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# The Chronic Fatigue Twin Registry: method of construction, composition, and zygosity assignment

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Chronic fatigue syndrome (CFS) and the symptom of chronic fatigue are conditions of unknown etiology. The Centers for Disease Control and Prevention (CDC) define CFS as an illness characterized by ≥ 6 months of disabling fatigue associated with muscle pain, pharyngitis, and alterations in mood, sleep and neurocognition. We constructed a registry of twins with chronic fatigue to facilitate research on the impact of illness, the associated medical and psychosocial factors, and the heterogeneous proposed mechanisms for these conditions. We have recruited 204 twin pairs in which one or both members reported persistent fatigue through patient support group newsletters (60%), clinicians/researchers familiar with CFS (12%), notices placed on electronic bulletin boards for CFS (11%), twin organizations and researchers (6%), relatives and friends (3%) and other sources (8%). Complete data are available for 177 pairs (87%). Twins completed an extensive questionnaire booklet that included measures of physical and mental health, functional status, and psychosocial factors; a structured psychiatric interview was also conducted by telephone. Twins were classified using three increasingly more stringent diagnostic criteria for chronic fatigue: 1) ≥ 6 months of fatigue (115 discordant and 61 concordant pairs); 2) chronic fatigue with additional symptoms and application of the medial exclusions of the CDC CFS case definition as obtained by self-report (92 discordant and 41 concordant pairs) and; 3) chronic fatigue with additional symptoms unexplained by self-reported medical conditions and psychiatric diagnoses as determined by the structured interview (69 discordant pairs and 25 concordant pairs). Despite the limitations of a volunteer registry, the Chronic Fatigue Twin Registry promises to be an important resource for research on CFS and chronic fatigue.

Keywords: chronic fatigue syndrome, fatigue, twins, genetics, registries

## Introduction

Fatigue is a common complaint in primary care settings[1–5] reported by at least 20% of patients seeking medical care. Likewise, large community surveys indicate that up to half of the general population experiences fatigue, typically of limited duration.[6–8] In most cases, the fatigue is transient, explained by prevailing circumstances, relieved by rest, and of little cause for concern. In both community and clinical settings, fatigue is observed more frequently among women than men.

Fatigue can, however, be both persistent and debilitating. In some cases, it may be the result of a recognized medical and psychological condition. Less commonly, such fatigue may be the hallmark of chronic fatigue syndrome (CFS), an illness of unknown etiology characterized by disabling fatigue associated with muscle pain, pharyngitis, and alterations in mood, sleep and neurocognition.[9] In clinical settings, CFS is reported most frequently among females.[10] Initially the prominence of infectious, neurocognitive and psychological symptoms suggested a viral illness or psychiatric disorder.[11,12] Subsequently a variety of findings related to sleep pathology, and neuroendocrine, immunological, and autonomic dysfunction have been observed in subgroups of CFS patients.[13–16] Physical examination and routine laboratory tests are typically normal.[9,10]

Of direct relevance to CFS, twins are especially helpful for the study of diseases of unknown cause, and those for which the appropriate comparison groups are ill-defined.[17] With this in mind, in 1995 we obtained funding from the National Institute of Allergy and Infectious Diseases to undertake the construction of the Chronic Fatigue Twin Registry to facilitate the investigation of the association of CFS and chronic fatigue with diverse measures of physical and mental health. The primary objectives of the project were to: 1) establish a national registry of twins with chronic fatigue and 2) conduct an intensive co-twin control study of CFS discordant

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monozygotic (MZ) twins in which both members of the pair underwent a comprehensive in-person examination. This paper describes the development, composition, and zygosity assignment in the Chronic Fatigue Twin Registry.

