Twin Analyses of Fatigue

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Prolonged fatigue equal to or greater than 1 month duration and chronic fatigue equal to or greater than 6 months duration are both commonly seen in clinical practice, yet little is known about the etiology or epidemiology of either symptom. Chronic fatigue syndrome (CFS), while rarer, presents similar challenges in determining cause and epidemiology. Twin studies can be useful in elucidating genetic and environmental influences on fatigue and CFS. The goal of this article was to use biometrical structural equation twin modeling to examine genetic and environmental influences on fatigue, and to investigate whether these influences varied by gender. A total of 1042 monozygotic (MZ) twin pairs and 828 dizygotic (DZ) twin pairs who had completed the University of Washington Twin Registry survey were assessed for three fatigue-related variables: prolonged fatigue, chronic fatigue, and CFS. Structural equation twin modeling was used to determine the relative contributions of additive genetic effects, shared environmental effects, and individual-specific environmental effects to the 3 fatigue conditions. In women, tetrachoric correlations were similar for MZ and DZ pairs for prolonged and chronic fatigue, but not for CFS. In men, however, the correlations for prolonged and chronic fatigue were higher in MZ pairs than in DZ pairs. About half the variance for both prolonged and chronic fatigue in males was due to genetic effects, and half due to individual-specific environmental effects. For females, most variance was due to individual environmental effects.

Fatigue is a common symptom in clinical practice; however, physicians have little empirical data on epidemiology or etiology. Fatigue is a presenting complaint for an estimated 7.6% to 13.6% of persons in primary care (Cathebras et al., 1992; Fuhrer & Wessely, 1995), and 5.0 to 7.7% of the general population suffers from prolonged fatigue (Jason et al., 1999). Chronic fatigue syndrome (CFS), where fatigue is disabling, is found at the extreme end of the spectrum. CFS is a clinically defined condition of unknown etiology that is characterized by profound fatigue of at least 6 months duration (Fukuda et al., 1994). Strictly defined, it appears to be comparatively rare in community-based samples (Jason et al., 1999; Reyes et al., 2003), and women are disproportionately afflicted (Afari & Buchwald, 2003; Reyes et al., 2003).

The etiology of the spectrum of fatiguing illness remains unclear. Recent family and twin studies have suggested a role for genetics in the etiology of prolonged and chronic fatigue as well as CFS (Buchwald et al., 2001; Hickie et al., 2001; Hickie et al., 1999; Walsh et al., 2001). Recently, Sullivan et al. (2005a) showed in a national Swedish Twin Registry study that genetic effects for varying levels of fatigue were moderate, accounting for about 30% of the variance across fatigue definitions and gender strata. Because relatively little is known about the genetic epidemiology of fatigue, the goal of this research was to use biometrical structural equation twin modeling to investigate whether genetic and environmental factors differed by gender, across three definitions of fatigue.

Methods

Sample

All twins were participants in the University of Washington Twin Registry, a community-based registry of twin pairs derived from applications for drivers' licenses in Washington State. The construction and characteristics of the University of Washington Twin Registry and its sample population are described in full elsewhere (Afari et al., 2006). Briefly, because drivers' license numbers are assigned on the basis of an individual's name and date of birth, the Department of Licensing asks each new applicant whether s/he is a member of a twin pair to avoid issuing duplicate license numbers. The University of Washington receives lists of applicants who are twins, and each member of the pair is invited to join the University of Washington Twin Registry and complete a health survey. All University of Washington Twin Registry procedures and the data collection involved in this study were approved by the University of

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Washington Institutional Review Board. Informed consent was obtained from all twins.

Zygosity Assignment

All twins completed a mailed questionnaire, in which they were asked questions about childhood similarity to assess zygosity. Studies have shown that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy that is 95% to 98% of that achieved by using biological indicators (Eisen et al., 1989; Torgersen, 1979). The following questions were asked: 'As children, were you and your twin as alike as two peas in a pod, or of ordinary family resemblance?' and 'When you were children, how often did [parents, other relatives, teachers, strangers] have difficulty in telling you apart?' The responses to these similarity questions were then used in a multi-step process to assign zygosity.

