Team 5: Fatigue

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Genetic Disposition and Patient-reported Quality of Life Outcomes
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Cancer Related Fatigue (CRF)

- Incidence of at least ≥ 60%
- Consistent definition of CRF lacking
  - Generally includes a “persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning.”
Pathophysiologic mechanisms of CRF

• Not completely understood
• Dysregulation of several systems, both biochemical and physiological, likely involved
• Proposed mechanisms of CRF include cytokine dysregulation, 5-HT neurotransmitter dysregulation, alterations in ATP and muscle metabolism, vagal afferent activation, and circadian rhythm disruption
Genetic Markers and Fatigue

- Two broad categories of research for studying genes that control human disease
  - Linkage methodology
  - Genome-wide scanning
  - Hypothesis-driven
    - candidate genes examined in specific pathways
    - appears to be most reasonable
Proposed mechanism for etiology of CRF involves the inflammation pathway:

- cytokines
- evidence suggests that increased inflammatory marker levels are related to increased fatigue
- sickness behavior and IL1
Genetic Markers and Fatigue


- Link between cancer-related fatigue and specific inflammatory markers
- Specific markers 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
Candidate Genes for Fatigue in the Inflammation Pathway

• Gene polymorphisms identified in the regulator (promoter) regions of genes that encode proinflammatory cytokines
  • could differentially influence susceptibility to CRF

• Likely that combination of gene polymorphisms will be associated with CRF
Candidate Genes for Fatigue in the Inflammation Pathway

• Genes that control other cancer-related symptoms (such as depression or pain) could influence fatigue
  • makes sense to examine the influence on fatigue of genes in the cytokine pathway that affect related symptoms such as pain and depression
Cytokine genes and their polymorphisms proposed as candidate markers for the study of CRF

- 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 & substantial under-representation of TT alleles in this group
Cytokine genes and their polymorphisms proposed as candidate markers for the study of CRF

- **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 2x greater representation in fatigued group
Cytokine genes and their polymorphisms proposed as candidate markers for the study of CRF

- TNFα—308 (G/A)
  - The TNFα—308 (G/A) polymorphism proposed for involvement in neoplastic cachexia 7 characterized, in part, by fatigue
  - However, none of the studies that examined the association between TNFα and fatigue demonstrated an association
Cytokine genes and their polymorphisms proposed as candidate markers for the study of CRF

- IL8—251 (T/A)
  - Variation in the promoter SNP IL8—251 (T/A) found to affect risk for pain severity in newly diagnosed untreated lung cancer patients by influencing concentrations of IL8
Cytokine genes and their polymorphisms proposed as candidate markers for the study of CRF

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

- Has been used in 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 found 839 genes to be associated with fatigue when contrasting 40 patients with chronic fatigue and 37 healthy controls.
  - genes regulated oxidative phosphorylation, glucogenesis, lipid metabolism, and several signal transduction pathways
  - 19,000 probes were analyzed - multiple testing problem is substantial
Global gene expression studies of fatigue

- Kerr et al - a two stage approach that identified 182 genes related to fatigue when examining the global gene expression of lymphocytes in 25 cases and 50 controls

- Genes were validated in 55 cases and 75 controls and differential expression was confirmed for 88 genes

- Genes had previously been shown to be associated with immune response, cancer, and cell death.
Global gene expression studies of fatigue - Issues with available data

- Few papers that address global gene expression and fatigue
- Common problem is lack of statistical precision
  - Data sets are small and measures to correct for multiple testing is not done or not described
  - Generally methods are not described in detail making inferences of the findings difficult
- Gene expression in blood cells may not be the optimal (but probably easiest accessible) biomarker of fatigue
Databases related to genes and fatigue

- Limited studies have been published on association between fatigue/QOL and genetic markers
- Most interesting study is available through the CDC (public health genomics office) concerning 227 individuals from Wichita with chronic fatigue syndrome
  - SNPs in HPA axis associated genes, in neuroendocrine effector and receptor genes and in genes in the serotonergic system found to be related to fatigue