Neuropathic pain as part of chronic widespread pain: environmental and genetic influences
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Abstract
Chronic widespread pain (CWP) has complex aetiology and forms part of the fibromyalgia syndrome. Recent evidence suggests a higher frequency of neuropathic pain features in those with CWP than previously thought. The aim of this study was to determine the prevalence of neuropathic pain features in individuals with CWP and to estimate the influence of genetic and environmental factors on neuropathic pain in CWP. Validated questionnaires (the London Fibromyalgia Screening Study questionnaire and PainDETECT questionnaire) were used to classify twins as having CWP and neuropathic pain, respectively. The prevalence of CWP was 14.7% \((n = 4324)\), and of the 1357 twins invited to complete neuropathic pain screening, 15.9% of those having CWP demonstrated features of neuropathic pain. Neuropathic pain was found to be heritable \((A = 37\%; 95\%\) confidence interval \[CI\]: 23%-50%) with unique environmental factors accounting for 63\% \((95\%\) CI: 49%-79\%) of the variance. Heritability of neuropathic pain and CWP were found to be correlated, 0.54 \((95\%\) CI: 0.42-0.66). Increasing age, raised body mass index, female gender, and smoking were all risk factors for neuropathic pain \((P < 0.05)\), and CWP \((P < 0.05)\). High socioeconomic status showed negative correlation with neuropathic pain \((P = 0.003)\) and CWP \((P = 0.001)\). Bivariate analysis of the 2 pain traits revealed that genetic predisposition to neuropathic pain is shared with that for CWP. This is the first study to provide formal heritability estimates for neuropathic pain in CWP. The findings suggest that at least some of the genetic factors underlying the development of neuropathic pain and CWP are the same.

Keywords: Chronic widespread pain, Neuropathic pain, Genetic, Fibromyalgia, Twin

Introduction
Chronic widespread pain (CWP) is a poorly understood complex condition with high prevalence ranging between 5% and 17% in the general population \(^{21,25}\) and is characterised by repeated or continuous musculoskeletal pain lasting more than 3 months. \(^{36}\) The American College of Rheumatology defines CWP as pain in at least 2 contralateral body quadrants (right and left sides of the body, above and below the waist) and in the axial skeleton. \(^{40}\) Diagnostic criteria for screening the general population for CWP have been developed. \(^{37}\) Chronic widespread pain is recognised as part of the affective spectrum disorders; there is increased prevalence of conditions such as irritable bowel syndrome \(^{17}\) and dry eye disease \(^{34}\) in people with CWP. Our recent work in TwinsUK suggests the presence of a shared genetic factor underlying such chronic pain syndromes. \(^{35}\) Furthermore, genetic factors are also thought to underlie the co-occurrence of CWP with anxiety and depression. \(^{17}\) Heritability estimates show that genetic and shared environmental influences account for approximately 50% of the variance in CWP. \(^{16}\) It has been suggested that neuropathic features in chronic pain may be more prevalent in the general population than previously thought. \(^{11}\)

Estimates for the prevalence of neuropathic pain (NP) in the population are 6% to 8% \(^{31}\); NP is experienced by 16% to 26% of patients with diabetes (diabetic neuropathy) \(^{15}\) and 8% to 19% of patients with herpes zoster virus infection (postherpetic neuralgia). \(^{30}\) In this study, we ascertained the prevalence of NP as part of CWP in TwinsUK (part of the NIHR BRC BioResource). Subjects have been shown to be similar to a singleton cohort for many traits and lifestyle factors \(^{22}\) and have been included in a number of chronic pain studies previously \(^{23,38,39}\) including a genome-wide association meta-analysis \(^{28}\) and exome sequencing in experimental pain sensitivity. \(^{38}\) In addition to defining the prevalence of NP in CWP, we estimated, using bivariate analysis, the genetic and environmental contribution shared between the traits. Similar genetic predisposition to CWP and NP might suggest similar underlying pathogenic mechanisms.

