Temporomandibular Disorder–Type Pain and Migraine Headache in Women: A Preliminary Twin Study

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Aims: *To determine whether shared genetic influences are responsible for the association between pain from temporomandibular disorders (TMD) and migraine headache.* ***Methods:*** *Data were obtained from 1,236 monozygotic and 570 dizygotic female twin pairs from the University of Washington Twin Registry. TMD pain was assessed with a question about persistent or recurrent pain in the jaw, temple, in front of the ear, or in the ear. The presence of migraine headache was determined by self-report of doctor-diagnosed migraine. Univariate and bivariate structural equation models estimated the components of variance attributable to genetic and environmental influences.* ***Results:*** *The best fitting univariate models indicated that additive genetic effects contributed 27% of the variance in TMD pain (95% confidence interval = 15% to 38%) and 49% of the variance in migraine headache (95% confidence interval = 40% to 57%). The best-fitting bivariate model revealed that 12% of the genetic component of TMD pain is shared with migraine headache.* ***Conclusion:*** *These preliminary findings suggest that the association between TMD pain and migraine headache in women may be partially due to a modest shared genetic risk for both conditions. Future studies can focus on replicating these findings with symptom- and diagnosis-based instruments.* J OROFAC PAIN 2012;26:91–98

Temporomandibular disorders (TMD) are a heterogeneous group of conditions characterized by pain in the temporomandibular joint and/or masticatory muscle and limited or painful jaw movements.[1,2] TMD are often associated with headaches,[3–5] with women affected more frequently than men.[6] The magnitude of association with TMD is highest for migraine compared to other types of headache.[4,5] A recent study indicated that 73% of patients with migraine headache also experience TMD and cutaneous allodynia.[3] In addition, the presence of TMD in patients with migraine headache predicts migraine persistence and chronicity, thus increasing the severity of pain.[3] The comorbidity of TMD and migraine headache causes physical and psychological disability and tremendous health care costs.[7,8] Therefore, studies investigating the nature of this comorbidity are warranted.

Multiple biopsychosocial factors including genetic and environmental factors may play a substantial role in the pathology of these conditions.[9,10] Both TMD and headache are mediated by the trigeminal nerve and characterized by pain in the head or face and pericranial tenderness.[5,11,12] Dysregulation of pain modulatory mechanisms

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in the central and peripheral nervous systems have been reported in both TMD and migraine headache.[13–16] In addition, inherent genetic differences among individuals may play an important role in the vulnerability to these types of pain.[17,18] In this regard, several studies have demonstrated the heritability of migraine headache[10,19] and a few investigations have addressed the heritability of TMD signs and symptoms.[20–22] To the authors' knowledge, no studies have examined the shared genetic influences that may be partially responsible for the association between TMD and migraine headache.

Twin studies offer a unique opportunity to investigate shared disease etiology by evaluating the relative contributions of genetic and environmental factors to more than one condition. This study examines the shared genetic influences on pain that is associated with TMD (ie, TMD pain) and migraine headache among female twins enrolled in a community-based twin registry in Washington State. The aims were to determine whether shared genetic influences are responsible for the association between pain from TMD and migraine headache.

Materials and Methods

Sample

The University of Washington Twin Registry is a community-based sample of twins derived from the driver license applications of the Washington State Department of Licensing.[23] In Washington State, driver license numbers are derived from a person's name and date of birth; thus, the Department of Licensing asks every new applicant if she or he is a twin to avoid issuing duplicate license and identification numbers to twins. Because state agencies in Washington are permitted by law to share data, the Department of Licensing has provided a list of all new drivers license applicants who are twins to the University of Washington since 1998. Upon receiving the names from the Department of Licensing, the University of Washington Twin Registry staff sends each twin an invitation to join, a brief survey to complete, and an incentive. The co-twin is mailed a survey using contact information provided by the index twin. The brief survey contains items on demographics, habits, doctor-diagnosed health conditions, symptoms, health care use, and various abridged, standardized measures of physical and mental health. A detailed description of strategies used for recruitment and maintaining the Twin Registry has been published.[23] All Registry procedures and data collection involved in this study were approved by the University of Washington Institutional Review Board. Informed consent was obtained from all twins. All authors had full access to study data.