## Methods

### Ascertainment of twins

Twin pairs used in this study were recruited through advertisements placed in twin organizations and patient support group newsletters, notices placed on electronic bulletin boards for CFS, general population twin registries, and through letters sent to clinicians and researchers familiar with CFS. Advertisements recruited twins in which one or both members reported persistent fatigue and specifically did not require a physician fatigue-related diagnosis. We took this approach for several reasons: 1) the criteria for CFS are often not strictly applied in community settings; 2) some individuals with fatigue may not have sought medical care for this complaint; and 3) we wished to classify twin pairs using increasing stringent and specific fatigue criteria and to apply an algorithm based on the 1994 Centers for Disease Control and Prevention (CDC) CFS case definition.[9]

In total 540 twins were mailed the Twin Registry Booklet (see below); of these 398 (74%) were returned. Of the 204 twin pairs identified in which one or both members reported persistent fatigue, 60% were recruited through patient support group newsletters, 12% through clinicians/researchers familiar with CFS, 11% through notices placed on electronic bulletin boards for CFS, 6% through twin organizations and researchers, 3% through relatives and friends, and 8% through other sources. Complete data were available for 177 pairs (87%). The twin making the initial inquiry was contacted, asked to provide their co-twin's name, address and telephone number, and to contact their twin to provide preliminary information on the study. Written, informed consent was obtained from each subject in accordance with regulations of our institutional Human Subjects Office.

### Data collection

A multi-stage data collection procedure was used to establish the Chronic Fatigue Twin Registry. After obtaining an inquiry from a twin who reported fatigue of $\geq 6$ months duration, a questionnaire booklet was mailed to both members of the pair. If after 6 weeks the completed booklet was not returned a research assistant attempted to telephone the potential Registry member to determine if they had received the booklet; a new booklet was sent in the event that the first mailing had not been received. Further follow-up was conducted as needed to obtain completed questionnaire booklets. Following receipt of the booklet the research assistant reviewed the information for completeness and then telephoned the respondent to conduct a structured psychiatric interview. This interview typically lasted $1\frac{1}{2}$ hours for fatigued and 1 hour for non-fatigued participants.

### Measures

The booklet and structured interview produced thousands of individual variables and numerous scaled scores relevant to chronic fatigue for each respondent. Broadly the data collected can be classified as items related to the assignment of zygosity, the classification of fatigue and CFS, and the identification of factors associated with fatigue either as a cause or consequence. Below we discuss the specific measures within each of these three domains of measurement.

### Assignment of zygosity

A prerequisite for the establishment of a useful chronic fatigue twin registry is the assignment of zygosity. Several items within the booklet were obtained to provide a way of assigning zygosity from the questionnaire without having to resort to the collection of biological samples for DNA assessment in all Registry members. The items collected included the 'peas in a pod' question, along with questions about childhood similarity and the frequency of being mistaken for one another as children (Table 1). We used these questions in a multi-step process similar to those suggested by Magnus[18] and Eisen.[19] In the first step of the method, we assigned zygosity to same sex twins who gave concordant answers to the 'peas in a pod' question; pairs who said they were of ordinary family resemblance were considered dizygotic (DZ) and pairs who were 'as alike as two peas in a pod' were considered MZ. It has been demonstrated that adult twins who give concordant answers to the 'peas in a pod' question correctly classify themselves as MZ or DZ with an accuracy of 95–98%.[20] Opposite-sex twin pairs were categorized as OZ. Non-OZ pairs with discordant responses were initially assigned to an indeterminate zygosity (IZ) category. The second step in the process constructed intra-pair mean scores from each of the childhood similarity and mistakenness questions; this was done by scoring the response categories for individuals as follows: 1 = similar or always mistaken, –1 = dissimilar or never mistaken, and all other responses = 0. These values led to

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Table 1 Questionnaire items and responses used for zygosity assignment

| Zygosity Questions | Response Category | | |
|---|---|---|---|
| | Alike | Don't know | Ordinary resemblance |
| 'Peas in a pod' | 1 | 0 | –1 |
| | | Some of the time or Don't | |
| Mistaken as children by | All the time | know | Never |
| Parents | 1 | 0 | –1 |
| Other brothers and sisters | 1 | 0 | –1 |
| Grandparents | 1 | 0 | –1 |
| Classmates | 1 | 0 | –1 |
| Teachers | 1 | 0 | –1 |
| Strangers | 1 | 0 | –1 |
| | | Somewhat similar | |
| Childhood similarity | Very similar | or Don't know | Not similar |
| Eye color | 1 | 0 | –1 |
| Hair color | 1 | 0 | –1 |
| Hair type | 1 | 0 | –1 |
| Height | 1 | 0 | –1 |
| Weight | 1 | 0 | –1 |
| Teeth | 1 | 0 | –1 |
| Voices | 1 | 0 | –1 |
| Muscular strength | 1 | 0 | –1 |
| Temperaments | 1 | 0 | –1 |
| Musical abilities | 1 | 0 | –1 |
| Language abilities | 1 | 0 | –1 |
| Manual skills (dexterity) | 1 | 0 | –1 |

