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Advancing the Biobehavioral Research of Fatigue With Genetics and Genomics

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Abstract

Purpose—To examine phenotypic considerations in the study of fatigue and to explore significant issues affecting the extension of biobehavioral research of fatigue by the inclusion of genetic and genomic markers.

Theoretical Organization—Fatigue is a condition that has an adverse effect on quality of life that has been a focus of nursing inquiry. Yet, the study of fatigue has been stymied by the lack of phenotypic clarity. To expand the biobehavioral inquiry of fatigue, phenotypic clarity is needed. In addition, examining genomic factors associated with fatigue may help to elucidate the pathophysiology of fatigue and, in the future, lead to targeted interventions that address the molecular basis of fatigue.

Conclusions—Given that nursing has been at the forefront of the study of fatigue, nurse scientists should consider enhancing phenotypic clarity by the development of a case-definition and use of a core measure of fatigue, one that can be augmented by condition- or population-specific measures as needed. Following the establishment of phenotypic clarity, the integration of genomics into biobehavioral research offers an opportunity for further clarity of phenotypes and for theoretical specification of the pathophysiology of conditions such as fatigue.

Clinical Relevance—The development of targeted interventions for fatigue depend on a more precise definition of fatigue and a better understanding of the biologic processes that contribute to its development and persistence.

Keywords

Genetics; fatigue; biobehavioral

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Biobehavioral research focuses on the impact of biological and behavioral factors on health conditions, disease prevention and assessment, and enhancing outcomes (Grady, 2006). As the science has matured, biobehavioral research has grown from examining single markers of biological phenomena and behavioral variables to examining complex patterns of biological responses and behavioral phenomena. The next challenge for advancement of the science is to thoughtfully integrate genetics and genomics into the conceptualization, measurement, and refinement of biobehavioral phenomena. Although the integration of genetics, the study of single genes, and genomics, the study of all genes in the genome and their interactions, into biobehavioral research is potentially complicated by the imprecision in the conceptualization, definition, and measurement of biobehavioral phenomena, there are benefits to the addition of genetic-genomic measures into biobehavioral research. In this article, we examine several conceptual and methodological issues of importance in the future development of biobehavioral research and discuss how genetics-genomics may potentially enhance the refinement and progression of the science. Using the phenomenon of fatigue as an exemplar, we discuss several strategies for the refinement and expansion of biobehavioral inquiry through the inclusion of relevant genetic and genomic measures into future research.

Fatigue as a Significant Biobehavioral Phenomenon

Fatigue has been associated with decreased quality of life in many areas of health and illness, as well as with increased healthcare services and lost wages (Sabes-Figuera et al., 2010). Fatigue has been a phenomenon of particular interest to nurse scientists: nurse researchers led the early research of fatigue, and nursing has long recognized fatigue as a commonly experienced, distressing patient complaint, often, but not always, associated with a diagnosed illness. Potempa, Lopez, Reid, and Lawson (1986) offered the first model of fatigue that was widely used for research in nursing. Their model presented a picture of fatigue as multidimensional and as an outcome associated with many factors. A later fatigue model by Piper (1989) theoretically differentiated between acute and chronic fatigue. In 2006, Ream and Richardson identified both physical and psychological attributes of fatigue. Other nurse researchers have explored patient characteristics that influence fatigue (Plach, Heidrich, &Jeske 2006) or its experience (Falk, Granger, Swedberg, & Ekman, 2007), and prominent nurse scientists have studied fatigue in relation to cancer and other serious illnesses (Nail, 2002; Schwartz, 1998). In recognition of the significance of fatigue to patient outcomes and societal costs, researchers from multiple scientific disciplines have developed programs of research devoted to the measurement and treatment of fatigue.

The Phenotypic Heterogeneity of Fatigue

Even with the increased focus on research in fatigue over the past decade, research findings are difficult to generalize, in part because of the phenotypic heterogeneity of the term fatigue. Currently, the study of fatigue remains muddied by the very use of the word fatigue to describe conceptually similar but operationally disparate phenomena. Fatigue has been conceptualized in multiple ways: as a condition, a symptom, a syndrome, an outcome, and as a component of a prominent symptom cluster (So et al., 2009). Further, fatigue has been considered unidimensional or multidimensional, and condition or disease dependent.

