

The Genetic Contribution to Carpal Tunnel Syndrome in Women: A Twin Study

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Objective. To assess the relative genetic and environmental contribution to carpal tunnel syndrome (CTS) using a classic twin study of monozygotic (MZ) and dizygotic (DZ) twins.

Methods. The study group comprised unselected female twin pairs, between 20 and 80 years of age, from the St Thomas' UK Adult Twin Registry. Individuals completed a questionnaire that included details on potential risk factors for CTS. The diagnosis of CTS was made using a standardized hand pain diagram and validated criteria. The genetic contribution to CTS was assessed using variance component and regression methods, the heritability was adjusted for environmental confounders. The role of individual risk factors was assessed by a nested case-control study.

Results. An overall prevalence of 14.2% for CTS was found in a population of 4,488 females, comprising 867 MZ and 970 DZ twin pairs, and 814 singletons. The concordance for CTS was significantly higher in MZ compared with DZ twins (case-wise concordance values of 0.35 and 0.24 respectively, with a significantly increased MZ:DZ ratio of 1.48; $P = 0.03$). Modeling produced a heritability estimate of 0.46 (95% CI 0.34–0.58) that was essentially unchanged after adjustment for environmental risk factors including age, body mass index, physical activities, and hormonal/reproductive factors. No major influence of any individual risk factor was seen in the case-control analysis of 520 cases and 3,154 controls, apart from a modest association with menopausal status with an increased risk of 1.53 and 1.43 in the peri and postmenopausal groups. There was no overall effect of age or body mass index.

Conclusion. This is the first study to explore the genetic component of CTS. Our data show that up to half of the liability to CTS in women is genetically determined, and this appears to be the single strongest risk factor, with only minor contributions from known environmental factors. Further studies should focus on genetic mechanisms that may lead to tests for susceptibility and detection of those at risk of developing CTS.

KEY WORDS. Carpal tunnel syndrome; Twins; Genetic epidemiology.

INTRODUCTION

Carpal tunnel syndrome (CTS), a disorder of median nerve entrapment at the wrist, is a very common and often disabling condition. Several epidemiologic studies have estimated the general population point prevalence of CTS in

females at between 7% and 18% (1–3) depending on definition, using combinations of a self-reporting screening questionnaire (4), clinical examination criteria, or nerve conduction studies. A number of studies have also looked at CTS in specific employment situations and found evidence of association with repetitive and/or forceful work activity (5,6).

The prevalence and incidence of CTS increase with age (1,7), and obesity is consistently reported as a risk factor (8–12). In clinical series, CTS has been associated with rheumatoid arthritis, diabetes, hypothyroidism, estrogen replacement therapy (13), oophorectomy (14), and pregnancy (15). Many of these studies have been conducted in highly selected populations and the individual contribution or “attributable risk” from each factor has been small. All studies have ignored an underlying genetic susceptibility that could explain much of the variation or liability to CTS. We present the results of a classic twin study assessing the relative genetic and environmental contribution to CTS.

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Table 1. Classification of hand pain diagram (4)

Classic
Pain, tingling, numbness and/or decreased sensation with or without pain in at least two of digits 1, 2, or 3
No symptoms in the palm or dorsum of the hand
Fifth digit symptoms, wrist pain or radiation proximal to the wrist allowed
Probable
Same as classic, except palmar symptoms allowed unless confined solely to the ulnar aspect
Possible
Pain, tingling, numbness and/or decreased sensation in at least one of digits 1, 2, or 3
Unlikely
No symptoms in digits 1, 2, or 3

SUBJECTS AND METHODS

The study subjects comprised female-female twin pairs recruited from the St Thomas' UK Adult Twin Registry, a volunteer-based group drawn from the UK population through successive media campaigns. The characteristics of this group have been documented in detail in previous studies (16). A postal self-administered questionnaire was sent to 6,600 individuals, all of whom were unaware of any interest or hypotheses in the study of musculoskeletal diseases or CTS. Data were collected on age, height, weight, smoking history, alcohol consumption, physical activity, occupation, estrogen replacement therapy, parity, menopausal status, oral contraceptive use, hysterectomy, oophorectomy, thyroxine replacement, and self-reported physician diagnosis of diabetes mellitus. All questions were standardized and had been used in other population-based surveys (17). Zygosity had been determined by a standard questionnaire and confirmed by DNA fingerprinting.