Measures

Questions about childhood similarity that correctly classify zygosity with an accuracy of 95% to 98% compared with biological indicators were used to determine zygosity.[24–27] Sociodemographic factors included age, sex, race, education, and marital status. The twins were given a list of conditions including TMD and migraine headache and asked: "Has your doctor ever told you that you have any of the following conditions?" In addition, all twins answered a question derived from the Life Pain Questionnaire, which was developed by researchers to screen for common chronic pain conditions such as TMD pain and headaches.[28] Twins were asked about TMD pain as follows: "In the past 3 months, have you had persistent or recurrent pain in the face, jaw, temple, in front of the ear, or in the ear?" This question has been validated and successfully used by other investigators to screen for TMD pain. The calculated sensitivity for a diagnosis of TMD ranges from 89% to 100% and specificity from 37% to 69%.[29,30] Because not all twins with TMD pain may have been diagnosed by a physician, the authors chose to use the TMD pain question as the primary variable in the analyses.

Finally, twins responded to a list of symptoms that accompany their typical headaches, including feeling sick to the stomach or vomiting and greater sensitivity to light and/or noise, two of the hallmark symptoms of migraine headaches. Because the headache symptom questions did not comprehensively assess migraine headache, the authors chose to use the self-reported physician's diagnosis of migraine headache as the primary variable from consecutive twins in the analyses.

Statistical Analysis

Descriptive statistics for demographic and health characteristics were calculated using means and standard deviations for continuous variables and percents for categorical variables. Logistic regression using generalized estimating equations to account for clustering within twin pairs was used to examine the association of TMD pain and headache symptoms with self-reported physician's diagnosis of TMDs and migraine headache, respectively. The association between TMD pain and migraine headache in monozygotic (MZ) and dizygotic (DZ) pairs was assessed by three types of tetrachoric

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correlations: phenotypic, twin, and cross-twin, cross-trait. Phenotypic correlations measure the association of TMD pain and migraine headache within individuals, whereas twin correlations examine the within-pair similarity for a trait. Cross-twin, cross-trait correlations assess the degree of association for two traits, eg, the relationship of TMD pain in twin 1 and migraine headache in twin 2, as well as TMD pain in twin 2 and migraine headache in twin 1.

Classic twin analyses compare phenotypic similarity in MZ twins and DZ twins; greater phenotypic similarity in MZ than DZ twins indicates a genetic component in the parameter of interest. The authors used univariate structural equation modeling to estimate the proportions of variance due to additive genetic (A), common environmental (C), and unique environmental (E) influences on TMD pain and migraine headache individually.[31] Models were fitted assuming an additive genetic correlation of 1.0 for MZ and 0.5 for DZ twins, a shared environmental correlation of 1.0 for all twins, and a unique environmental correlation of 0.0 for all twins. Modeling began by estimating parameters for the full model (ACE), and then reduced models were constructed by removing specific parameters. The goodness-of-fit of each reduced model was compared with the full model by using a likelihood ratio test. Parameter estimates, 95% confidence intervals (CIs), and goodness-of-fit statistics for the full model (ACE) are presented, as well as models in which all variance was attributable to genetic and specific environmental factors (AE), and common and specific environmental factors (CE). Parameters were removed from the model if doing so did not result in a significant degradation of model fit. Models were also evaluated using Akaike's Information Criterion (AIC),[32] where a lower value indicates a superior fit. Structural equation modeling can also be used to estimate the variability in two or more phenotypes due to shared vulnerabilities. The analyses used bivariate structural equation modeling to estimate shared genetic and environmental vulnerabilities with a full Cholesky decomposition that specified a general multivariate covariance structure and allowed for both specific and shared influences on TMD pain and migraine headache. The final best-fitting, most parsimonious model was identified by removing parameters that did not significantly degrade the fit of the model based on likelihood ratio tests and the AIC.[32] Goodness-of-fit statistics are presented for the full and reduced bivariate models, and trait-specific and shared variance components for the best-fitting model.

Descriptive analyses and tetrachoric correlations were computed using Stata 10.1 for Windows (Stata Corp). Structural equation models were fit using MxGui version 1.4.06 (Department of Psychiatry, Virginia Commonwealth University). A *P* value of .05 was considered the criterion for a significant degradation of model fit.