Methods
TwinsUK is the largest registry of monozygotic and dizygotic twins in the United Kingdom. It contains extensive genotype and phenotype data obtained at clinical visits and by mailed and online questionnaires. Twin volunteers having internet access completed a web-based TwinsUK pain questionnaire in 2013 to 2014, while the remainder received a paper questionnaire. A two-stage approach to questionnaires was adopted to minimise postage costs to those volunteers not having internet access.
First, a screening questionnaire was sent to 8465 volunteers of TwinsUK asking about symptoms of CWP. Any subject who replied "yes" to the question "In the past 3 months, have you had pain in your muscles, bones, and joints lasting at least 1 week?" (adapted from the London Fibromyalgia Epidemiology Screening [LFES] Study Questionnaire) was sent a further, more detailed, paper questionnaire. All the other active volunteers in the TwinsUK database received similar questionnaires by e-mail. Both e-mail and paper versions contained the adapted LFES questions followed by a modified version of the PainDETECT questionnaire. A single reminder was sent to nonresponders. Participants were unaware of the hypothesis being tested, as the first question was part of a much larger set of wide-ranging questions. Ethical approval for the study had been obtained from St Thomas’ Hospital Research Ethics Committee, and consent was obtained from all participants.

**Questionnaire and phenotype definitions**

The modified version of the LFES questionnaire contained 4 questions about musculoskeletal pain lasting over a week in the upper limbs, lower limbs, and thorax, neck or back, and 2 further questions about fatigue and its chronicity and severity. A diagnosis of CWP is made if respondents answer positively to all 4 pain items and positively to either both right- and left-side response or one both sides. A diagnosis of fibromyalgia is made if respondents answer positively for CWP as above and for the 2 fatigue questions. Sensitivity and specificity of the LFES pain criteria have been reported as 100% and 53%, respectively, with a test–retest reliability of 100% among those who screen negative and a positive predictive value of 57%. To generate a more accurate diagnosis for chronicity, participants were also asked whether the pain had lasted over 3 months. We considered the subjects to have CWP if they scored positive for the LFES questions and if pain lasted more than 3 months. The PainDETECT questions explored the nature of the pain and resulted in scores between −1 and 38. For clinical purposes, a score ≤12 indicates that NP is unlikely, whereas a score ≥19 indicates that NP is likely. Scores of 13 to 18 are ambiguous for the likelihood of NP. These scores were summarised for demographic description as a categorical NP variable taking values of 0, 1, and 2.

**Lifestyle factors**

Self-reported smoking data have been collected regularly since the TwinsUK study was set up in 1992. Participants were classified as nonsmokers, ex-smokers, or current smokers according to the most recent information available. Body mass index (BMI) was calculated using the measured height and weight of participants on clinical visit to the Department of Twin Research at St Thomas’ Hospital or using self-reported values when clinical visit data were not available. Socioeconomic status (SES) was measured using the Index of Multiple Deprivation based on the postcodes of the participants.

**Statistical analyses**

Statistical analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX), OpenMX 3.4 for the preliminary analyses and univariate heritability estimations and MAN 22 (http://www.tau.ac.il/~idak/hid_MAN.htm) were used for the bivariate analysis. The latter has a model formulation that incorporates Falconer’s polygenic threshold concept for the inheritance of dichotomous traits, allowing a bivariate quasi-variance component analysis where one variable is normally distributed and the other is dichotomous.

The association between CWP (as a dichotomous variable) and NP (PainDETECT final scores, as a continuous discrete variable) with covariates of interest was examined initially in a series of univariable regression models and next in a multivariable model that included all lifestyle factors (BMI, SES, and smoking) as well as age, sex, and as covariates. In both models, twin-relatedness was taken into account. The PainDETECT final scores are left-truncated; therefore, the associations were estimated using a truncated regression model.

For heritability estimates, the PainDETECT final scores were analysed both untransformed and transformed by quantile normalisation. The heritabilities were also estimated using the residuals from the truncated distribution and the residuals from the quantile-normalised distribution, both adjusted for age, BMI, and sex. As a high phenotypic correlation was observed between CWP and NP, a bivariate variance component genetic analysis was performed to determine what, if any, was the genetic correlation between the 2 pain states.

**Results**

Overall, 8465 twins received at least 1 questionnaire, with a response rate of 51.1%. Twin (n = 4324) volunteers replied to the LFESS section present in both questionnaires, and 1357 responded to the PainDETECT questions. In this study, 3879 subjects (89.7%) were female and 445 (10.3%) were male, with age ranging from 16 to 92 years. The overall prevalence of CWP in this sample was 14.7% (and for fibromyalgia, prevalence was 6.7%). The demographics of the cohort are detailed in Table 1. Twins having CWP were, on average, older (P < 0.001), more likely female (P < 0.001), heavier (P < 0.001), and also more likely to be a smoker (P = 0.001). In addition, they were of lower SES (P = 0.001).

