), genetic factors (e.g., heritability of 37% for PC), as well as cognitive-behavioural frameworks (e.g., operant learning and social learning models) give rise to the tendency to catastrophize pain sensations [8,15,23,26,27,28].

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 [4,24]. 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, e.g., chronic widespread pain) but also in pain-free individuals [7,11,13,26,28]. Chronic widespread musculoskeletal pain (CWP) is the cardinal symptom of fibromyalgia, which according to the definition of the American College of Rheumatology (ACR) 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 [32]. With a population prevalence of 10-15% 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 [5]. Recent research attempts to disentangle the pathoetiology have provided consistent evidence for a genetic influence on CWP, with heritability estimates of up to 58% [3,10]. In addition, numerous recent studies have demonstrated strong correlations between PC and

CWP/Fibromyalgia, albeit the source of the covariation remains unknown [7,9]. 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 psycho-affective correlates including anxiety sensitivity [3]. Apart from showing strong correlation with anxiety sensitivity, PC is also associated with a range of other traits and behaviours, such as neuroticism or fear of pain [2,8]. 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 [1,3]. Zygosity was established by using standardized questions about physical similarity that have over 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 by self-reported questionnaire was performed in two 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 over 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 co-twin did not participate. Twin pairs where one twin had data but the co-twin did not have data (treated as missing values) were also included in the study. Previous simulation studies have shown that this full information approach where all the available data is used is more powerful than the usual twin pair approach [6]. 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 ACR 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) [2,19,31]. This 6-item self-report questionnaire consists of 4 items relating to widespread pain (and 2 items relating to fatigue). According to the four pain items, pain left and right of the body and above and below diaphragm lasting at least 7 days in the previous 3 months were considered positive for CWP status. In order to be classified as having CWP,

participants had to respond “yes” to all four pain items with either both a right- and 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 three 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 alphas: total PCS = 0.87, rumination = 0.87, magnification = 0.66, and helplessness = 0.78) [18,25,29]. Cronbach’s α in our study was 0.94 for total PCS, 0.89 for helplessness, 0.74 for magnification, and 0.92 for rumination.

Statistical analysis and twin modelling

Data handling and all statistical analyses were carried out using Stata software (StataCorp, 2007). Genetic analyses were conducted using the R package “OpenMx”. PC was treated as a continuous trait whilst 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 twins, Mann-Whitney U tests (for continuous measures) and χ^2 tests (for categorical and dichotomous measures) were used. Point-biserial correlation between PCS and CWP was calculated. All tests were two-tailed. For all analyses, a P value less than 0.05 was considered statistically significant unless stated otherwise.

A liability threshold model was used to analyse the dichotomous variable CWP in the twin model. This liability threshold model assumes that cases or diseases measured by categorical responses result from an underlying continuous liability (or risk) which follows a

normal distribution [6,22]. The model assumes that when an individual exceeds a certain threshold, the individual manifests as a case [6]. In our twin model, liability was modelled by a latent variable for which the distribution followed a standard normal distribution [22].

Standard methods of quantitative genetic analysis were used to model latent genetic and environmental influence on the observed covariance of PC and CWP in both MZ and DZ twins. The classical twin design makes use of the fact that MZ twins share identical genotypes (>99.9%) whereas DZ twins share on average 50% of their segregating genes. By contrast, environmental influences that contribute to familial resemblance (shared environment) are assumed to affect MZ and DZ twins equally, meaning that any greater similarity between MZ as compared to DZ twin pairs is attributable to genetic factors [14]. By conducting quantitative genetic model fitting, the observed phenotypic variation can be decomposed into additive (A) and dominant (D) genetic effects, and common (C) and unique environmental (E) effects (which also includes measurement error) [20]. Initial assessment of the components (A, D, C, and E) may suggest non-significant values in C or D component when comparing the full ACE and ADE models with a fully saturated model by likelihood ratio test. The fully saturated model treats the variance-covariance matrix as a free parameter equivalent to the sample variance-covariance matrix. This initial assessment also shows whether the full ACE or ADE model satisfies the twin model assumption that the mean and variance of each observed variable is equal across twin order and zygosity. In a second step, the path coefficients from the components (A, C or D, and E) to the observed phenotypes are removed from the full ACE or ADE model and the deterioration in fit of the various sub-models assessed by likelihood ratio test. For additional evaluation of model parsimony, the Akaike Information Criteria ($AIC = \chi^2 - 2 \text{ df}$) can be considered, which combines the goodness of fit of a model (the discrepancy of expected to observed covariance matrixes) with its simplicity. Lower AIC values indicate a more suitable model.

