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Shared genetic factors underlie chronic pain syndromes

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ABSTRACT

Chronic pain syndromes (CPS) are highly prevalent in the general population, and increasingly the evidence points to a common etiological pathway. Using a large cohort of twins (n = 8564) characterized for chronic widespread musculoskeletal pain (CWP), chronic pelvic pain (PP), migraine (MIG), dry eye disease, and irritable bowel syndrome (IBS), we explored the underlying genetic and environmental factors contributing to CPS and the correlation between them. The sample was predominantly female (87.3%), with a mean age of 54.7 (±14.7) years. Prevalence of the different CPS ranged from 7.4% (PP) to 15.7% (MIG). For all CPS the within-twin correlation in monozygotic twin pairs was higher than in dizygotic pairs, suggesting a heritable component. Estimated heritability ranged from 19% (IBS) to 46% (PP). Except for MIG, we found significant pairwise phenotypic correlations between the CPS. The phenotypic correlation was highest between CWP and IBS (0.40; 95% confidence interval: 0.27 to 0.46). Excluding MIG from further analyses, cross-twin cross-trait correlations were higher in monozygotic compared with dizygotic twin pairs, suggestive of shared genetic factors between CWP, PP, IBS, and dry eye disease. Twin modeling analysis revealed the common pathway model as the model best explaining the observed pattern of correlation between the traits, with an estimated heritability of 66% of the underlying latent variable. These results are evidence of shared genetic factors in conditions manifesting chronic pain and justify the search for underlying genetic variants.

1. Introduction

Chronic pain is common among adults, with a prevalence ranging from 10% to 50% depending on the population studied and definition used [5,34,46,47]. It has significant impact on patients' functioning and quality of life [6]. The chronic pain syndromes (CPS) are a poorly defined constellation of syndromes with ongoing pain that show overlap in presenting symptomatology, such as fatigue, sleep disturbance, anxiety, depression, headache, and functional bowel disturbance. CPS are a serious challenge to health care providers because of their unclear and complex multifactorial pathophysiology, psychological element, and poor response to therapy. Chronic widespread musculoskeletal pain (CWP), chronic pelvic pain (PP), irritable bowel syndrome (IBS), and to a lesser extent migraine (MIG) are considered CPS that all lack gross tissue level abnormalities. Epidemiological studies have shown that such syndromes cluster in individuals [7,15,20,22]. Recently, we and others have found that dry eye disease (DED) is also associated with CWP, IBS, PP, and MIG [44,50,52]. Furthermore, DED is associated with increased sensitivity to heat pain on objective pain testing [45].

These findings are suggestive of a family of related disorders that has been termed affective spectrum disorder by Hudson et al. [20]. The term functional somatic syndromes also has been coined, often including chronic fatigue syndrome as well [18]. Further evidence for an association between these disorders comes from studies of family history and response to treatment [20]. A common underlying pathophysiology has been hypothesized, but clear mechanisms have yet to be identified. Twin and family

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studies have been used to estimate genetic and environmental contributions to several of the CPS. CWP [22], PP [59], and MIG [8] all have been shown to be heritable. Genetic factors have less influence on IBS but are still detectable [31].

The multivariate classic twin design may be used to estimate the degree to which the same genetic and environmental factors influence different CPS. This information can widen our understanding of CPS, and may provide clues to the interplay between different pathways underlying CPS, ultimately allowing identification of the pathways involved in chronic pain. The aims of the current study were to estimate the relative influence of genetic and environmental factors on CWP, PP, MIG, IBS, and DED, and particularly to investigate to what extent correlation between the CPS can be explained by genetic and environmental factors.

2. Methods

2.1. Subjects

Subjects for this study were twins recruited from the TwinsUK Adult Twin Registry, held at King's College London, UK [30]. This registry has been ascertained from the general population through national media campaigns. Twins from this registry have been shown to be comparable to the age-matched general population singletons for a broad variety of medical and behavioral traits [4]. For historical reasons, most enrolled twins are female. Local ethics committee approval was obtained for the study, and twin volunteers gave informed consent but were unaware of the precise hypotheses being tested. The research followed the tenets of the Declaration of Helsinki. Zygosity had been determined from standardized questionnaires and genomewide analyses.