Considering the PainDETECT questionnaire, relative to the entire sample, 3% of respondents showed a high likelihood of NP.

| Variable | CWP | Controls | Cases | P |
|----------|-----|----------|-------|---|
|          | n (%) | Mean (SD) | n (%) | Mean (SD) |
| Age, years | 3888 (85.3) | 58.5 (14.4) | 626 (14.7) | 64.2 (11.9) | <0.001 |
| Sex | | | | | <0.001 |
| Female 3275 (75.7) | 604 (14.0) | | | |
| Male 426 (9.9) | 19 (0.4) | | | |
| BMI, kg/m² | 3127 (84.8) | 25.8 (4.8) | 562 (15.2) | 27.9 (5.5) | <0.001 |
| Smoking | 3597 (85.2) | 627 (14.8) | | | 0.001 |
| Never 2087 (47.4) | 313 (7.4) | | | |
| Ever 1275 (30.2) | 259 (6.1) | | | |
| Current 235 (5.6) | 55 (1.3) | | | |
| SES | 2622 (83.8) | 545 (16.2) | | | 0.001 |
| 1 168 (5.0) | 56 (1.7) | | | |
| 2 338 (10.0) | 76 (2.3) | | | |
| 3 572 (17.0) | 94 (2.8) | | | |
| 4 744 (22.1) | 147 (4.4) | | | |
| 5 1000 (29.7) | 172 (6.1) | | | |

Summary of demographic and phenotypic measures of the 4324 respondents who completed the CWP questionnaires, separated by cases and controls according to the LFES definition. Cases and controls were compared by a χ² test (comparing the affected (1) and unaffected individuals (0), ANOVA (comparing the different levels of effects [0, 1, or 2]), or χ² test (comparing the different levels of effects for categorical variables).

ANOVA, analysis of variance; BMI, body mass index; CWP, chronic widespread pain; LFES, London Fibromyalgia Epidemiology Screening; SES, socioeconomic status.
(NP = 2); 77.1% of those reporting a high likelihood of NP (NP = 2) also reported having symptoms of CWP. Overall, 15.9% of those classified as having CWP had a high likelihood of NP (NP = 2). The sample characteristics are shown in Tables 2 and 3. From the 1357 twins who answered the PainDETECT questionnaire, 30 (2.2%) did not fulfil the criteria for CWP definition but still exhibited a high likelihood of NP (Table 2). From these 30 twins, 23 fulfilled 3 of the 4 CWP criteria; 7 of them had pain on only 1 side of the body, and 9 of them had pain lasting <3 months. Twins likely to have NP were more likely to have CWP symptoms ($P < 0.001$) and high BMI ($P < 0.001$); they were also more likely to be smokers ($P = 0.004$) and belong to lower SES ($P = 0.005$). Associations between CWP/NP and relevant risk factors were examined first individually in univariable regression and next together in multiple regressions (Table 3). The association between CWP and NP was highly statistically significant ($P < 0.001$, Table 2), and each also showed statistically significant association with potential risk factors (including age, age$^2$, BMI, smoking, SES, and sex). The risk factors that were statistically significant ($P < 0.05$) in the univariable regression were included in the multivariable regression and retained in the final analysis if they displayed at least the same level of statistical significance as in the univariable analysis. In the multivariable logistic regression, CWP was positively associated with age ($P = 0.003$), age$^2$ ($P = 0.027$), BMI ($P < 0.001$), current smoking ($P = 0.004$), and female sex ($P < 0.001$) and negatively associated with SES ($P = 0.001$ for the highest SES group). Similar results were found considering fibromyalgia instead of CWP (data not shown).

Heritability of neuropathic pain

Of the twins completing the PainDETECT questions, 79 pairs were dizygotic, 131 pairs were monozygotic, and 937 were unpaired twins. The heritability of NP was estimated using the classical twin model considering only the paired twins (implemented in OpenMX). Assessment of model fit was made by the Akaike information criterion, and the most suitable model describing the observed data was consistently found to be the AE model (Table 4), with estimates of contribution of additive genetic factors, $A = 37\%$ (95% confidence interval [CI]: 23%-50%) and unique environmental factors, $E = 63\%$ (95% CI: 49%-79%) to the total variance. The ACE models all estimated the common environment contribution ($C$) to be very close to zero.

