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Identification of Genetic Markers Associated With Self-Reported Attentional Function

by

John D. Merriman, MS, RN

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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by

John D. Merriman

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Abstract

Identification of Genetic Markers Associated With Self-Reported Attentional Function

John D. Merriman

Subgroups of individuals may be at greater risk for changes in attentional function before, during, and after cancer treatment. Proposed mechanisms for these changes may include genetic predisposition to cytokine and neurotransmitter dysregulation. The purposes of this dissertation research were to identify subgroups of individuals with distinct trajectories of attentional function and to evaluate for phenotypic and genotypic (i.e., variations in cytokine and neurotransmission genes) differences among these subgroups. Self-reported attentional function was evaluated in two independent samples using the Attentional Function Index. In the first sample of 167 oncology patients receiving radiation therapy and their 85 family caregivers, three latent classes were identified using growth mixture modeling: high (15.5%), moderate-to-high (48.0%), and moderate (36.5%) attentional function. Participants in the moderate class were younger, with more comorbidities and lower functional status. Multivariable models controlled for phenotypic differences among classes, population stratification due to race/ethnicity, and other genetic variations in the same gene. A cytokine gene variation (i.e., IL6 rs1800795) remained a significant genotypic predictor of latent class membership in multivariable models. In addition, two catecholaminergic gene variations (i.e., ADRA1D rs4815675, SLC6A3 rs37022), a gamma-aminobutyric acid (GABA)-ergic gene variation (i.e., SLC6A1 rs2697138), and two serotonergic gene variations (i.e., HTR2A rs2296972,

rs9534496) remained significant predictors of latent class membership. In the second sample of 397 patients with breast cancer, three latent classes were identified: high (41.6%), moderate (25.4%), and low-moderate (33.0%) attentional function. Patients in the low-moderate class were younger than those in the high class, with more comorbidities and lower functional status than the other two classes. Controlling for phenotypic differences among classes, population stratification due to race/ethnicity, and other genetic variations in the same gene, a cytokine gene variation (i.e., IL1R1 rs949963) remained a significant genotypic predictor of latent class membership. Findings provide evidence of subgroups of individuals with distinct trajectories of attentional function and of genetic associations with subgroup membership. These findings suggest that variations in genes that encode for inflammatory cytokines and for three distinct but related neurotransmission systems are involved in attentional function.

Keywords: attention, attentional fatigue, cancer, catecholamines, cognition, cytokine genes, gamma-aminobutyric acid, growth mixture modeling, inflammation, neurotransmitters, radiation therapy, serotonin

Table of Contents

Acknowledgements	iii
Abstract	v
Introduction to Dissertation	1
Chapter 1	
Proposed Mechanisms for Cancer- and Treatment-Related Cognitive Changes	10
Abstract	11
Introduction	12
Treatment-Related Mechanisms	13
Cytokine Upregulation	13
Hormonal Changes	16
Other Clinical Factors	18
Inter-Individual Differences	20
Genetic Variations	21
Co-Occurring Symptoms	23
Age	26
Conclusions	27
Clinical Implications	28
Recommendations for Future Research	28
References	30
Figure Legend	45
Figure	46

Chapter 2

Preliminary Evidence of an Association Between an Interleukin 6 Promoter Polymorphism and Self-Reported Attentional Function in Oncology Patients and Their Family Caregivers	47
Abstract	49
Introduction	50
Materials and Methods	52
Study Procedures	53
Phenotypic Analyses	53
Genotypic Analyses	54
Results	56
GMM Classes	56
Phenotypic Differences Among Classes	57
Genotypic Differences Among Classes	57
Discussion	58
References	63
Figure Legends	71
Tables and Figures	72
Table 1	72
Table 2	75
Table 3	76
Table 4	77
Figure 1	78

Figure 2	79
----------------	----

Chapter 3

Association Between an Interleukin 1 Receptor, Type I Promoter Polymorphism and Self-Reported Attentional Function in Women With Breast Cancer.....	80
Abstract	82
Introduction	83
Material and Methods	85
Study Procedures	85
Phenotypic Analyses	86
Genotypic Analyses	87
Results	90
GMM Classes.....	90
Phenotypic Differences Among Classes	90
Genotypic Differences Among Classes	91
Discussion	92
References	100
Figure Legends.....	110
Tables and Figures	111
Table 1	111
Table 2	112
Table 3	113
Table 4	115
Table 5	118

Figure 1	119
Figure 2	120

Chapter 4

Associations Between Catecholaminergic, GABAergic, and Serotonergic

Neurotransmission Genes and Self-Reported Attentional Function in Oncology Patients

and Their Family Caregivers

Abstract

Introduction

Methods

Study Procedures

Phenotypic Analyses

Genotypic Analyses

Results

Phenotypic Differences Among Latent Classes

Genotypic Differences Among Latent Classes

Discussion

Catecholaminergic System

GABAergic System

Serotonergic System

Conclusions

References

Figure Legends

Tables and Figures

Table 1	152
Table 2	157
Table 3	158
Table 4	159
Figure 1	160
Figure 2	161
Figure 3	162
Figure 4	163
Conclusions for Dissertation.....	164
Implications for Clinical Practice	165
Recommendations for Future Research	166
UCSF Library Release	174

Introduction to Dissertation

Attentional function is important for accomplishing meaningful goals and maintaining healthy social interactions during and following cancer treatment (Cimprich, Visovatti, & Ronis, 2011). However, attention may be impaired as a result of cognitive changes directly associated with cancer treatment or other clinical factors in patients with non-central nervous system (CNS) cancers (Merriman, Von Ah, Miaskowski, & Aouizerat, in press), as well as in their family caregivers (FCs; Merriman et al., 2013).

The current understanding of attentional function was derived from William James' rational description of two types of attention in *The Principles of Psychology* (James, 1890/1983): (1) voluntary attention, which requires effort and is directed by choice, and (2) involuntary attention, which pivots without effort or choice to things that affect survival or that are fascinating. While involuntary attention requires no effort, competing stimuli that capture this type of attention can lead to a state of distraction in which ever-increasing effort is required to direct voluntary attention (i.e., attentional fatigue; Cimprich, 1992; James, 1890/1983).

Neuroscientists expanded on James' ideas to propose three components of attention: (1) selectivity, which is the ability to focus on one stimulus while ignoring others; (2) alertness, which sustains selectivity over time; and (3) processing capacity, which is a ceiling on the number of stimuli that can be simultaneously processed (Posner & Boies, 1971). Importantly, these components of attention are measurable, which moved the study of attention from rational philosophy to testable hypotheses. Petersen & Posner (2012) proposed the following bases for the study of brain structures that are involved in the three components of attention: (1) attention is a system, like the motor or

sensory system; (2) this system encompasses one or more networks comprised of multiple brain structures; and (3) individual components of the network(s) have separate but complimentary functions.

Attention is integral to awareness, self-regulation, and executive function (Posner, 1994; Posner & Rothbart, 1998). Self-reported attentional function is an important quality of life indicator. While perceived cognitive changes present more subtly than physical or psychological symptoms, the personal impact of these changes can be devastating (e.g., inability to work; Boykoff, Moieni, & Subramanian, 2009). Although studies using objective neuropsychological tests have shown subtle or no changes in attentional function (e.g., Ahles et al., 2010; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Reid-Arndt, Hsieh, & Perry, 2010; Tager et al., 2010), patients may report these changes because of increased mental effort exerted to compensate for cognitive changes associated with cancer and its treatment (Ferguson, McDonald, Saykin, & Ahles, 2007). Indeed, functional magnetic resonance imaging studies support the hypothesis that subjective reports of cognitive changes are associated with increased mental effort (Ferguson et al., 2007; Reuter-Lorenz & Cimprich, 2013).

For both patients and FCs, the threatening nature of the cancer diagnosis, unfamiliar treatment environments, and confusing healthcare terminology contribute to pervasive distractions that contribute to diminished attentional function (Cimprich et al., 2011). A recent report from the International Cognition and Cancer Task Force highlighted a consistent finding in the literature that subgroups of patients are more vulnerable to cognitive changes (Wefel, Vardy, Ahles, & Schagen, 2011).

Characterization of vulnerable subgroups would allow clinicians to target educational programs and interventions to individuals most likely to benefit.

In a preliminary study to this dissertation research (Merriman et al., 2010), predictors of the trajectories of self-reported attentional function were evaluated in a sample of 73 women during radiation therapy (RT). Using hierarchical linear modeling, lower levels of attentional function were associated with younger age, not working, a higher number of comorbidities, and higher levels of trait anxiety. The trajectory of attentional function improved over time for women with a higher body mass index.

In a second preliminary study to this dissertation research (Merriman et al., 2011), differences in self-reported attentional function between 73 patients with breast cancer and 82 patients with prostate cancer were evaluated at the initiation of RT. After controlling for age, patients with breast cancer reported lower levels of attentional function. In both groups, lower levels of attentional function correlated with more anxiety, depressive symptoms, sleep disturbance, and physical fatigue. These correlations were stronger for the patients with breast cancer.

Cognitive changes may be mediated through genetic predisposition to dysregulation of cytokine and/or neurotransmission systems (Ahles & Saykin, 2007). Therefore, the purposes of this dissertation research, in two independent samples, were to identify latent classes (i.e., subgroups) of individuals with distinct trajectories of self-reported attentional function and to evaluate for phenotypic and genotypic (i.e., variations in cytokine and neurotransmission genes) differences among these subgroups.

In chapter one, the evidence is reviewed for various mechanisms that may underlie the development of diminished cognitive function in oncology patients. The

focus of this review is on studies of patients with cancer and cancer survivors. However, relevant findings in other populations and from pre-clinical studies are included. The chapter concludes with a discussion of the clinical implications and recommendations for future research. This chapter is a reprint of material in press in *Seminars in Oncology Nursing* (Merriman et al., in press).

In chapter two, growth mixture modeling (GMM) was used to identify latent classes of individuals with distinct trajectories of attentional function in a sample of 167 oncology patients and their 85 FCs during RT. Three latent classes were identified: high (15.5%), moderate-to-high (48.0%), and moderate (36.5%) attentional function. Differences among these latent classes in phenotypic and genotypic characteristics (i.e., variations in cytokine genes) were evaluated. Participants in the moderate class were younger, with more comorbidities and lower functional status. Controlling for phenotypic differences among the latent classes, population stratification due to race/ethnicity, and other genetic variations in the same gene, a cytokine gene variation (i.e., IL6 rs1800795) remained a significant predictor of latent class membership in multivariable models. This chapter is a reprint of material published in *Biological Research for Nursing* (Merriman et al., 2013).

In chapter three, we attempted to replicate findings from chapter two and identify novel associations in a more homogenous sample. GMM was used to identify latent classes of patients with distinct trajectories of attentional function in a sample of 397 women being treated for breast cancer. Three latent classes were identified: high (41.6%), moderate (25.4%), and low-moderate (33.0%) attentional function. Patients in the low-moderate class were younger than those in the high class, with a higher level of

comorbidity and lower functional status than the other two classes. Controlling for phenotypic differences among the latent classes, population stratification due to race/ethnicity, and other genetic variations in the same gene, a cytokine gene variation (i.e., IL1R1 rs949963) remained a significant genotypic predictor of latent class membership in multivariable models.

In chapter four, associations between neurotransmission gene variations and the three GMM latent classes previously identified in the sample of oncology patients and their FCs (Merriman et al., 2013) were evaluated. Multivariable models were fit controlling for phenotypic differences among the latent classes, population stratification due to race/ethnicity, and other genetic variations in the same gene. Two catecholaminergic gene variations (i.e., ADRA1D rs4815675, SLC6A3 rs37022), a gamma-aminobutyric acid (GABA)-ergic gene variation (i.e., SLC6A1 rs2697138), and two serotonergic gene variations (i.e., HTR2A rs2296972, rs9534496) remained significant predictors of latent class membership.

Taken together, these findings provide preliminary evidence of subgroups of individuals with distinct trajectories of attentional function and of phenotypic and genotypic associations with subgroup membership. These findings suggest that age, comorbidities, and functional status are important phenotypic predictors of self-reported attentional function. In addition, these findings suggest that variations in genes that encode for inflammatory cytokines and for three distinct but related neurotransmission systems are involved in attentional function.

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Chapter 1:

Proposed Mechanisms for Cancer- and Treatment-Related Cognitive Changes

John D. Merriman, Diane Von Ah, Christine Miaskowski, and Bradley E. Aouizerat

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This chapter is a reprint of material in press: Merriman, J. D., Von Ah, D., Miaskowski, C, & Aouizerat, B. E. (in press). Proposed mechanisms for cancer- and treatment-related cognitive changes. *Seminars in Oncology Nursing*.

Abstract

This review describes the proposed mechanisms of cognitive changes associated with non-central nervous system cancers and cancer treatment through a review and synthesis of data-based publications and review articles. Proposed mechanisms include cytokine upregulation, hormonal changes, neurotransmitter dysregulation, attentional fatigue, genetic predisposition, and comorbid symptoms. Oncology nurses need to understand the multiple mechanisms that may contribute to the development of cancer- and treatment-related cognitive changes so that they can identify patients at high risk and can help patients understand why these changes occur.

Keywords: cognition, cancer, cytokines, inflammation, neurotransmitters

Proposed Mechanisms for Cancer- and Treatment-Related Cognitive Changes

A patient's cognitive function is important for navigating treatment, maintaining social support, and accomplishing meaningful goals during and following cancer treatment (Cimprich, Visovatti, & Ronis, 2011). However, attention and other components of cognitive function (e.g., working memory, information processing speed) may be impaired as a result of cognitive changes directly associated with cancer treatment or other clinical factors in patients with non-central nervous system (CNS) cancers.

Cancer- and treatment-related cognitive changes may be mediated through inflammatory cytokine upregulation and hormonal changes (Ahles & Saykin, 2007). In addition, the biology of the cancer (Allavena & Mantovani, 2012), as well as stress (Juster, McEwen, & Lupien, 2010) and attentional fatigue (Cimprich, 1992a) may contribute to cognitive changes. Finally, genetic predisposition (Ahles & Saykin, 2007) and co-occurring symptoms (De Raedt & Koster, 2010) may explain some of the inter-individual variability in these cognitive changes. The severity of cognitive changes may be moderated by age (Ahles, Root, & Ryan, 2012).

The purpose of this article is to review the evidence for various mechanisms that may underlie the development of diminished cognitive function in oncology patients (see Figure 1). The focus of this review is on studies of patients with cancer and cancer survivors. However, relevant findings in other populations and from pre-clinical studies are included. The article concludes with a discussion of clinical implications and recommendations for future research.

Treatment-Related Mechanisms

Evidence suggests that cancer treatments play a role in cognitive changes. Chemotherapy (CTX) is the most frequently evaluated treatment for its effects on cognitive function (Ahles, 2012). Some CTX drugs cross the blood-brain barrier (e.g., 5-fluorouracil) or may be administered intrathecally (e.g., methotrexate), potentially damaging the CNS directly (Ahles & Saykin, 2007). High-dose CTX may cause more damage to the CNS than standard-dose CTX (van Dam et al., 1998). In addition, treatment-induced cardiotoxicity may impact cognitive function by reducing the flow of blood to the brain (Ahles & Saykin, 2007). Alternatively, systemic CTX may induce CNS damage through inflammatory pathways upregulated by non-apoptotic cell death (Seruga, Zhang, Bernstein, & Tannock, 2008).

Other treatments may contribute to cognitive changes. Surgery (Cibelli et al., 2010) and radiation therapy (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008) may result in cognitive changes through peripheral tissue damage that activates inflammatory pathways. In addition, anesthesia administered during surgery could impact cognitive function directly (Janelins et al., 2011). Finally, hormonal therapy could influence cognition through changes in hormone levels (Bender, Paraska, Sereika, Ryan, & Berga, 2001).

Cytokine Upregulation

Peripheral inflammation may mediate cognitive changes associated with cancer treatment (Seruga et al., 2008). A peripheral inflammatory state can be communicated to the CNS in many ways (e.g., through afferent nerves such as the vagus nerve; Capuron & Miller, 2011; Watkins et al., 1995). In response, proinflammatory cytokines are produced

by microglial cells in the CNS (Capuron & Miller, 2011). These central cytokines damage neurons by inducing oxidative stress (Joshi et al., 2005). Therefore, peripheral inflammation may negatively impact cognitive function (Wilson, Finch, & Cohen, 2002).

CTX may damage the CNS indirectly through the production of free radicals (e.g., reactive oxygen species; Ahles & Saykin, 2007; Chen, Jungsuwadee, Vore, Butterfield, & St Clair, 2007). When cellular antioxidants are unable to neutralize free radicals, cells enter a state of oxidative stress in which cellular structures and DNA are damaged (Chen et al., 2007; Tangpong et al., 2007). Mitochondria, which produce cellular energy, are susceptible to oxidative damage because of their involvement with free radical production and their poor DNA repair capabilities (Chen et al., 2007; Tsutsui, Ide, & Kinugawa, 2006). Damage to mitochondria may reduce neuronal energy production, leading to poorly functioning neurons (Chen et al., 2007; Martin, 2006). Damaged or poorly functioning neurons may be destroyed by apoptosis, contributing to cognitive changes (Geller et al., 2001).

