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# Chronic fatigue syndrome: Is it one discrete syndrome or many? Implications for the "one vs. many" functional somatic syndromes debate

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**Abstract**

There is a current debate as to whether "functional somatic syndromes" (FSSs) are more similar to or different from each other. While at the same time, there is evidence of heterogeneity within single syndromes. So, it could be that these syndromes are all part of one big process/illness, are discrete in their own right, or that they are heterogeneous collections of different illnesses lumped together by common symptoms but separated by uncommon pathophysiologies. The example of chronic fatigue syndrome (CFS) is instructive. There is evidence to support all three models of understanding. Three recent large studies have suggested that FSSs are both similar and dissimilar at the same time. The solution to the debate is that we need to both "lump" and "split." We need to study both the similarities between syndromes and their dissimilarities to better understand what we currently call the FSSs.



*Keywords:* Functional somatic syndromes; Chronic fatigue syndrome; heterogeneity; homogeneity; risk markers

## Introduction

In order to understand the cause or pathophysiology of an illness or disease the usual first step is to define the phenotype of that illness and then seek associations with putative risk markers. Without doing that, no amount of markers will be shown to be consistently associated with one distinct illness or disorder. The example of one particular "functional somatic syndrome" (FSS), namely, chronic fatigue syndrome (CFS), provides insights into the difficulties of trying to define the phenotype in the absence of the biomarkers that usually help us to define a disease phenotype in the first place, The literature about CFS also provides the possible solution to this problem for both CFS and for all FSSs in general.

## Does a phenotype of CFS exist?

There are several operationalized criteria used for defining CFS [1–3]. These criteria provide reliability across different studies [4], but the tests of validity suggest that they do not "cleave nature at the joint" [5], omitting more patients that have chronic unexplained disabling fatigue than they include. At the same time, large empirical studies suggest that there is a more broadly defined phenotype of chronic unexplained fatigue with associated symptoms (thus a CFS) with good cross-cultural and international empirical data supporting the broad phenotype of CFS [5–8]. In addition to these cross-sectional studies, cohort studies of at-risk populations, such as patients with incident infections, suggest that a CFS exists independently of mood disorders, the most common alternative diagnosis [9,10]. Therefore, there is good evidence that CFS exists as a discrete illness phenotype.

## Is CFS homogeneous or heterogeneous?

There have been several attempts to test the heterogeneity of CFS, using symptoms and demographic data to define the phenotypes [5,6,11–15]. Some studies used principal components or other factor analyses to define the syndromes themselves, whereas others used latent class analysis to seek clusters of patients. The early studies found a broad phenotype in the majority and a separate polysymptomatic phenotype in the minority, labeled as a somatization disorder

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[11,12]. Later studies, mainly using latent class analysis, found between three and five subphenotypes, some clustering with comorbid mood disorders and other clusters labeled musculoskeletal and infectious on the basis of symptoms [5,13–15]. Although similar clusters of symptoms are found across studies, no work has looked at the validity of these empirically defined subphenotypes, such as longitudinal studies with risk marker associations. We therefore cannot be sure that these symptom clusters define valid subphenotypes. A second problem is that these attempts to define the heterogeneity of CFS have relied on symptoms and demographic variables alone, excluding associated biological abnormalities, such as down-regulated hypothalamic-pituitary-adrenal axis activity [16]. Adding such biomarkers might reveal subphenotypes that are defined by the underlying biological processes, which are called endophenotypes [17].

A large population-based study has attempted to elucidate the underlying endophenotypes of the broad phenotype of CFS. That is, the authors used biomarkers in addition to symptoms and demographic variables in an attempt to delineate the endophenotypes. The Centers for Disease Control (CDC), based in Atlanta, GA, in the USA, has produced several epidemiological studies derived from populations. One of these was based in Wichita, KS, chosen as it is demographically representative of the USA [18]. The CDC did a nested case-control study of those with a CFS-like illness and healthy controls. They studied clinical variables, such as symptoms and comorbid disorders, but also biomarkers, measuring immune and endocrine variables as well as polysomnography [18]. The authors first of all used principal components analysis to reduce the large number of variables to the smaller number of only those that contributed to defining the components, and then latent class analysis to seek clusters of individual women (men being too small in number to analyze) [19]. The best statistical solution defined four classes, but interpretations were possible for five and six classes [19]. Interpretation of the six classes is as follows: Class 1 (26% of subjects) was primarily delineated by obesity and sleep disordered breathing (hypnea). Class 2 (24%) was healthy. Class 3 (15%) contained obese and hypneic subjects, but with low heart rate variability during sleep and low 24-h urinary cortisol levels (consistent with physiological evidence of chronic stress). Class 4 (14%) had sleep disturbance and myalgia without obesity or significant depression. The two remaining classes (Class 5 with 14% and Class 6 with 7%) consisted of subjects who reported most symptoms and were depressed, but without obesity or its related hypnea. Class 5 had normal sleep indices. Class 6 was characterized by disturbed sleep, with low sleep heart rate variability, low 24-h urinary cortisol levels, and the subjects were postmenopausal.

It is vital to validate and replicate these findings in order to avoid being sidetracked by spurious findings. The authors tested the validity against variables not used in the original analyses. Firstly, they found that fatigue and disability differentiated ill classes from each other [20]. Secondly, they found that gene expression differentiated three classes out of both the five and six class solutions [21]. Thirdly, they reported that single nucleotide polymorphisms of candidate genes, related to monoamine transmission and cortisol receptors, differentiated three out of six classes [22]. These authors went on to replicate this work in an independent population sample, also studied by the CDC, this time in Georgia, USA. They were not able to directly replicate this work in this replication study because the same biomarkers had not been studied. However, by using proxy variables, they were able to partially replicate this work, finding four out of five classes were similar to those found in the original Wichita study [23].

Testing the heterogeneity of other FSSs is less well developed, but preliminary studies suggest that other FSSs may also be heterogeneous [24,25], as well as sharing commonalities [26].

## Is CFS part of another FSS?

A related but seemingly paradoxical issue is the need to explain the clinical associations between the FSSs. Why is CFS strongly associated with both chronic widespread pain ("fibromyalgia") and irritable bowel syndrome (IBS) [13,26–28]? Could it be that there is only one general functional somatic disorder [29,30]? One way to answer these questions was attempted in a primary care prospective case-control study of risk markers of patients with fatigue syndromes (postinfectious and CFSs) matched by age, gender, and general practice with two comparison groups: patients attending primary care of other ill health reasons and patients attending with IBS [31]. These authors used the UK General Practice Research Database and found that, although the fatigue syndromes were heterogeneous, those with CFS had the same predisposing risk markers as those with IBS (primarily premorbid mood disorders and other FSSs). In contrast, triggering risk markers differentiated the syndromes, with systemic viral infections triggering CFS and gastrointestinal infections triggering IBS. Using a cohort study of Epstein-Barr virus and *Campylobacter* infections, Moss-Morris and Spencer [32] had previously found this specificity regarding triggering infections, with EBV triggering CFS and *Campylobacter* even more convincingly triggering IBS.

A large study of Swedish twins seems to support this novel conclusion. Kato et al. [33] studied mainly symptom profiles in over 30,000 twins obtained from the population, looking for the latent traits supporting four FSSs: CFS, chronic widespread pain, IBS and recurrent headaches, along with two mood disorders (major depression and generalized anxiety). When examining women, they found that two latent traits explained the main variance, with one loaded with the two mood disorders, and the other (which included all four FSSs) without them. Furthermore, all four FSSs had their own specific heritability, but environmental