**Table 2**

| Variable      | NP = 0 |             | NP = 1 |             | NP = 2 |             | P     |
|---------------|--------|-------------|--------|-------------|--------|-------------|-------|
|              | n (%)  | Mean (SD)   | n (%)  | Mean (SD)   | n (%)  | Mean (SD)   |       |
| Age, years   | 1008 (74.3) | 60.3 (13.6) | 218 (16.1) | 62.0 (10.7) | 131 (9.6) | 62.1 (10.8) | 0.12  |
| Sex          | Female | 914 (67.3)  | 203 (15.0) | 126 (9.3)   | 0.07   |
|              | Male   | 94 (6.9)    | 15 (1.1)   | 5 (0.4)     |        |
| BMI, kg/m$^2$| 884 (74.3) | 26.3 (5.2)  | 196 (16.5) | 27.8 (5.9)  | 110 (8.2) | 28.8 (6.7)  | <0.001|
| Smoking      | Never  | 974 (74.3)  | 211 (16.1) | 125 (9.5)   | 0.004  |
|              | Ever   | 531 (40.5)  | 101 (7.7)  | 49 (3.7)    |        |
| Ever         | 382 (29.2) | 92 (7.0)    | 60 (4.6)   |        |
| Current      | 61 (4.7)  | 18 (1.4)    | 16 (1.2)   |        |
| SES          | 825 (73.5) | 191 (17.0)  | 107 (9.5)  | 0.005  |
| 1            | 49 (4.4)  | 18 (1.6)    | 13 (1.2)   |        |
| 2            | 81 (7.2)  | 28 (2.5)    | 19 (1.7)   |        |
| 3            | 153 (13.6)| 34 (3.0)    | 23 (2.0)   |        |
| 4            | 220 (19.6)| 53 (4.7)    | 24 (2.1)   |        |
| 5            | 322 (28.7)| 58 (5.2)    | 28 (2.5)   |        |
| CWP          | 0       | 761 (56.1)  | 94 (6.9)   | 30 (2.2)  | <0.001  |
|              | 1      | 247 (18.2)  | 124 (9.1)  | 101 (7.4) |        |

Summary of demographic and phenotypic measures of the 1357 individuals who responded to the PainDETECT questionnaire grouped as 1) NP = 0: non-NP (PainDETECT score ≤12), 2) NP = 1: ambiguous result (PainDETECT score between 13 and 18), and 3) NP = 2: NP (PainDETECT score ≥19). These were compared by ANOVA (comparing the different levels of effects [0, 1, or 2]) or $\chi^2$ test (comparing the different levels of effects for categorical variables).

ANOVA, analysis of variance; BMI, body mass index; CWP, chronic widespread pain; NP, neuropathic pain; SES, socioeconomic status.
independent and dependent of C-fibre nociceptor activity.\(^4\)\(^1\) However, as this is the type of pain that features in various conditions, the relationship between the mechanism of pain, symptomatology, and aetiology is complex and multifaceted. One of the main mechanisms by which NP is mediated is the spontaneous activity of the nociceptive primary sensory neurons after damage to these neurons.\(^4\)\(^1\) Neuropathic pain can either be stimulus-evoked (hyperalgesia and allodynia) or stimulus-independent, as in CWP/fibromyalgia. Mechanisms of pain in CWP are heterogeneous and show varying symptomatology, which is also a characteristic of NP. A recent study by de Tommaso et al.\(^7\) demonstrated small nerve fibre (C-fibre) neuropathy in patients with fibromyalgia, which replicated the findings of a previous study\(^3\)\(^2\) and may explain the idiopathic peripheral sensory nerve involvement and neuropathic nature of chronic pain. We wished to explore the genetic contributions to CWP and NP features and determine their similarity as a way of understanding better the aetiology of the underlying pain mechanism in both traits.