Results of one study demonstrated that administration of doxorubicin, which is not known to cross the blood-brain barrier (Chen et al., 2007; Ohnishi et al., 1995), was associated with increased levels of the proinflammatory cytokine tumor necrosis factor- α in the periphery (Janelins et al., 2012). This upregulation of peripheral cytokine levels may be communicated to the CNS, subsequently damaging neurons via oxidative stress (Ahles & Saykin, 2007; Tangpong et al., 2006; Wilson et al., 2002).

Study results suggest that upregulated peripheral cytokine levels and peripheral oxidative stress mirror oxidative stress in the CNS. Researchers conducting pre-clinical studies found that mice treated with doxorubicin had higher levels of CNS neuronal

oxidation (Aluise et al., 2010; Joshi et al., 2005). Similarly, in a recent study of breast cancer survivors an average of six years after CTX, oxidative DNA damage in peripheral white blood cells was associated with decreased grey matter density in the brain (Conroy et al., 2013). These findings support the pathway whereby treatments that do not pass the blood-brain barrier can damage CNS neurons indirectly. It is possible that DNA damage induced by inflammation contributes to further immune activation, potentially perpetuating a cycle of DNA damage and inflammation (Ahles & Saykin, 2007).

Although damage to CNS neurons may explain partially the cognitive changes patients experience, neural progenitor cells and neuroglial cells also are important. Neural progenitor cells replenish damaged neurons and neuroglia in the hippocampus (Dietrich, Han, Yang, Mayer-Proschel, & Noble, 2006). These cells are active in building neural tissue in the hippocampus, which is responsible for consolidation of short-term memories (Dietrich et al., 2006). If the pool of neural progenitor cells is decreased due to treatment-induced toxicity, the CNS has less ability to repair damaged neurons and maintain hippocampal tissue (Dietrich et al., 2006). In addition, damage to oligodendrocytes, a type of neuroglial cell, impairs myelination of white matter tracts, thereby reducing processing speed (Dietrich, Monje, Wefel, & Meyers, 2008).

Results from pre-clinical studies using mouse models indicated that systemic CTX damages lineage-restricted neural progenitor cells and oligodendrocytes (Dietrich et al., 2006; Han et al., 2008). After CTX administration, neuronal cell death continued at an increased rate for at least six weeks (Dietrich et al., 2006), and white matter tracts remained impaired for at least six months (Han et al., 2008). Taken together, injury to neural progenitor cells and oligodendrocytes partially may explain long-term and delayed

cognitive changes experienced by cancer survivors, particularly changes in memory and processing speed (Dietrich et al., 2006).

Hormonal Changes

Estrogen. Estrogen is important for verbal memory (Bender et al., 2001) and learning (Jenkins, Atkins, & Fallowfield, 2007). The hormone increases production of acetylcholine, which is important for memory (Bender et al., 2001). Estrogen promotes the development of synapses in areas of the brain involved in memory, such as the hippocampus (Liu et al., 2008). In addition, the hormone is important for neuronal cell growth and maintenance (Turgeon, Carr, Maki, Mendelsohn, & Wise, 2006). Decreases in estrogen levels may occur because of systemic CTX, which can damage hormone-producing tissue, or as a result of anti-estrogen therapy (Bender et al., 2001). Anti-estrogen therapies include aromatase inhibitors, which block the conversion of androgens to estrogen, and selective estrogen receptor modulators (e.g., Tamoxifen; Jenkins et al., 2007). These treatments are used to prevent the recurrence of hormone-sensitive tumors (Jenkins et al., 2007).

Treatment-induced menopause may occur in pre-menopausal women undergoing systemic treatment (Bender et al., 2001). Women who experience the precipitous decline in estrogen levels that occurs as a result of treatment-induced menopause, as opposed to the more gradual hormonal changes that occur with natural menopause, may report more pronounced cognitive changes. Moreover, because estrogen is thought to be neuroprotective (Turgeon et al., 2006), women who enter treatment-induced menopause earlier in life may be at greater risk for more severe cognitive changes (Bender et al., 2001).

Testosterone. Testosterone is important for cognitive function, particularly for visuospatial ability (Cherrier et al., 2005) and working memory (Nelson, Lee, Gamboa, & Roth, 2008; Sandstrom, Kim, & Wasserman, 2006), as well as the maintenance of synaptic density in the hippocampus (Leranth, Petnehazy, & MacLusky, 2003). Administration of testosterone is associated with elevated mood and cognitive function. In contrast, low levels of the hormone are associated with deficits in neurotransmission, fatigue, poor mood, and worse cognitive function (Bain, 2010). Administration of testosterone to men with Alzheimer's disease or mild cognitive impairment has been shown to improve cognitive function (Beauchet, 2006).

Androgen deprivation therapy (ADT) is used to prevent growth of hormone-sensitive prostate cancer (Cannata, Kirschenbaum, & Levine, 2012). ADT severely reduces testosterone levels, which may impact cognitive function in subtle but meaningful ways for patients (Nelson et al., 2008). Because aromatase converts testosterone to estrogen, blocking testosterone lowers estrogen levels (Alibhai, Gogov, & Allibhai, 2006). Therefore, some of the cognitive changes these men experience may be related to estrogen deprivation (Cherrier et al., 2005; Nelson et al., 2008).

Findings from clinical studies about the effects of ADT are mixed. In one recent study of men post radiation therapy, no significant differences were found in the cognitive functioning of men who received ADT compared to men who did not (Wiechno, Sadowska, Kalinowski, Michalski, & Demkow, 2013). Another recent study (Chao et al., 2012) was conducted to explore this relationship using functional magnetic resonance imaging. Men treated with ADT showed decreased activity in cortical structures important for top-down cognitive control compared to men not treated with ADT,

although both groups performed similarly on objective tests of cognitive function. Therefore, imaging may be more sensitive to treatment-induced cognitive changes than objective tests (Chao et al., 2012).

Other Clinical Factors

In a number of recent studies, cognitive changes were found in patients before adjuvant treatment for cancer. For example, researchers found worse verbal memory and attention in women before adjuvant treatment for breast cancer compared to women without breast cancer (Bender et al., 2013). Although the effects of surgery may account for these findings (Bender et al., 2013; Cibelli et al., 2010), other clinical factors may explain cognitive changes before treatment.

Tumor-associated macrophages release proinflammatory cytokines that alter the micro-environment surrounding the tumor (Allavena & Mantovani, 2012). This alteration promotes an environment that is hospitable to growth and metastasis (Allavena & Mantovani, 2012). Tumor-induced inflammatory changes could contribute to a chronic inflammatory state before treatment, which may affect cognitive function through the same mechanisms attributed to treatment-induced inflammation (Seruga et al., 2008). Comorbidities may impact cognitive function directly (e.g., heart failure; Bauer, Johnson, & Pozehl, 2011). Moreover, management of multiple comorbidities may strain the cognitive systems of the brain (Merriman et al., 2010).

The high, sustained levels of stress experienced by patients after diagnosis of cancer could contribute to cognitive changes. The allostatic load hypothesis suggests that physical and psychological stressors impact common biological pathways to produce cognitive changes via cytokine upregulation (Juster et al., 2010; McEwen, 2008; Miller,

Maletic, & Raison, 2009; Seruga et al., 2008). Through the process of allostasis, the body adjusts to stress by adaptations (McEwen, 2008). However, chronic stress may tip these adjustments into allostatic overload, negatively impacting cognitive function through dysregulation of immune function (McEwen, 2008).

Attentional fatigue is an important contributor to cognitive changes (Cimprich et al., 2011). Three networks are thought to compose the attention system of the brain: the alerting, orienting, and executive networks (Posner, 2012). Together, these networks allow for normal attentional function. Of particular importance to attentional fatigue is the executive network, which is responsible for synthesizing conflicting input from separate brain areas into a coherent response. This “effortful control” (Posner, 2012) is experienced in part as making rational decisions, planning to meet goals, monitoring the self during social interactions, and controlling the expression of emotions.

The pervasive distractions that oncology patients experience after diagnosis can lead to reduced ability to continue to exert effortful control (i.e., attentional fatigue; Cimprich, 1992b; Posner, 2012). Because effortful control has high metabolic demands and its effectiveness is sensitive to variations in glucose levels, short-term attentional fatigue may be mediated by depletion of glucose (Gailliot et al., 2007). However, long-term attentional fatigue can be experienced as burn-out that is not dependent on glucose levels (Baumeister, Vohs, & Tice, 2007).

In one study, patients who more recently completed CTX or who had received higher doses of CTX had a significantly lower cerebral glucose metabolic rate than patients who completed treatment earlier, received lower doses of CTX, or received no CTX (Baudino et al., 2011). Using positron emission tomography, the frontal lobes were

shown to have the most severe reductions in glucose metabolism, which is consistent with reduced efficiency of the executive attention network. Although patients scored within the normal ranges on neuropsychological tests, they reported cognitive difficulties. Therefore, patients may have noticed the extra effort required to successfully complete neuropsychological tasks due to impaired glucose metabolism.

This impairment pattern parallels age-related changes in cerebral glucose metabolism, which may occur due to an accumulation of neuronal damage due to oxidative stress and mitochondrial dysfunction (Baudino et al., 2011; Maccormick, 2006; Mattson & Magnus, 2006). Support for this hypothesis was found in high levels of oxidative DNA damage in peripheral lymphocytes after CTX in women with breast cancer (Blasiak et al., 2004), as well as higher mutation rates in the mitochondrial DNA of cancer patients (Wardell et al., 2003). Changes in glucose metabolism may contribute to uncontrolled glucose levels and insulin resistance, which in turn contribute to inflammatory cytokine production, oxidative stress, and hypothalamic-pituitary-adrenal (HPA) axis disruption (Greenwood & Winocur, 2005).

Inter-Individual Differences

Inter-individual differences in cognitive changes before and during cancer treatment and into survivorship may be due to multiple mechanisms that confer susceptibility to, or protection from, cognitive changes. These mechanisms include genetic variations and co-occurring symptoms (e.g., affective symptoms, sleep disturbance; Ahles & Saykin, 2007). In addition, the severity of cognitive changes may be moderated by age (Cimprich et al., 2011).

Genetic Variations

Inflammatory cytokines. Variations in genes that encode for pro- and anti-inflammatory cytokines partially may explain inter-individual differences in cognitive function among oncology patients (Ahles & Saykin, 2007). For example, researchers recently found an association between IL6 rs1800795 and level of self-reported attentional function (Merriman et al., 2013). In that study, each additional copy of the “G” rare allele conferred increased odds of belonging to a subgroup of participants with lower attentional function. In another recent study, this allele was associated with memory complaints among women with breast cancer (Bower et al., 2013). The G allele is associated with elevated peripheral levels of interleukin-6 (Hulkkonen, Pertovaara, Antonen, Pasternack, & Hurme, 2001) and inflammation that may contribute to cognitive changes (Naugler & Karin, 2008).

Neurotransmitters. The neurotransmitters norepinephrine, acetylcholine, and dopamine are important for cognitive function (Petersen & Posner, 2012). Therefore, variations in genes that encode for adrenergic, cholinergic, and dopaminergic pathways may contribute to inter-individual variability in cognitive function (Posner, Rothbart, & Sheese, 2007). For example, candidate genes that encode for the dopaminergic pathway important to the executive attention network include catechol-O-methyltransferase (COMT), dopamine transporter (DAT1), dopamine receptor D4 (DRD4), dopamine beta-hydroxylase (DBH), and monoamine oxidase A (MAOA; Green et al., 2008; Posner, 2012; Posner et al., 2007). Likely because of its involvement in dopamine metabolism (Fossella et al., 2002), COMT is associated with conflict resolution, a function of the executive attention network thought to be dependent on the anterior cingulate cortex

(ACC; Posner, 2012).

In one study, each additional copy of the “Val” allele in COMT rs4680 was associated with greater activity in the ACC and poorer performance on an attentional task (Blasi et al., 2005). The effect was most pronounced during the most difficult attentional tasks that required the highest level of conflict resolution. The Val allele is associated with faster dopamine metabolism (Goldberg & Weinberger, 2004; Savitz, Solms, & Ramesar, 2006), which suggests that this relationship may exist because of less dopamine available to the executive attention network (Posner, 2012). This finding is consistent with less efficient operation of the ACC due to reduced dopamine availability (Blasi et al., 2005). In a study of 130 women treated for breast cancer compared to non-cancer controls (Small et al., 2011), carriers of the Val allele performed significantly worse on tests of attention regardless of cancer history. In addition, women treated with CTX who were carriers of the Val allele performed significantly worse than healthy controls on these tests.

In summary, variations in genes that encode for neurotransmitters may account for some of the inter-individual variability in cognitive function reported by oncology patients. These effects are partially mediated through changes in the efficiency of inter-neuronal communication in attention networks (Posner et al., 2007).

Other variants. The epsilon 4 ($\epsilon 4$) allele in the gene that encodes for apolipoprotein E (APOE) is associated with cognitive decline in other populations, notably patients with Alzheimer’s disease (Mahley & Huang, 2012). Carriers of the APOE $\epsilon 4$ allele are at higher risk for cognitive decline, perhaps through susceptibility to neuronal damage (Mahley & Huang, 2012). A study of the effects of this allele in

survivors of breast cancer or lymphoma found associations with changes in visual memory and spatial ability (Ahles et al., 2003).

Variation in genes that encode for DNA repair mechanisms may impact the efficiency of DNA repair (Ahles & Saykin, 2007). Because decreased efficiency of DNA repair may contribute to cytokine-induced neuronal damage (Ahles & Saykin, 2007), future studies should determine whether these variants contribute to cancer and treatment-related cognitive changes.

Co-Occurring Symptoms

Affective symptoms. Affective symptoms may explain some of the variability in cognitive function. Difficulty concentrating is a depressive symptom (American Psychiatric Association, 2000). Psychosocial stressors may contribute to dysregulation of the HPA axis (De Raedt & Koster, 2010). This dysregulation results in subsequent changes in serotonin metabolism, negatively impacting cognitive control in frontal brain structures that depend on serotonin (De Raedt & Koster, 2010). In particular, dysregulation of serotonin metabolism in the dorsolateral prefrontal cortex may reduce attentional control of emotional responses (Carver, Johnson, & Joormann, 2008). Evidence supporting this hypothesis includes reduction in serotonergic activity in the rat prefrontal cortex (Mizoguchi, Yuzurihara, Ishige, Sasaki, & Tabira, 2002) and downregulation of serotonin receptors (Lopez, Liberzon, Vazquez, Young, & Watson, 1999) during chronic stress. In addition, because estrogen is important for serotonin production and function (Bethea, Lu, Gundlah, & Streicher, 2002; Pandaranandaka, Poonyachoti, & Kalandakanond-Thongsong, 2009), anti-estrogen treatments may contribute to this relationship.

Deficits in attentional control may contribute to affective symptoms, given that the ACC exerts control over limbic brain structures involved with emotion (e.g., the amygdala; Beauregard, Levesque, & Bourgouin, 2001; Posner, 2012). In particular, diminished attentional function may contribute to depressive symptoms (De Raedt & Koster, 2010). The orienting network of the attention system enables disengagement from some stimuli in order to focus on others (Petersen & Posner, 2012). Persons with diminished attentional function may be less able to change the focus of their attention from negative to positive thoughts (De Raedt & Koster, 2010). Moreover, persons may have an attentional bias toward thoughts with negative emotional connotations and ruminate on these thoughts, which predisposes them to prolongation of negative affect and risk for depression (De Raedt & Koster, 2010; Nolen-Hoeksema, 2000; Nolen-Hoeksema, Morrow, & Fredrickson, 1993).

Anxiety was found to be associated with diminished self-reported attentional function in a sample of breast and prostate cancer patients (Merriman et al., 2011). As state anxiety increases, concentration may be more difficult (Lehto & Cimprich, 1999). Changes in attention may contribute to state anxiety, particularly among individuals for whom the ability to concentrate is highly valued (e.g., individuals whose work is mentally demanding; Beadle, 2006). In addition, high trait anxiety may be a surrogate for neuroticism (Costa & McCrae, 1987). Individuals high in neuroticism may be more likely to report changes in attentional function because of their tendency to focus on subtle internal changes (Mora, Halm, Leventhal, & Ceric, 2007).

Recent findings suggest that genetic variations may influence affective symptoms through changes in the efficiency of the executive attention network (Posner, 2012). For

example, carriers of the short allele of a 44-base-pair variable number tandem repeat (5HTTLPR) in the promoter region of a serotonin transport gene (SLC6A4) reported worse anxiety (Hariri et al., 2002). The short allele is associated with three-fold lower gene transcription, which results in lower levels of serotonin transporter production (De Neve, 2011). These results were linked to decreased ACC control of the amygdala (Pezawas et al., 2005) and increased sensitivity of the amygdala to stimuli (Mattay & Goldberg, 2004). While this relationship has not been evaluated in oncology patients, results of a recent study indicated that reduction of serotonin levels through acute tryptophan depletion was associated with diminished verbal memory and psychomotor ability (Von Ah et al., 2012).