intra-pair mean scores that could take on five values (–1, –0.5, 0, + 0.5, + 1) with negative scores indicating a lack of similarity and positive scores a high degree of similarity. The third step in the process involved the creation of a summary score by adding together the intra-pair mean scores that were derived from each item. As a fourth step, we fitted a logistic regression model predicting zygosity (derived exclusively from the 'peas in a pod' question) from the childhood similarity and mistakenness summary score. The fifth step used the regression coefficients estimated from the model to obtain predicted probabilities of zygosity (i.e. the probability of being an MZ twin) for twin pairs that were initially classified as IZ. These probabilities were used to reassign the IZ pairs a final zygosity status as MZ or DZ.

## Classification of fatigue

Several different approaches were used to measure the multi-faceted phenomena of fatigue (Table 2). All twin pairs completed the Multidimensional Assessment of Fatigue, a 14-item survey that ascertains the characteristics of fatigue across a variety of domains including duration, intensity, perceived and functional impact, and behavioral consequences of fatigue.[21] A second brief scale was the six-item fatigue attribution scale which was developed for use in fatigued patients.[22] It inquires about an individual's perception of disease, in particular, physical (e.g. viral) versus psychological etiologies.

We used three progressively more stringent methods to classify chronic fatigue. The first method defined chronic fatigue based on the response to the single question: 'Have you been fatigued for at least 6 months?' No further inclusionary or exclusionary conditions were applied.

The second method defined chronic fatigue that was not explained by medical exclusions, classifying all twins according to the CDC CFS research criteria using data obtained solely from the mailed questionnaire. An algorithm was developed that defined chronic fatigue using both the inclusionary and medical exclusionary (including obesity) components of the CDC case definition.[9] To be classified as having medically unexplained chronic fatigue, twins were required to report fatigue of ≥ 6 months duration that was not lifelong and that resulted in a substantial reduction of occupational, educational, social, or personal activities. Furthermore, fatigued twins had to endorse the presence of four or more of the following eight CDC CFS symptom criteria: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multi-joint pain, new headaches, unrefreshing sleep, and post-exertional fatigue.[9] Twin were excluded from this definition of chronic fatigue if they were obese (body

Table 2 Fatigue measures and definitions of chronic fatigue

| |
|---|
| Fatigue measures |
| Multidimensional Assessment of Fatigue |
| Fatigue Attribution Scale |
| Criteria for classification of chronic fatigue |
| Definition 1 |
| ≥ 6 months of chronic fatigue |
| Definition 2 |
| ≥ 6 months of chronic fatigue |
| Medical exclusions (e.g. steroid-dependent, asthma, infectious hepatitis, diabetes, malignancies other than skin cancer, congestive heart failure, stroke, cirrhosis, multiple sclerosis, and systemic lupus erythematosus) |
| Definition 3 |
| ≥ 6 months of chronic fatigue |
| Medical exclusions (e.g. steroid-dependent, asthma, infectious hepatitis, diabetes, malignancies other than skin cancer, congestive heart failure, stroke, cirrhosis, multiple sclerosis, and systemic lupus erythematosus) |
| Psychiatric exclusions due to: |
| current alcohol or substance abuse/dependence |
| lifetime mania, hypomania, bipolar disorder, schizophrenia, major depression with psychotic or melancholic features, anorexia or bulimia nervosa |

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mass index > 45) or self-reported any of the exclusionary medical conditions.

To determine health conditions, we used a checklist of self-reported medical problems; twins indicated whether a condition was currently active or was resolved and whether it had been evaluated by a physician. The application of the CDC defined exclusionary medical conditions to the checklist was determined by consensus of two general internists, a psychiatrist with expertise in CFS, an infectious disease specialist and an internist/emergency room physician with knowledge of, but little exposure to, patients with CFS. Examples from the comprehensive list of exclusionary disorders included (but was not limited to) steroid-dependent asthma, infectious hepatitis, diabetes, cancer (other than skin), congestive heart failure, stroke, cirrhosis, multiple sclerosis, and systemic lupus erythematosus. To assess the performance of our list of exclusionary conditions, subjects' self-reported health conditions were compared with physician confirmation of these diagnoses via chart review and telephone contact with treating physicians for a subsample of twins. Among 40 participants, we did not find any fatigued participant to be ineligible due to a exclusionary condition that was missing or inaccurately obtained in the self-reported questionnaire. Conversely, no exclusionary conditions were observed in any twin who was reported to be in good health.

