Genetic Predictors of Fatigue in Prostate Cancer Patients Treated with Androgen Deprivation Therapy: A Pilot Study

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Androgen Deprivation Therapy

- Androgen deprivation therapy (ADT) used to treat prostate cancer at intermediate or high risk of recurrence or local metastasis
- Eliminates testosterone, which slows the growth of cancer
- Associated with fatigue, which can be very distressing to patients and is associated with worse quality of life
- Important to examine which patients at greatest risk of fatigue
Genetic Predictors of Fatigue in Cancer

- Relatively few studies, none in prostate cancer patients treated with ADT
- Fatigue associated with single nucleotide polymorphisms (SNPs), expression of genes involved in production of pro-inflammatory cytokines in various other cancer types, although data are conflicting
  - Interleukin 1-beta (IL1B), interleukin-6 (IL6), tumor necrosis factor alpha (TNFA)

Cytokines and Fatigue in Cancer Patients

• Genes regulating pro-inflammatory cytokines are a logical focus of research:
  – Circulating IL-1B, IL-6, TNF-α associated with greater fatigue in breast cancer survivors and breast cancer patients undergoing radiation
  – Fatigue can be induced in animals and humans through experimental or therapeutic administration of inflammatory cytokines

Testosterone and Cytokines

- Cytokines may be particularly important in fatigue secondary to ADT
  - Testosterone modulates inflammation
    - Attenuates production of IL6 and TNF by macrophages, monocytes, immature T cells, and other immune cells
    - Animal and human studies show increased IL-1B, IL-6, and TNF-α associated with decreased testosterone

Study Aim

• To examine whether SNPs in IL1B, IL6, and TNFA predict changes in fatigue in men treated with ADT for prostate cancer
  – Hypothesis: men with variants in these genes would display greater increases in fatigue following initiation of ADT
Methods: Study Design

- **Longitudinal**

- **3 groups of men:**
  - Diagnosed with prostate cancer undergoing ADT (ADT+)
  - Diagnosed with prostate cancer treated with surgery only (ADT-)
  - Non-cancer controls (CA-)

- **Matched on:**
  - Age (within 3 years)
  - Education (3 levels)
  - Time since diagnosis (ADT+ & ADT-)
## Methods: Eligibility Criteria

### All participants
- ≥ 18 years of age
- ≥ 6\textsuperscript{th} grade education
- Able to speak/read English
- Able to provide informed consent

### ADT+
- Diagnosed with non-metastatic/asymptomatic metastatic prostate cancer
- Scheduled to be treated with ADT for at least 12 months
- No previous ADT treatment
Methods: Procedures

• Recruitment:
  – Men in the ADT+ group were recruited at Moffitt Cancer Center and the James A. Haley VA

• Participants were assessed at the following time points:
  – ADT+ group: prior to beginning ADT & 6 months later
Methods: Measures

- **Genetic variation**
  - Taq-man PCR assays performed on whole blood specimens collected at baseline
  - Assays included 3 negative controls and 5% duplicates per assay
    - *IL1B-511*: rs16944 (G → A)
    - *IL6-174*: rs1800795 (G → C)
    - *TNFA-308*: rs1800629 (G → A)

- **Fatigue Symptom Inventory (FSI)**
  - Completed at baseline, 6 months
    - Fatigue severity (mean of most, least, average, current)
    - Fatigue interference (e.g., in general activities, work, social activities)
    - Fatigue frequency (days fatigued)
    - Fatigue duration (how much of the day patient felt fatigued)
  - Higher scores indicate greater fatigue
Methods: Measures

- **Center for Epidemiological Studies – Depression (CES-D)**
  - Baseline assessment examined as a potential confound
  - Higher scores indicate greater depressive symptomatology
- **Sociodemographic data**
  - Self-report: age, education, race, marital status, annual household income
Methods: Statistical Analyses

• Examined mean fatigue in three genotypes for each gene to select genetic model
• Factorial ANOVA used to examine mean-level changes in fatigue outcomes
  – Primary interest genotype*time interactions, indicating differential change in fatigue by genotype
• Cumulative effect of multiple SNPs created by summing number of variant alleles
  – Linear regression used to predict fatigue at 6 months from number of variants (i.e., 0 to 3), controlling for fatigue at baseline
  – *IL1B*: G/A or A/A
  – *IL6*: G/C or C/C
  – *TNFA*: G/A or A/A
## Results: Genotype Frequency