Subsequently, even though fatigue has been of great research interest, the study of fatigue is riddled with imprecision, similar to the study of other complex disorders with a high degree of subjectivity, such as psychiatric disorders (e.g., anxiety disorders). Although many conditions can be examined using an animal model, fatigue is difficult to study in animal models due to the “intrinsically human nature of these complex behavioral phenotypes” (Mehta, Menke, & Binder, 2010, p. 139). Moreover, most research in which fatigue has been

studied has not isolated fatigue from closely related conditions such as mood disorders, sleep disorders, and pain. Researchers have also mixed the terms fatigue, implying a state of being, and fatiguability, implying a state of physical capacity for specific muscular fatigue, which has further blurred the biobehavioral inquiry of fatigue (Kennedy, 1988).

Toward the Concept Clarification and Phenotypic Specification of Fatigue

Refining the ontological and epistemological lenses has led to enhancements in both the precision and breadth for better understanding the nature of nursing phenomena (Fawcett, Watson, Neuman, Walker, & Fitzpatrick, 2001). Because the integral concepts undergirding nursing science are generally quite complex, much attention has been directed to concept analysis and concept derivation in order to more precisely define and measure nursing phenomena. The challenge of developing phenotypic precision for biobehavioral research can be understood as concept clarification. For biobehavioral researchers, it is important to conceptually and operationally define fatigue and its measures prior to integrating genetic-genomic factors into biobehavioral studies. If fatigue is not defined in a precise and replicable manner, cross-study knowledge cannot be exploited and science cannot be accelerated in an efficient manner. Thus, while there are multiple measures of “fatigue” that have well-established psychometric properties; those measures may or may not be measuring the same phenomenon. The advancement of knowledge about fatigue or any other phenomenon depends on measurement of the same phenomenon using the same or similar measures.

To move the science of patient outcomes toward shared conceptualization and measures, the Patient-Reported Outcomes Measurement Information System (PROMIS; Cella et al., 2007) initiative was established to support the development and testing of psychometrically sound measures of patient-reported outcomes that may be used across a broad array of conditions. Fatigue is one of the outcome domains supported by the PROMIS initiative. The definition of fatigue as addressed by the PROMIS initiative is as follows:

> Fatigue at its highest level is defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one’s ability to carry out daily activities, including the ability to work effectively and to function at one’s usual level in family or social roles. Similar subjective feelings, yet fewer behavioral consequences are associated with lower levels of fatigue. Fatigue is divided conceptually into the experience of fatigue (such as its intensity, frequency and duration), and the impact of fatigue on physical, mental, and social activities. (Cella et al., 2007, p. 9)

The PROMIS initiative has also created a tool for measuring fatigue that is beginning to be used more widely in research. The continuing development of the PROMIS instruments for fatigue and other phenomena will be enhanced by additional psychometric data, particularly from concurrent and predictive validity studies using condition- and population-specific measures.

Integrating Genetics-Genomics in the Biobehavioral Study of Fatigue

Although the PROMIS initiative and its work to define and measure patient-reported phenomena are laudable, the work of PROMIS is generally limited to behavioral measurement. Little systematic effort has been undertaken to date to include biological measures into the study of fatigue in the PROMIS initiative. Yet, the integration of genomic and genetic factors into biobehavioral research offers an opportunity to further enhance the science of fatigue in several ways. Genetics is a term that generally refers to the study of single genes. Genomics is a term that encompasses “the study of all the genes in a person, as

well as interactions of those genes with each other and with that person's environment" (http://www.genome.gov/Glossary/index.cfm?id=532; Centers for Disease Control and Prevention, 2010; see Table 1). We present examples of several genetic-genomic approaches that may increase the precision and clarity of the biobehavioral inquiry of fatigue, including candidate gene studies and genome-wide association studies (GWAS), which may lead to enhanced theoretical specification, and gene expression approaches, including epigenetic studies, which may be important in understanding the mechanisms by which fatigue occurs in various health conditions as a patient symptom. While these current examples are useful, genetic-genomic analysis technologies are rapidly evolving, and more powerful strategies and techniques continue to be developed. Biobehavioral researchers should be aware of technological advances and consider the whole continuum of available analysis strategies.