The third method defined chronic fatigue that was not explained by medical and psychiatric exclusions; this method further restricted our sample on the basis of psychiatric diagnoses considered exclusionary by the CDC case definition.[9] Psychiatric conditions were ascertained from the structured telephone interview using the Diagnostic Interview Schedule (DIS), Version III-A.[23] The DIS assigns current and lifetime diagnoses by computer algorithm based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Version III-Revised.[24] The specific exclusionary diagnoses obtained include: lifetime mania, hypomania, bipolar disorder, schizophrenia, major depression with psychotic or melancholic features, anorexia or bulimia nervosa, and current alcohol or substance abuse/dependence. Identical psychiatric exclusionary criteria were applied to both the chronically fatigued and non-fatigued twins.

## Other measures

We used a variety of measures to examine diverse factors potentially associated with chronic fatigue (Table 3). Physical health and habits were determined with a questionnaire on past and current medical and psychological problems that included the symptoms characteristic of CFS; a control version was used for non-fatigued individuals. This questionnaire has been used in over 2000 chronic fatigue patients in three study sites during the past 13 years. Items constituting the temporo-mandibular disorders Research Diagnostic Criteria[25] and the International Criteria for Sjogrens Syndrome[26] were also collected. An atopy and allergy section obtained detailed information on drug and respiratoy/nasal allergies (hay fever), asthma, dermatitis, eczema, exposures, and family history of atopy. Sleep was evaluated with the Sleep Disorders Questionnaire which was designed to describe quality and quantity of sleep and to predict the presence of common sleep disorders based on clustering of self-report responses.[27] It has four subscales: psychiatric, narcolepsy, sleep apnea, and restless legs/periodic limb movements. Participants also completed a 2-week sleep diary.

To assess the social environment we used the Social Support Questionnaire to elicit the number of available others to whom a person can turn in times of need in a variety of situations and the level of satisfaction with the perceived support.[28] The Revised Ways of Coping Checklist prompts subjects to indicate their response to stressful events yielding scores on eight scales: problem-focused, seeks social support, blamed self, wishful thinking, avoidance, blamed others, count your blessings, and religiosity.[29] The Medical Outcomes Short-Form General Health Survey is a widely used 36-item functional

Table 3 Assessment of factors associated with chronic fatigue

| | |
|---|---|
| Demographics, health history, health habits | |
| Demographics | Age, sex, race, socioeconomic status, occupation, employment, marital status, children |
| Health history | Medical and psychiatric history, atopy and allergies; temporomandibular disorders questionnaire (using Research Diagnostic Criteria); Sjogrens Syndrome items (International Criteria), chronic pain screener |
| Health habits | Smoking, alcohol consumption, exercise, Sleep Disorders Questionnaire, sleep diary |
| Assessment of social environment | |
| Social Support Questionnaire | |
| Revised Ways of Coping Checklist | |
| Medical Outcomes Study Short-Form 36 General Health Survey | |
| Threatening life events/victimization and abuse | |
| Victimization/abuse survey | |
| Brugha Threatening Life Events | |
| Neuropsychological measures | |
| Diagnostic Interview Schedule (DIS) | |
| General Health Questionnaire | |
| Personality Diagnostic Questionnaire-Revised | |
| NEO Five Factor Inventory | |
| Multiple Ability Self-Report Questionnaire | |

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status measure that contains eight subscales: physical, emotional, social and role-functioning, body pain, mental health, vitality, and general health.[30]

Specific life events were catalogued with a semi-structured screening questionnaire administered on the telephone following the structured psychiatric interview. Items inquired about included ever having been assaulted by a stranger or being physically or sexually abused in childhood or adulthood. Additional information was collected on age at the time of the offense, relationship of the offender, whether anyone was told, and abuse frequency and duration. To assess stress associated with 12 events such as moving, divorce or death of a loved one, we used the Brugha Threatening Life Events Inventory.[31]