Genetic modelling was extended to bivariate model fitting to explore quantitatively the phenotypic covariation between PC and CWP and to test whether the same genetic and environmental factors contribute to their covariance [16,20]. For the bivariate analyses, a Cholesky decomposition was considered, in which a basic model includes two independent genetic and environmental factors. The first factor loads on both phenotypes and the second factor loads only on the second phenotype, therefore offering the fullest potential explanation of the data. Similar to the univariate modelling, the lowest AIC is used as an indicator to choose the most parsimonious model in determining the degree of shared genetic and environmental influences. Here we present the correlations from genetic and environment (r_G and r_E , respectively), which describes the degree of overlap in genetic and environment effects on the two phenotypes PC and CWP.

To compare models and obtain standardized path coefficients with 95% confidence intervals (CIs), we performed SEM with full information maximum-likelihood estimation. All observed variables were adjusted for age in the models.

Results

The mean age of the sample was 62.7 years (SD 11.2) and the prevalence of CWP was 17.3%. MZ and DZ twins did not differ in terms of CWP prevalence or levels of PC. However, by chance, DZ twins were older than MZ twins (64.2 vs. 61.4, $p < 0.001$). Pain catastrophizing correlated significantly with CWP ($r = 0.14$; $p < 0.001$). Women with CWP were significantly older and also reported significantly higher levels of PC compared to women without CWP (11.8 vs 7.9, $p < 0.001$ and 66.1 vs 61.9, $p < 0.001$; results not shown). Univariate heritabilities revealed moderate genetic influence on phenotypic variation, with heritabilities of 40% for PC and 77% for CWP. No influence of C or D could be detected on either of the two phenotypes.

Bivariate Twin Modelling

For the bivariate twin modelling, the fully saturated model was compared to the full ACE and the full ADE Cholesky model (Table 1). The Cholesky factorization provides the correlations between the 3 independent genetic and environmental factors (A, C or D, and E) and decomposes the variance and covariance of the two phenotypes into distinct additive genetic and distinct non-shared environmental effects, providing the fullest potential explanation of the data. Based on the AIC value, the ACE Cholesky model provided the best balance between model fit and parsimony, indicating that dominant genetic factors (D) were negligible for the covariance in CWP and PC and could therefore be removed for subsequent analyses (Table 1).

Further modelling indicated that C could be dropped without significant loss in parsimony, resulting in a best-fitting AE Cholesky model (Table 2). According to this model, an additive genetic factor (A1) loading on both PC and CWP, as well as an additive genetic factor (A2) loading on CWP alone could be detected (Figure 1). In terms of environmental influences, two individual environmental factors could be identified loading separately on PCS (E1) and CWP (E2). With 59%, the phenotypic variance in PC explained by E1 was considerably higher than the 23% of variance in CWP explained by E2. The variance explained by additive genetic factors, however, was higher for CWP compared to PC (77% vs. 40%, respectively). The genetic correlation (i.e., overlap in genetic effects between PC and CWP) was $r_G = 0.40$, whereas no evidence of an environmental correlation could be detected ($r_E = 0.0$; results not shown).

Discussion

In the present study we were interested in exploring the phenotypic covariation between pain-related catastrophizing and CWP by disentangling the proportion of shared and non-shared genetic and environmental influences on the two phenotypes. To the best of our knowledge this is the first study of twins to explore the source of phenotypic covariation between PC and CWP.