Studies reporting a relationship between higher levels of anxiety (Merriman et al., 2010) and/or depressive symptoms (Chen, Miaskowski, Liu, & Chen, 2012; Cimprich, 1992a, 1999; Cimprich, So, Ronis, & Trask, 2005; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Lehto & Cimprich, 1999; Von Ah, Russell, Storniolo, & Carpenter, 2009) with diminished self-reported attentional function support the hypothesis that these symptoms share a common etiology. In addition, attentional function and affective symptoms are influenced by common molecular mechanisms. For example, variations in 5HTTLPR may contribute to anxiety, depressive symptoms, and diminished attentional function through a reduction in executive control of the amygdala (Pezawas et al., 2005). Therefore, variations in genes that encode for serotonin pathways may account for some of the inter-individual differences in attentional function experienced by oncology patients (Pezawas et al., 2005).

Sleep disturbance. The suprachiasmatic nucleus controls multiple circadian

rhythm clocks in the brain (Wulff, Gatti, Wettstein, & Foster, 2010). Disruption of these physiological clocks can have detrimental cognitive effects. For example, in a recent study of women with breast cancer, higher levels of sleep disturbance were associated with lower levels of self-reported attentional function (Van Onselen et al., 2012).

Changes in circadian rhythms due to sleep disturbance may negatively impact cognitive function through disruption of neurotransmitter production (Wulff et al., 2010).

Furthermore, the importance of neurotransmitters to brain health in general, including emotional health, may link findings of impaired attentional function and increased levels of affective symptoms. Support for these hypotheses was found in intervention studies in patients with psychiatric or neurodegenerative disease that showed improved cognition and affective symptoms with improved sleep quality (Wulff et al., 2010).

Age

Younger patients report worse cognitive changes than older patients (Cimprich et al., 2011). However, older patients perform worse than younger patients on neuropsychological tests (Cimprich et al., 2005). These differences may be explained by younger patients noticing more subtle cognitive changes due to the impact on work or home life (Cimprich et al., 2011). In contrast, older patients may have adapted to previous cognitive changes that allow them not to worry as much about cognitive changes associated with cancer and its treatment (Cimprich et al., 2011).

An interesting hypothesis is that treatment for cancer may accelerate the aging process (Ahles et al., 2012). Specifically, cognitive changes associated with treatment may parallel age-related changes and occur earlier for oncology patients than for age-matched controls (i.e., diminished cognitive function compared to population norms at

the same age due to an initial insult to the CNS from treatment).

Conclusions

The focus of this review was the potential mechanisms that underlie diminished cognitive function reported by oncology patients. In summary, multiple mechanisms may contribute to diminished cognitive function in patients with non-CNS cancers. In particular, cancer- and treatment-related cognitive changes may be mediated through inflammatory cytokine upregulation and hormonal changes (Ahles & Saykin, 2007). Other clinical factors including the biology of cancer (Allavena & Mantovani, 2012), stress (Juster et al., 2010), and attentional fatigue (Cimprich, 1992a) may contribute to cognitive changes. In addition, genetic predisposition (Ahles & Saykin, 2007) and co-occurring symptoms (De Raedt & Koster, 2010) may explain some of the inter-individual variability in these cognitive changes. Potential underlying mechanisms include variations in candidate genes involved in the regulation of inflammatory cytokines and neurotransmitters. The severity of cognitive changes may be moderated by age (Ahles et al., 2012).

The diagnosis and treatment of cancer may amplify the impact of underlying cytokine dysregulation through induction of chronic peripheral inflammation (Ahles & Saykin, 2007). The distracting environment associated with cancer treatments may negatively impact cognitive function through attentional fatigue (Cimprich et al., 2011). In addition, sleep disturbance may amplify the negative effects of neurotransmitter dysregulation through disruption of circadian rhythms (Wulff et al., 2010). Affective symptoms may impact cognitive function directly or share common underlying mechanisms, such as reduced ACC control of the amygdala (Pezawas et al., 2005).

Clinical Implications

While progress has been made in understanding mechanisms of cancer and treatment-related cognitive changes, uncertainty remains for what causes these changes. Moreover, clinicians cannot accurately predict the severity of cognitive changes patients will experience so that patient education and interventions can be targeted. For now, oncology nurses need to understand the mechanisms that contribute to cognitive changes so that they can identify high-risk patients and explain to patients the reasons for these changes. In addition, the treatment of co-occurring affective symptoms and sleep disturbance is important (Merriman et al., 2011).

Recommendations for Future Research

Three important areas for future research are: (1) elucidation of mechanisms, (2) determination of factors that increase susceptibility to cognitive changes, and (3) interventions to prevent or reduce cognitive changes. Genetic studies provide information about hypothetical mechanisms (Conley et al., 2013) by showing associations among cognitive changes and genetic variation. However, the mechanisms underlying these associations are poorly understood. Animal studies may bolster our understanding of the genetic associations found in humans. In addition, the emerging synergy in combining the disciplines of symptom research, immunology, genetics, neuropsychology, and imaging may provide strong evidence for the hypothesized mechanisms of cognitive changes reported by oncology patients (Wefel, Vardy, Ahles, & Schagen, 2011). Determination of risk factors will allow clinicians to target education and interventions appropriately. While additional research on underlying mechanisms and risk factors is warranted, the information available today can be used to develop and test interventions to improve this

important clinical problem.

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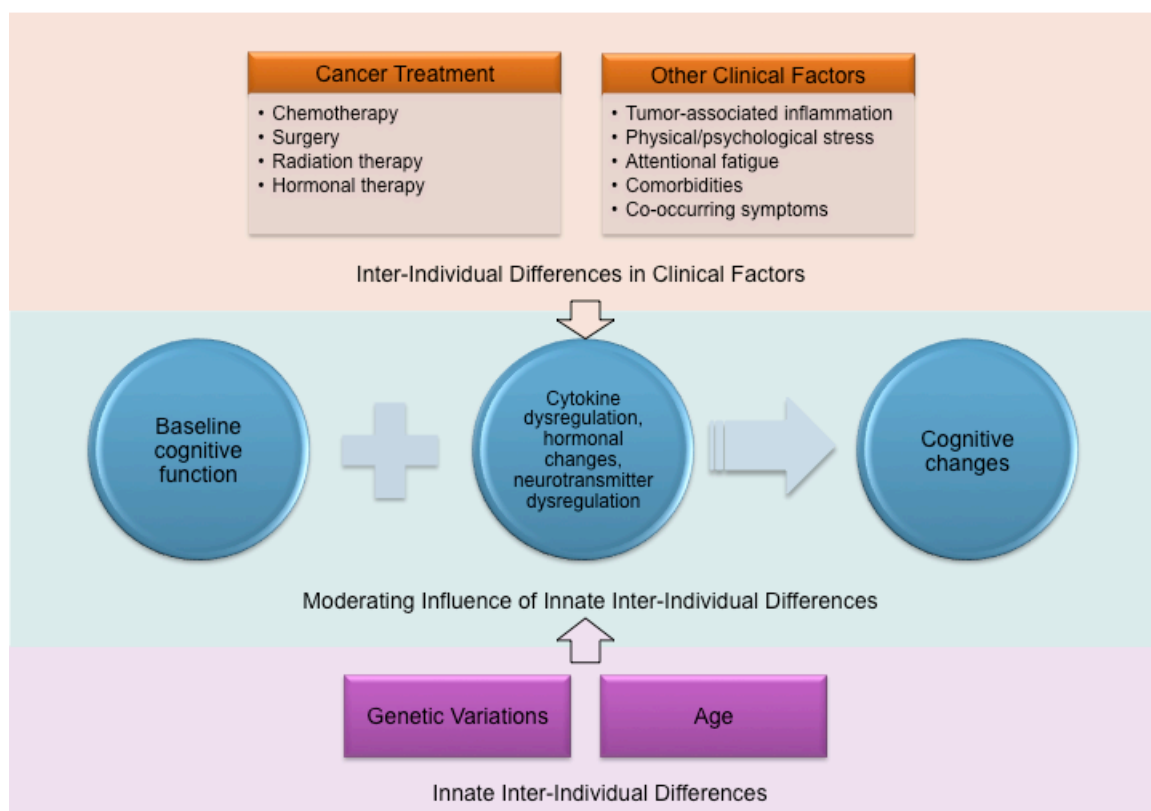
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Figure Legend

Figure. Proposed Mechanisms for Cancer and Treatment-Related Cognitive Changes.

Clinical factors impact baseline cognitive function to produce cognitive changes. These changes may be mediated by upregulation of inflammation, hormonal changes, and neurotransmitter dysregulation. Innate inter-individual differences moderate cognitive changes. The effects of clinical factors and innate inter-individual differences on the mechanisms producing cognitive changes overlap and interact.



Chapter 2:

Preliminary Evidence of an Association Between an Interleukin 6 Promoter

Polymorphism and Self-Reported Attentional Function in

Oncology Patients and Their Family Caregivers

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Abstract

Subgroups of individuals may be at greater risk for cytokine-induced changes in attentional function. The purposes of this study were to identify subgroups of individuals with distinct trajectories of attentional function and evaluate for phenotypic and genotypic (i.e., cytokine gene polymorphisms) differences among these subgroups. Self-reported attentional function was evaluated in 252 participants (i.e., 167 oncology patients and 85 family caregivers) using the Attentional Function Index before radiation therapy and at six additional assessments over six months. Three latent classes of attentional function were identified using growth mixture modeling: high (15.5%), moderate-to-high (48.0%), and moderate (36.5%) attentional function. Participants in the moderate class were significantly younger, with more comorbidities and lower functional status. However, only functional status remained significant in multivariable models. Ninety-two single nucleotide polymorphisms among 15 candidate genes were included in the genetic association analyses. Additive, dominant, and recessive genetic models were assessed for each single nucleotide polymorphism. Controlling for functional status, only IL6 rs1800795 remained a significant genotypic predictor of class membership in multivariable models. Each additional copy of the rare “G” allele was associated with a four-fold increase in the odds of belonging to the lower attentional function class (95% confidence interval: 1.78, 8.92; $p=.001$). Findings provide preliminary evidence of subgroups of individuals with distinct trajectories of attentional function and of a genetic association with an IL6 promoter polymorphism.

Keywords: attention, cancer, cytokines, inflammation, genetic association studies, radiotherapy

Preliminary Evidence of an Association Between an Interleukin 6 Promoter
Polymorphism and Self-Reported Attentional Function in
Oncology Patients and Their Family Caregivers

Three networks comprise the attention system of the brain: the alerting, orienting, and executive attention networks (Posner, 2012). The alerting network enables vigilance (i.e., maintaining attention). The orienting network is necessary for selecting one stimulus out of the many stimuli in the internal (i.e., thoughts) and external environments for processing. The executive network is responsible for synthesizing input from multiple brain areas into a coherent response and for voluntarily directing attention. This “effortful control” of the executive network is experienced as planning to meet goals, monitoring the self during social interactions, and moderating the expression of emotions (Posner, 2012).

Self-reported attentional function is an important quality of life indicator, for while perceived cognitive changes present more subtly than physical or psychological symptoms, the personal impact can be devastating (e.g., inability to work; Boykoff, Moieni, & Subramanian, 2009). The Attentional Function Index (AFI; Cimprich, Visovatti, & Ronis, 2011) is a commonly used self-report measure of attentional function. Multiple studies have used the AFI in patients with breast cancer before (Cimprich, 1999; Cimprich, So, Ronis, & Trask, 2005; Lehto & Cimprich, 1999) and after (Cimprich, 1992) surgery and chemotherapy (CTX; Jansen, Cooper, Dodd, & Miaskowski, 2011). Additional studies have used the measure across multiple treatment modalities (Chen, Miaskowski, Liu, & Chen, 2012) and in long-term survivors (Von Ah, Russell, Storniolo, & Carpenter, 2009).

Implicit in the colloquial term “chemo brain” is that changes in cognitive function are due solely to treatment (Hess & Insel, 2007). However, for both patients and family caregivers (FCs), the threatening nature of the cancer diagnosis, unfamiliar treatment environment, and confusing healthcare terminology contribute to pervasive distractions (Cimprich et al., 2011). Effortful control in the face of these distractions can fatigue the attention system of the brain (Cimprich et al., 2011).

In addition, both patients and FCs experience chronic stress (Schulz & Beach, 1999). The allostatic load hypothesis states that stressors from any source impact common biological pathways to produce deleterious changes in the body (Juster, McEwen, & Lupien, 2010). Chronic stress contributes to immune dysregulation (Miller, Maletic, & Raison, 2009), which may contribute to these cognitive changes in both patients and FCs (Seruga, Zhang, Bernstein, & Tannock, 2008).

Cytokines and their receptors exercise a major influence on inflammatory processes. A leading hypothesis for how immune dysregulation can result in decrements in attentional function is that peripheral inflammation is communicated to the central nervous system (CNS) through afferent nerves (e.g., vagus nerve; Capuron & Miller, 2011; Watkins et al., 1995). Other possible routes of communication include peripheral cytokine interactions with circumventricular organs (Banks & Erickson, 2010), active transport of cytokines (Plotkin, Banks, & Kastin, 1996), second messengers (e.g., prostaglandins; Konsman, Vignes, Mackerlova, Bristow, & Blomqvist, 2004), and direct entry of peripherally activated monocytes (Capuron & Miller, 2011; D'Mello, Le, & Swain, 2009). Microglial cells respond by producing central pro-inflammatory cytokines that damage the CNS directly or through secondary mechanisms such as oxidative stress

(Joshi et al., 2005), dysregulation of hypothalamic-pituitary-adrenal axis function (Raison et al., 2010), or diminished growth factor signaling (Tong, Balazs, Soiampornkul, Thangnipon, & Cotman, 2008; Wilson, Finch, & Cohen, 2002).

Given these possible mechanisms, variations in genes that encode for pro- and anti-inflammatory cytokines may explain some of the inter-individual variability in attentional function for both patients and FCs. Genes that encode for pro-inflammatory cytokines include interferon gamma receptor 1 (IFNGR1), interleukin 1 receptor 1 (IL1R1), IL2, IL8, IL17A, and tumor necrosis factor alpha (TNFA). Genes that encode for anti-inflammatory cytokines include IL1R2, IL4, IL10, and IL13. Genes that encode for cytokines with both pro- and anti-inflammatory functions include IFNG1, IL1B, and IL6. Genes that encode for transcription factors, which moderate levels of cytokine production, include nuclear factor kappa B 1 (NFKB1) and NFKB2. (Seruga et al., 2008)

Previous studies have found that subgroups of individuals are at greater risk for significant cognitive changes (Wefel, Vardy, Ahles, & Schagen, 2011). Growth mixture modeling (GMM) is a sophisticated technique for identifying subgroups (i.e., latent classes) of individuals that differ in their growth trajectories for a particular characteristic (Jung & Wickrama, 2008). Therefore, the purposes of this study, in a sample of oncology patients and their FCs, were to identify latent classes of individuals with distinct trajectories of attentional function and to evaluate for differences among these subgroups in phenotypic and genotypic characteristics.

Materials and Methods

This descriptive, longitudinal study is part of a larger study that evaluated multiple symptoms in patients who underwent primary or adjuvant radiation therapy (RT)

for breast, prostate, lung, or brain cancer and their FCs (Miaskowski et al., 2012). An abbreviated version of the methods is provided below. The complete version of the methods is available as an online supplement.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF) and at the second site. Prior to RT, a research nurse invited patients and FCs to participate, explained the protocol, and determined eligibility. After written informed consent, participants completed baseline questionnaires. Follow-up questionnaires were completed at four weeks after the initiation of RT; at the end of RT; and at four, eight, 12, and 16 weeks after completion of RT (i.e., seven assessments over six months).

Participants completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977), and the AFI. The AFI consists of 16 items designed to measure attentional function (Cimprich et al., 2011). Higher mean scores on a 0 to 10 numeric rating scale indicate greater capacity to direct attention (Cimprich et al., 2011). Scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function; Cimprich et al., 2005). The AFI has well established reliability and validity (Cimprich et al., 2011). In this study, Cronbach's alpha was .95 for both patients and FCs.

Phenotypic Analyses

Data were analyzed using SPSS 19 (IBM, Armonk, New York) and Mplus 6.11 (Muthén & Muthén, Los Angeles). Descriptive statistics and frequency distributions were generated for sample characteristics and AFI scores. GMM with robust maximum

likelihood estimation identified latent classes of participants with distinct trajectories of attentional function. Because 65% of participants were in patient-FC dyads, models were estimated with dyad as a clustering variable to control for intra-dyadic dependency. The GMM methods are described in detail elsewhere (Dunn et al., 2012).

Analyses of variance and Chi-square analyses evaluated for differences in participant characteristics among classes. The cohort for each analysis was dependent on the largest set of available data across classes. Differences were considered statistically significant at $p < .05$. Post hoc contrasts used the Bonferroni correction to control overall family alpha. For any one of three possible pairwise contrasts, $p < .017$ was considered statistically significant. Effect sizes were determined using Cohen's d (Cohen, 1988).

A backwards stepwise approach was used to create the most parsimonious phenotypic regression model. Except for self-reported race/ethnicity and ancestry informative markers (AIMs), only predictors with a p -value of $< .05$ were retained in the final model.

Genotypic Analyses

Genomic DNA was extracted from archived buffy coats using the Puregene DNA Isolation System (Invitrogen, Carlsbad, CA). Of 287 participants, DNA could be recovered for 252 (i.e., 167 patients and 85 FCs). No differences were found in demographic and clinical characteristics for those participants from whom DNA could not be recovered.

