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)

Aouizerat et al. *Biol Res Nurs* 2009; 11:27-41.
Collado-Hidalgo et al. *BBI* 2008; 22: 1197-1200.
Rausch et al. *Cancer* 2010; 116: 4103-4113.
Rienertsen et al. *BBI* 2011; 25: 1376-1383.

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

Bower et al. *Psychosom Med* 2002; 64: 604-611.
Bower et al. *Clin Cancer Res* 2009; 15: 5534-5540.
Kelley et al. *BBI* 2003; 17 Suppl 1: S112-118.
Schubert et al. *BBI* 2007; 21: 413-427.
Wang et al. *BBI* 2010; 24: 968-974.

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

Bellido et al. *J Clin Invest* 1995; 95: 2285-2895.
Maggio et al. *J Clin Endocrinol Metab* 2006; 91: 345-347.
Mustabak et al. *Clin Exp Immunol* 2003; 132: 265-270.

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
- ≥ 6th 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

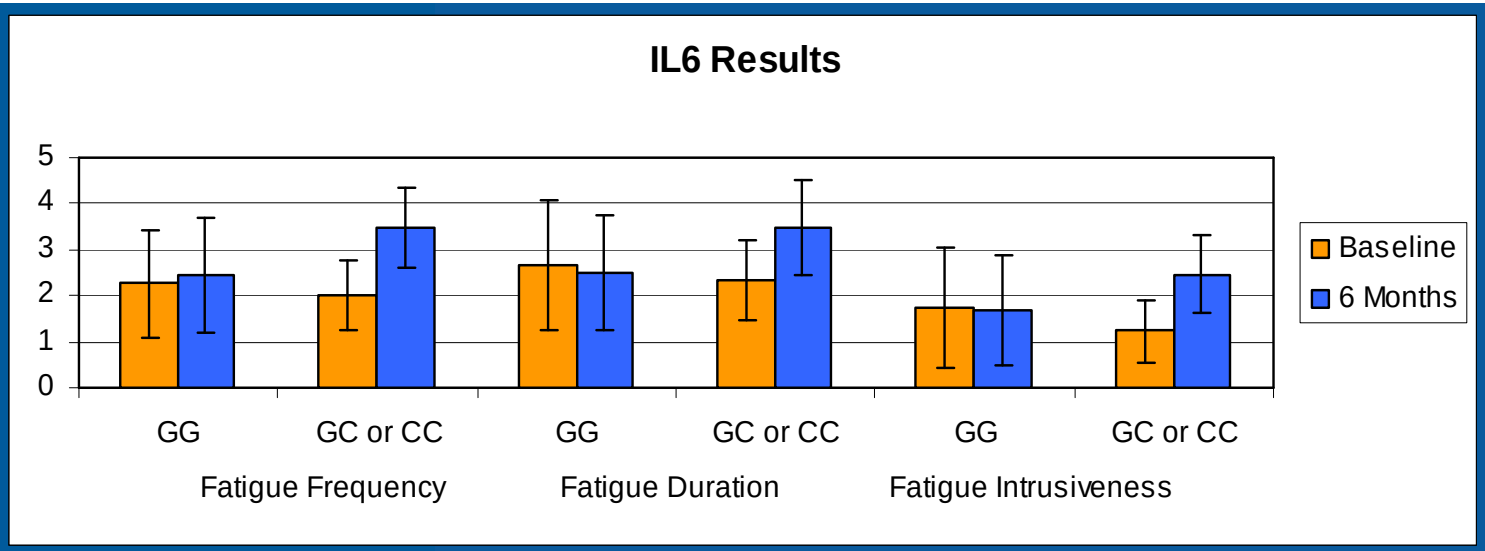
	rs16944 (*IL1B*)	rs1800795 (*IL6*)	rs1800629 (*TNFA*)
Homozygous major allele	28 (53%) G/G	18 (34%) G/G	33 (62%) G/G
Heterozygous	17 (32%) G/A	29 (55%) G/C	20 (38%) G/A
Homozygous minor allele	8 (15%) A/A	6 (11%) C/C	0 (0%) A/A
Minor allele frequency	0.31	0.39	0.19