2.2. Measures

Classification of the different CPS was based on standard, validated criteria when possible. Questions relating to the CPS were contained within a number of different questionnaires sent to twins between 2001 and 2010 and were among questions on other phenotypes. Thus the questionnaires did not appear to be specifically collecting chronic pain information. Questions to determine presence of MIG were based on the University of California–San Diego Migraine Questionnaire (including at least 5 episodes of unilateral, pulsating headache over the previous year, with a duration of 4 to 72 hours, with noise and light sensitivity) [43]. A questionnaire based on the Rome III criteria [13] was used to assess the presence of IBS. In short, to be assigned as having IBS, participants needed to have recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) for at least 3 days per month in the last 3 months, together with 2 or more of the following criteria: (1) improvement with defecation, (2) onset associated with a change in stool frequency, and (3) onset associated with a change in form (appearance) of stool. PP was defined as recurrent or constant lower abdominal pain lasting for at least 6 months. A custom-made questionnaire was used to assess this in female subjects only [59]. A modified version of the London Fibromyalgia Symptom Screening Questionnaire was used to assess the presence of CWP syndrome [53]. CWP was defined as pain in the left and right sides of the body, above and below the diaphragm, and in the axial skeleton, following the Fibromyalgia Criteria of the American College of Rheumatology [56]. No gold standard for a diagnosis of DED exists [11]. DED was classified by asking about a clinician's diagnosis of dry eye disease together with the concomitant use of artificial tear eye drops or gel, as used in another population-based study [14].

2.3. Analysis

The aims of our analyses were twofold: (1) to estimate the relative influence of genetic and environmental factors on the observed phenotypic variance in all CPS separately, and (2) to assess the extent to which phenotypic correlations between CPS may be explained by genetic and environmental factors.

2.3.1. Twin model fitting

The rationale of the twin design is to compare the degree of similarity of resemblance among monozygotic (MZ) twins, who share 100% of their genetic makeup, and dizygotic (DZ) twins, who share on average 50% of their segregating genes. Relative differences between within-pair correlations are then used to estimate the relative contributions of the additive genetic effects (A), the shared environmental effects (C) and the non-shared environmental effects, which also include measurement error (E) [38]. Confidence intervals of parameter estimates were obtained by maximum likelihood [32]. Age and gender were entered into the models as covariates.

2.3.2. Univariate analysis

CPS were defined categorically as present or absent, and prevalence and probandwise concordance rates were calculated. Because the traits in question were dichotomous, similarity between twins was further examined using tetrachoric correlations with a liability-threshold model [40], performed in the program Mx [33]. The liability-threshold model assumes an underlying continuous liability that follows a normal distribution. The threshold is estimated from the population frequency of the phenotype [42]. The difference between correlations in MZ and DZ pairs can be used to quantify genetic (A) and shared and nonshared environmental sources (C and E, respectively) of variation in liability in the population using maximum likelihood structural equation model fitting.

2.3.3. Multivariate analysis

Multivariate models assess the genetic and environmental contributions to the covariance between traits. The ratio of MZ to DZ cross-twin cross-trait covariance is used to decompose the covariance between measures into genetic, shared, and nonshared environmental components [32]. Higher cross-twin cross-trait correlations for MZ vs DZ twins suggest a genetic influence on the covariance between traits.

Three different multivariate models, with different assumptions about the underlying relationships between variables, were fitted to the data: the correlated factors solution, the independent pathway model, and the common pathway model. The first model, the correlated factors solution, decomposes variance into A, C, and E and estimates correlations between the variance components (Appendix Fig. 1). This model provides a baseline comparison for subsequent models, as it makes no a priori assumptions regarding covariation between the traits [19]. The second model, the independent pathway model, allows for common genetic and environmental factors to influence the observed variables directly without an intermediate higher-order factor [37]. This model tests the hypothesis that common etiological factors influence the CPS, accounting for their correlation, in addition to variable specific factors. Third, the common pathway model decomposes variance into that which is shared—a single underlying phenotypic latent variable—and that which is unique to each trait. This latent variable has genetic and environmental components of variance with variable specific genetic and environmental sources of variances also estimated [38].

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