In accordance with previous studies reporting a robust link between PC and chronic pain, a significant albeit rather weak phenotypic link between PC and CWP could be found in our study [7,26]. While the heritability for PC was rather moderate (40%), CWP showed a significantly higher heritability with an estimate of 77% - indicating that genes contribute to a much larger extent to the phenotypic variance in CWP compared to PC. The moderate heritability of PC is in line with previous study reports and reflects the general tendencies of modest heritabilities commonly observed for human psycho-behavioural traits whereas anatomical/biological phenotypes such as CWP tend to show stronger genetic influence [2,27]. However, it should be borne in mind that such heritability estimates have been found to offer no guide to the likelihood of identifying the genetic variants responsible, or their effect size. Rather, the interest lies in identifying shared genetic variants and in providing a framework to conceptualise better the risk factors for CWP.

Bivariate twin analyses revealed the AE Cholesky model to provide the best fit to our data (Fig 1), with the co-occurrence of CWP and PC being best explained by one shared additive genetic factor loading heavily on PC and to a lesser degree on CWP. In addition, a genetic factor unique to CWP and explaining 64% of its variance could be detected (i.e., variances can be calculated by squaring the factor loads in Figure 1). Our bivariate model therefore provides support for previous theoretical and empirical findings on the relationship between CWP and PC by showing that the genetic influence on PC is entirely shared with the genetic influences on CWP [7,11,13,26,28]. This suggests that high levels of PC may

partially account for high levels in CWP. The finding of “a shared” genetic factor does, however, not imply that the genes/risk alleles underlying both phenotypes are identical but that most likely there is a subset of genes/risk alleles that contributes to the underlying factor that may overlap. In other words, PC represents an important dispositional trait that may explain genetic influences on CWP.

The environmental correlation of our phenotypes was zero, indicating no shared environmental aetiology underlying PC and CWP. Instead, two phenotype-specific non-shared environmental factors could be identified, explaining 59% of variance in PC and 23% in CWP, respectively. A likely scenario could be that repeated episodes of pain experiences create a sense of learned helplessness which fuels the negative cognitive-affective schemata eventually creating more PC, while episodes of chronic pain or their severity, instead, might be triggered and aggravated by stressful life events. Also noteworthy is the fact that, according to our model, the environmental influences that influence PC and CWP are comprised of an entirely non-shared nature (i.e. unique environment). In other words, familial factors such as attitudes within families, socioeconomic status, and psychosocial factors shared within the families do not seem to contribute to either PC or CWP, nor to the relationship between them.

In a recent quantitative genetic study of psychological correlates in CWP in TwinsUK, our team found that pain reporting is intimately linked to mood, in particular depression, and that a range of psycho-affective variables (such as emotional instability and intelligence, anxiety sensitivity) share a common genetic basis with CWP [3]. In that study, we found a second genetic factor that was more “clinical” in its expression by loading only on CWP and depression. In addition, and comparable to the present study, an important role for individual experiences such as stressful life events, social learning, coping, etc., in CWP development and maintenance could be postulated. Overall, the results from the previous

research and the present study are analogous as they suggest that the covariation between CWP and its psychobehavioral and affective correlates is of an entirely genetic nature and although environmental factors play a crucial role in all phenotype expression, these factors tend to be unique to the individual traits, therefore they do not contribute to the observed phenotypic covariation.