### Table 3

| Variable     | CWP Univariable |   |   |   | Multivariable |   |   |   |
|--------------|-----------------|---|---|---|---------------|---|---|---|
|              | n               | OR | 95% CI | P  | n | OR | 95% CI | P  |
| Age          | 4324            | 1.03 | 1.03-1.04 | <0.001 | 2998 | 1.13 | 1.04-1.22 | 0.003 |
| Age\(^2\)    | 4324            | 1.00 | 1.00-1.00 | <0.001 | 2998 | 1.00 | 1.00-1.00 | 0.027 |
| BMI          | 3689            | 1.08 | 1.06-1.10 | <0.001 | 2998 | 1.07 | 0.15-1.09 | <0.001 |
| Smoking      | 4224            |    |   |   | 2998 |    |   |   |
| 1            | 1.35            | 1.13-1.63 | 0.001 | 2998 | 1.28 | 1.04-1.58 | 0.02 |
| 2            | 1.56            | 1.12-2.17 | 0.008 | 2998 | 1.79 | 1.20-2.67 | 0.004 |
| SES          | 3667            |    |   |   | 2998 |    |   |   |
| 2            | 0.67            | 0.45-1.01 | 0.06 | 2998 | 0.63 | 0.40-1.01 | 0.06 |
| 3            | 0.49            | 0.33-0.73 | <0.001 | 2998 | 0.49 | 0.31-0.75 | 0.001 |
| 4            | 0.59            | 0.41-0.86 | 0.006 | 2998 | 0.54 | 0.36-0.82 | 0.004 |
| 5            | 0.52            | 0.36-0.74 | <0.001 | 2998 | 0.50 | 0.33-0.76 | 0.001 |
| Sex          | 4324            | 0.42 | 0.28-0.62 | <0.001 | 2998 | 0.36 | 0.22-0.59 | <0.001 |

The univariable analyses (logistic regression for CWP or truncated ordinary regression for NP) included the factor shown adjusted for twin-relatedness. The multiple regressions included all risk factors shown and were adjusted for twin-relatedness.\(^b\) \(b\), effect size; BMI, body mass index; CI, confidence interval; CWP, chronic widespread pain; NP, neuropathic pain; OR, odds ratio; SES, socioeconomic status.

### Table 4

| Variable       | n | Adjusted? | Model | AIC | Heritability, % |
|----------------|---|-----------|-------|-----|-----------------|
| PainDETECT     | 1353 | No        | ACE   | 6258.3 | A 37 (0-50) C 0 (0-37) E 63 (50-78) |
|                |     |           | AE    | 6256.4 | A 37 (23-50) E 63 (50-77) |
| PainDETECT (truncreg residuals) | 1185 | Yes       | ACE   | 5451.4 | A 35 (0-50) C 2 (0-36) E 63 (0-81) |
|                |     |           | AE    | 5449.4 | A 37 (20-50) E 63 (49-79) |

Model fit was based on maximum likelihood estimation as assessed by the AIC.\(^1\) The full ACE model was compared with the reduced nested model (AE). Contribution of additive genetic factors \(A\), common environment \(C\), and unique environment \(E\) was determined. Adjustments were made for age, age\(^2\), sex, and BMI. AIC, Akaike information criterion; BMI, body mass index.
The observation that NP is seen as part of the CWP spectrum is not new. The cohort also contributed to the international CWP genome-wide association study meta-analysis of CWP. The observation that NP is seen as part of the CWP spectrum is not new but has not been extensively studied. The study of twins having CWP and risk factor information allows dissection of the environmental and genetic factors, which may point to similar underlying predisposing factors.

We evaluated the association between CWP and NP and found evidence of NP in 15.9% of CWP cases. Of note, when we studied the fibromyalgia subset of CWP, we found the prevalence of NP in fibromyalgia to be substantially higher, at 24.5%. There was a strong phenotypic correlation and genetic correlation (r = 0.54) between CWP and NP, and it was this subgroup that was of particular interest. Neuropathic pain heritability is difficult to determine solely based on family history and classic genetic techniques due to sporadic changes in neural damage and its complex aetiology, thus requiring the use of mice models and twin studies. To our knowledge, this is the first twin study to provide a formal demonstration of the heritability estimates of NP in humans (A = 37%; 95% CI: 20%-50%).

Of the 4 SNPs reported by TwinsUK, 2 SNPs were studied in the 1958 British birth cohort; but a role for COMT was not identified in chronic pain, although 2 SNPs of the β2-adrenergic receptor gene did show association with CWP. A recent candidate gene meta-analysis showed an association between COMT Val158-Met and fibromyalgia in all subjects (10 studies, 993 cases, 778 controls) but failed to show an association between COMT and fibromyalgia susceptibility in the European and Turkish population when stratified according to ethnicity. Although serotonin and dopamine have long been known to play significant role in central pain processes, more profound studies on genetic polymorphisms of serotonin and dopamine receptors/transporters are still lacking in the current literature. A meta-analysis of 3 studies for the serotonin 5-HT2A receptor 102T/C polymorphism conferred susceptibility to fibromyalgia; a meta-analysis of 5-HTLPR S/L allele (5 studies) and COMT Val158Met polymorphism (4 studies) failed to show an association with fibromyalgia. Finally, a genome-wide association meta-analysis, which included the subjects from this study, tested over 2 million SNPs for association and identified genetic variant rs13361160 at the FAM173B (located 81 kB upstream and 57 kB downstream, 5p15.2) locus associated with CWP, suggesting CCT5 and SUCLG1 being implicated in chronic pain with a common amino acid allele change, also known as the “valine risk allele” (n = 1359). A significant association has also been found between a SCN9A SNP and pain score as per nociceptive stimulus (n = 1277).