In terms of neuropsychological measures, the General Health Questionnaire was used to ascertain somatic and psychological distress; elevated scores correlate with psychiatric diagnoses.[32] The Personality Diagnostic Questionnaire-Revised is a self-report instrument that yields presence/absence classifications for 11 personality disorders, with the advantage of being a self-report instrument and the resultant decreased need for professional time.[33] We also used the Neuroticism and Introversion–Extraversion subscales of the Revised NEO (Neuroticism, Extraversion, Openness) Personality Inventory which defines broad domains of the 5-factor model of personality.[34] The Multiple Ability Self-Report Questionnaire assessed language, visuo-perceptual, verbal memory, visual memory, and attention and correlates well with objective performance on tests assessing the same domains.[35]

## Clinical study

One of the primary reasons for establishing the Chronic Fatigue Twin Registry was to identify 20 MZ CFS-discordant twins who would be willing to undergo an intensive 7-day clinical evaluation. The protocol included a complete physical examination and extensive laboratory studies that tested many of the major hypotheses concerning the pathophysiology and etiology of CFS (e.g. tilt table testing, viral assays, studies of immune function). Using information from the mailed questionnaire, psychiatric interview, medical records obtained from all physicians seen during the previous 5 years, and telephone interview with twins' physicians, potentially eligible twin pairs were screened for the presence of CFS in one twin and good health in the other. All 20 MZ CFS-discordant sets have been examined in person; the data from the evaluation of this highly selected subsample will be reported elsewhere.

## Results

The initial 'peas in the pod' classification of zygosity identified 107 MZ and 41 DZ twins; 20 additional OZ DZ twins were also available (Table 4). Nine pairs could not be readily classified using the 'peas in the pod' question. The childhood similarity and mistakenness summary score was constructed using those same-sex twins initially classified as MZ and DZ; the mean value of the score differed according to zygosity (MZ mean = 10.9, DZ mean = –6.2; $P < .001$). Using the estimated regression coefficients from a logistic regression between initial zygosity and the summary score, a predicted probability of being an MZ was calculated for each of the IZ pairs. Five of the pairs had a very high probability ($> 0.90$) of being MZ and three of the pairs had a very low probability ($< 0.15$) of being MZ twins. The remaining pair had a probability of 0.57 that we assigned as MZ. Thus our final Registry zygosity classification resulted in 113 same sex MZs, 44 same sex DZs and 20 OZ DZs.

Table 5 displays the sociodemographic characteristics of the Registry. Most of the twins in the Registry are middle-aged adults, with a mean age of 47 as of 1999. The Registry also has a high proportion of females (89%). The vast preponderance of the twins are white and the majority have some college education. Most are married and on average have 1.5 children. Virtually all the twins were reared together. For fatigued twins, the average duration of fatigue is 9 years.

The basic concordance data for the three increasingly more stringent definitions of fatigue is presented in Figure 1 according to zygosity. The concordance rate for ≥ 6 months of fatigue (definition 1) was greater in MZ (41%) than DZ (24%) pairs suggesting a genetic influence on chronic fatigue

Table 4 Classification of zygosity

| | Initial 'Peas in a pod' classification, n (%) | Predicted probabilities | Final classification n (%) |
|---|---|---|---|
| Zygosity | | | |
| MZ | 107 (61) | – | 113 (64) |
| DZ | 41 (23) | – | 44 (25) |
| OZ | 20 (11) | – | 20 (11) |
| IZ | 9 (5) | – | – |
| IZ Twin identification | | | |
| A | | 1.00 | |
| B | | 1.00 | |
| C | | 0.99 | |
| D | | 0.91 | |
| E | | 0.91 | |
| F | | 0.57 | |
| G | | 0.14 | |
| H | | 0.01 | |
| I | | 0.00 | |