Subjects were asked whether they had ever experienced pain, numbness, tingling, or reduced sensation in their hands and to shade in areas on a standardized hand diagram, marking where they had felt any of these symptoms. Each hand diagram was read by a single observer (SZ) and coded according to validated classification criteria (4) (Table 1). Subjects were considered to have had symptoms of CTS if they fulfilled the criteria for "classic" or "probable" disease. The observer was blinded to the pairing of the twins. A second observer (AJH) independently re-coded a random sample of 20% of the diagrams, which revealed an acceptable error rate of 0.4%.

A telephone survey of a random sample of 60 nonresponders (30 MZ and 30 DZ subjects), was also performed. Although the mean age was slightly lower, 45.6 ± 2.8 years in the nonresponders compared with 51.0 ± 12.9 years in the responders, there were no other clear differences between the groups.

The premise in the classic twin study is that variation in phenotype can be accounted for by genetic influences, environmental influences shared between each twin pair, and random environmental influences unique to each twin. Convention assigns this phenotypic variance to a composite of additive (A) and dominance (D) genetic components, and shared/common (C) and unique (E) environmental components. MZ twins are genetically identical

and DZ twins have the genetic similarity of ordinary siblings, sharing an average of 50% of their genetic material. The model assumes twin siblings to have been reared together. Given that covariance among DZ twins therefore has a smaller contribution from shared genetics than that of MZ twins, quantitative genetic analysis using a variance approach with standard regression techniques (18,19) compares the distribution characteristics in MZ and DZ twins, estimating and examining the significance of each of the components of variation in a phenotype. Different models may be applied in the variance analysis. Initial assessment of the components (A, D, C, and E), may suggest nonsignificant values in one or more component. Further analysis may then use models of ACE or AE, for example, to estimate the heritability. Heritability is defined as the proportion of total phenotypic variance in a trait that can be attributed to genetic components. Using logistic regression techniques, the initial estimate for heritability can then be adjusted for potential confounders, assessing the effect on heritability of individual or combined environmental risk factors.

Evidence for heritability may be assessed by comparing case-wise concordance for a disease or trait in the two zygosity groups. Concordance provides a measure of the proportion of co-twins of affected twins that have the disease or trait themselves. Case-wise concordance (P_c) is the probability that a twin is affected, given that the co-twin is affected. The P_c is calculated from the number of concordant pairs (cn) and discordant pairs (dn) using the formula

$$P_c = 2cn \div (2cn + dn)$$

The two groups, MZ and DZ twins, were compared for their compatibility in terms of prevalence of CTS and other characteristics. Statistical analysis was performed with Stata (release 6.0, Stata Corporation, College Station, TX). A case-control design using logistic regression methods, including the generalized estimation equation xtgee to account for codependency within twin pairs, was used to analyze potential risk factors for CTS (20). Each risk factor was adjusted for age and body mass index (BMI).

Case-wise concordance for CTS was calculated as described above. The AE model of variance analysis was used having found the D and C components to be nonsignificant. The crude heritability estimate for CTS was then adjusted for the simultaneous combination of age, height, weight, menopausal status, and physical activity as potential confounders, having found no significant effect from other environmental risk factors in the initial case-control analysis.

RESULTS

A total of 4,488 women (comprising 867 MZ and 970 DZ twin pairs, and 814 singletons) returned the questionnaire. The overall response rate was 68% and there were no differences in response rates or characteristics between the MZ and DZ groups (Table 2).

Of 520 individual cases classified as having symptoms compatible with CTS, 92% were "classic" and 8% "prob-

Table 2. Characteristics of the twins by zygosity

Variable	Monozygotic*	Dizygotic*	Number of responders in paired data set
Age in years, mean (SD)	51.0 (12.97)	50.6 (12.38)	3674
BMI mean (SD) kg/m ²	22.5 (4.22)	23.1 (4.18)	3122
Height mean (SD) cm	169.6 (6.87)	169.9 (6.87)	3122
Weight mean (SD) kg	64.7 (11.99)	66.7 (12.27)	3122
Home activity			
None	3.0	2.6	3640
Light	27.1	28.1	3640
Moderate	63.9	62.9	3640
Heavy	6.0	6.4	3640
Leisure activity			
None	7.2	6.8	3622
Light	30.4	36.1	3622
Moderate	53.1	50.6	3622
Heavy	9.3	6.5	3622
Occupation			
None	40.0	36.0	3520
Nonmanual	38.0	42.0	3520
Clerical	20.0	19.0	3520
Manual	2.0	3.0	3520
Current smoker	14.1	17.9	3674
% parity	80.8	88.6	3610
Median (interquartile range)	2 (2–3)	2 (2–3)	3610
Postmenopausal	39.5	42.0	3446
Current use of oral contraceptive	10.1	7.2	2718
Current use of HRT	19.9	22.7	3674
Hysterectomy	22.7	19.6	3616
Oophorectomy	6.4	6.0	3674
Thyroxine replacement	5.4	5.6	3674
Diabetes mellitus	1.0	1.5	3674