DNA was quantitated using spectrophotometry and normalized to a concentration of 50 ng/ μ L (diluted in 10 mM Tris/1 mM EDTA). Genotyping was performed blinded to clinical status. Samples were genotyped using the GoldenGate genotyping platform and

processed using GenomeStudio (Illumina, San Diego). Genotype calls for each single nucleotide polymorphism (SNP) were visually inspected by two blinded reviewers. Disagreements were adjudicated by a third reviewer.

SNP selection. A combination of tagging SNPs and literature-driven SNPs (i.e., associated with altered function, symptoms) were selected for analysis. Tagging SNPs were required to be common, defined as having minor allele frequencies (MAFs) $\geq 5\%$ in public databases. SNPs with call rates $< 95\%$ or Hardy-Weinberg $p < .001$ were excluded.

Statistical analyses. Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by the Chi-square or Fisher Exact test. Measures of linkage disequilibrium (LD; i.e., D' and r^2) were computed from the participants' genotypes with Haploview 4.2 (Broad Institute, Cambridge, Massachusetts). LD-based haplotype block definition was based on the D' confidence interval method (Gabriel et al., 2002). Haplotypes were constructed using PHASE 2.1 (Stephens Lab, University of Chicago), as described previously (Miaskowski et al., 2012). AIMs were used to minimize confounding due to population stratification (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008). One hundred six AIMs were included in the analysis, as described previously (Miaskowski et al., 2012).

Additive, dominant, and recessive genetic models were assessed in association tests for each SNP. Barring trivial improvement (i.e., $\Delta < 10\%$) from the additive model, the model that best fit the data, by maximizing the significance of the p-value, was selected for inclusion in the multivariable analyses. To estimate the magnitude (i.e., odds ratio, OR) and precision (i.e., 95% confidence interval, CI) of the association of

genotype with odds of class membership, logistic regression models were fit that treated class as a discrete categorical variable. Model fit and unadjusted/covariate-adjusted odds ratios were estimated using Stata 12 (StataCorp, College Station, Texas). If the overall model included a statistically significant genotype term, pairwise post hoc models (e.g., high versus moderate-to-high) were fit. Only post hoc models with Bonferroni-corrected statistical significance for genotype were retained.

Based on recommendations in the literature (Hattersley & McCarthy, 2005; Rothman, 1990), the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. In addition, significant SNPs identified in the bivariate analyses were evaluated further using regression analyses that controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variation in other SNPs/haplotypes within the same gene. Only SNPs that remained significant were included in the final results. Therefore, the significant independent genetic association reported is unlikely to be due solely to chance. In addition, unadjusted (i.e., bivariate) associations are reported for all SNPs passing quality control criteria (Table 1) to allow for subsequent comparisons and meta-analyses.

Results

GMM Classes

Three distinct classes of attentional function trajectories were identified (Figure 1). A three-class solution provided the best model fit because it had a significant Vuong-Lo-Mendell-Rubin likelihood ratio test (Table 2). It had greater entropy and more differentiating growth trajectories than the two-class solution, with each class

maintaining reasonable size and interpretability (Jung & Wickrama, 2008).

Participants in the high attentional function (“high”) class (15.5%) had estimated AFI scores of 8.98 at enrollment that remained high throughout the study (Table 3). Participants in the moderate-to-high (“moderate-to-high”) class (48.0%) had estimated AFI scores of 7.47 at enrollment that improved over time to high attentional function (i.e., >7.5). Participants in the moderate attentional function (“moderate”) class (36.5%) had estimated AFI scores of 5.55 at enrollment that did not improve during the study.

Phenotypic Differences Among Classes

Participants in the moderate class were significantly younger and reported lower functional status than the other two classes (Table 4). They had significantly more comorbidities than the high class. A significantly lower percentage of participants in the moderate class were married/partnered than in the high class. A significantly higher percentage of patients were in the moderate class than the high class. No differences were found among the classes in years of education, gender, or race/ethnicity. Using a backwards stepwise approach, only functional status (i.e., KPS score) significantly predicted class membership when controlling for population stratification due to race/ethnicity.

Genotypic Differences Among Classes

Ninety-two SNPs among 15 candidate genes passed quality control filters (Table 1). Genotype distributions differed significantly among classes for six SNPs and two haplotypes. After adjustment for functional status and race/ethnicity, only models fit for IL6 rs1800795 ($p=.002$) and haplotype A6 ($p=.003$) remained significant. Because haplotype A6 was collinear with rs1800795, the model fit for rs1800795 was retained for

parsimony. (See Figure 2.)

Post hoc contrasts revealed that the relationship with IL6 genotype was driven by the high versus moderate-to-high classes ($p=.002$). The final model explained 14.6% of variance in class membership. Controlling for covariates, each additional copy (i.e., additive model) of the rare “G” allele was associated with a four-fold increase in the odds of belonging to the moderate-to-high class (OR: 3.98; 95% CI: 1.78, 8.92; $p=.001$).

Discussion

This study is the first to identify subgroups of oncology patients and FCs with distinct trajectories of self-reported attentional function prior to, during, and after RT, and to evaluate for phenotypic and genotypic differences among these subgroups. Differences in mean AFI scores among the subgroups at enrollment represent clinically meaningful differences (Wyrwich et al., 2005) in self-reported attentional function ($d=1.21$ for high versus moderate-to-high classes and $d=1.16$ for moderate-to-high versus moderate classes).

The only phenotypic predictor of class membership that remained significant in multivariable regression models was functional status. The moderate class reported significantly lower functional status than other classes. Clinically, this KPS score was a categorical change from “I have no complaints or symptoms” for the high and moderate-to-high classes to “I have minor signs or symptoms of my illness.” While previous studies did not report an association between functional status and self-reported attentional function, one possible explanation is that the higher number of comorbidities reported by the moderate class mediated this relationship. For example, managing multiple comorbidities during cancer treatment may contribute to attentional fatigue

(Merriman et al., 2011), or specific comorbidities may be directly associated with cognitive changes (Bauer, Johnson, & Pozehl, 2011; Wefel et al., 2011).

Although not a significant predictor of class membership after controlling for other covariates, the moderate class was significantly younger. Younger patients generally report lower levels of attentional function than older patients (Cimprich et al., 2011), which may also be true for FCs. Younger individuals may notice subtle attentional changes more than older adults, who may have adjusted to some alterations in attentional function (Cimprich et al., 2011). For these reasons, in a post hoc evaluation age was entered as a covariate in the multivariable regression analysis, and the reported results for IL6 did not change.

Twelve patients were diagnosed with brain tumors. Although brain tumors and treatment for CNS disease can impact cognitive function (Correa, 2010), no differences were found in AFI scores at enrollment for patients with brain tumors (mean=6.98, SD=1.88) versus breast (mean=6.77, SD=1.87), prostate (mean=7.59, SD=1.50), or lung cancer (mean=6.26, SD=2.15). In addition, only breast and prostate cancer patients differed in class membership. One possible explanation for the higher proportion of breast cancer compared to prostate cancer patients in the moderate (50.0% and 27.2%, respectively) versus moderate-to-high (36.6% and 55.1%, respectively) classes ($p=.001$) is that all of these women had surgery and approximately 55% had CTX prior to RT. In contrast, only 10% of the men with prostate cancer had prostatectomy and none had CTX prior to RT. Surgery (Chen et al., 2012) and CTX (Jansen et al., 2011) were associated with lower levels of attentional function in previous studies.

Only one SNP in IL6 (rs1800795) significantly predicted class membership after

controlling for covariates. Each additional copy of the rare G allele was associated with an increased odds of belonging to a lower attentional function class. Genotype uniquely explained 0.5% of variance in class membership.

High levels of IL-6 are associated with poor treatment outcomes (DeMichele et al., 2009). In addition, administration of recombinant IL6 to healthy adults produces symptoms of sickness behavior, including difficulty concentrating (Spath-Schwalbe et al., 1998). IL6 is produced as part of a cytokine cascade (Capuron & Miller, 2011) and contributes to pro-inflammatory cytokine production in the CNS (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Its anti-inflammatory properties include downregulation of other pro-inflammatory cytokines (Muller-Steinhardt, Ebel, & Hartel, 2006). Therefore, high levels of IL6 suggest an underlying inflammatory state (Naugler & Karin, 2008).

Several studies found poorer outcomes in carriers of the G allele. For example, patients treated with interferon-alpha for hepatitis C infection who carried the G allele reported significantly more depressive symptoms (Bull et al., 2009) and patients with breast cancer who carried the G allele had worse disease-free survival (DeMichele et al., 2009). Furthermore, this allele is associated with elevated levels of IL6 in peripheral circulation (Hulkkonen, Pertovaara, Antonen, Pasternack, & Hurme, 2001).

Study limitations should be acknowledged. Because inclusion of both patients and FCs was necessary due to sample size requirements, future studies should confirm these results with more homogenous samples. Studies of patients with additional cancer diagnoses and different treatments may clarify the association of attentional function with cytokine genes. Because of the heterogeneity of treatments other than RT received by

patients before the study or during the six months of the study, as well as inclusion of FCs in the analyses, it was not possible to evaluate the effects of treatment in the models. Future studies with more homogenous patient samples should evaluate treatment effects.

The relationship of IL6 rs1800795 to attentional function class membership warrants replication before clinical implications are evaluated. Larger samples could uncover additional latent classes and genetic associations. Serum cytokine levels could support genetic associations. Studies of genes that encode for other physiological pathways (e.g., dopaminergic, serotonergic; Posner, Rothbart, & Sheese, 2007) may further clarify the etiology of reduced attentional function in oncology patients and their FCs.

Objective tests may evaluate a different construct of attention than subjective measures such as the AFI. Current neuropsychological tests may not be sensitive to the attentional demands that patients and FCs report when completing instrumental activities of daily living and thus may have limited ecological validity (Schagen, Das, & van Dam, 2009). However, inclusion of objective tests in future studies could improve understanding of the phenotype of diminished attentional function. In addition, future studies should evaluate for changes in other cognitive domains (e.g., working memory, executive function) that may be associated with genetic variation in IL6.

This study provides preliminary evidence for a relationship between IL6 rs1800795 and distinct trajectories of self-reported attentional function. The fact that a significant relationship was found between the SNP in IL6 and AFI class membership despite the heterogeneity of the sample suggests that this SNP influences attentional function regardless of the etiology of diminished attentional function. Specifically, this

association suggests that cytokine dysregulation negatively impacts attentional function for both oncology patients and FCs at a time when the capacity to direct attention is particularly important for successfully navigating the cancer treatment experience.

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Figure Legends

Figure 1. Observed and estimated (i.e., model-predicted) Attentional Function Index (AFI) score trajectories for participants in each latent class, as well as mean AFI scores for the total sample.

Figure 2. Differences among the attentional function (AF) latent classes in the percentages of participants who were homozygous for the common “C” allele, heterozygous, or homozygous for the rare “G” allele for rs1800795 in interleukin 6 (IL6).

Table 1. Differences in Cytokine Gene Single Nucleotide Polymorphism (SNP) Allele and Haplotype Frequencies Among the Latent Classes of Attentional Function

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IFNG1	rs2069728	66834051	12	.079	G>A	1.15	.887	A
IFNG1	rs2069727	66834490	12	.411	A>G	2.94	.568	A
IFNG1	rs2069718	66836429	12	.442	C>T	1.90	.754	A
IFNG1	rs1861493	66837463	12	.264	A>G	1.14	.888	A
IFNG1	rs1861494	66837676	12	.279	T>C	1.19	.880	A
IFNG1	rs2069709	66839970	12	.008	G>T	n/a	n/a	n/a
IFNG1	HapA3		12			1.14	.888	
IFNG1	HapA5		12			2.94	.568	
IFNGR1	rs9376268	137574444	6	.246	G>A	3.26	.516	A
IL1B	rs1071676	106042060	2	.198	G>C	3.81	.433	A
IL1B	rs1143643	106042929	2	.331	G>A	4.28	.370	A
IL1B	rs1143642	106043180	2	.095	C>T	1.15	.887	A
IL1B	rs1143634	106045017	2	.196	C>T	4.17	.383	A
IL1B	rs1143633	106045094	2	.345	G>A	2.69	.610	A
IL1B	rs1143630	106046282	2	.103	C>A	6.86	.144	A
IL1B	rs3917356	106046990	2	.432	A>G	8.08	.089	A
IL1B	rs1143629	106048145	2	.353	T>C	7.11	.130	A
IL1B	rs1143627	106049014	2	.390	T>C	6.65	.156	A
IL1B	rs16944	106049494	2	.380	G>A	6.38	.173	A
IL1B	rs1143623	106050452	2	.248	G>C	4.01	.405	A
IL1B	rs13032029	106055022	2	.428	C>T	7.70	.103	A
IL1B	HapA1					4.86	.302	
IL1B	HapA3					0.05	.977	
IL1B	HapA4					4.23	.375	
IL1B	HapA5					4.05	.400	
IL1B	HapB1					2.79	.594	
IL1B	HapB7					4.07	.397	
IL1B	HapB9					7.67	.105	
IL1B	HapB11					6.01	.198	
IL1R1	rs949963	96533648	2	.213	G>A	4.89	.299	A
IL1R1	rs2228139	96545511	2	.066	C>G	5.75	.218	A
IL1R1	rs3917320	96556738	2	.068	A>C	4.13	.127	A
IL1R1	rs2110726	96558145	2	.333	C>T	4.26	.372	A
IL1R1	rs3917332	96560387	2	.124	T>A	5.28	.260	A
IL1R2	rs4141134	96370336	2	.401	T>C	5.53	.237	A
IL1R2	rs11674595	96374804	2	.233	T>C	6.03	.197	A
IL1R2	rs7570441	96380807	2	.393	G>A	8.66	.070	A
IL1R2	HapA1					2.82	.588	
IL1R2	HapA2					6.16	.187	
IL1R2	HapA4					5.03	.284	
IL2	rs1479923	119096993	4	.302	C>T	1.74	.784	A
IL2	rs2069776	119098582	4	.244	T>C	2.38	.666	A
IL2	rs2069772	119099739	4	.238	A>G	3.57	.467	A
IL2	rs2069777	119103043	4	.054	C>T	0.45	.798	A
IL2	rs2069763	119104088	4	.287	T>G	3.28	.512	A
IL2	HapA1					5.83	.212	
IL2	HapA2					4.00	.406	