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Table 5 Characteristics of participants in the Chronic Fatigue Twin Registry

| | | |
|---|---|---|
| Sex and zygosity, [a]n (%) | | |
| Male-male MZ | 7 | (4) |
| Female–female MZ | 106 | (60) |
| Male–male DZ | 3 | (2) |
| Female–female DZ | 41 | (23) |
| Male–female DZ | 20 | (11) |
| Demographics | | |
| Age, mean years in 1999 (±SE) | 47 | (±0.8) |
| White, n (%) | 170 | (96) |
| Education, mean years (±SE) | 14.8 | (±0.13) |
| Children, mean number (±SE) | 1.5 | (±0.1) |
| Married, n (%) | 243 | (64) |
| Raised together, n (%) | 171 | (97) |
| Length of fatigue, years[b] | 9 | (±0.6) |

[a]based on 177 complete twin pairs; [b]for 188 fatigued twins

(P = 0.031 by Fisher's exact test). This difference in concordance rates became progressively more pronounced after first applying the medical exclusion criteria (definition 2, P = 0.020) and next applying both medical and psychiatric exclusion criteria (definition 3, P = 0.006).

## Discussion

Many theories on the pathophysiology of CFS have been suggested, but research has failed to demonstrate a unifying mechanism. Most findings remain questionable and/or controversial for a number of reasons. Some have not been readily replicated whilst others appear to be isolated observations with poorly understood relationships to other clinical or laboratory features associated with CFS. In addition, an ongoing methodological dilemma is the choice of appropriate control subjects for CFS patients; recent studies have compared patients with normal persons, patients with chronic medical and psychiatric disorders, and sedentary health subjects. Furthermore, although most prior studies have used a case-control design, CFS cases have not always been well-matched to controls even for age, sex and psychiatric illness.[36,37] Much has also been made of predisposing and precipitating factors, yet no study of CFS has examined these factors while controlling for genetic and common familial effects of childhood and youth. These design limitations, and the lack of a diagnostic test, have led to major limitations in our understanding of CFS and chronic fatigue.

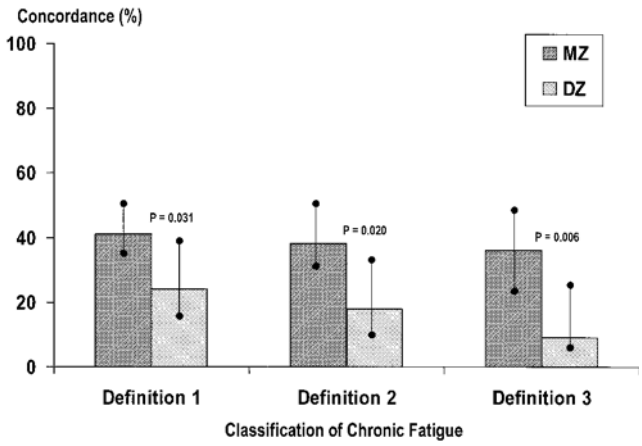


Figure 1 Concordance rates for chronic fatigue in MZ and DZ twins

Twin studies have not been widely used to examine CFS and other chronically fatiguing conditions. In this regard, an exhaustive, computerized search of the medical literature of the past decade failed to yield a single citation on twins and CFS. However, whilst CFS has not been investigated using a twin study design, there have been some recent classical studies using a scaled measure of fatigue and several papers on energy metabolism. Using the Australian Twin Registry, researchers have demonstrated that fatigue appears to be under genetic influence that is distinct from the genetic influence on depression and anxiety.[38] Moreover, important factors in energy expenditure such as level of habitual physical activity, resting metabolic rate, energy cost of exercise, endurance performance response to training and $VO_2$ max are all, to some extent, genotype-dependent.[39–44] Taken together, the poorly understood nature of the illness, the lack of clarity about appropriate controls, and the success of twin studies in examining energy metabolism all suggested to us that a Chronic Fatigue Twin Registry would be a fruitful approach to the study of fatigue.

This approach has several potential limitations. It is important to acknowledge that the method we used to identify the chronically fatigued twin sample was not ideal. Solicitation by advertisement resulted in a volunteer sample of twin pairs with the potential for ascertainment problems. However, the more desirable strategy of systematically identifying twins with CFS and chronic fatigue from a well-defined, truly population-based twin registry would have been extremely difficult and inordinately costly. There are few population-based registries in the United States and those containing only male veterans (the National Academy of Science WW-II Twin Registry and Vietnam Era Twin Registry) represent a highly inefficient sampling frame for

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studying a disorder that is concentrated in females. Even if we had attempted to ascertain CFS twins from a population-based twin registry that contains large numbers of females (such as the Mid-Atlantic Twin Registry) it would have proved extremely difficult because the prevalence of CFS is low (< 2%), the diagnoses of CFS and other chronically fatiguing illnesses are not typically available in these registries, and until recently CFS did not have an assigned International Classification of Disease (ICD) code. It was because of these difficulties that we used a volunteer sample to form our Chronic Fatigue Twin Registry.

