Chronic fatigue syndrome

Is chronic fatigue syndrome (CFS/ME) heritable in children, and if so, why does it matter?

Esther Crawley, George Davey Smith

We need a clear definition of CFS/ME in children and sample sizes for genetic studies need to be much larger

Chronic fatigue syndrome or ME (CFS/ME) is surprisingly common in children with a prevalence of between 0.19% and 2% based on telephone surveys in the UK and the USA.[1–3] Lifetime prevalence (up to 30 years old) of self-reported CFS/ME, uncorroborated by a physician, of 0.8% has been reported from the 1970 British Birth Cohort.[4] Lifetime prevalences (age 8–17) of disabling fatigue of 3 months' and 6 months' duration of 2.34% and 1.29% have been reported from a longitudinal cohort of twins.[5] This means that almost all paediatricians reading this article will have seen and managed children with CFS/ME. Some paediatricians will have noted a family history of CFS/ME and may have wondered whether this was due to genetic heritability or an environmental factor. The causes of CFS/ME have long been debated, which has not necessarily been helpful to the clinical management of children with CFS/ME.[6–8] This article examines the evidence base for the genetic heritability of CFS/ME. This is an important area of knowledge for paediatricians as it will inform our discussions with children, young people and their families.

FAMILIAL AGGREGATION

The familial aggregation of CFS/ME was first described 16 years ago in Lyndonville, New York State. In this study, a questionnaire asking about symptoms of CFS/ME and possible risk factors (allergies, asthma, risk factors for infection and family history) was distributed to all 914 students at the Lyndonville Central School. Having a family member with CFS/ME was a strong predictor of CFS/ME, with a risk ratio of 35.9[9] (it is not clear from the study whether the authors only asked about first degree relatives or ''any'' relatives). The authors concluded that this could be due to either the transmission of an infectious agent, the presence of genetic factors or some environmental factor yet to be defined. In another small study 3 years later, 50% of children with CFS/ME had a family history of CFS/ME.[10] However once again, it is not clear whether these were first degree or ''any'' relatives.

TWIN STUDIES

Investigators have used twin methodology to determine how much of the family aggregation described is due to genetic factors and how much to the environment. Twin studies in adults have shown consistently higher concordance rates in monozygotic twins compared to dizygotic twins for CFS/ME, with the monozygotic correlation usually at least twice that of the dizygotic correlation[11–14] (for example 0.55 and 0.19[14] and 0.43 and 0.16,[12] respectively). As environmental factors (eg, infections or parental up-bringing) during early life should have been similar within monozygotic and dizygotic twin pairs, the difference between monozygotic twins who share 100% of their DNA and dizygotic twins, who on average share 50%, can be used to calculate the contribution made by genetic heritability. The difference in concordance rates increases with increasingly stringent case definition in adults.[14] This provides evidence that there is a core CFS/ME group among whom genetic factors play an important role.

Repeating the studies in children is difficult for many reasons, not least because there are currently no agreed criteria for CFS/ME in children. The Royal College of Paediatrics and Child Health do not recommend a minimum time frame before making a diagnosis in children but merely require that they have fatigue which is disabling and without another identifiable cause.[6] The NICE guidance for CFS/ME published in August 2007 suggest that a diagnosis of CFS/ME is made in children when symptoms have persisted for 3 months.[15]

Nevertheless, twin studies investigating fatigue in children are consistent with those in adults. In the UK, carers of 670 twin pairs were questioned about disabling fatigue lasting more than a week and more than a month. In both cases the concordance was higher in monozygotic twins compared to dizygotic twins (0.81 vs 0.59 for 1 week, 0.75 vs 0.47 for 1 month).[16] This suggests that the genetic contribution to the experience of disabling fatigue is high. This study was extended and length of time for fatigue was defined as a few days, more than a week and more than 1, 3 or 6 months, and the relationship between fatigue and depression was investigated in 1468 pairs of twins.[17] For short duration fatigue, genetic heritability was high and no shared environmental contribution (from environmental factors shared by twins, as many background family-based factors would be expected to be) could be detected. However, for prolonged fatigue, there appeared to be substantial environmental influences and a modest genetic contribution.