Biobehavioral Theory Refinement

Candidate gene—Studies focus on genes that are selected because of a priori hypotheses about their role in the etiology of a condition or disease (Tabor, Risch, & Myers, 2002). Candidate genes may inform the understanding of genetic predisposition for a condition using a case-control design, with care taken to maximize the homogeneity of controls (e.g., age, gender, ethnicity). Once identified, the statistical methods needed to analyze studies that include candidate genes are not complex (Zhu & Zhao, 2007). Candidate gene data are typically coded as binary (e.g., present or absent); thus, traditional statistical methods are sufficient without the need for the newer bioinformatics or statistical approaches. In the biobehavioral inquiry of fatigue, candidate genes may help illuminate theoretically plausible associations of genes with fatigue. To date, the study of candidate genes and fatigue has been derived from several current biobehavioral theories focused on inflammatory alterations and fatigue. However, other theories could undergird the search for candidate genes. Three classes of genes may have theoretically plausible links to fatigue: inflammatory, monoamine, and clock genes. These classes of candidate genes are used as examples that are consistent with a biobehavioral framework of fatigue.

Inflammatory genes—The "sickness behavior" theory has been a useful guide for understanding the multiple ways in which inflammation may affect biobehavioral outcomes (Cleeland et al., 2003). Conditions that are associated with inflammation initiate a neuroendocrine cascade, affecting the hypothalamic pituitary axis. Central or peripheral induction and interaction of cytokines are involved in the onset and maintenance of the various sickness behaviors (Seruga, Zhang, Bernstein, & Tannock, 2008). Experimental studies have shown that systemic administration of proinflammatory cytokines produces the systemic inflammatory response syndrome, manifested by multiple nonspecific symptoms, including fever, fatigue, hypersomnia, and depression. To date, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) have been documented as central mediators of such symptoms (Raison, Capuron, & Miller, 2006). Interferon-γ (IFN-γ), administered for the treatment of a variety of cancers, also has been found to induce fatigue (Seruga et al., 2008).

Nurse scientists are leading the way in testing biobehavioral theories using circulating markers of inflammation to examine genetic predispositions for fatigue and related concepts. A connection between inflammatory gene polymorphisms and fatigue is one of the first published associations between a genetic variant and fatigue. This association was demonstrated by the seminal work of Miaskowski and colleagues at the University of California, San Francisco (Aouizerat et al., 2009), who recently documented an association between a TNF-α promoter polymorphism (rs1800629) and sleep disturbance and fatigue in persons with cancer as well as their care providers ($N = 288$). Similarly, Hidalgo and colleagues found a significant relationship between promoter sequence polymorphisms in IL-1β and persistent fatigue in breast cancer survivors (Collado-Hidalgo, Bower, Ganz,

Irwin, & Cole, 2008). These studies represent an important step in associating fatigue and potential genetic variants in the context of biobehavioral theory.

Monoamine genes—Derived from neurotransmitter theories of depression and related psychiatric conditions, another theoretically plausible link to genetic variants and fatigue is alterations in genes of the monoaminergic system (Wichers & Maes, 2002). The existence of variations in monoamine levels (serotonin, dopamine, and norepinephrine) in the brain underlies considerable psychiatric research. Interestingly, fatigue is a condition that is present in many psychiatric disorders; however, most current psychiatric modalities are ineffective in treating fatigue, even with the resolution of concomitant depressive and anxiety symptoms. To date, there are no published studies specifically examining polymorphisms in monoamine genes and fatigue other than in patients with chronic fatigue syndrome. Further analysis of monoamine genes may be particularly important for the study of fatigue that is defined with a subjective component versus fatigue that is defined as muscle weakness.