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IL2	HapA3					2.24	.692	
IL2	HapA5					1.74	.784	
IL4	rs2243248	127200946	5	.101	T>G	3.79	.435	A
IL4	rs2243250 ^a	127201455	5	.260	C>T	n/a	n/a	n/a
IL4	rs2070874	127202011	5	.219	C>T	6.26	.181	A
IL4	rs2227284	127205027	5	.399	C>A	12.67	.013	A
IL4	rs2227282	127205481	5	.401	C>G	12.75	.013	A
IL4	rs2243263	127205601	5	.124	G>C	1.11	.574	A
IL4	rs2243266	127206091	5	.203	G>A	5.66	.226	A
IL4	rs2243267	127206188	5	.205	G>C	5.29	.259	A
IL4	rs2243274	127207134	5	.262	G>A	11.70	.020	A
IL4	HapA1					10.48	.033	
IL4	HapA10					5.09	.278	
IL6	rs4719714	22643793	7	.196	A>T	7.21	.125	A
IL6	rs2069827	22648536	7	.071	G>T	12.51	.002	D
IL6	rs1800796 ^a	22649326	7	.095	G>C	n/a	n/a	n/a
IL6	rs1800795 ^b	22649725	7	.355	C>G	13.19	.010	A
IL6	rs2069835	22650951	7	.066	T>C	1.50	.474	A
IL6	rs2066992 ^a	22651329	7	.091	G>T	n/a	n/a	n/a
IL6	rs2069840	22651652	7	.308	C>G	3.56	.469	A
IL6	rs1554606	22651787	7	.405	T>G	6.91	.141	A
IL6	rs2069845	22653229	7	.405	G>A	6.91	.141	A
IL6	rs2069849	22654236	7	.039	C>T	n/a	n/a	n/a
IL6	rs2069861	22654734	7	.083	C>T	2.79	.248	A
IL6	rs35610689	22656903	7	.242	A>G	1.89	.755	A
IL6	HapA4					4.42	.352	
IL6	HapA6					14.73	.005	
IL8	rs4073	70417508	4	.498	T>A	2.31	.679	A
IL8	rs2227306	70418539	4	.366	C>T	3.79	.435	A
IL8	rs2227543	70419394	4	.374	C>T	3.45	.486	A
IL8	HapA1					3.17	.529	
IL8	HapA3					3.79	.435	
IL8	HapA4					2.31	.679	
IL10	rs3024505	177638230	1	.138	C>T	2.35	.672	A
IL10	rs3024498	177639855	1	.236	A>G	4.31	.366	A
IL10	rs3024496	177640190	1	.459	T>C	0.34	.987	A
IL10	rs1878672	177642039	1	.452	G>C	0.94	.920	A
IL10	rs3024492	177642438	1	.207	A>T	4.18	.382	A
IL10	rs1518111	177642971	1	.267	G>A	3.38	.496	A
IL10	rs1518110	177643187	1	.267	G>T	3.38	.496	A
IL10	rs3024491	177643372	1	.448	T>G	1.00	.909	A
IL10	HapA5					6.78	.148	
IL10	HapA6					3.18	.529	
IL10	HapA8					4.27	.371	
IL10	HapA9					2.39	.664	
IL13	rs1881457	127184713	5	.192	A>C	2.07	.723	A
IL13	rs1800925	127185113	5	.227	C>T	0.99	.911	A
IL13	rs2069743	127185579	5	.021	A>G	n/a	n/a	n/a
IL13	rs1295686	127188147	5	.252	G>A	3.37	.498	A
IL13	rs20541	127188268	5	.174	C>T	3.92	.417	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IL13	HapA1					3.92	.417	
IL13	HapA4					2.91	.573	
IL17A	rs4711998	51881422	6	.293	G>A	5.30	.258	A
IL17A	rs8193036	51881562	6	.255	T>C	4.93	.295	A
IL17A	rs3819024	51881855	6	.374	A>G	0.16	.997	A
IL17A	rs2275913	51882102	6	.345	G>A	4.03	.401	A
IL17A	rs3804513	51884266	6	.027	A>T	n/a	n/a	n/a
IL17A	rs7747909	51885318	6	.225	G>A	5.15	.272	A
NFKB1	rs3774933	103645369	4	.444	T>C	2.85	.583	A
NFKB1	rs170731	103667933	4	.397	T>A	2.18	.703	A
NFKB1	rs17032779	103685279	4	.023	T>C	n/a	n/a	n/a
NFKB1	rs230510	103695201	4	.366	T>A	2.66	.615	A
NFKB1	rs230494	103706005	4	.477	A>G	3.97	.410	A
NFKB1	rs4648016	103708706	4	.017	C>T	n/a	n/a	n/a
NFKB1	rs4648018	103709236	4	.025	G>C	n/a	n/a	n/a
NFKB1	rs3774956	103727564	4	.479	C>T	3.92	.417	A
NFKB1	rs10489114	103730426	4	.025	A>G	n/a	n/a	n/a
NFKB1	rs4648068	103737343	4	.366	A>G	1.96	.742	A
NFKB1	rs4648095	103746914	4	.052	T>C	0.78	.677	A
NFKB1	rs4648110	103752867	4	.205	T>A	2.09	.719	A
NFKB1	rs4648135	103755716	4	.060	A>G	1.02	.600	A
NFKB1	rs4648141	103755947	4	.188	G>A	2.25	.690	A
NFKB1	rs1609798	103756488	4	.337	C>T	1.86	.761	A
NFKB1	HapA1					2.54	.637	
NFKB1	HapA9					1.84	.765	
NFKB2	rs12772374	104146901	10	.157	A>G	1.75	.782	A
NFKB2	rs7897947	104147701	10	.229	T>G	6.09	.048	D
NFKB2	rs11574849	104149686	10	.085	G>A	2.37	.669	A
NFKB2	rs1056890	104152760	10	.317	C>T	7.75	.101	A
TNFA	rs2857602	31533378	6	.360	T>C	1.70	.791	A
TNFA	rs1800683	31540071	6	.388	G>A	6.09	.193	A
TNFA	rs2239704	31540141	6	.370	G>T	1.41	.842	A
TNFA	rs2229094	31540556	6	.256	T>C	8.35	.080	A
TNFA	rs1041981	31540784	6	.388	C>A	6.09	.193	A
TNFA	rs1799964	31542308	6	.202	T>C	8.21	.084	A
TNFA	rs1800750	31542963	6	.019	G>A	n/a	n/a	n/a
TNFA	rs1800629	31543031	6	.157	G>A	8.89	.064	A
TNFA	rs1800610	31543827	6	.105	C>T	1.70	.791	A
TNFA	rs3093662	31544189	6	.072	A>G	5.16	.272	A
TNFA	HapA1					5.53	.237	
TNFA	HapA5					9.17	.057	
TNFA	HapA8					1.84	.766	

Abbreviations: Chr = chromosome, MAF = minor allele frequency, A = additive model, D = dominant model, n/a = not assayed because SNP violated Hardy-Weinberg expectations ($p < .001$) or because MAF $< .05$.

^aSNPs that violated Hardy-Weinberg expectations ($p < .001$).

^bOnly IL6 rs1800795 was retained in multivariable analyses.

Table 2. Fit Indices for Attentional Function Growth Mixture Model (GMM) Solutions Over Seven Assessments, with Dyad as a Clustering Variable

GMM	LL	AIC	BIC	Entropy	VLMR ^c
1-class ^a	-2320.300	4668.600	4718.012	n/a	n/a
2-class	-2262.120	4568.241	4645.888	0.685	116.359***
3-class ^b	-2251.400	4556.800	4652.094	0.693	21.441*
4-class	-2245.108	4554.217	4667.158	0.745	12.583

Abbreviations: LL = log likelihood, AIC = Akaike information criterion, BIC = Bayesian information criterion, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test.

^aRandom intercepts latent growth curve model with linear and quadratic components; $\chi^2 = 82.842$, 28 df, $p < .001$, comparative fit index (CFI) = .956, root mean square error of approximation (RMSEA) = .088.

^bA three-class solution provided the best model fit because it had a significant VLMR, as well as greater entropy and more differentiating growth trajectories than the two-class solution, with each class maintaining reasonable size and interpretability. Further, VLMR was not significant for the four-class solution.

^cThis statistic is the Chi-square statistic for VLMR. When significant, this test provides evidence that the K-class solution fits the data better than the K-1-class solution.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3. Growth Mixture Model (GMM) Parameter Estimates (Mean [SE])

Parameter Estimates ^a	High Attentional Function n = 39 ^b (15.5%)	Moderate-to-High Attentional Function n = 121 (48.0%)	Moderate Attentional Function n = 92 (36.5%)
Intercept	8.979*** (0.120)	7.467*** (0.198)	5.549*** (0.240)
Linear slope	0.150* (0.073)	0.200** (0.068)	-0.222 (0.119)
Quadratic slope	-0.012 (0.010)	-0.021* (0.010)	0.043** (0.016)
Variances			
Intercept	0 ^c	0.629*** (0.137)	1.438*** (0.256)
Linear slope	0 ^c	0 ^c	0.048*** (0.014)

Abbreviation: SE = standard error.

^aParameter estimates were obtained with robust maximum likelihood, with dyad as a clustering variable to account for dependency between patients and family caregivers.

^bTrajectory class sizes are for classification of individuals based on most likely latent class membership.

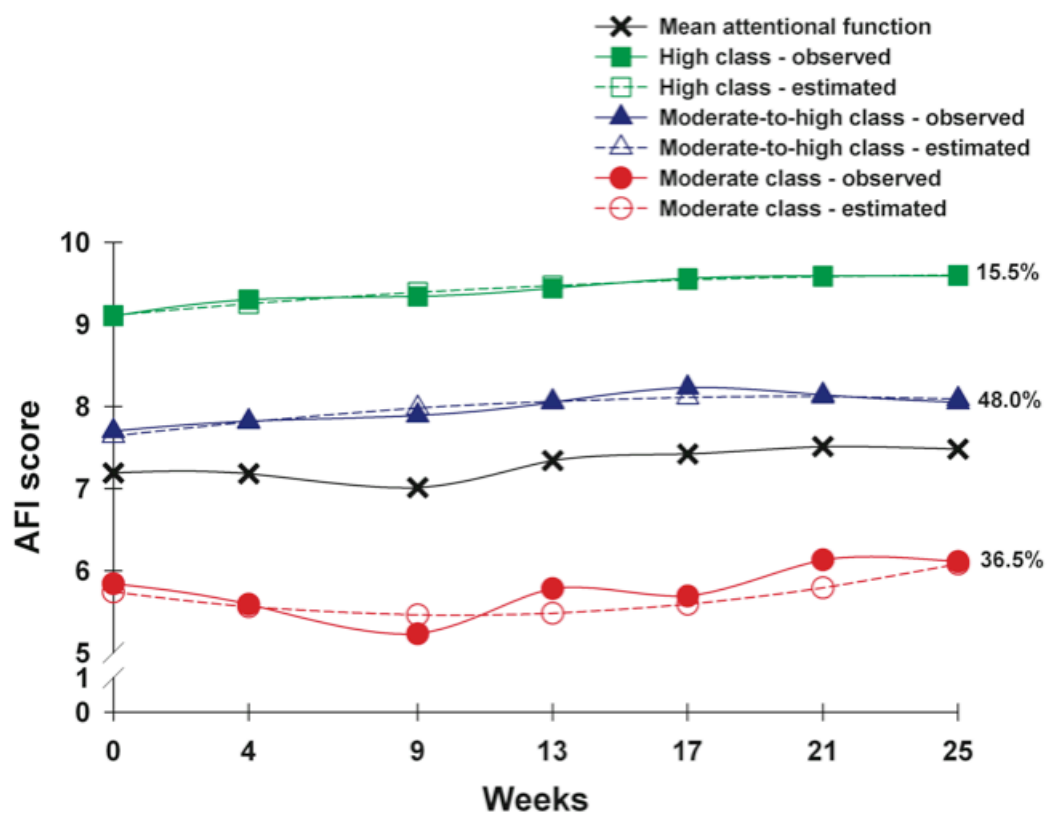
^cFixed at 0 to improve estimation.

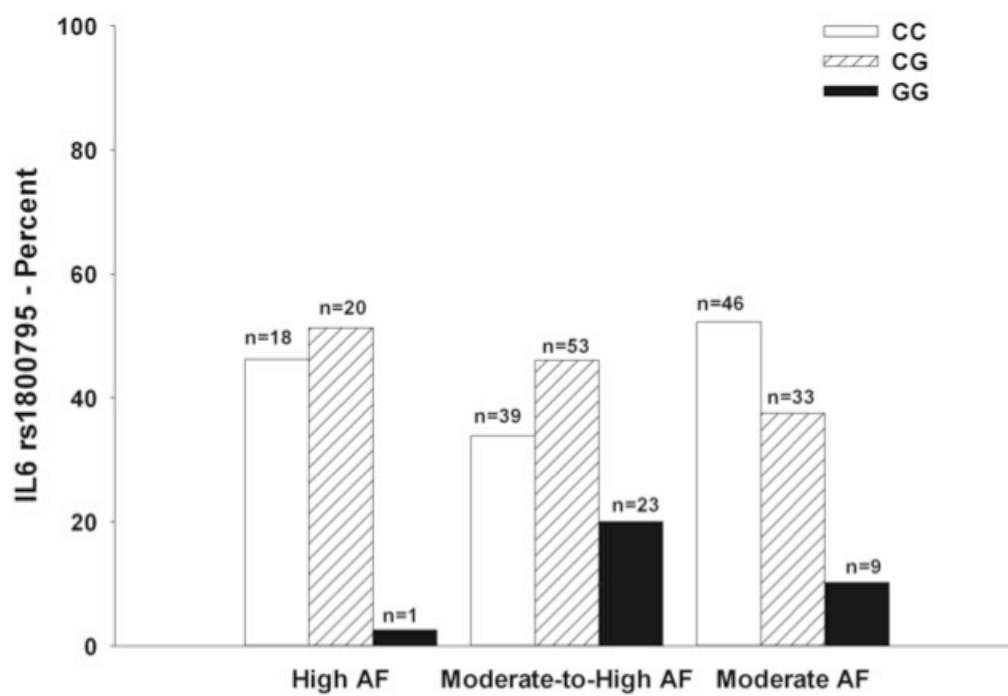
*p < .05. **p < .01. ***p < .001.

Table 4. Differences in Demographic and Clinical Characteristics at Enrollment

Characteristic	High Attentional Function (0) n = 39 (15.5%)	Moderate-to-High Attentional Function (1) n = 121 (48.0%)	Moderate Attentional Function (2) n = 92 (36.5%)	Statistics and Post Hoc Comparisons
	Mean (SD)			
Age (years)	65.3 (8.7)	62.6 (10.3)	58.4 (12.7)	F(2,113)=6.5, p=.002; 2<0,1
Education (years)	15.9 (3.1)	16.2 (3.3)	15.6 (2.5)	NS
Number of comorbidities	3.8 (2.4)	4.5 (2.7)	5.1 (2.7)	F(2,249)=3.6, p=.030; 2>0
Weight (pounds)	175.6 (38.8)	177.1 (37.6)	174.1 (41.7)	NS
KPS score	96.2 (8.8)	93.6 (9.5)	87.9 (13.7)	F(2,108)=9.0, p<.001; 2<0,1
	n (%)			
Gender (female)	20 (51.3)	59 (48.8)	56 (60.9)	NS
Ethnicity (White)	32 (82.1)	94 (78.3)	61 (66.3)	NS
Lives alone (yes)	6 (31.6)	24 (30.8)	24 (34.3)	NS
Married or partnered (yes)	33 (84.6)	87 (72.5)	54 (59.3)	$\chi^2=9.160$, p=.010; 2<0
Children at home (yes)	3 (9.4)	14 (14.3)	18 (22.2)	NS
Older adult at home (yes)	0 (0.0)	4 (4.1)	3 (3.6)	NS
Work for pay (yes)	20 (51.3)	55 (46.2)	40 (44.9)	NS
Patient/FC (patient)	19 (48.7)	78 (64.5)	70 (76.1)	$\chi^2=9.518$, p=.009; 2>0

Abbreviations: SD = standard deviation, NS = not significant, KPS = Karnofsky Performance Status, FC = family caregiver.





Chapter 3:

Association Between an Interleukin 1 Receptor, Type I Promoter Polymorphism and Self-Reported Attentional Function in Women With Breast Cancer

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Abstract

Subgroups of patients with breast cancer may be at greater risk for cytokine-induced changes in cognitive function after diagnosis and during treatment. The purposes of this study were to identify subgroups of patients with distinct trajectories of attentional function and evaluate for phenotypic and genotypic (i.e., cytokine gene polymorphisms) predictors of subgroup membership. Self-reported attentional function was evaluated in 397 patients with breast cancer using the Attentional Function Index before surgery and for six months after surgery. Using growth mixture modeling, three attentional function latent classes were identified: high (41.6%), moderate (25.4%), and low-moderate (33.0%). Patients in the low-moderate class were significantly younger than those in the high class, with more comorbidities and lower functional status than the other two classes. No differences were found among the classes in years of education, race/ethnicity, or other clinical characteristics. Eighty-two single nucleotide polymorphisms among 15 candidate genes were included in the genetic association analyses. After controlling for age, comorbidities, functional status, and population stratification due to race/ethnicity, IL1R1 rs949963 remained a significant genotypic predictor of class membership in the multivariable model. Carrying the rare “A” allele (i.e., GA+AA) was associated with a two-fold increase in the odds of belonging to a lower attentional function class (OR: 1.98; 95% CI: 1.18, 3.30; $p=.009$). Findings provide evidence of subgroups of women with breast cancer who report distinct trajectories of attentional function and of a genetic association between subgroup membership and an IL1R1 promoter polymorphism.

Keywords: attention; breast cancer; inflammation; cytokine genes; interleukin 1 receptor, type I; growth mixture modeling

Association Between an Interleukin 1 Receptor, Type I Promoter Polymorphism and Self-Reported Attentional Function in Women With Breast Cancer

Self-reported attentional function is an important aspect of quality of life for patients with breast cancer (Boykoff, Moieni, & Subramanian, 2009; Cimprich, Visovatti, & Ronis, 2011; Myers, 2012). Perceived changes in attentional function after diagnosis and during treatment negatively impact women's ability to maintain meaningful activities that require the direction of attention for sustained periods of time (Cimprich et al., 2011). Attentional function is closely tied to working memory (Gazzaley & Nobre, 2012) and is a component of executive function (Cimprich et al., 2011). Therefore, changes in attentional function interfere with planning and goal-directed activities for these women (Cimprich et al., 2011). Although studies using objective neuropsychological tests have shown subtle or no changes in attentional function, women may report these changes because of increased mental effort exerted to compensate for cancer- and cancer-treatment-related cognitive changes (Ferguson, McDonald, Saykin, & Ahles, 2007). Indeed, functional magnetic resonance imaging studies support the hypothesis that subjective reports of cognitive changes are associated with increased mental effort (Ferguson et al., 2007; Reuter-Lorenz & Cimprich, 2013).

A recent report of the International Cognition and Cancer Task Force highlighted a consistent finding in the literature that subgroups of patients are more vulnerable to cognitive changes (Wefel, Vardy, Ahles, & Schagen, 2011). Characterization of vulnerable subgroups would allow clinicians to target education and interventions to patients most likely to benefit. Phenotypic characteristics (e.g., age, functional status) and clinical characteristics (e.g., disease stage, treatment), as well as differences in peripheral

inflammatory processes (Seruga, Zhang, Bernstein, & Tannock, 2008), may be associated with vulnerability to changes in attentional function in these women.

