Genetic Disposition of Fatigue

Team 5: Michele Halyard, MD; Andrea Barsevick, PhD, RN, AOCN; Aeilko Zwinderman, PhD; Per Hall, MD, PHD; Marlene Frost, PhD.

Background

Cancer related fatigue (CRF) is an extremely prevalent condition, with reported incidence of at least 60% or higher in some studies. A consistent definition of cancer related fatigue is lacking, but generally includes a “persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning.” The pathophysiologic mechanisms involved in cancer related fatigue are not completely understood. Dysregulation of several systems, both biochemical and physiological, are likely involved in CRF. Proposed mechanisms of CRF include cytokine dysregulation, 5-HT neurotransmitter dysregulation, alterations in ATP and muscle metabolism, vagal afferent activation, and circadian rhythm disruption. Circadian rhythms play a significant role in the concept of fatigue through the modulation of arousal and sleep. Arousal and sleep are modulated through the central circadian system and downstream network of relay stations in the hypothalamus. This system is most significantly affected by the input of light that creates neurophysiological changes in the hypothalamus and melatonin which affects the darkness period, neurons in the suprachiasmatic nuclei (SCN) that regulate 24 hour sleep patterns, and by afferent nerve fibers groups that relay signals from the SCN to the hypothalamus. Signals from the hypothalamus effect the parasympathetic and sympathetic autonomic centers in the brainstem and in turn affect the secretion of stress and physiology regulating hormones.

Alterations in any part of the circadian system can result in disruption of arousal and sleep patterns. SCN ablation has resulted in the permanent loss of rhythmic rest, activity and sleep behaviors. Specific SCN peptides, ligands of EGFR, identified as having the ability to regulate activity and sleep patterns include epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), and neuregulin-1 (NRG-1), prokineticine-2 (PK2), and cardiotrophin-like cytokine (CLc). All five of these peptides have been shown to reversibly inhibit activity and deregulate 24-hour sleep patterns. The EGFR ligands can be released by the cancer or in response to the stress of the cancer. Circadian rhythm may also be affected through SCN downstream signal disruption that may occur in the dorsal or ventral nuclei or from input from the brain’s visceral, limbic, and cortical systems. Input from the brain’s visceral, limbic and cortical systems may explain how the tumor itself can effect the rhythmic circadian activity. Circadian rhythms have been shown to be affected significantly in advanced stage or metastatic disease. Little or no effect is noted with early-stage cancers. Additionally, flattening of the circadian rhythms were noted in patients receiving chemotherapy. Specific mediators of circadian rhythms, including cortisol levels and melatonin, have been shown to change in patients with cancer.
**Genetic Markers and fatigue**

There are two broad categories of research for studying genes that control human disease and other health problems. The first category is linkage studies which are used to identify familial inheritance patterns of disease using families as the sampling unit. Although genetic linkage studies have been reported for pain and depression, the linkage methodology is not optimal for the study of most cancer-related symptoms.

Another broad approach to the study of genetic variation is the association study. This type of study has been aided by the Human Genome Project and the HapMap Project which provided basic information about human genetic variation. Advances in molecular and genetic technology now enable the use of whole genome scanning as one approach to conducting genetic association studies. Genome-wide scanning can be done without a specific hypothesis or proposed pathway because thousands of single nucleotide polymorphisms (SNP) can be examined simultaneously. There have been no genome-wide association studies of cancer-related symptoms probably due to the prohibitive cost and the need for very large samples.

Another type of association study is hypothesis-driven with candidate genes examined in specific pathways. SNP with frequency of at least 5% are prevalent enough to be candidates for study in genetic association studies. The pathway-based approach requires prior knowledge of SNP, gene function, and pathophysiologic processes.

At this point in the evolution of the science, the pathway-based hypothesis-driven approach appears to be the most reasonable. Most genetic association studies of cancer pain have focused on gene SNP involved in pharmacokinetics and pharmacodynamics. For example, studies of polymorphisms of the mu opioid receptor gene, OPRM1, demonstrated that individuals who were homozygous for the variant G allele needed significantly more morphine to alleviate pain than individuals with the A allele.

A mechanism that has been proposed for the etiology of cancer-related fatigue involves the inflammation pathway. Cytokines, soluble proteins that mediate cell to cell communication among immune cells, are activated by inflammatory processes. Several lines of evidence suggest that increased inflammatory marker levels are related to increased fatigue. Animal studies have demonstrated that direct application of the cytokine IL1 into the brain led to “sickness behavior” with symptoms such as fatigue, fever, appetite suppression, and lower physical activity. In humans, the administration of recombinant proinflammatory cytokines to boost immune defenses against cancer has been associated with severe dose-limiting fatigue. This converging evidence provides a rationale for further examination of the association between cancer-related fatigue and activation of the immune system.

