Gene Research: A Scientific 'Signature' for ME/CFS?

How does it work?
A key component of the gene research is the use of microarray technology to analyze the genetic material of a person with CFS. Researchers take a sample of blood or tissue; apply it to a glass slide, called a "microarray," which contains more than 20,000 gene identifiers; and are able to determine which genes in the sample are being "expressed," that is, turned on or off, or turned up or down. This gene expression profile provides a window into the disease process.

Dr John Gow and colleagues (University Department of Neurology, University of Glasgow), to whom MERGE has contributed interim funding for the verification of potentially important genes, are seeking to identify a genes specific to ME/CFS using novel microarray technology. One phase of their project consists of verifying the key genes/pathways predicted by DNA microchip assay as having the highest fold change between patients and controls, and the next will focus on the development of diagnostic biomarkers. The project will utilise peripheral blood mononuclear cells isolated from whole blood from patients with ME/CFS and matched healthy controls. As has been reported in a series of articles in the press in the Autumn of 2005, pilot data obtained by Dr Gow's team have suggested alterations to genes controlling the metabolism of prostaglandin and those regulation-specific immune cells. This is interesting work which deserves to be supported into its mature phase when a specific "gene signature" for particular proteins may be revealed.

The Glasgow team is one of a number of world-wide research groups investigating the genetic characteristics of people with this illness. One group, led by Dr Jonathan Kerr at St Mary's Campus Imperial College London, have just published some early results (in the *Journal of Clinical Pathology*): they compared levels of gene expression in the white blood cells of 25 healthy individuals with those in 25 patients, and found differences in 35 of the 9522 genes analysed using DNA chip technology. Using real-time PCR, 15 of the genes were up to four times as active in people with ME/CFS, while one gene was less active. Dr Kerr is shortly to study 1000 ME/CFS patients and healthy controls, this time looking at 47,000 gene products.

Another group, led by Suzanne Vernon of the Centers for Disease Control and Prevention's molecular epidemiology programme in Atlanta, USA, has been investigating gene expression profiles in the large Wichita clinical data set, and her preliminary findings suggest dysregulation of genes involved in immune pathways, supporting the many reports in the literature of immune dysregulation in the development of the illness. This team has been able to show differences among people with ME/CFS, confirming that the broad diagnostic category ME/CFS contains different kinds of patient groups. Examining 3,800 genes in 23 women, they found that those with sudden-onset illness (developing in one week) had a different gene expression profile than those with gradual onset (developing over several months), and they may find particular patterns that are specific to other subgroups as well. While their hope is that the microarray could become

a routine diagnostic tool for ME/CFS, their realise that finding effective treatment for CFS is the long-term goal, and as Dr Vernon says, "With a better understanding of the disease process, specific therapeutic interventions may one day be possible".

These developments are welcome: few areas of biomedical research into ME/CFS can boast more than two separate research groups simultaneously engaged on a common quest. But it is a long complicated process. Experience from the use of genome-wide scanning technologies for cancer screening has shown that discovery and validation of biomarkers requires multiple phases of research over some years. Nevertheless, the work is one of the most exciting recent developments in ME/CFS, and could open the door to development of pharmacological interventions. As Dr Russell Lane, a neurologist at Charing Cross Hospital in London has said of the work on genes, if the researchers succeed and identify "*clear physical changes in people with CFS, the lingering opinion that it is "all in the mind" could finally be laid to rest.*"

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ME/CFS - the research problems

Of course, the same problems that confront all researchers in ME/CFS also apply to research groups using microarray technology. One is that 'diagnosis' of the illness is most often based on a ragbag of common non-specific symptoms, resulting in a diverse group of patients. As Jason et al. (2005) have pointed out in an excellent recent review, "Subgrouping is the key to understanding how CFS begins, how it is maintained… and in the best case, how it can be prevented, treated and cured." It is unlikely, therefore, that a single biomarker or cluster will be found able to detect all cases as currently defined, although microarray technology does have the potential to make diagnosis more precise in the long term. Another problem is that obtaining and maintaining funding haunts the efforts of all biomedical researchers in ME/CFS, and it is particularly acute in these gene biomarker studies which will require million of dollars to come to a definitive conclusion. As Alex Fergusson MSP said in the Parliamentary members' business debate in June 2005 (motion S2M-2852) on the subject of a cure for myalgic encephalomyelitis, it is entirely unacceptable that major funding bodies seem uninterested in novel gene research— particularly when large traunches of money have been allocated to research on non-curative psychosocial strategies designed to 'manage' symptoms.

Illnesses are most easily accepted when they have a specific clinical or scientific 'signature'— a biochemical test, a cluster of specific symptoms or signs, etc. — that confers legitimacy in the eyes of healthcare professionals. Until then, patients are in a no-man's land between the living and the well, subject to a variety of quasi-therapeutic interventions. ME/CFS has been called the "disease of a thousand names", but it has also been the disease of a thousand false dawns and a thousand broken promises. Yet, the discovery of a clinical or scientific 'signature' for ME/CFS, indicative of the physical terrain, would transform this situation at a single sharp stroke. In the longer term, work using genome-wide scanning technologies has the potential to reveal such a 'signature': to quote Steinau et al. (2004), "Biomarkers characteristic of CFS could contribute to precision in case ascertainment, identify heterogeneity in the CFS population to clarify

contributing pathways to disease, suggest novel therapeutic targets, and provide indicators of disease progression and prognosis." 382 words