IS THE HERITABILITY OF FATIGUE DUE TO DEPRESSION?

The fatigue being measured might actually be part of a mood disorder such as depression, also known to be heritable. In the paediatric study described above, for both the short and prolonged fatigue most of the genetic and environmental variance was shown to be specific to disabling fatigue and different from factors contributing to depression.[17] This is consistent with an adult study where depression, anxiety and psychological distress were measured in 1004 adult twin pairs.[12] Structural equation modelling suggested that the familial aggregation for fatigue was largely due to additive genetic factors, which were not shared by the other measures of psychological distress. In other words, chronic fatigue is heritable and this heritability is aetiologically distinct from psychological

Table 1 Turkheimer's laws of behavioural genetics[18]

Law 1	Everything is heritable
Law 2	The environmental effect of being raised in the same family is substantially smaller than the genetic effect and is often close to zero
Law 3	Most behavioural variability remains in the error term after genetic effects and the effects of being raised in the same family have been accounted for

Table 2 Gene expression studies

Author, year	Patients and controls	Number of genes tested	Differentially expressed genes
Vernon *et al*, 2002[31]	5 patients, 17 controls	1764 genes	CMRF35 antigen, IL-8, HD protein
Powell *et al*, 2003[29]	7 patients, 4 controls	Differential display	Cathepsin C and MAIL1, TNFα, Moesin
Kaushik *et al*, 2005[30]	25 patients, 25 controls	9522 genes	ABCD4, PRKCL1, MRPL23, CD2BP2, KHSRP, BRMS1, GABARAPL1 (IL-10RA ↓)

distress. These studies are important as they suggest that fatigue is not just a variant of depression.

Therefore, CFS/ME seems to at least partially obey Turkheimer's laws of behavioural genetics (table 1).[18] Many conditions that obey these laws are, however, also environmentally determined when changes in risk over time and between populations are considered. For example, obesity shows high heritability – typically around 70% – but at the same time we have witnessed a dramatic increase in prevalence, clearly implicating changing environmental factors. Estimates of genetic and environmental contributions to disease risk from twin studies cannot, of course, reflect the contribution of near-universal environmental exposures, or ones that are changing across all strata of society, such as the balance between energy expenditure and energy intake.[19] Furthermore, the assumption that apparently shared exposures – such as parental divorce – have the same effect on two individuals is not necessarily justified, as prior experiences and individual characteristics may lead to such exposures producing different effects in different people.[18]

ASSOCIATION STUDIES

As in many conditions with evidence of substantial heritability, and in some without, much recent work has involved candidate gene association studies in population based case-control studies. The candidate genes have been chosen to reflect the postulated mechanisms through which CFS/ME arises, for example, variants in the hypothalamo-pituitary adrenal (HPA) axis. If variants related to different HPA activity profiles were associated with risk of CFS/ME, this would provide good evidence that potentially modifiable environmental influences on HPA function are causally related to the risk of developing CFS/ME. The reasoning here is complex but important. If we continue to use the HPA axis as an example, we can see that potential environmental influences on a child's HPA function, say parental discord, or even direct measures of HPA function, will be associated with a large array of other potential causes of CFS/ME. Therefore, the associations will be confounded by these factors and it is not possible to isolate the aetiological processes that could be modified to prevent or treat CFS/ME from spurious confounders. Furthermore, the disease process involved in CFS/ME may alter HPA function, rather than disturbed HPA function leading to CFS/ME, a situation referred to as reverse causation. Genotypes are not, however, associated with confounding factors, nor do disease processes alter germline genetic variants. Thus a genotype related to HPA function can be taken as a marker of such function that is neither confounded nor susceptible to reverse causation, and thus provides better evidence of causality. This approach to using genetic data has been referred to as Mendelian randomisation and applied in other clinical settings.[20 21] This approach to genetic epidemiology utilises genetic data to understand potentially modifiable causes of disease rather than to provide a basis for predictive genetic testing.