Measures of Fatigue

Several different measures of fatigue-related variables were possible, given the data collected by questionnaire. *Prolonged fatigue* was defined as the presence of self-reported fatigue of equal to or greater than 1 month duration. *Chronic fatigue* was the presence of self-reported fatigue for 6 months or longer. Chronic fatigue was therefore a subset of prolonged fatigue. These definitions are consistent with other studies of the epidemiology and genetics of fatigue (Furberg et al., 2005; Sullivan et al., 2005a). Exclusionary criteria were not applied to these variables. CFS was coded through an affirmative response to the question 'Has your doctor ever told you that you have chronic fatigue syndrome?' Pairs with missing data for CFS were excluded from these analyses.

Statistical Analyses

As described at length elsewhere (Neale & Cardon, 1992), we applied a standard approach to structural equation twin modeling of a discrete trait. Briefly, our goal was to assess the magnitudes of latent components of variation underlying the observed trait (e.g., CFS). These analyses postulate that the observed similarity of members of a twin pair results from variance in three types of causes. Additive genetic effects (a^2) are the cumulative impact of multiple genes, individually of small effect, that contribute twice as much to the monozygotic (MZ) as to the dizygotic (DZ) twin correlation, under the assumption that MZ twins are genetically identical while DZ twins share about half of their genes. Shared environmental effects (c^2) to which both members of a twin pair are exposed contribute equally to the correlation in MZ and DZ twins. Individual-specific environmental effects (e^2) reflect environmental experiences that are not shared by the members of a twin pair and tend to make them different in liability to illness. The sum of a^2, c^2, and e^2 is set to 1. The goal of univariate twin analysis is to decompose the variance in liability to the disorder in the population studied into the proportion due to a^2, c^2, and e^2, with 95% confidence intervals. Our primary intention was to assess the confidence intervals on a^2, c^2, and e^2 (Sullivan & Eaves, 2002). Mx was used for all analyses (Neale & Cardon, 1992), employing a script from the GenomEUtwin library (GenomEUtwin) to analyze contingency tables and perform confidence interval calculations (Neale & Miller, 1997).

Results

Participants

At the time of these analyses, a total of 3982 individual twins (1991 twin pairs) had completed the University of Washington Twin Registry survey. Participants ranged from 18 to 90 years of age (mean = 32.4 ± 14.7) and were predominantly female (61%). Most of the participants were White (87%), 33% were married, and 42% had fewer than 12 years of education. There were 1042 MZ twin pairs (52%), 828 DZ twin pairs (42%), and 121 pairs of unknown zygosity (6%). The prevalence rate of prolonged fatigue was 16% and of chronic fatigue was 12%. CFS was reported by 2.5% of all twins.

Twin Correlations

Tetrachoric correlations and associated data for the three definitions of fatigue by zygosity groupings are given in Table 1. For prolonged fatigue, the tetrachoric correlations between female MZ and DZ twins were similar (.39 vs. .32), while correlations between male MZ and DZ twins differed substantially (.55 vs. –.02). The female DZ twin correlation was considerably larger (.32) than the other DZ correlations (–.02, .05, –.20).

The results for analyses of chronic fatigue were similar. The tetrachoric correlations between female MZ and DZ twins were comparable (.36 vs. .32), but the correlation for male monozygotic twins was substantially larger (.51) than the correlation for male DZ twins (–.07).

In contrast, the female MZ correlation for CFS exceeded the female DZ correlation (.61 vs. .40). The MZ male correlation for CFS was similar to the MZ male correlations for prolonged and chronic fatigue; however, due to low cell sizes, we were not able to calculate tetrachoric correlations for CFS among DZ males.