Results

Twin Characteristics

The initial registry sample consisted of 1,919 same-sex female pairs. Both members of 113 pairs were excluded because of undetermined zygosity or missing data for one or both twins, leaving a total of 1,236 MZ and 570 DZ female pairs (n = 1,806 pairs). The twins' mean age was 32 years (SD = 15), with a range of 18 to 90 years; 85% of the sample were white, reflecting the demographics of Washington State. The majority of the sample (93%) had completed at least a high school education, and 30% had completed a 4-year college degree or higher; 43% were married or cohabitating.

TMD Pain and Migraine Headache Characteristics

The overall prevalence of TMD pain was 13%. Similarly, 20% of twins reported a doctor's diagnosis of migraine headache, and 4% reported both TMD pain and migraine. Twins reporting TMD pain were more likely than those without self-reported TMD pain to endorse a doctor's diagnosis of TMD (20% versus 4%, $P < .001$). Compared to twins not reporting a migraine headache diagnosis, twins who had a doctor's diagnosis of migraine headache more frequently reported their typical headaches were accompanied by nausea or vomiting (44% versus 11%, $P < .001$), and photophobia or phonophobia (79% versus 41%, $P < .001$).

Tetrachoric Correlations

Table 1 presents phenotypic, twin, and cross-twin, cross-trait tetrachoric correlations for TMD pain and migraine headache by zygosity. Phenotypic correlations ranged from 0.32 to 0.33 in MZ twins and from 0.16 to 0.18 in DZ twins. Larger MZ than DZ twin correlations for TMD pain (0.27 versus 0.10) and migraine headache (0.50 versus 0.20) suggested a genetic basis for each trait. The higher cross-twin, cross-trait correlations in MZ compared with DZ pairs suggested modest shared genetic influences on both traits.

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Table 1 Tetrachoric Correlations for TMD Pain and Migraine Headache in Female Twin Pairs According to Zygosity

	Twin 1		Twin 2	
	TMD pain	Migraine	TMD pain	Migraine
MZ (n = 1,236 pairs)				
Twin 1				
TMD pain	1.00			
Migraine	0.33 (0.22, 0.44)*	1.00		
Twin 2				
TMD pain	0.27 (0.15, 0.40)†	0.18 (0.06, 0.30)‡	1.00	
Migraine	0.09 (–0.03, 0.21)‡	0.50 (0.41, 0.59)†	0.32 (0.21, 0.43)*	1.00
DZ (n = 570 pairs)				
Twin 1				
TMD pain	1.00			
Migraine	0.16 (–0.03, 0.35)*	1.00		
Twin 2				
TMD pain	0.10 (–0.12, 0.31)†	0.14 (–0.04, 0.32)‡	1.00	
Migraine	0.03 (–0.17, 0.22)‡	0.20 (0.04, 0.36)†	0.18 (0.00, 0.36)*	1.00

*Phenotypic correlation between TMD pain and migraine headache; †Twin correlation; ‡Cross-twin, cross-trait correlation.

Table 2 Univariate Structural Equation Models of TMD Pain and Migraine Headache in Female Twin Pairs

	Estimates of variance components*			Test of model fit			
Model	Additive genetic (A)	Common environment (C)	Unique environment (E)	χ^2	*df*	*P* value	AIC†
TMD pain							
ACE	0.27 (0.00, 0.38)	0.00 (0.00, 0.31)	0.73 (0.61, 0.86)	–	–	–	–
AE	**0.27 (0.15, 0.38)**	**–**	**0.73 (0.62, 0.85)**	**0.00**	**1**	**> .99**	**–2.00**
CE	–	0.23 (0.12, 0.33)	0.77 (0.67, 0.88)	1.70	1	.19	–0.30
Migraine headache							
ACE	0.49 (0.23, 0.57)	0.00 (0.00, 0.23)	0.51 (0.43, 0.60)	–	–	–	–
AE	**0.49 (0.40, 0.57)**	**–**	**0.51 (0.43, 0.60)**	**0.00**	**1**	**> .99**	**–2.00**
CE	–	0.41 (0.33, 0.49)	0.59 (0.53, 0.67)	10.73	1	< .01	8.73

*Proportion of variance (and 95% CI) caused by additive genetics, common environment, and unique environment according to each model; †AIC is a global measure of goodness of fit; the best-fitting and most parsimonious models are shown in **bold**.