Genetic association studies of CFS/ME to date have only been carried out in adults. The findings so far have been mixed, and are summarised below.

Table 3 Explanation of terms used in this paper

Term	Definition or explanation
Principle components methodology[40]	A method used to find a few combinations of variables, called components, that adequately explain the overall observed variation, and thus to reduce the complexity of the data
Latent class analysis	A statistical method for finding subtypes of related cases (latent classes) from multivariate categorical data
Single nucleotide polymorphism	DNA sequence variation occurring when a single nucleotide A, T, C or G in a genome differs between members of a species

HPA axis

Variants in the corticosteroid binding globulin (CBG) gene have been described in an isolated kindred and were associated with idiopathic chronic fatigue and CFS/ME (as defined by the Centers for Disease Control and Prevention (CDC)).[22] However, when investigated in a case-control study, there was no robust difference in CBG prevalence in a group of 248 patients with CFS/ME compared to 248 controls.[23] Further single nucleotide polymorphisms (SNPs) of interest in the HPA axis are described below.

HLA genotype

Whether HLA genotypes are associated with CFS/ME or not is controversial. One study showed no significant associations compared to controls[24] and one study suggested an increased frequency of HLA-DQA1*01.[25] Both studies were small (58 and 49 patients in each group, respectively) and in the second study, the association was not corrected for multiple tests.

Cytokines

One study in Italian patients with CFS/ME investigated promoter polymorphisms of IL-10, IL-6 and IFNγ and demonstrated an increase in TNF genotypes compared to controls with a decrease in IFNγ low producers.[26] However, this is only a single study and to date the findings have not been replicated.

Association studies in this field are massively underpowered, so it is not unexpected that no robust findings have emerged. Realistic assumptions about the effect sizes that might exist between common genetic variants and a complex non-homogenous illness like CFS/ME would suggest that studies at least an order of magnitude larger than current studies are required if they are to be informative.[27] The effort is worth it, however, as they have the potential to inform us about modifiable risk factors for CFS/ME through utilisation of the Mendelian randomisation approach discussed above. Furthermore, if adequately powered studies yield validated associations between genetic variants and risk of CFS/ME, then this suggests that the CFS/ME patient group studied at the very least contacts a subgroup with a coherent

Table 4 Gene expression studies from Centers for Disease Control and Prevention data

Author, year	Method	Result
Fang *et al*, 2006[36]	Selected patients with most or least depression or fatigue. Principle components analysis to select genes which were common to both pathways and separated patients with CFS/ME	24 identified genes, 11 common pathways with the following functions: immune responses and apoptosis; metal ion binding, ion transport and ion channel activity; cascade, signal transduction, cell–cell signalling, regulation of cell growth; neuronal activity genes; a photosensitive gene and DNA fragmentation and TNF signalling pathway
Whistler *et al*, 2006[37]	Quantitative trait analysis was used to identify correlation of gene expression with fatigue	839 genes identified which mapped to the following cellular functions: metabolism, transcriptional regulation and cell signalling pathways
Carmel *et al*, 2006[38]	A computational approach was developed to identify genes that could discriminate the classes identified using microarray expression data on 15 315 genes	32 and 26 genes which can discriminate between the 5 and 6 class solution. Most classes were distinguished by: ZNF350, SLC1A6, FBXO7, VAC14 and some by PTH2 and TCL1A
Broderick *et al*, 2006[39]	Applied principle components analysis (PCA) to 59 variables which made up CFS/ME and then to rotated gene expression data to find gene expression that correlates with illness	39 genes; single most influential gene was Sestrin1, also calcium channel activity and transcription peptidase MBTPS1, protein kinase C-like 1 (PRKCL-1) and KHSRP

diagnosis, since if the diagnosis is actually completely incoherent, no true associations could be found.