* Except where indicated otherwise, values are the % in each group answering positively. BMI = body mass index; HRT = hormone replacement therapy.

able” with no difference between the MZ and DZ groups. The prevalence of these symptoms was 14.5% in the MZ pairs, 13.9% in the DZ pairs, and 14.3% in the sample of 60 nonresponders. There were 163 discordant and 44 concordant symptomatic MZ pairs, and 205 discordant and 32 concordant DZ pairs.

Pc for CTS symptoms in MZ twin pairs was 0.35 (95% CI 0.28–0.43) compared with 0.24 (95% CI 0.17–0.31) in DZ pairs, with a significantly increased MZ:DZ ratio of 1.48 ($P = 0.03$). The difference in Pc for each environmental risk factor, although generally higher in the MZ pairs, did not reach the level of significance. Using the AE model, the heritability to the phenotype of CTS was estimated at 0.46 (95% CI 0.34–0.58). This did not alter after adjustment for confounders; either the simultaneous combination of age,

BMI, and menopausal status, or the former 3 with the addition of physical activity scores for home, leisure, and work (Table 3).

A case-control analysis of environmental factors was performed using the 867 MZ and 970 DZ twin pairs, taking account of pair codependency (Table 4). Based on 520 cases and 3,154 controls, the analysis suggested a modest association between symptoms of CTS and menopausal status, with an increased risk of 1.53 and 1.43 in the peri and postmenopausal groups. There was no overall effect of age or BMI other than a modest increase in the group aged 45–50 years. The prevalence of symptoms was 20% in this group, compared with 11% for the group <45 years of age, and 14% in each of those groups >50 years of age. An apparent association with hysterectomy was lost when menopausal status was taken into account and no other significant association was found with any other factor on crude analysis, and after adjusting for age and BMI.

DISCUSSION

In this study, we found symptoms consistent with CTS to be common, with a greater concordance in MZ twins than in DZ twins and a considerable genetic influence equating to an estimate of heritability of 46%. None of the individual environmental risk factors we measured were strongly related to CTS.

Important considerations in the analysis include whether the twins are truly representative of a general population, and the suitability of symptom reporting alone as a tool for defining cases. Selection bias is unlikely to be a problem because the study questionnaire did not focus on a particular disease and all the twin pairs recruited were unselected volunteers. Our twin population has also been found to be similar to a population-based singleton sample for a range of diseases including osteoporosis and osteoarthritis (21). No significant associations with risk

Table 3. Heritability estimates for carpal tunnel syndrome (CTS)

	Genetic component of variance*	95% Confidence intervals
Crude* (i.e. CTS alone)	0.46	0.34–0.58
CTS and simultaneous analysis with age, body mass index (BMI) and menopausal status	0.46	0.32–0.59
CTS and simultaneous analysis with age BMI and menopausal status, along with simultaneous analysis of occupation, leisure, and home activity	0.47	0.34–0.59

* Heritability estimated through regression methods and based on an additive/unique environmental model.