Table 3 Bivariate Structural Equation Models of TMD Pain and Migraine Headache in Female Twin Pairs

Shared component*	χ^2	*df*	*P* value	AIC
ACE	–	–	–	–
CE	0.94	1	.33	–1.07
AE	**0.00**	**1**	**.99**	**–2.00**
AC	12.92	1	< .01	10.92
A	12.92	2	< .01	8.92
C	19.15	2	< .01	15.15
E	9.14	2	.01	5.14

*The best-fitting and most parsimonious model is shown in **bold**.

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Table 4 Unique and Shared Additive Genetic and Environmental Effects for TMD Pain and Migraine Headache in Female Twin Pairs*

	Proportion of variance (95% CI)		
Effect	Additive genetic (A)	Common environment (C)	Unique environment (E)
Trait specific			
TMD pain	0.26 (0.01, 0.38)	0.00 (0.00, 0.24)	0.74 (0.65, 0.86)
Migraine	0.49 (0.25, 0.57)	0.00 (0.00, 0.21)	0.51 (0.43, 0.60)
Shared	0.12	–	0.06

*Based on best-fitting bivariate model specified in Table 3.

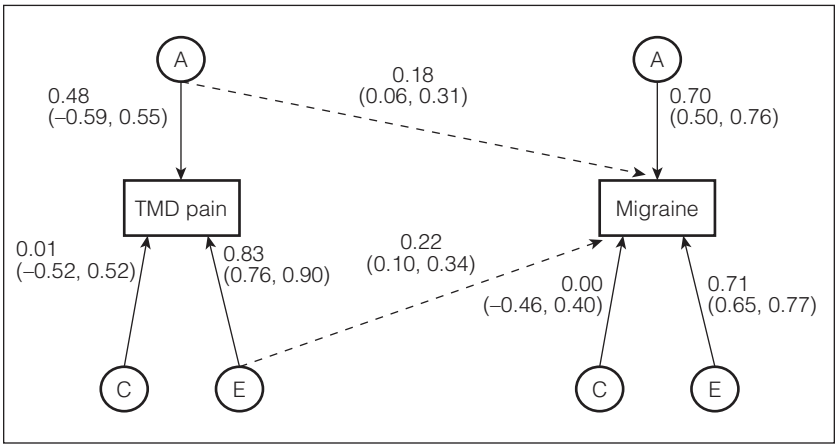

Fig 1 Path diagram depicting additive genetic and unique environmental effects *shared* by TMD pain and migraine headache (*dotted lines*) plus additive genetic (A), common environmental (C), and *unique* environmental (E) effects unique to each trait (*solid lines*). The parameter estimates and 95% CI are path coefficients, indicating the relative importance of the latent variables A, C, and E to TMD pain and migraine headache.

Univariate Structural Equation Modeling

Table 2 shows the results of the univariate structural equation models for TMD pain and migraine headache. The best-fitting model for TMD pain included both additive genetic effects (27%) and unique environmental effects (73%). The best-fitting model for migraine headache included additive genetic effects (49%) and unique environmental exposures (51%).

Bivariate Structural Equation Modeling

The best-fitting, most parsimonious bivariate model included shared additive genetic and unique environmental influences for TMD pain and migraine headache, as presented in Table 3. Based on the best-fitting model, it was estimated that 12% of the genetic component of TMD pain is shared with migraine headache (Table 4). Figure 1 illustrates the best-fitting model with standardized pathway coefficients and the relative magnitude of shared and unique influences on both traits.

Discussion

To the authors' knowledge, this is the first study to examine the shared genetic contribution to TMD pain and migraine headache in a twin population. TMD pain was associated with self-reported physician's diagnosis of migraine headache. A modest but significant genetic component to TMD pain and a significant genetic component to migraine headache in female twins was found. The analyses also suggested that the association between TMD pain and migraine headache in women may be partially due to shared genetic risk factors for both conditions.

Only a handful of twin studies have examined the heritability of TMD pain and symptoms,[20,21] with equivocal findings. For example, Makchalowicz and colleagues found a nonsignificant heritability of 24% in a small sample of twins, concluding that individualized environmental factors were the major determinants of variance.[21] Given the present finding of a significant heritability of 27% in a much larger sample of twins, it is possible that the Makchalowicz et al study was hampered by issues of statistical power. In addition, the present findings are consistent with candidate gene studies that have identified several polymorphisms that may be involved in the development of TMD.[33]

The finding of a significant genetic basis to migraine headache supports previous research on the topic. Migraine headache appears to be a familial disorder,[34–36] with a multifactorial inheritance pattern.[35]