Clock genes—Another theoretically plausible link to fatigue is alteration in clock genes. Research examining whether the variants in inflammatory genes lead to a greater propensity for fatigue or whether the inflammatory variants lead to disturbances in other biologically plausible pathways, such as circadian clock genes, also is a promising avenue for researchers. Recent studies of clock genes have implicated *Period 3* (*Per3*) variant genotypes and circadian disruptions, fatigue, and other sickness behaviors to inflammatory and growth-regulating cytokines-chemokines (IL-1β, IL-6, TNF-α, IFN-γ, IL-1 receptor antagonist, and vascular endothelial growth factor (Guess et al., 2009). Animal models suggest that the increase of TNF-α and IL-1β, as seen in infectious and autoimmune diseases, impairs clock gene functions and causes fatigue (Cavadini et al., 2007). Circadian disruption and inflammation appear to be causally linked, but the complex mechanisms remain to be discerned. The roles of clock genes, particularly period circadian protein homolog 3 (*Per3*) and the two *Cryptochrome* (*Cry*) genes, in circadian period sleep disruption and, by extension, symptomatic fatigue are actively being explored (von Schantz, 2008).

Potential associations of clock genes and inflammatory genes clearly need to be examined within this paradigm as well. Both monoamine genes and clock genes have theoretically supported relationships with inflammatory genes, but the empirical relationships between and among these genetic variants will need to be further clarified. Although further development of biobehavioral theories can be enhanced with the addition of theoretically plausible candidate genes, it is unlikely that studies of a few candidate genes will be sufficient to fully expand knowledge of factors underlying fatigue. Rather, pathway-based genotyping approaches are indicated, such as that used by Reyes-Gibby et al. (2009) in a study of 37 inflammatory genes associated with pain severity among persons with lung cancer. A systems approach to examine candidate genes that may have interaction or reciprocal effects will be needed to better explain the interrelated biological systems. Nonetheless, the focus on candidate genes will assist in further developing and testing core tenets of biobehavioral theories. The study of candidate genes may also help to further clarify the distinction between fatigue and related conditions, such as sleep disturbances and mood disorders, particularly depressive disorders.

Genome-Wide Association Studies: Biobehavioral Theory Development

In contrast to a candidate gene approach that has a theoretical basis, GWAS use a non-hypothesis-driven approach to identifying genetic variants that are associated with different traits or phenotypes. Technical advances in high-throughput, high-accuracy genotyping

platforms have permitted the concurrent examination of hundreds of thousands of single-nucleotide polymorphisms (SNPs; Panoutsopoulou & Zeggini, 2009) and haplotypes. GWAS have produced evidence that specific DNA sequence differences among people influence their genetic susceptibility to more than 40 different common diseases (Cichon et al., 2009; Psychiatric GWAS Consortium Coordinating Committee (2009). Many of these findings have identified previously unsuspected candidate genes and generated new hypotheses regarding the etiology of various conditions (Cichon et al., 2009). Although GWAS have led to identification of genetic susceptibility for human diseases, this approach has not yet led to identification of genes involved in less discretely defined disorders, such as psychiatric conditions, or in phenomena that are categorized as patient symptoms, such as fatigue.

Due to the non-hypothesis-driven approach to the examination of thousands of data points, the statistical methodology for GWAS analysis requires making inferences based on thousands of data points. Consequently, incorporating GWAS into biobehavioral research has several major limitations. A major limiting factor of GWAS in clinical research is the requirement for very large sample sizes to detect relationships between genetic variants and phenotypes. For example, highly significant associations have been documented for alleles with genotypic relative risks of 1.1 to 1.4 (mostly between 1.12 and 1.20); however, these studies required samples of 8,000 to 20,000 case subjects (plus comparison subjects; Cichon et al., 2009). An additional limiting factor of GWAS is the potential for false positives, given the large number of data points and the resultant inflation of Type I error. Although not yet reported for fatigue-related research, GWAS are potentially useful for biobehavioral research, given the caveat that GWAS are highly dependent on clarifying a specific phenotype prior to undertaking complex bioinformatic and statistical approaches to data analysis (Moore, Asselbergs, & Williams, 2010).

Gene Expression: Biobehavioral Mechanisms

Gene expression applications are used for the identification of differentially expressed genes by comparing the condition samples with the control samples (Fang et al., 2006) or examining within-individual levels over time, approaches that are appropriate for biobehavioral research. Unlike candidate genes, gene expression levels are potentially modifiable. Gene expression studies include heritable aspects of the genome as well as gene-environment (epigenetic) modifications. Gene expression studies have potential utility as biomarkers to monitor changes in levels of protein expression over time and, as such, may shed light on the mechanisms associated with biobehavioral phenomena. Further knowledge of gene expression patterns may lead to better prediction of risk and the identification of biological markers of fatigue onset, progression, and resolution as well as response to behavioral interventions.