Cytokines and their receptors regulate inflammatory processes (Seruga et al., 2008). Peripheral inflammation, due to cancer and its treatment, could induce inflammation in the central nervous system (CNS) through activation of afferent nerves such as the vagus nerve (Capuron & Miller, 2011; Watkins et al., 1995), peripheral cytokine interactions with circumventricular organs (Banks & Erickson, 2010), active transport of cytokines across the blood-brain barrier (Plotkin, Banks, & Kastin, 1996), activation of second messengers (Konsman, Vigues, Mackerlova, Bristow, & Blomqvist, 2004), and/or direct entry of peripherally activated monocytes into the CNS (Capuron & Miller, 2011; D'Mello, Le, & Swain, 2009). Microglial cells within the CNS respond by producing central pro-inflammatory cytokines that contribute to oxidative stress (Joshi et al., 2005), dysregulation of hypothalamic-pituitary-adrenal axis function (Raison et al., 2010), and diminished growth factor signaling (Tong, Balazs, Soiampornkul, Thangnipon, & Cotman, 2008; Wilson, Finch, & Cohen, 2002). Therefore, the effects of peripheral cytokines could have a negative impact on cognitive function (Ahles & Saykin, 2007). Given this hypothesized relationship, variations in genes that encode for inflammatory cytokines and their receptors may explain some of the variability in attentional function reported by women with breast cancer.

In a previous study using growth mixture modeling (GMM; Merriman et al., 2013), we identified three subgroups of participants with clinically meaningful differences in trajectories of attentional function during and after radiation therapy. In these patients with breast, prostate, brain, or lung cancer and their family caregivers, a

single nucleotide polymorphism (SNP) in IL6 (rs1800795) predicted subgroup membership. In the current study, we attempt to replicate these findings and identify novel associations in a larger, more homogenous sample. Therefore, the purposes of this study, in a sample of women with breast cancer, were to identify latent classes (i.e., subgroups of patients) with distinct trajectories of attentional function and to evaluate for phenotypic and genotypic characteristics associated with latent class membership.

Material and Methods

This analysis is part of a larger study that evaluated for multiple symptoms in patients who underwent surgery for breast cancer (McCann et al., 2012). Patients were recruited from breast care centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices. Patients were eligible to participate if they were ≥ 18 years of age; underwent surgery on one breast; were able to read, write, and understand English; and gave written informed consent. Patients with distant metastases at the time of diagnosis were excluded. Of the 516 patients who were approached, 410 enrolled in the study (79.5% response rate) and 397 completed baseline assessments. The most common reasons for refusal were being too busy or feeling overwhelmed.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the institutional review boards at each of the other study sites. During preoperative visits, a clinical staff member explained the study and invited patients to participate. Those women who were willing to participate were introduced to a research nurse, who determined eligibility. After providing written informed consent, patients completed baseline questionnaires a mean of four days prior to

surgery. Follow-up questionnaires were completed each month for six months after surgery (i.e., seven assessments over six months). Medical records were reviewed for disease and treatment information.

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977), the Self-administered Comorbidity Questionnaire (SCQ; Sangha, Stucki, Liang, Fossel, & Katz, 2003), and the Attentional Function Index (AFI). The AFI consists of 13 items designed to measure self-reported attentional function (i.e., ability to voluntarily direct and sustain attention; Cimprich et al., 2011). Higher mean scores on a 0 to 10 numeric rating scale indicate greater capacity to direct attention. Scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function; Cimprich, So, Ronis, & Trask, 2005). Multiple studies have used the AFI in patients with breast cancer before (Cimprich, 1999; Cimprich et al., 2005; Lehto & Cimprich, 1999) and after (Cimprich, 1992) surgery and chemotherapy (Jansen, Cooper, Dodd, & Miaskowski, 2011). Additional studies have used the measure across multiple treatment modalities (Chen, Miaskowski, Liu, & Chen, 2012) and in long-term survivors (Von Ah, Russell, Storniolo, & Carpenter, 2009). The AFI has established reliability, as well as construct and convergent validity (Cimprich et al., 2011). In this study, Cronbach's alpha was .93.

Phenotypic Analyses

Data were analyzed using SPSS 19 (IBM, Armonk, New York) and Mplus 6.11 (Muthén & Muthén, Los Angeles). Descriptive statistics and frequency distributions were generated for sample characteristics and AFI scores. GMM with robust maximum likelihood estimation identified latent classes of patients with distinct trajectories of

attentional function. The GMM methods are described in detail elsewhere (Dunn, Aouizerat, Cooper, et al., 2012).

Analyses of variance and Chi-square analyses were used to evaluate for differences in patient characteristics among classes. The cohort of patients for each analysis was dependent on the largest set of available data across classes. Differences were considered statistically significant at $p < .05$. Post hoc contrasts used the Bonferroni correction to control the overall family alpha. For any one of three possible pairwise contrasts, $p < .017$ was considered statistically significant. Effect sizes were determined using Cohen's d (Cohen, 1988).

Genotypic Analyses

Genomic DNA was extracted from archived buffy coats using the Puregene DNA Isolation System (Invitrogen, Carlsbad, CA). Of 397 patients who completed the baseline assessment, DNA was recovered for 302.

DNA was quantitated using spectrophotometry and normalized to a concentration of 50 ng/ μ L (diluted in 10 mM Tris/1 mM EDTA). Genotyping was performed blinded to clinical status. Samples were genotyped using the GoldenGate genotyping platform and processed using GenomeStudio (Illumina, San Diego). Genotype calls for each SNP were visually inspected by two blinded reviewers. Disagreements were adjudicated by a third reviewer.

Gene and SNP selection. Genes that encode for pro-inflammatory cytokines include interferon gamma receptor 1 (IFNGR1), interleukin (IL) 1, IL1 receptor 1 (IL1R1), IL2, IL8, IL17A, and tumor necrosis factor alpha (TNFA). Genes that encode for anti-inflammatory cytokines include IL1R2, IL4, IL10, and IL13. Genes that encode

for cytokines with both pro- and anti-inflammatory functions include IFNG1, IL1B, and IL6. Genes that encode for transcription factors, which moderate the levels of cytokine production, include nuclear factor kappa B 1 (NFKB1) and NFKB2. (Seruga et al., 2008)

A combination of tagging SNPs and literature-driven SNPs (i.e., associated with altered function, symptoms) for these genes were selected for analysis. Tagging SNPs were required to be common, defined as having minor allele frequencies (MAFs) $\geq 5\%$ in public databases. SNPs with call rates $< 95\%$ or Hardy-Weinberg expectation $p < .001$ were excluded.

Statistical analyses. Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg expectation was assessed by the Chi-square or Fisher Exact test. Measures of linkage disequilibrium (LD; i.e., D' and r^2) were computed from patients' genotypes with Haploview 4.2 (Broad Institute, Cambridge, Massachusetts). LD-based haplotype block definition was based on the D' confidence interval (CI) method (Gabriel et al., 2002). Haplotypes were constructed using PHASE 2.1 (Stephens, Smith, & Donnelly, 2001), as described previously (Miaskowski et al., 2012). One hundred six ancestry informative markers (AIMs) were included in the analyses, as described previously (Miaskowski et al., 2012). A backwards stepwise approach was used to create the most parsimonious phenotypic regression model. Except for self-reported race/ethnicity and AIMs, which were included to minimize confounding due to population stratification (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008), only predictors with a p-value of $< .05$ were retained in the final model.

Additive, dominant, and recessive genetic models were assessed in association

tests for each SNP. Barring trivial improvements (i.e., $\Delta < 10\%$) from the additive model, the model that best fit the data, by maximizing the significance of the p-value, was selected for inclusion in the multivariable analyses. To estimate the magnitude (i.e., odds ratio, OR) and precision (i.e., 95% CI) of the association of genotype with odds of class membership, logistic regression models were fit that treated class as a discrete categorical variable. Model fit and both unadjusted and covariate-adjusted ORs were estimated using Stata 9 (StataCorp, College Station, Texas). If the overall model included a statistically significant genotype term, pairwise post hoc models (e.g., high versus moderate attentional function) were fit. Only post hoc models with Bonferroni-corrected statistically significant genotype terms were retained.

As was done in our previous studies (Dunn, Aouizerat, Langford, et al., 2012; Merriman et al., 2013; Miaskowski et al., 2012) and based on recommendations in the literature (Hattersley & McCarthy, 2005; Rothman, 1990), the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. Significant SNPs identified in the bivariate analyses were evaluated further using regression analyses that controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variation in other SNPs/haplotypes within the same gene. Only SNPs that remained significant were included in the final results. Therefore, the significant independent genetic association reported is unlikely to be due solely to chance. In addition, unadjusted (i.e., bivariate) associations are reported for all SNPs passing quality control criteria to allow for subsequent comparisons and meta-analyses.

Results

GMM Classes

Three distinct classes of attentional function trajectories were identified (Figure 1). A three-class solution provided the best model fit because it had the smallest Bayesian information criterion (BIC) and a significant bootstrapped likelihood ratio test (BLRT), as well as greater entropy and more differentiating growth trajectories than the two-class solution, with each class maintaining reasonable size and interpretability (Table 1). Further, the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) was not significant for the four-class solution (Jung & Wickrama, 2008).

Patients in the high attentional function (“high”) class (41.6%) had estimated AFI scores of 7.78 at enrollment that increased significantly and remained high throughout the study (Table 2). Patients in the moderate attentional function (“moderate”) class (25.4%) had estimated AFI scores of 6.58 at enrollment that decreased and then increased significantly but remained moderate throughout the study. Patients in the low-moderate attentional function (“low-moderate”) class (33.0%) had estimated AFI scores of 5.23 at enrollment that did not change significantly during the study.

Phenotypic Differences Among Classes

Patients in the low-moderate class were significantly younger than those in the high class (Table 3). They had significantly more comorbidities and lower functional status than the other two classes. While a significant difference in body mass index (BMI) was found among the classes, post hoc contrasts were not significant. Although no differences were found among the classes in the proportion of patients who worked for pay, a greater proportion of patients making <\$30,000/year than $\geq$ \$30,000/year were in

the low-moderate class compared to the high class. Likewise, a greater proportion of patients making <\$30,000/year than $\geq$ \$100,000/year were in the low-moderate class compared to the moderate class. No differences were found among the classes in years of education, race/ethnicity, or other clinical characteristics.

Using a backwards stepwise approach, only age, comorbidities (i.e., SCQ score), and functional status (i.e., KPS score) significantly predicted class membership in multivariable models unadjusted for genotype. For each five-year increase in age, patients had a 12% decrease in the odds of belonging to a lower attentional function class (OR: 0.88; 95% CI: 0.80, 0.97; $p=.012$). For every one point increase in SCQ score (i.e., indicating a greater number, severity, and/or functional impact of comorbidities), patients had a 14% increase in the odds of belonging to a lower attentional function class (OR: 1.14; 95% CI: 1.04, 1.24; $p=.004$). For every ten-point increase in KPS score (i.e., indicating a clinically meaningful increase in functional status), patients had a 30% decrease in the odds of belonging to a lower attentional function class (OR: 0.70; 95% CI: 0.55, 0.90; $p=.006$).

Genotypic Differences Among Classes

Eighty-two SNPs among 15 candidate genes passed all of the quality control filters. Genotype distributions differed significantly among classes for four SNPs and one haplotype (Table 4). Controlling for age, comorbidities, functional status, and population stratification due to race/ethnicity, only the model fit for IL1R1 rs949963 remained significant ($p<.001$; Table 5). Pairwise post hoc contrasts did not meet Bonferroni-corrected thresholds for significant between-class differences by genotype (OR: 2.10; 95% CI: 1.12, 3.94; $p=.021$ for high versus moderate classes. OR: 2.01; 95% CI: 1.10, 3.68;

$p=.023$ for high versus low-moderate classes. OR: .90; 95% CI: .46, 1.75; $p=.750$ for moderate versus low-moderate classes). See Figure 2 for allelic distributions.

The final model explained 7.5% of variance in class membership ($p<.001$). Controlling for covariates, carrying the rare “A” allele (i.e., GA or AA genotype) was associated with a two-fold increase in the odds of belonging to a lower attentional function class (OR: 1.98; 95% CI: 1.18, 3.30; $p=.009$).

Discussion

This study is the first to use GMM to identify subgroups of women with breast cancer who reported distinct trajectories of attentional function prior to and after surgery and to evaluate for phenotypic and genotypic differences among these subgroups. Differences in mean AFI scores among the subgroups prior to surgery represent clinically meaningful differences (Wyrwich et al., 2005) in self-reported attentional function ($d=0.68$ for high versus moderate classes and $d=0.89$ for moderate versus low-moderate classes). The GMM solution found in this study partially confirms findings from our previous study (Merriman et al., 2013). Both studies found that a three-class solution best fit the data. However, AFI scores in the current study for each of the classes were lower than in the previous study. In addition, the trajectories of attentional function in each of the three classes varied between the studies.

These differences in AFI scores and trajectories may be due to the inclusion of male patients and male family caregivers in the previous sample. Since gender differences in the severity of other symptoms have been reported (Dunn, Aouizerat, Langford, et al., 2012; Hagedoorn, Buunk, Kuijer, Wobbles, & Sanderman, 2000; Hagedoorn, Sanderman, Bolks, Tuinstra, & Coyne, 2008; Illi et al., 2012; Reyes-Gibby,

Aday, Anderson, Mendoza, & Cleeland, 2006; Walsh, Donnelly, & Rybicki, 2000), additional research is warranted to evaluate for gender differences in self-reported attentional function. Future studies of patients with cancer diagnoses that affect both men and women (e.g., colorectal cancer) may provide insights into these relationships.

An alternative explanation is that the different treatments that patients underwent in the two studies may have differentially impacted attentional function. However, treatment was not associated with attentional function class membership in either study. While none of the clinical characteristics differentiated among the classes, visual inspection of the class trajectories (Figure 1) suggests that the moderate class had a significant decrease in attentional function after surgery followed by a significant increase in attentional function approximately three months later. This trajectory was possibly influenced by treatment. While larger sample sizes may identify treatment-related predictors of attentional function, our findings suggest that several patient characteristics (i.e., younger age, higher number and/or severity of comorbidities, lower functional status) are risk factors for poorer attentional function after diagnosis of breast cancer and during treatment.

The phenotypic predictors of class membership that remained significant in multivariable models were age, comorbidities, and functional status. Consistent with previous reports (Cimprich et al., 2011; Merriman et al., 2011; Merriman et al., 2010), younger patients were more likely to belong to a lower attentional function class. It is hypothesized that younger patients may notice changes in their attentional function in response to the diagnosis and treatment of cancer more than do older adults, who may have adjusted to previous age-related alterations in attentional function (Cimprich et al.,

2011).

Consistent with our previous study (Merriman et al., 2013), functional status was a phenotypic predictor of attentional function class membership. The low-moderate class reported a pre-treatment mean KPS score of 88.83 (± 12.77), which is a clinically meaningful difference from 95.74 (± 8.62) for the high class and 94.90 (± 6.89) for the moderate class ($d=0.62$ and $d=0.55$, respectively). One possible explanation is that the higher comorbidity score reported by the low-moderate class in the present study influenced this relationship. Managing multiple comorbidities may decrease a patient's capacity to direct and sustain attention before the diagnosis of cancer (Merriman et al., 2011), or cognitive changes may be associated with specific comorbidities (Bauer, Johnson, & Pozehl, 2011; Wefel et al., 2011).

The most commonly reported comorbidities regardless of class membership were high blood pressure (30.9%), back pain (28.1%), and depression (21.9%). While the low-moderate class reported the same top three comorbidities, the proportions of patients who reported back pain (35.1%) and depression (29.0%) were higher. It is possible that the greater proportions of patients with pain and depression in this class at enrollment accounts for its lack of improvement in attentional function during cancer therapy. Future studies should evaluate the effects of these symptoms on attentional function class membership.

In a previous study by our group (Merriman et al., 2010), higher BMI before radiation therapy was associated with improvement in attentional function over time in women with breast cancer. Although BMI was associated with differences in latent class membership in the current study, no significant relationships were apparent between

higher versus lower BMI and class membership. Future studies may clarify these relationships.

Income was significantly different among the classes. The lowest annual household income level (i.e., <\$30,000) was associated with membership in the lowest attentional function class. Although income level did not remain a significant predictor of class membership in multivariable models, it is possible that stress associated with lower income (Hauksdottir, McClure, Jonsson, Olafsson, & Valdimarsdottir, 2013) in the context of the cost of breast cancer treatment contributed to these class differences. Chronic stress negatively impacts immune system function (Miller, Maletic, & Raison, 2009), which may contribute to cognitive changes in these patients (Seruga et al., 2008). This finding warrants more research in terms of social and environmental characteristics associated with socio-economic status that may influence attention.

One SNP in IL1R1 (rs949963) significantly predicted class membership after controlling for covariates. Genotype uniquely explained 1.5% of variance in class membership. Carrying the rare A allele was associated with an increased odds of belonging to a lower attentional function class. Although significant pairwise post hoc class comparisons were not found after correction for multiple testing, examination of these relationships is warranted in future studies.

IL1R1 rs949963 is located in the promoter region, 616 base pairs upstream of the transcription start site. Although no studies have demonstrated a link between transcription factors involved in regulation of gene expression and this SNP, the A allele is predicted to have decreased affinity for two transcription factors (i.e., Yin Yang 1 [YY1], upstream stimulatory factor 1 [USF1]), as compared to the “G” allele (Grabe,

2000). YY1 is a pleiotropic human transcription factor involved in the regulation of inflammation (Landvik, Tekpli, Anmarkrud, Haugen, & Zienolddiny, 2012) and neural plasticity (Gao et al., 2010). USF1 is involved in regulation of inflammation (Ratajewski, Walczak-Drzewiecka, Salkowska, & Dastych, 2012) and lipid metabolism genes involved in cognition (e.g., APOE; Isotalo et al., 2012). Given the predicted differential binding sites for these two mechanistically plausible transcription factors at IL1R1 rs949963, it is reasonable to hypothesize that variation in this SNP may influence the regulation of IL1R1 in a manner that is associated with differences in attentional function. Functional studies to determine if either of these theoretical binding sites are active and influenced by rs949963 are warranted.