Limitations

As is common in genetic epidemiology studies, several limitations have to be considered when interpreting the results. Although we used a validated and well established self-report measure of CWP – the LFESSQ – this does not replace a clinical diagnosis of CWP or fibromyalgia and therefore results may not be extrapolated to samples having a clinical diagnosis. Second, information on CWP and PC were collected in two separate assessment waves which were 3 years apart. We were unable to determine how many individuals were still suffering from CWP during the collection of information on PC. The low temporal proximity of the assessment waves might have led to an under- or overestimation of the phenotypic correlation and potentially have biased the results of twin modelling. Although some recent research reports have assessed PC in a situation-specific, dynamic manner, PC has typically been conceptualized as a trait-like or dispositional variable, with the PCS representing a trait measure of PC [21]. Fourth, significant links between depression and CWP, as well as with PC have been previously reported. In this study, however, we were unable to control for depression as a covariate as it resulted in instable models, most likely due to the small subsample for which data on depression was available. Fifth, only female Caucasian twins were included in the study, thus limiting the generalizability of our findings to the male population or to ethnic and racial groups other than Caucasians. Similarly, the mean age of the participants was relatively high, consequently we cannot exclude the fact that

some of them might have suffered from other musculoskeletal disorders, of which osteoarthritis would be the most prevalent. Sixth, the presence of potential gene–environment interactions were not taken into account in this study. Thus, the reported estimates have to be regarded as a first approximation of the relative contributions of genetic and environmental influences. Finally, CWP was measured in a dichotomous manner assuming a standard normal distribution by using the liability threshold model which may have reduced statistical power. Consequently, the association between CWP and PC, and effects of genetic and environmental factors on CWP might have been underestimated.

Conclusion

Overall, our results add to the knowledge on the nature of CWP and the basis of its close relationship with other psycho-affective conditions and behavioural correlates by suggesting a shared genetic-aetiological structure with PC. The findings therefore highlight a potential avenue for future research and provide additional utility for the clinical management of pain and pain coping. For example, early identification of people with abnormal pain coping mechanisms – people for whom rumination, magnification, and helplessness are signs that they cope poorly – might lead to trials of intervention to prevent CWP developing in mid-life. Also, increasing knowledge on the shared influences on PC and CWP offers one further step towards understanding the mechanisms underlying individual differences in these phenotypes. In a next step, identifying which specific environmental experiences and which specific DNA variations are involved may reveal important mechanistic information for both phenotypes as well as potential novel therapeutic targets.

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Table 1 Results of the model comparison between the fully saturated, the full ACE Cholesky, and the full ADE Cholesky modelling. The best fitting model by AIC is the ACE Cholesky model highlighted in bold.

Table 2 Results of the model comparison among the full ACE Cholesky model and the sub-models.

Figure 1. Path diagram of the best fitting AE Cholesky model depicting the sources of covariance between pain catastrophizing and chronic widespread pain. Standardized factor loadings with 95% confidence interval are displayed. Abbreviations: CWP = chronic widespread pain; PCS = Pain Catastrophizing Scale.

Table 1 Results of the model comparison between the fully saturated, the full ACE Cholesky, and the full ADE Cholesky modelling. The best fitting model by AIC is the ACE Cholesky model highlighted in bold.

Model	Differences of log likelihood	Differences of df	P vales of likelihood ratio tests	AIC
The fully saturated model	Reference	Reference	Reference	-361.58
The full ACE Cholesky model	18.99	19	0.46	-380.59
The full ADE Cholesky model	19.77	19	0.40	-379.80

Abbreviations: A = additive genetic factors; C = shared environmental factors; D = dominant genetic factors; E = non-shared environmental factors; AIC = Akaike information criterion; df = degree of freedom.

Table 2 Results of the model comparison among the full ACE Cholesky model and the sub-models.

Model name	Differences of log likelihood	Differences of df	P vales of likelihood ratio tests	AIC
The full ACE Cholesky model	Reference	Reference	Reference	-380.59
The full AE Cholesky model (Model 1 without all C factors)	0.79	3	0.85	-385.80
The best model (Model 2 without a path from E1 to CWP)	1.02	4	0.91	-387.58

Abbreviations: A = additive genetic factors; C = shared environmental factors; E = non-shared environmental factors; AIC = Akaike information criterion; df = degree of freedom.

Highlights

- Genes explain approximately 40% of the variance in pain catastrophizing (PC)
- The correlation between PC and chronic widespread pain (CWP) was 0.14
- PC and CWP share a genetic aetiology
- The environmental factors influencing PC and CWP are distinct