Although gene expression studies have potential utility in biobehavioral research of fatigue, there are several methodological considerations. Like the technologies for candidate gene studies and GWAS, microarray technology enables simultaneous measurements of thousands of gene expression levels in parallel (Wu et al., 2009). DNA microarray technology involves large-scale monitoring of relative differences in RNA abundance between samples (Lockhart & Winzeler, 2000). Thus, gene expression studies require specialized bioinformatics-statistical analysis due to the large number of data points (Slonim & Yanai, 2009). Gene expression studies also require careful consideration of the source of specimens. For example, many psychiatric studies have been conducted on postmortem brain tissue because of the intent to measure the most biologically relevant source of gene expression. Even though this is the closest approximation of actual biological activity, recent studies have found no evidence of correlations in gene expression with major depression and suicide. For the study of fatigue, consideration of the specimen source for gene expression is

important. Depending on the case-definition of fatigue, the source of specimens could vary from muscle or brain tissue to peripheral blood.

Epigenetic Inquiry

Epigenetic factors involve changes in the regulation of the expression of gene activity without alteration of genetic structure (Unified Medical Language System, National Library of Medicine, National Library of Medicine, 2010). Such changes in expression resulting from factors other than DNA sequence are also likely to contribute to the etiology and manifestations of fatigue. Epigenetic factors influence expression of DNA and include genetic regulatory controls that result in different levels of gene products from identical sequences under different environmental conditions.

Many epigenetic mechanisms have been identified, and many more have been hypothesized. Two examples of potential epigenetic influences on fatigue, sex hormones, and messenger RNA (mRNA) regulation, are provided here. Sex hormones are differentially expressed by age and gender and are important pleiotropic genetic regulators. Sex hormones induce DNA methylation and modify histones, which results in increased or decreased expression of target genes (Kaminsky et al., 2006; Wilson, 2008). Even if individuals have identical sequences for particular genes, their regulation of those genes will be affected by differing levels of sex hormones, resulting in differences between them in gene expression. Thus, differences in fatigue by gender might result from the influence of such epigenetic regulatory hormones. mRNA interactions have been proposed as regulatory elements for inflammatory factors and thus might influence fatigue. mRNA regulation influences translation of proteins, causing increasing or decreasing amounts of specific cellular products even if transcription remains constant. Numerous promising hypotheses related to epigenetic influences on biobehavioral phenomena, such as fatigue, remain to be explored.

Future Directions

Nurse scientists have been at the forefront in the study of fatigue and similar phenomena. To further refine this work and build a future for research in this priority area, there are several steps in the process for better clarifying fatigue (Table 2).

First, to further refine this work and build a future for research in this priority area, the adoption of a consistent definition of fatigue is needed. In order to realize the potential for genetic and genomic measures to expand biobehavioral science, reducing phenotypic heterogeneity is the first step. The background work and a focus on developing a case-definition of symptoms that are prominent in nursing clinical care and research could start by defining fatigue using an analogous process to the consensus building that has guided the development of the Diagnostic and Statistical Manual of Mental Disorders in psychiatry. In that situation, it would be important to develop a case definition of fatigue that integrates global perspectives of this phenomenon to facilitate cross-study analyses and meta-analyses (Sale, Mychaleckyj, & Chen, 2009). Appropriate venues for this important work could include, for example, a consensus conference sponsored by the National Institute of Nursing Research or a forum at the Council for the Advancement of Nursing Science meeting. Discussions could also be held at meetings with an international nursing audience, such as Sigma Theta Tau's research conferences. What is most important is that there should be conceptual distinction and phenotypic clarity of fatigue as well as other biobehavioral phenomena. Only with conceptual and phenotypic precision can we logically incorporate relevant genetic and genomic measures to expand and refine our understanding of phenomena.

Along with the adoption of a standard case-definition, the use of well-validated and psychometrically sound measures will further enhance outcomes research and facilitate comparisons among research findings. Researchers might start with the case-definition of fatigue instead of fatigue in the context of a particular population or disease state. For instance, research has focused on cancer-related fatigue, pregnancy fatigue, and other conditionally defined types of fatigue. With a case-definition and shared measures, the biobehavioral science of fatigue can be more rapidly advanced. Thus, although there may be increased item burden resulting from using the PROMIS instruments in addition to other measures of fatigue such as population-specific measures, the future of biobehavioral research depends on having core definitions and measures of conditions of great public health interest such as fatigue.