No studies were found that described a relationship between IL1R1 rs949963 and clinical outcomes. However, in mouse models, the inhibition of interleukin 1 receptor, type I production decreased joint inflammation (Torres et al., 2009) and reduced the behavioral outcome of despair (i.e., immobility during tail suspension and forced swim tests; Zhu et al., 2010). In addition, inhibiting the receptor blocked the development of stress-related glucocorticoid resistance, which is a possible mechanism for chronic inflammation (Engler et al., 2008). The relationships of this interleukin 1 receptor to inflammation (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008) and cognition (Cibelli et al., 2010) are hypothesized to extend to humans.

Given the numerous mechanisms by which inflammation may negatively impact attentional function (Ahles & Saykin, 2007; Banks & Erickson, 2010; Capuron & Miller, 2011; D'Mello et al., 2009; Joshi et al., 2005; Konsman et al., 2004; Plotkin et al., 1996; Raison et al., 2010; Tong et al., 2008; Watkins et al., 1995; Wilson et al., 2002), it is

reasonable to suggest that carriers of the rare A allele for IL1R1 rs949963 have increased production of this interleukin 1 receptor. Therefore, interleukin-1 production at the time of diagnosis and treatment for breast cancer would be more efficient in producing an inflammatory state that could impact the CNS. However, future studies must evaluate for differences in expression of IL1R1 in carriers of the rare A allele to determine whether this hypothesis is tenable.

In our previous study (Merriman et al., 2013), this SNP was not associated with attentional function class membership. The MAFs for the SNP in the two studies were similar, which suggests that the lack of an association in the previous study was not due to differences in allele frequency. Moreover, in the previous study no significant associations were found between IL1R1 SNPs and class membership in bivariate analyses. The lack of a significant finding may be due to sample variation or to different composition of the GMM groups. Also, AFI scores for the three classes identified in the present study were lower than in the previous study, which may have contributed to differences in SNP associations.

The present study did not replicate the finding of our previous study that variation in IL6 rs1800795 predicted attentional function class membership (Merriman et al., 2013). Moreover, no significant associations were found between IL6 SNPs and class membership in bivariate analyses. This lack of replication could be due in part to the fact that the MAF for this SNP in the present study was 19.7% lower than in the previous study. An alternative hypothesis is that the classes are phenotypically distinct.

Because it is possible that the revised AFI used in the present study (Cimprich et al., 2011) is not directly comparable to the original AFI used in the previous study

(Merriman et al., 2013), analyses were run with the original instrument. These analyses showed no differences in results for these two SNPs (data not shown). For both IL1R1 rs949963 and IL6 rs1800795, larger samples could resolve whether their relationships to attentional function can be replicated.

Study limitations should be acknowledged. The relationship of IL1R1 rs949963 to attentional function class membership warrants replication and functional studies before clinical implications are evaluated. Measuring serum cytokine levels could support the hypothesized relationship between cytokine levels and cognitive function (Ahles & Saykin, 2007; Banks & Erickson, 2010; Capuron & Miller, 2011; D'Mello et al., 2009; Joshi et al., 2005; Konsman et al., 2004; Plotkin et al., 1996; Raison et al., 2010; Tong et al., 2008; Watkins et al., 1995; Wilson et al., 2002). Studies of genes that encode for other physiological pathways (e.g., dopaminergic, serotonergic; Posner, Rothbart, & Sheese, 2007) may clarify the etiology of reduced attentional function in women with breast cancer.

Although neuropsychological tests may not be sensitive to the changes in attentional function that patients report (Schagen, Das, & van Dam, 2009), inclusion of objective tests could improve understanding of subgroups of patients at risk for diminished attentional function. In addition, studies should evaluate for changes in other cognitive domains (e.g., working memory, executive function) that may be associated with genetic variation in IL1R1.

The low-moderate class was the only class not to report significantly improved attentional function over the six months of the study. It is possible that acute deficits in attentional function may lead to chronic deficits. An alternative hypothesis is that class

trajectories may be influenced by co-occurring symptoms. Future studies may clarify long-term trends.

This study provides evidence for a relationship between IL1R1 rs949963 and distinct trajectories of self-reported attentional function. The finding suggests that cytokine dysregulation negatively impacts attentional function in women with breast cancer at a time when the capacity to direct and sustain attention is important for quality of life during treatment for breast cancer.

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Figure Legends

Figure 1. Observed and estimated attentional function trajectories for patients in each latent class (high class, n=165; moderate class, n=101; low-moderate class, n=131), as well as mean Attentional Function Index (AFI) scores for the total sample.

Figure 2. Differences among the attentional function (AF) latent classes in the percentages of patients who were homozygous for the common “G” allele versus heterozygous or homozygous for the rare “A” allele for rs949963 in interleukin 1 receptor, type I (IL1R1) (p=.016).

Table 1. Fit Indices for Attentional Function Growth Mixture Model Solutions Over Seven Assessments

Model	LL	AIC	BIC	Entropy	VLMR ^c	BLRT ^d
1-class ^a	-4286.758	8597.516	8645.323	n/a	n/a	n/a
2-class	-4239.001	8518.003	8597.682	0.461	135.636**	135.636**
3-class ^b	-4218.660	8485.321	8580.935	0.554	40.682*	40.682**
4-class	-4220.918	8497.836	8609.386	0.642	23.514 ^{ns}	23.514*** ^e

Abbreviations: LL = log likelihood, AIC = Akaike information criterion, BIC = Bayesian information criterion, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test, BLRT = bootstrapped likelihood ratio test, n/a = not applicable, ns = not significant, CFI = comparative fit index, RMSEA = root mean square error of approximation.

^aRandom intercepts latent growth curve model with linear components; $\chi^2=49.470$, 23 df, $p<.01$, CFI=.975, RMSEA=.054.

^bA three-class solution provided the best model fit because it had the smallest BIC and a significant BLRT, as well as greater entropy and more differentiating growth trajectories than the two-class solution, with each class maintaining reasonable size and interpretability. Further, VLMR was not significant for the four-class solution.

^cThis statistic is the Chi-square statistic for VLMR. When significant, this test provides evidence that the K-class solution fits the data better than the K-1-class solution.

^dBLRT p-values are approximated based on varying numbers of bootstrap draws.

^eAlthough BLRT was significant, one of the classes comprised <5% of the sample (n=18), indicating an unreliable model.

* $p<.05$, ** $p<.001$.

Table 2. Growth Mixture Model Parameter Estimates

Parameter Estimates ^a	High Attentional Function n=165 ^b (41.6%)	Moderate Attentional Function n=101 (25.4%)	Low-moderate Attentional Function n=131 (33.0%)
	Mean (SE)	Mean (SE)	Mean (SE)
Intercept	7.779*** (0.222)	6.576*** (0.196)	5.227*** (0.231)
Linear slope	0.110*** (0.017)	-0.304* (0.129)	-0.010 (0.027)
Quadratic slope	0 ^c	0.062** (0.021)	0 ^c
Intercept variance	0.678*** (0.174)	2.329*** (0.486)	1.020** (0.354)
Linear slope variance	0 ^c	0.761*** (0.191)	0 ^c
Quadratic slope variance	0 ^c	0.019*** (0.005)	0 ^c

Abbreviation: SE = standard error.

^aParameter estimates were obtained with robust maximum likelihood.

^bTrajectory class sizes are for classification of individuals based on most likely latent class membership.

^cFixed at zero to improve estimation.

*p<.05, **p<.01, ***p<.001.

Table 3. Differences in Demographic and Clinical Characteristics Among the Three Latent Classes for Attentional Function

Characteristic	High Attentional Function (0)	Moderate Attentional Function (1)	Low-moderate Attentional Function (2)	Statistics and Post Hoc Comparisons
	Mean (SD)			
Age (years)	56.7 (11.2)	55.2 (10.3)	52.6 (12.6)	F(2,394)=4.9, p=.008; 2<0
Education (years)	15.8 (2.7)	15.8 (2.9)	15.6 (2.4)	ns
SCQ score	3.8 (2.5)	4.0 (2.6)	5.1 (3.2)	F(2,393)=8.8, p<.001; 2>0,1
BMI (kg/m ²)	25.9 (5.7)	27.6 (6.6)	27.4 (6.3)	F(2,388)=3.4, p=.033; no significant post hoc contrasts
KPS score	95.7 (8.6)	94.9 (6.9)	88.8 (12.8)	F(2,387)=19.6, p<.001; 2<0,1
	n (%)			
Race/ethnicity				ns
White	113 (69.3)	70 (69.3)	72 (55.0)	
Black	15 (9.2)	7 (6.9)	18 (13.7)	
Asian/Pacific Islander	17 (10.4)	14 (13.9)	19 (14.5)	
Hispanic/mixed/other	18 (11.0)	10 (9.9)	22 (16.8)	
Live alone (% yes)	39 (23.9)	19 (19.2)	36 (27.7)	ns
Married or partnered (% yes)	69 (42.1)	36 (36.0)	60 (46.2)	ns
Work for pay (% yes)	84 (51.5)	52 (51.5)	53 (40.8)	ns
Household income level				KW=13.2, p=.001 ^a
<\$30,000	19 (14.3)	15 (16.7)	36 (34.0)	
\$30,000-\$99,999	61 (45.9)	33 (36.7)	40 (37.7)	
≥\$100,000	53 (39.8)	42 (46.7)	30 (28.3)	
Regular exercise (% yes)	118 (71.5)	74 (74.0)	82 (63.6)	ns
Stage of disease				ns
Stage 0	30 (19.1)	18 (18.8)	16 (12.8)	
Stage I	65 (41.4)	38 (39.6)	40 (32.0)	
Stage II	50 (31.8)	35 (36.5)	53 (42.4)	
Stages III and IV	12 (7.6)	5 (5.2)	16 (12.8)	
Postmenopausal (% yes)	106 (65.4)	64 (66.7)	78 (60.9)	ns
Neoadjuvant therapy (% yes)	27 (16.4)	17 (17.0)	35 (26.7)	ns
Type of surgery (% mastectomy)	30 (18.2)	24 (23.8)	25 (19.1)	ns
Postoperative complications (% yes)	32 (19.4)	19 (19.0)	32 (24.8)	ns
Adjuvant chemotherapy (% yes)	48 (29.1)	40 (39.6)	45 (34.4)	ns
Radiation therapy (% yes)	95 (57.6)	52 (51.5)	77 (58.8)	ns
Estrogen receptor (% positive)	137 (83.5)	74 (73.3)	96 (73.3)	ns
Progesterone receptor (% positive)	124 (75.6)	70 (69.3)	85 (64.9)	ns
HER2/neu (% positive)	21 (14.3)	15 (17.0)	23 (18.7)	ns
HRT before diagnosis (% yes)	22 (13.3)	24 (24.0)	21 (16.2)	ns

Abbreviations: SD = standard deviation, ns = not significant, SCQ = Self-administered Comorbidity Questionnaire, BMI = body mass index, KPS = Karnofsky Performance Status, KW = Kruskal-Wallis test, HER2/neu = human epidermal growth factor receptor 2, HRT = hormone replacement therapy.

^aPost hoc contrasts revealed that a greater proportion of patients making <\$30,000/year than $\geq$ \$30,000/year were in the low-moderate class compared to the high class. Likewise, a greater proportion of patients making <\$30,000/year than $\geq$ \$100,000/year were in the low-moderate class compared to the moderate class.

Table 4. Differences in Cytokine Gene Single Nucleotide Polymorphism (SNP) Allele and Haplotype Frequencies Among the Latent Classes of Attentional Function

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IFNG1	rs2069728	66834051	12	.110	G>A	1.27	.867	A
IFNG1	rs2069727	66834490	12	.384	A>G	2.65	.617	A
IFNG1	rs2069718	66836429	12	.494	C>T	3.17	.530	A
IFNG1	rs1861493	66837463	12	.266	A>G	0.92	.921	A
IFNG1	rs1861494	66837676	12	.273	T>C	0.67	.955	A
IFNG1	rs2069709	66839970	12	.003	G>T	n/a	n/a	n/a
IFNG1	HapA3					0.80	.939	-
IFNG1	HapA5					2.79	.593	-
IFNGR1	rs9376268	137574444	6	.254	G>A	3.75	.441	A
IL1B	rs1071676	106042060	2	.189	G>C	4.87	.301	A
IL1B	rs1143643	106042929	2	.383	G>A	1.64	.802	A
IL1B	rs1143642	106043180	2	.082	C>T	1.14	.887	A
IL1B	rs1143634	106045017	2	.187	C>T	4.66	.324	A
IL1B	rs1143633	106045094	2	.392	G>A	2.03	.731	A
IL1B	rs1143630	106046282	2	.115	C>A	6.82	.146	A
IL1B	rs3917356	106046990	2	.450	G>A	4.48	.345	A
IL1B	rs1143629	106048145	2	.389	T>C	6.64	.156	A
IL1B	rs1143627	106049014	2	.397	T>C	5.09	.278	A
IL1B	rs16944	106049494	2	.386	G>A	5.63	.229	A
IL1B	rs1143623	106050452	2	.277	G>C	6.61	.158	A
IL1B	rs13032029	106055022	2	.448	C>T	3.02	.554	A
IL1B	HapA1					6.20	.185	-
IL1B	HapA4					1.55	.818	-
IL1B	HapA6					4.84	.304	-
IL1B	HapB1					2.72	.605	-
IL1B	HapB6					5.93	.205	-
IL1B	HapB8					3.37	.498	-
IL1R1	rs949963 ^a	96533648	2	.223	G>A	8.32	.016	D
IL1R1	rs2228139	96545511	2	.053	C>G	2.09	.720	A
IL1R1	rs3917320	96556738	2	.047	A>C	n/a	n/a	n/a
IL1R1	rs2110726	96558145	2	.317	C>T	1.11	.893	A
IL1R1	rs3917332	96560387	2	.187	A>T	3.75	.441	A
IL1R1	HapA1					1.67	.797	-
IL1R1	HapA2					2.26	.689	-
IL1R1	HapA3					3.81	.432	-
IL1R2	rs4141134	96370336	2	.362	T>C	2.62	.623	A
IL1R2	rs11674595	96374804	2	.258	T>C	4.50	.343	A
IL1R2	rs7570441	96380807	2	.408	G>A	5.21	.266	A
IL1R2	HapA1					6.36	.174	-
IL1R2	HapA2					3.84	.147	-
IL1R2	HapA4					1.50	.827	-
IL2	rs1479923	119096993	4	.308	C>T	1.30	.862	A
IL2	rs2069776	119098582	4	.184	T>C	n/a	n/a	n/a
IL2	rs2069772	119099739	4	.241	A>G	5.08	.279	A
IL2	rs2069777	119103043	4	.047	C>T	n/a	n/a	n/a
IL2	rs2069763	119104088	4	.277	T>G	5.17	.270	A
IL2	HapA1					2.46	.653	-