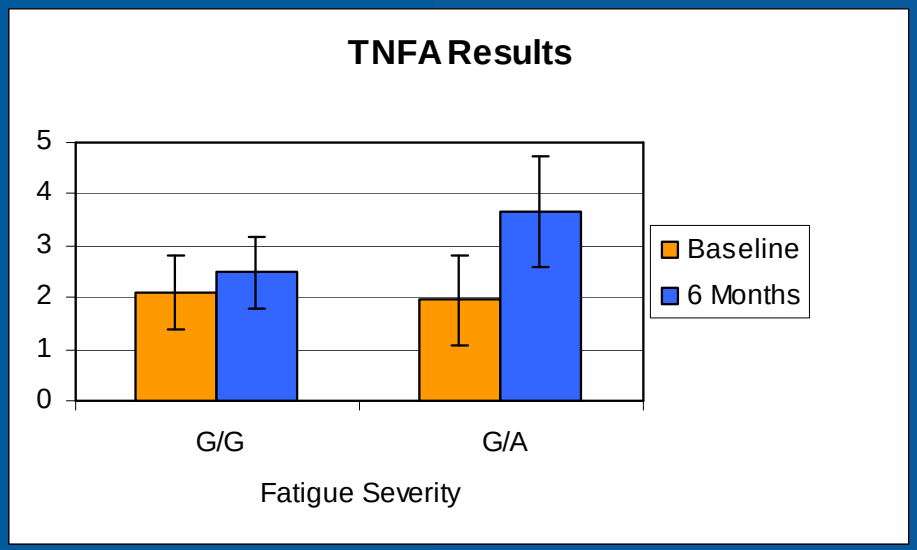
Results: Dominant Model

	IL1B				Genotype* Time *F*	*p*
	G/G		G/A or A/A			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	2.13 (2.11)	3.21 (1.95)	1.94 (1.96)	2.60 (2.46)	.56	.46
Fatigue interference	1.48 (2.21)	2.11 (1.95)	1.29 (2.42)	2.30 (3.12)	.54	.46
Frequency of fatigue	2.21 (2.25)	3.43 (2.57)	1.96 (2.35)	2.80 (2.68)	.35	.56
Duration of fatigue	2.68 (2.57)	3.39 (2.71)	2.20 (2.96)	2.88 (3.15)	.00	.96
	IL6					
	G/G		G/C or C/C			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	2.24 (2.26)	2.49 (2.44)	1.94 (1.92)	3.15 (2.08)	2.72	.11
Fatigue interference	**1.71 (2.76)**	**1.68 (2.56)**	**1.23 (2.03)**	**2.47 (2.54)**	**5.71**	**.02**
Frequency of fatigue	**2.28 (2.47)**	**2.44 (2.64)**	**2.00 (2.21)**	**3.49 (2.57)**	**4.17**	**.05**
Duration of fatigue	**2.67 (3.01)**	**2.50 (2.68)**	**2.34 (2.63)**	**3.49 (3.00)**	**4.18**	**.05**
	TNFA					
	G/G		G/A			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	**2.10 (2.08)**	**2.48 (2.00)**	**1.95 (1.98)**	**3.65 (2.39)**	**5.67**	**.02**
Fatigue interference	1.35 (2.25)	1.92 (2.50)	1.46 (2.42)	2.66 (2.63)	1.43	.24
Frequency of fatigue	2.09 (2.34)	2.73 (2.53)	2.10 (2.25)	3.80 (2.69)	2.77	.10
Duration of fatigue	2.30 (2.73)	2.58 (2.77)	2.70 (2.81)	4.10 (2.95)	3.19	.08

Note: Unadjusted means, standard deviations, and repeated measures ANOVAs are shown.

Results: Dominant Model





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

					No control variables	Control for age, race, baseline CESD
	IL1B				Genotype* Time F	Genotype* Time F
	G/G		G/A or A/A			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	2.13 (2.11)	3.21 (1.95)	1.94 (1.96)	2.60 (2.46)	.56	.49
Fatigue interference	1.48 (2.21)	2.11 (1.95)	1.29 (2.42)	2.30 (3.12)	.54	.94
Frequency of fatigue	2.21 (2.25)	3.43 (2.57)	1.96 (2.35)	2.80 (2.68)	.35	.20
Duration of fatigue	2.68 (2.57)	3.39 (2.71)	2.20 (2.96)	2.88 (3.15)	.00	.01
	IL6					
	G/G		G/C or C/C			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	2.24 (2.26)	2.49 (2.44)	1.94 (1.92)	3.15 (2.08)	2.72	2.53
Fatigue interference	1.71 (2.76)	1.68 (2.56)	1.23 (2.03)	2.47 (2.54)	**5.71***	3.85†
Frequency of fatigue	2.28 (2.47)	2.44 (2.64)	2.00 (2.21)	3.49 (2.57)	**4.17***	2.91†
Duration of fatigue	2.67 (3.01)	2.50 (2.68)	2.34 (2.63)	3.49 (3.00)	**4.18***	3.04†
	TNFA					
	G/G		G/A			
	Time 1	Time 2	Time 1	Time 2		
Fatigue severity	2.10 (2.08)	2.48 (2.00)	1.95 (1.98)	3.65 (2.39)	**5.67***	**5.39***
Fatigue interference	1.35 (2.25)	1.92 (2.50)	1.46 (2.42)	2.66 (2.63)	1.43	1.46
Frequency of fatigue	2.09 (2.34)	2.73 (2.53)	2.10 (2.25)	3.80 (2.69)	2.77	2.75
Duration of fatigue	2.30 (2.73)	2.58 (2.77)	2.70 (2.81)	4.10 (2.95)	3.19	3.16†

Note: Unadjusted means, standard deviations, and repeated measures ANOVAs are shown.
†p≤.10, *p≤.05

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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