Structural Equation Modeling

We next conducted structural equation twin modeling to estimate the genetic architecture of these three traits. Results of twin models are depicted in Table 2. For prolonged fatigue, the heritability (a^2) was estimated at 51% in males (95% CI: 13–69%) and considerably exceeded that in females (18%), whose 95% CI included zero. For males, about half the variance was due to genetic effects, and half was due to environmental effects specific to individuals. For females, most of the variance was due to individual-specific environmental effects, but a substantial component of shared environmental effects could not be compellingly excluded.

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Table 1

Tetrachoric Correlations and Other Descriptive Data for Three Fatigue Definitions by Zygosity Groupings

Phenotype	Zygosity	Tetrachoric correlation	ASE	Contingency table cell counts* (*N*)			
				T1–/T2–	T1–/T2+	T1+/T2–	T1+/T2
Prolonged fatigue	MZ-F	.39	.07	474	82	66	39
	DZ-F	.32	.11	171	34	39	20
	MZ-M	.55	.10	316	20	31	14
	DZ-M	–.02	.22	109	14	17	2
	DZOS-MF	.05	.17	133	38	15	5
	DZOS-FM	–.20	.15	151	23	53	4
Chronic fatigue	MZ-F	.36	.08	521	63	55	22
	DZ-F	.32	.12	191	29	31	13
	MZ-M	.51	.12	329	18	25	9
	DZ-M	–.07	.26	116	11	14	1
	DZOS-MF	.16	.18	146	30	11	4
	DZOS-FM	–.04	.16	167	19	41	4
Chronic fatigue syndrome†	MZ-F	.61	.12	616	14	13	5
	DZ-F	.40	.21	237	11	8	2
	MZ-M	.51	.25	362	3	9	1
	DZ-M	—	—	139	2	1	0
	DZOS-MF	—	—	181	5	0	0
	DZOS-FM	.72	.24	217	1	5	1

Note: MZ = monozygotic; DZ = dizygotic; DZOS = DZ opposite sex; F = female; M = male; ASE = asymptotic standard error; T1 = twin 1; T2 = twin 2.

*Counts of T1 by T2 for each phenotype-zygosity grouping; – means absent and + means present.

†Unable to calculate all correlations due to low cell sizes.

For chronic fatigue, the same general pattern of results was found as for prolonged fatigue. However, the male heritability 95% CI included zero, due to the smaller numbers of affected individuals and decreased statistical power. For CFS, the low prevalence in males (Afari & Buchwald, 2003) meant that several cells were empty in the zygosity contingency tables. As a consequence, twin models could be conducted only in females. Compared to the other fatigue definitions, the heritability estimate for CFS in females was larger (51%), and the precision was lower (95% CI: 0–82%). Environmental variance was split between shared (12%) and unshared (36%) components.

Discussion

The goal of this study was to examine genetic and environmental influences on fatigue, and investigate whether these influences vary by gender. We found intriguing differences in the patterns of genetic influences for women and men. In women, correlations for prolonged and chronic fatigue were quite similar for MZ and DZ pairs, but not for CFS. This was in contrast to the much higher correlations in male MZ pairs than in male DZ pairs. Structural equation modeling results confirmed a possible genetic contribution to CFS in females. In contrast, for prolonged and chronic fatigue definitions, individual environmental effects predominated for females, whereas for males, approximately half the variance was due to genetic effects, and half was due to individual-specific environmental effects. Shared environmental effects were minimal for both females and males, but could not be definitively excluded.