Although we repeatedly emphasized in all advertisements and contacts with support groups and physicians that probands were desired regardless of either the health of their co-twin or a definitive diagnosis, it is likely that subjects screened themselves as either eligible or ineligible for the Registry. This possibility is not likely to be a major impediment for co-twin control studies using CFS discordant pairs. For classical twin studies using the Registry careful attention needs to be given to the possibility of ascertainment bias. One type of ascertainment bias would result if twin pairs in which both members were fatigued were more likely to volunteer for the Registry and complete the lengthy booklet. Furthermore, it is possible that MZ twins who were concordant for fatigue and CFS had a higher probability of participation than DZ concordant twins. These biases might lead to an overestimate of the concordance and genetic influence for chronic fatigue and CFS. On the other hand, if MZ discordant twins were more likely than DZ discordant to volunteer, their over-representation might deflate the difference in concordance rates even if an actual difference exists in the population. This pattern could occur if MZ discordant twins were more likely to participate since, in a second phase, a week-long intensive evaluation was offered to selected CFS discordant MZ, but not DZ, twins.

Another possible limitation is the method we used to define and measure fatigue and exclusionary medical conditions. Whilst a clinical examination of all twins was not feasible, we closely followed the CFS diagnostic criteria articulated by CDC. In addition, our three increasingly more stringent measures of fatigue were consistent with those employed by several recent large epidemiological studies (L Jason, L Steele, S Reyes, personal communication, 1999). We were likewise concerned with the use of self-reported health conditions. This methodology could result in either an overestimate or underestimate of the actual rate of chronic fatigue for definitions 2 and 3 depending on whether individuals did not report conditions which might be exclusionary or incorrectly claimed to have been diagnosed with conditions they did not actually have. Nonetheless, in our clinical subsample we found that the measurement of exclusionary medical conditions using self-report was adequate; in no case was a CFS twin participating in the intensive in-person study found to be ineligible due to an exclusionary condition that was inaccurately obtained in the self-reported questionnaire.

Finally, we have appointed a committee to establish policy and review requests for use of the Chronic Fatigue Registry. A wide range of applications for use of the Registry are being considered including mailed questionnaires, telephone interviews, in-person assessments, examinations of biological specimens, and requests for use of currently available information. Once a study is completed, all data collected becomes a permanent part of the Registry and is available for use by other investigators. To encourage continued participation, all twins receive birthday cards, small gifts, and the annual Twin Registry Newsletter that provides general information on the Registry, updates on CFS, and progress reports on studies using the Registry. A questionnaire which accompanies the Newsletter collects longitudinal data on all twins and has achieved a response rate of up to 85%. Using these follow-up questionnaires, we have collected self-report measures that assess domains for which objective data has been collected in the clinical evaluation. This paradigm allows comparisons not possible with the smaller sample size of the intensive study.

The development of the Chronic Fatigue Twin Registry was prompted by the need to identify a pool of MZ CFS-discordant twins for participation in an intensive clinical evaluation. However, the Registry has proved to be an invaluable adjunct to the intensive clinical co-twin study in a number of ways. First, many questions regarding sleep patterns, psychiatric co-morbidity, overlapping syndromes, and functional status can be examined using self-report data obtained from the mailed questionnaire and psychiatric diagnoses from the structured interview. Second, although a volunteer twin registry of chronic fatigue twins is imperfect, it does provide an opportunity to investigate potential genetic and non-genetic predisposing factors for CFS. Third, the use of three definitions of chronic fatigue that apply increasingly more restrictive diagnostic criteria enhances the utility of the Registry for future genetic epidemiological studies of fatigue. Data on the accuracy and reliability of self-report for CFS from the Twin Registry also has broader implications for both research and clinical practice. In summary, this Registry provides a unique resource for examining

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diverse domains among highly motivated, chronically fatigued twins within the context of a genetically informative sample.

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