Similarly, SNPs in catechol-O-methyltransferase (COMT), a key regulator of pain perception, have been shown to be likely candidates in modulating nociceptive and dysfunctional (in their case, temporomandibular joint disorder) pain. Of the 4 SNPs studied by Diatchenko et al., 2 SNPs were studied in the 1958 British birth cohort; but a role for COMT was not identified in chronic pain, although 2 SNPs of the β2-adrenergic receptor gene did show association with CWP. A recent candidate gene meta-analysis showed an association between COMT Val158-Met and fibromyalgia in all subjects (10 studies, 993 cases, 778 controls) but failed to show an association between COMT and fibromyalgia susceptibility in the European and Turkish population when stratified according to ethnicity. Although serotonin and dopamine have long been known to play significant role in central pain processes, more profound studies on genetic polymorphisms of serotonin and dopamine receptors/transporters are still lacking in the current literature. A meta-analysis of 3 studies for the serotonin 5-HT2A receptor 102T/C polymorphism conferred susceptibility to fibromyalgia; a meta-analysis of 5-HTLPR S/L allele (5 studies) and COMT Val158Met polymorphism (4 studies) failed to show an association with fibromyalgia. Finally, a genome-wide association meta-analysis, which included the subjects from this study, tested over 2 million SNPs for association and identified genetic variant rs13361160 at the F5p15.2 locus associated with CWP, suggesting CCT5 and FAM173B (located 81 kB upstream and 57 kB downstream, respectively) as promising targets for pain regulation.

With the heritability results in our study showing moderate genetic influence on NP, the next step would be to determine through agnostic methods, genome-wide association study, the specific genes implicated in NP and to establish genes overlapping between NP and CWP.

We found similar environmental factors for NP as for CWP, with age, sex, BMI, and smoking all implicated. There is also a role for SES, which is recognised to be a complex risk factor and beyond the scope of this study. While the lowest SES group did not show an association with NP, the other SES groups demonstrated negative association (determined by β with NP). Our results are consistent with the findings of the large 1958 British birth cohort study of CWP and with those of other cohorts. In the 1958 cohort, poor diet in women, smoking, high BMI, lack of physical exertion, and smoking were associated with CWP.

There were some limitations to the study, meriting further consideration. The questionnaires were sent in 2 waves to reduce postal cost, which could have resulted in response bias. Although not perfect, the use of questionnaires allows the collection of a much larger sample than if recruited and examined at clinical visit. Second, as the TwinsUK cohort is predominantly female, results cannot necessarily be extrapolated to males; it is noteworthy however that CWP largely affects females.

This study is the first of its kind to provide formal results of NP heritability in individuals with CWP. These results not only provide figure 1. Path diagram summarising the results of the bivariate variance component analysis of chronic widespread pain (CWP) and neuropathic pain (NP).

Figure 1. Path diagram summarising the results of the bivariate variance component analysis of chronic widespread pain (CWP) and neuropathic pain (NP). Path diagram reflecting the magnitude (and significance) of the genetic (heritability, h²) and unique environmental (e²) effects and reflect the order of the connections between these factors and CWP and NP. The contribution of the genetic factors to variation in CWP and NP was 0.53 and 0.33, respectively, and these effects are not independent. The genetic correlation between them is 0.54; similarly is seen with respect to environmental factors. The circles indicate latent additive genetic (h²) and environmental (e²) factors affecting CWP and NP variations, respectively. The arrows show the direction and strength (variance attributable to) of the respective effects. Squares represent measured pain phenotypes, CWP and NP, respectively. Paths with double-headed arrows connecting the corresponding circles represent the genetic (rG) and environmental (rE) correlation between CWP and NP, respectively. The path diagram allows one to estimate the covariance shared by CWP and NP.
insight into CWP and NP aetiology but also affirm the need for studies investigating the specific genetic variants underlying these pain conditions, which may further provide diagnostic tools and targets for treatment.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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