Given the state of the science of fatigue, it may seem premature to include biomarkers such as genetic-genomic measures in fatigue research. However, the inclusion of these measures may help to further refine the biobehavioral science of fatigue. Current genomic analysis methods such as GWAS are part of a continuum of evolving genomic analysis technologies. In order for GWAS to become feasible, genotyping methods had to become sufficiently sophisticated to enable high-throughput screening of hundreds of thousands of SNPs efficiently, and statistical methods to analyze complex volumes of data had to be developed (Hirschhorn & Gajdos, 2011). What is possible today will change as newer analysis methods continue to be developed and refined. The development of genome-wide sequencing, although not yet widely available, is an excellent example of a technology that may yield useful information for answering a wide range of scientific questions.

In the future, the integration of genetic-genomic measures into biobehavioral research may lead to better prediction of risk as well as the identification of biological markers of symptom onset, progression, and resolution. Ultimately, clarifying the phenotype of fatigue and standardizing its measurement will ultimately guide interventions for management of this troubling symptom. Moreover, interventions to reduce risks for fatigue might be possible by identifying genotypes and gene expression profiles associated with fatigue. Identifying epigenetic factors that “turn on” fatigue genes may also be an important avenue for the future development of targeted preventive strategies and interventions for fatigue amelioration. With the refinement of the biobehavioral paradigm to include genetic and genomic factors, the specificity of nursing interventions focused on both prevention of fatigue as well as the refinement of targeted interventions may be achievable outcomes for nursing research.

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Clinical Resources

- Fatigue (PDQ), http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/healthprofessional/allpages
- Patient Reported Outcomes Measurement Information System (PROMIS), http://www.nihpromis.org/
- Talking Glossary of Genetic Terms, http://www.genome.gov/Glossary/
- NINR Mission & Strategic Plan, http://www.ninr.nih.gov/AboutNINR/NINRMissionandStrategicPlan/

Table 1

Glossary of Terms

Term	Definition
Genetics	Genetics is the study of genes and heredity, the passing of genetic information and traits (such as eye color and an increased chance of getting a certain disease) from parents to offspring.[a]
Genomics	Genomics refers to the study of the entire genome of an organism, whereas genetics refers to the study of a particular gene.[b]
Epigenetics	Epigenetics is an emerging field of science that studies heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism.[b]
Phenomics	Phenomics is anemergingtransdiscipline dedicated to systematic study of phenotypes.[c]
Phenotype	A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors.[b]
Genotype	A genotype is an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype.[b]
Genome sequencing	Process for determining the relative order of base pairs in a DNA fragment, gene, chromosome, or an entire genome.[d]
Candidate genes	A candidate gene is a gene whose chromosomal location is associated with a particular disease or other phenotype. Because of its location, the gene is suspected of causing the disease or other phenotype.[b]
Genome-wide association study (GWAS)	A GWAS is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease.[b]

[a] Definition from *NCI Dictionary of Cancer Terms*, by National Institutes of Health, National Cancer Institute. Retrieved October 11, 2010, from http://www.cancer.gov/dictionary.

[b] National Institutes of Health. National Human Genome Research Institute. Retrieved October 6, 2010, from http://www.genome.gov/glossary.

[c] National Institutes of Health. Retrieved October 11, 2010, from http://commonfund.nih.gov/interdisciplinary/consortia/neuro.asp.

[d] Mapping and Sequencing the Human Genome, http://www.ornl.gov/sci/techresources/Human_Genome/publicat/primer/prim2.html.

Table 2

Steps to Enhance the Biobehavioral Inquiry of Fatigue

1.	Refine the homogeneity of the fatigue conceptualization
2.	Operationalize the refined conceptualization of fatigue.
3.	Develop valid and reliable measures of fatigue.
4.	Examine theoretically related genotypes (e.g., through candidate gene studies).
5.	Explore the contribution of the genome (e.g., through GWAS).
6.	Examine the epigenetic triggers of fatigue.

GWAS = genomewide association study.