The prevalence of fatigue and its gender distribution were similar to findings in a Swedish Twin Registry (Evengard et al., 2005) and in US samples (Furberg et al., 2005). However, studies of heritability among the Swedish twins did not find strong evidence for a genetic contribution as definitions of fatigue became more refined (Sullivan et al., 2005a). By contrast, our findings in this US sample do suggest a genetic contribution to CFS, as evidenced among females in this study. Several other studies have examined interactions between gender and genetic contributions to fatigue, with inconsistent findings. One study investigated fatigue that interfered with daily activities for 5 days or more, and found evidence for etiological heterogeneity, with a stronger genetic effect in women, and shared environmental effects in men (Sullivan et al., 2003). More recently, however, a large study among 12,407 Swedish twin pairs revealed remarkably consistent findings between women and men (Sullivan et al., 2005a). On the whole, the literature from twin research provides little consensus as to gender differences in genetic and environmental contributors for fatigue. Further research is needed, with

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Table 2

Structural Equation Twin Models for Three Fatigue Definitions

	Prolonged fatigue	Chronic fatigue	Chronic fatigue syndrome
Type of twin model	6-group sex limitation	6-group sex limitation	2-group (females only)
Model GOF	$\chi^2 = 18.7$, $df = 11$, $p = .07$	$\chi^2 = 17.4$, $df = 11$, $p = .10$	$\chi^2 = 2.91$, $df = 3$, $p = .41$
Male — a^2 (95% CI)	51% (13–69%)	47% (0–68%)	—
Male — c^2	0% (0–33%)	0% (0–39%)	—
Male — e^2	49% (31–71%)	53% (32–79%)	—
Female — a^2	18% (0–54%)	12% (0–53%)	51% (0–82%)
Female — c^2	23% (0–48%)	26% (0–48%)	12% (0–72%)
Female — e^2	59% (46–74%)	62% (47–78%)	36% (18–65%)

Note: GOF = goodness-of-fit; *df* = degrees of freedom; CI = confidence interval; a^2 = proportion of variance in liability due to additive genetic effects; c^2 = proportion of variance in liability due to environmental effects common or shared between co-twins; e^2 = proportion of variance in liability due to environmental effects unshared between co-twins.

an emphasis on recruiting adequate numbers of males into studies.

Recently, association studies and microarray analyses have revealed potential genes that may play an important part in chronic, disabling fatigue. Candidate genes that distinguished fatigued individuals from well individuals have been identified (Carmel et al., 2006), as well as markers that consistently identified subjects with CFS (Goertzel et al., 2006). Associations have also been found with 11 candidate genes involved in hypothalamic–pituitary axis functioning among CFS sufferers (Smith et al., 2006). These analyses take us one step closer to definitively classifying the spectrum of disabling fatiguing illness. The same line of research may also uncover the physiologic basis for this perplexing condition, and guide clinicians in treating fatigue complaints.

A major strength of this study was the use of a community-based, US registry of twins, distinguishing it from prior epidemiologic studies in Scandinavia (Evengard et al., 2005; Sullivan et al., 2005a), and disease-specific registries for chronic fatigue sufferers (Buchwald et al., 2001). In addition, our results are generalizable, because we obtained data on a variety of definitions of fatigue with relevance to clinical settings. Finally, we performed analyses stratified by gender, which add a more nuanced understanding to the genetic epidemiology of fatigue.

This study does, however, have several limitations. While twin studies are exceptionally well-suited to examine hypotheses that polygenic or recessive genes, for example, might contribute to fatigue, we cannot verify the underlying assumptions of polygenic inheritance, nor can we confirm that MZ and DZ twins grew up in equal environments. Moreover, CFS was assessed by a single-item self-report of a doctor's diagnosis, which can be subject to response bias. This format also excludes symptomatic individuals who have not been formally diagnosed, or who have limited access to health care. Even when a clinical diagnosis of CFS has been made, there is concern that the 1994 Center for Disease Control case definition of CFS may not accurately classify all individuals with impairing levels of fatigue (Sullivan et al., 2005b). Finally, small cell sizes in several analyses limit the conclusiveness of our findings, and we were in fact unable to complete analyses of CFS in males, because too few individuals were affected.

Nonetheless, this study adds further insight into the complexity of the genetic basis for fatigue. We would recommend further work on gender differences in fatigue presentation and among larger samples of men. Given the promising results of early association studies, continued investigation of genetics and gene-environment interactions in the etiology of persistent fatigue is warranted.

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