Schubert and colleagues examined the link between cancer-related fatigue and specific inflammatory markers. Conclusions of this review were limited by the small number of studies, small sample sizes, heterogeneity of study populations, and inconsistency in
selection of inflammatory markers for study. However, general analyses based on weighting of sample size demonstrated a significant positive correlation between fatigue and circulating levels of inflammatory markers. Specific markers that were associated with fatigue included IL6, IL1ra, and neopterin. Although IL1β or TNFα have been proposed as markers in the fatigue pathway, neither correlated with fatigue in several studies of cancer-related fatigue. The findings to date provide initial support for further exploration of the inflammatory pathway in the etiology of fatigue.

**Candidate Genes for Fatigue in the Inflammation Pathway**

Gene polymorphisms have been identified in the regulator (promoter) regions of genes that encode proinflammatory cytokines; these polymorphisms could differentially influence susceptibility to cancer-related fatigue. Because cancer-related symptoms are complex, they are likely to be influenced by the cumulative effect of several gene polymorphisms. Also cytokine genes are pleiotropic in that the activity of one gene can have more than one effect. Based on these premises, it is likely that a combination of gene polymorphisms will be associated with cancer-related fatigue. Also, genes that control other cancer-related symptoms (such as depression or pain) could influence fatigue. Therefore, it makes sense to examine the influence on fatigue of genes in the cytokine pathway that affect related symptoms such as pain and depression.

Several cytokine genes and their polymorphisms have been proposed as candidate markers for the study of cancer-related fatigue.

- **IL1B—511 (C/T):** Analysis of the IL1B—511 (C/T) polymorphism in breast cancer survivors revealed a substantial over-representation of the CC alleles among fatigued survivors and a substantial under-representation of TT alleles in this group.

- **IL6—174 (G/C):** In breast cancer survivors, homozygosity for both the variant C allele and the wild-type G allele of the IL6—174 (G/C) polymorphism were associated with a twofold greater representation in the fatigued group.

- **TNFα—308 (G/A):** The TNFα—308 (G/A) polymorphism has been proposed for involvement in neoplastic cachexia which is characterized, in part, by fatigue. However, none of the studies that examined the association between TNFα and fatigue demonstrated an association.

- **IL8—251 (T/A):** Variation in the promoter SNP IL8—251 (T/A) was found to affect risk for pain severity in newly diagnosed untreated lung cancer patients by influencing concentrations of IL8.

- **IL2—330 (T/G):** This genetic polymorphism is believed to regulate IL2 production which has been implicated in complex regional pain syndrome and painful neuropathy.
Global gene expression studies of fatigue

An alternative to analyzing DNA using SNPs is examining the transcript of genes, RNA. RNA synthesis is the process where DNA nucleotide sequence information is transcribed into RNA nucleotide sequence information. If the DNA codes for a protein, transcription is the first step that leads to the expression of a gene. This is done by the production of mRNA, a “chemical blueprint” for a protein product.

As discussed, it is possible to measure the expression of the whole genome. The technique has successfully been used in cancer research for different purposes, for example, prognostication or biological influence of specific alterations. \(^{19,20}\) While the genetic variation in DNA is constant throughout life, RNA changes over time and is found to be tissue specific, that is, not all genes are similarly expressed in all tissues.

Global gene expression has been used in some few studies in an attempt to associate regulation of specific genes and fatigue. In most cases gene expression of blood lymphocytes has been used. Whistler et al. found 839 genes to be associated with fatigue when contrasting 40 patients with chronic fatigue and 37 healthy controls. \(^{21}\) The genes regulated oxidative phosphorylation, gluconeogenesis, lipid metabolism, and several signal transduction pathways. Given the fact that 19,000 probes were analyzed the multiple testing problem is substantial. A simple Bonferroni correction indicates that a p-value of \(10^{-6}\), and not 0.05, should be considered significant. A significance level probably not reached.

Later the same group adopted a different approach by using candidate genes. \(^{22}\) Gene sets for T- and B-cell regulation were constructed and expression was contrasted between cases with fatigue and healthy controls. The results pointed at a B cell dysfunction in the blood array profiles.

Kerr adopted a two stage approach in that they firstly identified 182 genes related to fatigue when examining the global gene expression of lymphocytes in 25 cases and 50 controls. \(^{23}\) These genes were validated in 55 cases and 75 controls and differential expression was confirmed for 88 genes. The genes had previously been shown to be associated with immune response, cancer, and cell death.

Few papers could be found that addressed global gene expression and fatigue. Those referenced in this section should be considered fairly representative. The common problem is the lack of statistical precision. The data sets are small and measures to correct for multiple testing is not done or at least not described. Generally methods are not described in detail making inferences of the findings difficult. One could also argue that gene expression in blood cells is not the optimal (but probably easiest accessible) biomarker of fatigue.

Databases related to genes and fatigue

For fatigue and QOL in general, a very limited number of studies have been published on association between fatigue/QOL and genetic markers. The most interesting study is available through the CDC (public health genomics office) concerning 227 individuals from Wichita with chronic fatigue syndrome. \(^{24}\) SNPs in HPA axis associated genes, in
neuroendocrine effector and receptor genes and in genes in the serotonergic system were found to be related to fatigue. Others papers can be found that report on the association of one or more genetic markers and fatigue or QOL in general but these data are usually not publicly available.

References