<table>
<thead>
<tr>
<th></th>
<th>rs16944 (<em>IL1B</em>)</th>
<th>rs1800795 (<em>IL6</em>)</th>
<th>rs1800629 (<em>TNFA</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Homozygous major allele</strong></td>
<td>28 (53%) G/G</td>
<td>18 (34%) G/G</td>
<td>33 (62%) G/G</td>
</tr>
<tr>
<td><strong>Heterozygous</strong></td>
<td>17 (32%) G/A</td>
<td>29 (55%) G/C</td>
<td>20 (38%) G/A</td>
</tr>
<tr>
<td><strong>Homozygous minor allele</strong></td>
<td>8 (15%) A/A</td>
<td>6 (11%) C/C</td>
<td>0 (0%) A/A</td>
</tr>
<tr>
<td><strong>Minor allele frequency</strong></td>
<td>0.31</td>
<td>0.39</td>
<td>0.19</td>
</tr>
</tbody>
</table>
### Results: Dominant Model

<table>
<thead>
<tr>
<th>Genotype*</th>
<th>Time</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL1B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severity</td>
<td>2.13 (2.11)</td>
<td>3.21 (1.95)</td>
<td>1.94 (1.96)</td>
</tr>
<tr>
<td>Fatigue interference</td>
<td>1.48 (2.21)</td>
<td>2.11 (1.95)</td>
<td>1.29 (2.42)</td>
</tr>
<tr>
<td>Frequency of fatigue</td>
<td>2.21 (2.25)</td>
<td>3.43 (2.57)</td>
<td>1.96 (2.35)</td>
</tr>
<tr>
<td>Duration of fatigue</td>
<td>2.68 (2.57)</td>
<td>3.39 (2.71)</td>
<td>2.20 (2.96)</td>
</tr>
<tr>
<td>IL6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severity</td>
<td>2.24 (2.26)</td>
<td>2.49 (2.44)</td>
<td>1.94 (1.92)</td>
</tr>
<tr>
<td>Fatigue interference</td>
<td>1.71 (2.76)</td>
<td>1.68 (2.56)</td>
<td>1.23 (2.03)</td>
</tr>
<tr>
<td>Frequency of fatigue</td>
<td>2.28 (2.47)</td>
<td>2.44 (2.64)</td>
<td>2.00 (2.21)</td>
</tr>
<tr>
<td>Duration of fatigue</td>
<td>2.67 (3.01)</td>
<td>2.50 (2.68)</td>
<td>2.34 (2.63)</td>
</tr>
<tr>
<td>TNFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue severity</td>
<td>2.10 (2.08)</td>
<td>2.48 (2.00)</td>
<td>1.95 (1.98)</td>
</tr>
<tr>
<td>Fatigue interference</td>
<td>1.35 (2.25)</td>
<td>1.92 (2.50)</td>
<td>1.46 (2.42)</td>
</tr>
<tr>
<td>Frequency of fatigue</td>
<td>2.09 (2.34)</td>
<td>2.73 (2.53)</td>
<td>2.10 (2.25)</td>
</tr>
<tr>
<td>Duration of fatigue</td>
<td>2.30 (2.73)</td>
<td>2.58 (2.77)</td>
<td>2.70 (2.81)</td>
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</tbody>
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Note: Unadjusted means, standard deviations, and repeated measures ANOVAs are shown.
Results: Dominant Model

**IL6 Results**

<table>
<thead>
<tr>
<th>Fatigue Frequency</th>
<th>Fatigue Duration</th>
<th>Fatigue Intrusiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>GC or CC</td>
<td>GG</td>
</tr>
<tr>
<td>6 Months</td>
<td></td>
<td>GG</td>
</tr>
</tbody>
</table>

**TNFA Results**

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<tr>
<td>G/G</td>
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<td>6 Months</td>
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Baseline vs. 6 Months comparison for Fatigue Frequency, Duration, and Intrusiveness.
Results: Cumulative Effect of Multiple Variants

- Examined IL1B: G/A or A/A, IL6: G/C or C/C, TNFA: G/A
- Four patients had 0 variants, 24 patients had 1, 19 patients had 2, 6 patients had 3
- Number of variants significantly predicted fatigue interference and duration (ps≤.02) but not fatigue severity or frequency (ps>.08)
# Results: Adjusted Dominant Model

<table>
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<tr>
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<th>IL1B</th>
<th>IL6</th>
<th>TNFA</th>
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<tr>
<td></td>
<td>G/G</td>
<td>G/A or A/A</td>
<td>G/A</td>
</tr>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
<td>Time 1</td>
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* p≤.05, ** p≤.01
Summary of Findings

- Variation in IL6 gene predicted increases in fatigue intrusiveness, frequency, and duration
  - Relationships attenuated by addition of age, race, and depressive symptomatology to model
- Variation in TNFA gene predicted increases in fatigue severity
- Variation in IL1B gene did not predict changes in fatigue
- Patients with multiple variants of the three genes showed greater increases in fatigue duration and interference (i.e. “multiple hit”)
Discussion

• Our IL1B findings contrary to previous evidence showing a significant relationship with cancer-related fatigue
• Our IL6 and TNFA findings congruent with previous literature, although there is mixed evidence regarding at-risk variant and correlation with circulating cytokines
  – Complexity of multiple regulatory regions
• Future research: gene regulation, downstream gene products (e.g. mRNA)
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