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Twin studies consistently have documented[10,37,38] heritability estimates ranging from 34%[10] to 61%,[37] with stronger genetic effects in women.[38]

The association between TMD pain and migraine headache could be due to multiple biopsychological factors, including the influence of each trait on the other, shared environmental determinants, and shared genetic factors. Both TMD and headache are mediated by the trigeminal nerve and manifest pain in the head or face and pericranial tenderness.[5,11,12] In both TMD and migraine headache, dysregulation of pain modulatory mechanisms in the central and peripheral nervous systems has been reported.[13–16] The present study revealed a modest overlap in the genetic risk factors that increase liability to both TMD pain and migraine headache. However, a review of the relevant literature indicates that studies on shared genetics of the two conditions are lacking. Since both conditions appear to be polygenic, multiple genes likely contribute small amounts to each condition. Recent studies have identified several candidate genes related to TMD and pain sensitivity, such as catecholamine-O-methyltransferase, beta-2 and -3 adrenergic, and serotonin transporter genes.[39–42] Although findings have been mixed,[43,44] other investigations also have found variants of the serotonin transporter gene to be related to migraine headache, especially in women.[45–47] These findings further highlight the potential for shared genetic influences on TMD pain and migraine headache. By focusing attention on shared pathways, researchers can better elucidate two common health conditions simultaneously.

A common feature of TMD and migraine headache is the role of female hormones in the timing and severity of symptoms.[48] Hormonal mediation based on genetic susceptibility also could account for the link between TMD pain and migraine headache. For example, hormonally related candidate gene studies are examining the interaction of female hormones and genetic susceptibility in migraine headache during specific points during the menstrual cycle.[49,50] The authors' own epidemiological data on the comorbidity of TMD with severe headache have substantiated a high prevalence during the reproductive years that decreases in later life, again pointing to potential shared hormonal mediation.[51]

The present findings also suggest that unique environmental and behavioral factors play a role in the influence of each trait on the other. Marital status and psychosocial stress are among commonly reported factors involved in both conditions.[52,53] Clearly, identifying modifiable behavioral factors such as managing stress or changing eating habits, as well as examining the genetic, environmental, social, and cultural mechanisms underlying the relationship between TMD and migraine headache inform effective prevention and treatment strategies for both conditions.

This study had several limitations. First, because the variables were intended as screening items on a large survey, the study was limited to the use of self-reported doctor-diagnosed conditions and brief symptom questions. Of note, however, the study's prevalence estimates for both TMD pain (13%) and migraine headache (20%) were consistent with previous reports of these conditions in women.[1,2,8] Nonetheless, the potentially high level of error in brief assessments would be expected to reduce estimates of genetic effects. Therefore, the estimates of the shared genetic contribution to TMD pain and migraine headache are likely conservative. Second, self-reported physician's diagnosis of migraine headache could have resulted in response biases or misclassification, especially since many individuals with migraine headache may not have been diagnosed by a physician. Furthermore, there was a high correlation between diagnosis and self-reported symptoms characteristic to migraine. However, because both TMD pain and migraine headache were assessed through self-report, potential misclassification due to self-report is unlikely to affect significantly the estimates of association and would not be expected to differ between MZ and DZ twin pairs. Third, it is possible that the phenotypic association of TMD pain and migraine headache in this study is an overestimate because the TMD pain measure included pain in the temple, which is also a symptom of migraine headache.[54] Therefore, the study should be replicated with validated measures of TMD pain and migraine headache. Fourth, no measure of current migraine headache was available, thus the findings are restricted to the association between current TMD pain and lifetime migraine headache. Finally, because the sample was overwhelmingly white and highly educated, the authors were unable to address the role of these factors in the relationship between TMD pain and migraine headache.

Conclusions

The present findings from a community-based sample of twins provide evidence for a modest shared genetic vulnerability to TMD pain and migraine headache in women. Although these results need to be confirmed in future studies using standardized clinical criteria to diagnose TMD pain and migraine headache, this effort highlights the need for more systematic approaches to examining shared genetic

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and environmental factors that link these two conditions. Such research may yield new insights into the common pathophysiology and risk factors for these conditions. Additionally, examining the environmental, social, and cultural mechanisms in these two conditions jointly can identify targets for effective prevention and treatment strategies for individuals with comorbid TMD pain and migraine headache.

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