Table 4. Odds ratios for risk factors in carpal tunnel syndrome

Variable	Crude odds ratio	95% Confidence interval	Age and BMI adjusted odds ratio	95% Confidence interval
Age in years				
≤ 45	1.00	Referrant	–	–
46–50	1.99	1.42–2.79	2.01	1.44–2.81
51–55	1.26	0.90–1.78	1.30	0.92–1.83
56–59	1.29	0.90–1.86	1.33	0.92–1.92
≥ 60	1.24	0.91–1.68	1.28	0.94–1.75
BMI, kg/m ²				
≤ 21.0	1.00	Referrant	–	–
21.1–23.0	0.94	0.71–1.25	0.91	0.69–1.22
23.1–25.0	0.91	0.66–1.24	0.89	0.65–1.23
25.1–28.0	0.86	0.60–1.22	0.84	0.59–1.21
≥ 28.1	0.85	0.58–1.24	0.84	0.57–1.23
Activity				
Home (low vs. high level)	1.13	0.83–1.64	1.21	0.95–1.55
Leisure (low vs. high level)	1.04	0.70–1.55	1.00	0.80–1.26
Occupation (clerical vs. nonclerical)	1.11	0.72–1.73	1.13	0.90–1.43
Premenopausal	1.00	Referrant	–	–
Perimenopause	1.46	1.06–2.00	1.53	1.01–2.32
Postmenopause	1.20	0.93–1.55	1.43	0.89–2.29
Hysterectomy	1.33	1.06–1.65	–	–
After accounting for menopause	1.12	0.70–1.75	1.20	0.89–1.63
Current use of HRT	0.87	0.67–1.13	0.85	0.62–1.16
Current thyroxine replacement therapy	1.15	0.78–1.69	1.13	0.72–1.78

BMI = body mass index; HRT = hormone replacement therapy.

factors were found. Most of our subjects were aged between 35 and 65 years, and had a BMI between 21 and 25. A broader range may have demonstrated stronger associations found in other studies of more extreme populations. Similarly we may have lacked power in demonstrating occupation in clerical or manual employment as a risk factor, given the small number of cases in these groups. However, it is probable that there are a large number of environmental factors imposing small effects on the development of CTS and it is highly unlikely that these could have a large effect on the heritability estimate.

Criteria for the definition of CTS have been developed by a consensus approach (22). There is no absolute gold standard for CTS. Nerve conduction studies alone are insufficient, but when performed in conjunction with assessment of symptom characteristics offer the most accurate information. The use of symptom characteristics and/or physical examination alone is likely to lead to greater misclassification. Our prevalence data was consistent with other population studies (2) that have used the screening hand diagram (4). Nerve conduction studies would probably have defined a smaller group of cases and possibly separated nerve entrapment at the wrist from that at the neck. However nerve conduction studies, as well as being difficult and expensive to perform in our large paired data set, may also falsely dismiss a number of subclinical cases as negative, depending upon the criteria used to define delayed nerve conduction. If a more specific and severe phenotype for CTS had been available, it is likely that we would have shown a larger genetic effect than that seen in this study.

A further, theoretical criticism of the twin design is the potential for greater environmental sharing in MZ than DZ twins. This might bias the estimate of heritability upwards only if these factors were both strongly associated with CTS and showed a marked excess sharing in MZ twins (23). Although there were slightly higher concordance figures in the MZ group for several variables, none of them significantly contributed to the risk of disease and they did not affect the estimates after adjustment.

The genetic component of CTS could arise from a range of different sources and might include molecular or structural differences, psychological factors, or pain mechanisms. A small number of family pedigrees with autosomal dominant CTS have been studied. Potocki et al observed the presence of a deletion of the peripheral myelin protein 22 (PMP 22) gene on chromosome 17 in members of one family with entrapment neuropathies (24). The population distribution of this PMP 22 deletion is not known and similar gene abnormalities are likely to exist.

Abnormalities of collagen formation or repair may also occur. However, one study of 130 cases by Nakamichi and Tachibana did not demonstrate any consistent or typical changes in histology of the transverse carpal ligament or the flexor tenosynovium in idiopathic CTS (25). At a macroscopic level, a number of studies have examined the use of ultrasound or magnetic resonance imaging as tools for CTS diagnoses and staging. There remains a difference of opinion as to their value in demonstrating anatomic changes useful for staging the condition (26–29). It is possible that there is considerable genetic variation in the

width or dimensions of the carpal tunnel, although this remains to be tested.

Pain perception and behavior should also be considered. Levels of pain sensitivity have been shown to be similar within families (30). Genetic mechanisms for pain perception have also been demonstrated in animal studies and genetic polymorphisms identified (31,32). However, learned patterns of behavior within families, and shared environmental influences may be the predominant determinants of pain perception and not genetic components (33). This is an area that needs further study. Assessment of the components of pain behavior may demonstrate traits that could account in part for the genetic contribution to conditions as CTS.

In summary, the strongest risk factors for CTS appear to be genetic, although the mechanisms by which these genes might act are unclear. Further study of these mechanisms may aid in assessing susceptibility to CTS and other entrapment neuropathies.

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