In addition to studies of genetic variants and CFS/ME risk, there have been studies of differences in gene expression (ie, levels of RNA transcription products) in patients with CFS/ME compared to controls. These studies are informative in that they tell us about potential mechanisms of disease development, but ultimately gene expression data are measures of bodily state and reaction, unlike genotype data. As patients who receive a diagnosis of CFS/ME are distinguished from those who do not by phenotypic differences, it is expected that differences in gene expression will exist. Problems arise, however, because sedentary activity itself, as well as differences in medication or diet, may well alter gene expression. Gene expression studies are therefore less informative about the ontology of CFS/ME than are genetic association studies, although the combination of gene expression and genetic variant studies can, when they provide congruent information, be particularly powerful.[28]

Three relatively small studies have described altered gene expression in patients with CFS/ME compared to controls.[29–31] Each study identified genes with differential expression patterns (table 2). However, the associations identified have not been replicated and each study has described different biological pathways. This is likely to be due to the small sample size in what is likely to be a non-homogenous illness together with the problems discussed above.

More recently, further genetic information has emerged from an elaborate investigation involving 227 residents of Wichita,[32] carried out by the CDC. During a 2-day hospital stay, data were collected on the participants' psychiatric status, sleep characteristics and cognitive function. Biological samples were collected to measure neuroendocrine status, autonomic nervous system function, systemic cytokines and peripheral blood gene expression. Twenty investigators from the disciplines of medicine, mathematics, biology, engineering and computer science were then given the task of analysing and interpreting the data over 6 months. The results give a clearer understanding of CFS/ME, but perhaps more importantly, describe a novel method of analysing large datasets in a complex illness.

In the first part of the study, the CDC used principle components methodology and latent class analysis (see table 3 for explanation) to divide a group of women with fatigue and chronic fatigue syndrome and controls into five separate groups which could be explained by their symptoms and clinical and laboratory findings.[32 33] They then used several methods to analyse gene expression and demonstrated several different results (see table 4 for summary of gene expression results).

As well examining gene expression, the CDC group also investigated genomic DNA. One group tested whether SNPs (table 3) could distinguish the five groups described above, whilst another group investigated whether SNP profiles could be used to predict whether a patient had CFS/ME or not. In the first study, they found that three of the classes described on clinical and laboratory grounds were associated with genes involved in the HPA axis function or mood related neurotransmitter systems (monoamine oxidase A and B and tryptophan hydroxylase).[34] In the second study, one particular combination of five SNPs was able to identify patients versus controls (OR 8.94, $p<0.001$).[35] The most important genes for this study coded for neuronal tryptophan hydroxylase (TPH2), catechol-o-methlyltransferase and a glucocorticoid receptor, NR3C1 (TPH2 is the rate-limiting enzyme in the synthesis of serotonin, itself a precursor of melatonin). Genes for corticotropin releasing hormone receptors were also implicated. Although potentially interesting in terms of the biological pathways involved, these studies are heavily underpowered and replications are required before the findings are given any credence.

CONCLUSIONS

In summary, there is now increasingly strong evidence that CFS/ME is heritable. It seems likely that the heritability contributes to the experience of fatigue as well as to the development of CFS/ME itself. It should therefore not be surprising that CFS/ME runs in families and paediatricians will see families where more than one person is affected. Although there is some agreement that a model involving the joint action of genes and environment is required, there is currently little agreement on the actual genes and environmental factors involved.

The fact that CFS/ME is heterogeneous hampers research in this area. However, learning more about the different biological processes and the genes involved in CFS/ME is an important step in understanding and developing methods for preventing or treating this important condition. Genetic studies may drive this research forward and provide an anchorage point around which CFS/ME can be understood and the modifiable risk factors that influence risk can be determined.

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Authors' affiliations
Esther Crawley, Centre for Child and Adolescent Health, Hampton House, Cotham Hill, Bristol, UK
George Davey Smith, MRC Centre for Causal Analyses in Translational Epidemiology (CaiTE), Department of Social Medicine, University of Bristol, Bristol, UK

Correspondence to: Esther Crawley, Centre for Child and Adolescent Health, Hampton House, Cotham Hill, Bristol BS6 6JS, UK; Esther.crawley@bristol.ac.uk

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