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IL2	HapA2					4.99	.289	-
IL2	HapA3					5.08	.279	-
IL4	rs2243248	127200946	5	.086	T>G	2.93	.570	A
IL4	rs2243250	127201455	5	.269	C>T	n/a	n/a	n/a
IL4	rs2070874	127202011	5	.245	C>T	n/a	n/a	n/a
IL4	rs2227284	127205027	5	.387	C>A	n/a	n/a	n/a
IL4	rs2227282	127205481	5	.390	C>G	n/a	n/a	n/a
IL4	rs2243263	127205601	5	.124	C>G	4.28	.369	A
IL4	rs2243266	127206091	5	.237	G>A	n/a	n/a	n/a
IL4	rs2243267	127206188	5	.237	G>C	n/a	n/a	n/a
IL4	rs2243274	127207134	5	.261	G>A	n/a	n/a	n/a
IL4	HapA1					0.39	.983	-
IL4	HapA3					2.18	.704	-
IL4	HapX1					3.64	.457	-
IL6	rs4719714	22643793	7	.255	A>T	0.88	.927	A
IL6	rs2069827	22648536	7	.069	G>T	1.11	.892	A
IL6	rs1800796	22649326	7	.134	C>G	n/a	n/a	n/a
IL6	rs1800795	22649725	7	.285	C>G	3.10	.542	A
IL6	rs2069835	22650951	7	.061	T>C	n/a	n/a	n/a
IL6	rs2066992	22651329	7	.049	G>T	4.11	.391	A
IL6	rs2069840	22651652	7	.333	C>G	4.51	.341	A
IL6	rs1554606	22651787	7	.319	G>T	2.21	.697	A
IL6	rs2069845	22653229	7	.319	A>G	2.44	.655	A
IL6	rs2069849	22654236	7	.024	C>T	n/a	n/a	n/a
IL6	rs2069861	22654734	7	.056	C>T	7.92	.094	A
IL6	rs35610689	22656903	7	.259	A>G	2.49	.646	A
IL6	HapA1					4.39	.356	-
IL6	HapA5					4.85	.303	-
IL6	HapA8					2.70	.610	-
IL8	rs4073	70417508	4	.455	T>A	2.39	.665	A
IL8	rs2227306	70418539	4	.366	C>T	3.76	.440	A
IL8	rs2227543	70419394	4	.368	C>T	3.36	.500	A
IL8	HapA1					2.39	.665	-
IL8	HapA4					3.91	.419	-
IL10	rs3024505	177638230	1	.129	C>T	4.13	.389	A
IL10	rs3024498	177639855	1	.204	A>G	2.66	.617	A
IL10	rs3024496	177640190	1	.421	T>C	4.87	.301	A
IL10	rs1878672	177642039	1	.416	G>C	4.71	.319	A
IL10	rs3024492	177642438	1	.190	T>A	n/a	n/a	n/a
IL10	rs1518111	177642971	1	.303	G>A	4.36	.359	A
IL10	rs1518110	177643187	1	.301	G>T	4.69	.321	A
IL10	rs3024491	177643372	1	.408	G>T	4.39	.356	A
IL10	HapA1					4.25	.373	-
IL10	HapA2					2.94	.567	-
IL10	HapA8					1.99	.738	-
IL13	rs1881457	127184713	5	.210	A>C	6.44	.169	A
IL13	rs1800925	127185113	5	.233	C>T	1.56	.816	A
IL13	rs2069743	127185579	5	.019	A>G	n/a	n/a	n/a
IL13	rs1295686	127188147	5	.265	G>A	5.70	.223	A
IL13	rs20541	127188268	5	.212	C>T	4.18	.383	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
IL13	HapA1					5.27	.261	-
IL13	HapA4					4.20	.379	-
IL17A	rs4711998	51881422	6	.346	G>A	2.96	.565	A
IL17A	rs8193036	51881562	6	.327	T>C	6.08	.193	A
IL17A	rs3819024	51881855	6	.372	A>G	4.97	.291	A
IL17A	rs2275913	51882102	6	.361	G>A	4.06	.398	A
IL17A	rs3804513	51884266	6	.023	A>T	n/a	n/a	n/a
IL17A	rs7747909	51885318	6	.217	G>A	4.06	.398	A
NFKB1	rs3774933	103645369	4	.409	T>C	6.29	.043	R
NFKB1	rs170731	103667933	4	.358	A>T	0.93	.920	A
NFKB1	rs17032779	103685279	4	.011	T>C	n/a	n/a	n/a
NFKB1	rs230510	103695201	4	.410	T>A	7.14	.028	D
NFKB1	rs230494	103706005	4	.434	A>G	4.37	.358	A
NFKB1	rs4648016	103708706	4	.010	C>T	n/a	n/a	n/a
NFKB1	rs4648018	103709236	4	.018	G>C	n/a	n/a	n/a
NFKB1	rs3774956	103727564	4	.435	C>T	3.84	.429	A
NFKB1	rs10489114	103730426	4	.018	A>G	n/a	n/a	n/a
NFKB1	rs4648068	103737343	4	.363	A>G	1.55	.818	A
NFKB1	rs4648095	103746914	4	.052	T>C	5.92	.052	A
NFKB1	rs4648110	103752867	4	.170	T>A	1.23	.873	A
NFKB1	rs4648135	103755716	4	.061	A>G	6.05	.049	A
NFKB1	rs4648141	103755947	4	.180	G>A	2.61	.625	A
NFKB1	rs1609798	103756488	4	.337	C>T	2.83	.587	A
NFKB1	HapA1					10.11	.039	-
NFKB1	HapA9					1.09	.895	-
NFKB2	rs12772374	104146901	10	.168	A>G	7.51	.112	A
NFKB2	rs7897947	104147701	10	.221	T>G	5.70	.223	A
NFKB2	rs11574849	104149686	10	.070	G>A	3.73	.444	A
NFKB2	rs1056890	104152760	10	.305	C>T	1.24	.872	A
TNFA	rs2857602	31533378	6	.341	T>C	3.41	.492	A
TNFA	rs1800683	31540071	6	.390	G>A	1.25	.871	A
TNFA	rs2239704	31540141	6	.335	G>T	3.37	.497	A
TNFA	rs2229094	31540556	6	.278	T>C	2.81	.591	A
TNFA	rs1041981	31540784	6	.386	C>A	1.07	.900	A
TNFA	rs1799964	31542308	6	.224	T>C	2.66	.616	A
TNFA	rs1800750	31542963	6	.016	G>A	n/a	n/a	n/a
TNFA	rs1800629	31543031	6	.149	G>A	1.30	.861	A
TNFA	rs1800610	31543827	6	.100	C>T	8.12	.087	A
TNFA	rs3093662	31544189	6	.074	A>G	7.38	.117	A
TNFA	HapA1					1.22	.874	-
TNFA	HapA5					3.18	.528	-
TNFA	HapA6					2.15	.708	-

Abbreviations: Chr = chromosome, MAF = minor allele frequency, A = additive model, D = dominant model, R = recessive model, n/a = not assayed because SNP violated Hardy-Weinberg expectation ($p < .001$) or because $MAF < .05$, Hap = haplotype.

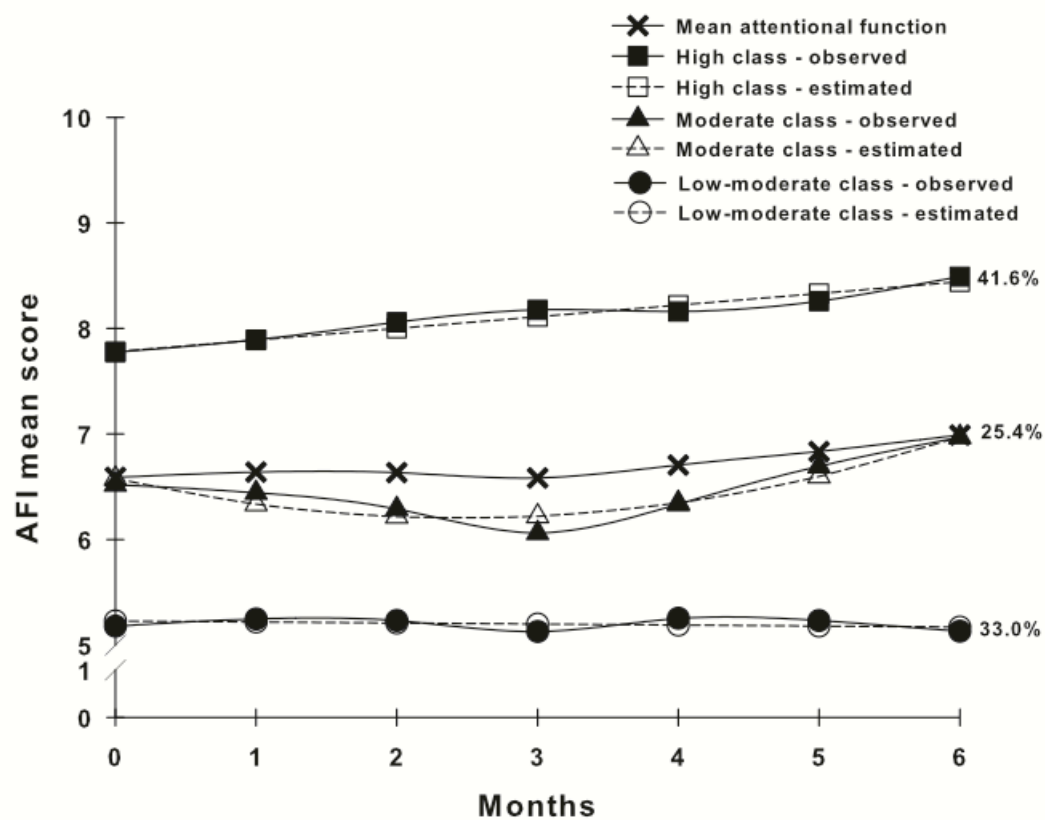
^aOnly IL1R1 rs949963 was retained in multivariable analyses.

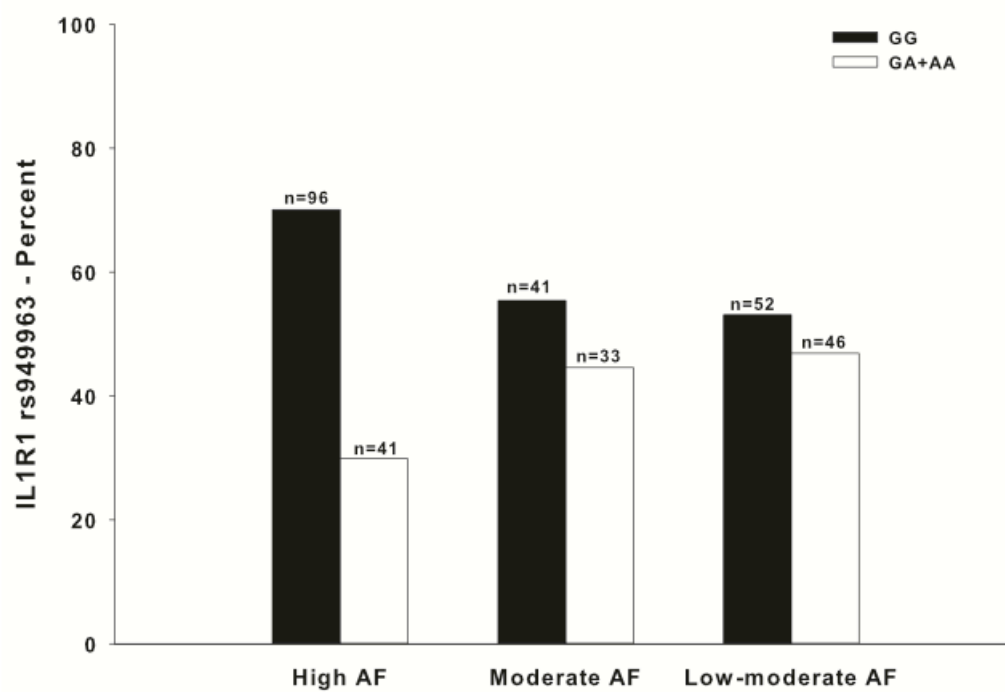
Table 5. Multiple Logistic Regression for IL1R1 rs949963

GMM Class Comparison	Predictor ^a	Odds Ratio	Standard Error	95% CI	z	p-value
High versus moderate and low-moderate attentional function classes	Genotype	1.98	0.52	1.18, 3.30	2.61	.009
	Age	0.87	0.51	0.78, 0.98	-2.35	.019
	SCQ score	1.14	0.06	1.02, 1.26	2.41	.016
	KPS score	0.77	0.11	0.58, 1.02	-1.84	.066
Overall model fit (n=300): $\chi^2 = 31.00$, $p < .001$, $R^2 = 0.075$						

Abbreviations: GMM = growth mixture model, CI = confidence interval, SCQ = Self-administered Comorbidity Questionnaire, KPS = Karnofsky Performance Status.

^aSelf-reported race/ethnicity and the first three principle components identified in the analysis of ancestry informative markers were retained in the model to adjust for potential confounding due to population stratification (data not shown). The genotypic predictor evaluated in the model was IL1R1 rs949963 genotype (GG versus GA+AA). Age is in 5-year increments. KPS score is in 10-point increments.





Chapter 4:
Associations Between Catecholaminergic, GABAergic, and Serotonergic Genes and
Self-Reported Attentional Function in Oncology Patients and
Their Family Caregivers

John D. Merriman

Abstract

Subgroups of individuals may be at greater risk for changes in attentional function during cancer treatment because of variations in neurotransmission genes. In our previous analysis using growth mixture modeling, three subgroups of participants with distinct trajectories of self-reported attentional function (i.e., high, moderate-to-high, and moderate latent classes) were identified among 167 oncology patients and their 85 family caregivers. The purpose of the current analysis was to evaluate for associations between variations in candidate genes involved in catecholaminergic, gamma-aminobutyric acid (GABA)-ergic, and serotonergic mechanisms of neurotransmission and these attentional function latent classes. Multivariable models controlled for age, number of comorbidities, functional status, and population stratification. Two catecholaminergic gene variations (i.e., ADRA1D rs4815675, SLC6A3 rs37022), a GABAergic gene variation (i.e., SLC6A1 rs2697138), and two serotonergic gene variations (i.e., HTR2A rs2296972, rs9534496) remained significant genotypic predictors of latent class membership in the multivariable models. These findings suggest that genetic variations in three distinct but related neurotransmission systems are involved in attentional function.

Keywords: cancer, radiation therapy, serotonin, catecholamines, gamma-aminobutyric acid, neurotransmission, attention, cognition, attentional fatigue

Associations Between Catecholaminergic, GABAergic, and Serotonergic Genes and Self-Reported Attentional Function in Oncology Patients and Their Family Caregivers

The attention system of the brain is comprised of multiple networks, including the alerting and executive networks (Posner, 2012). While these networks use different brain structures and neurotransmitters (Fan, McCandliss, Sommer, Raz, & Posner, 2002), they operate collectively as a single attention organ system (Posner, 2012). Deficits in the alerting network may be experienced as difficulty staying on task (Posner, 2012). Deficits in the executive network may be experienced as difficulty with planning, impulse control, and emotional regulation (Posner, 2012). During treatment for cancer, normal attentional function within these networks is important for patients and family caregivers (FCs) to maintain purposeful activity and social support and to navigate the healthcare system (Cimprich, Visovatti, & Ronis, 2011).

The alerting attention network is composed of the reticular activating system and broad areas of the brain. This network has both tonic and phasic functions. The tonic function of the alerting network enables long attentional cycles and circadian rhythms. The phasic function of the alerting network enables short attentional cycles (e.g., attention to tasks). Together, the tonic and phasic functions of the alerting attention network provide diurnal fluctuations in attentional function. (Petersen & Posner, 2012)

Catecholaminergic neurotransmitters include epinephrine, norepinephrine (NE) and dopamine (DA). Epinephrine and NE regulate sympathetic nervous system function during homeostasis and times of psychological or physical stress (Johnson & Liggett, 2011). NE, produced by the locus coeruleus, is the major transmitter used by adrenergic neurons in the alerting attention network (Fan, Wu, Fossella, & Posner, 2001).

Adrenergic neurons project from the locus coeruleus to cortical structures throughout the brain (Aston-Jones & Cohen, 2005). This widespread innervation suggests that adrenergic activity is important for general alertness (Aston-Jones & Cohen, 2005). Alertness appears to have an inverted U-shaped relationship with attentional function so that too much (i.e., hypervigilance) or too little alertness negatively impacts attentional function (Aston-Jones & Cohen, 2005). Therefore, changes in NE production or function outside an optimal range may adversely effect the functioning of the alerting attention network.

The executive attention network is composed of the anterior cingulate cortex (ACC), the anterior insula, and the dorsolateral prefrontal cortex (Posner, 2012). The dorsal ACC exerts control over cognition and the ventral ACC over emotion (Posner, 2012). DA, which is produced in the ventral tegmental area, is the primary neurotransmitter for the executive attention network (Fernandez-Duque & Posner, 2001). Dopaminergic neurons project from the ventral tegmental area and the substantia nigra into brain regions involved in cognition (i.e., prefrontal cortex) and emotion (i.e., limbic system). In addition, dopaminergic neurons project into reward systems (i.e., the striatum) that may influence cognition and emotion (Eriksen, Jorgensen, & Gether, 2010). DA levels are associated with working memory performance (Frank & Fossella, 2011), which is closely related to attentional function (Cimprich et al., 2011; Gazzaley & Nobre, 2012). Increased dopamine levels improve working memory in patients with low performance but impair working memory in patients with good performance (Frank & Fossella, 2011).

Neurotransmitter systems that may moderate the functioning of the alerting and executive attention systems including gamma-aminobutyric acid (GABA) and serotonin.

GABA is the principal inhibitory neurotransmitter in the central nervous system (CNS; Antonucci et al., 2012). GABAergic neurons are located in multiple cortical and subcortical structures in the CNS (Conti, Minelli, & Melone, 2004; McDonald, Muller, & Mascagni, 2011). The inhibitory action of GABA prevents over-excitation of neurons in these structures (Antonucci et al., 2012). Therefore, GABA may affect the functioning of the alerting attention network by moderating the excitatory state of the network so that it functions at an optimal level.

Serotonin is another neurotransmitter that may impact attentional function. Serotonergic neurons are located in cortical and subcortical structures involved, in part, in impulsivity and the regulation of mood (Fineberg et al., 2010). Recent evidence suggests that serotonin moderates the functioning of the executive attention network, which impacts mood (Posner, 2012). Major psychosocial stressors that can occur during cancer treatment may dysregulate serotonin metabolism, which can have an impact on the executive attention network (De Raedt & Koster, 2010). Specifically, decreased serotonergic function in the dorsolateral prefrontal cortex may weaken executive attentional control of emotion (Carver, Johnson, & Joormann, 2008).

Taken together, catecholaminergic, GABAergic, and serotonergic pathways have a major influence on the alerting and executive attention networks. Cognitive changes such as diminished attentional function may occur when these neurotransmitter systems are dysregulated (Ahles & Saykin, 2007). Therefore, variations in genes that encode for the receptors and transporters used by these neurotransmitters, as well as for metabolism and synthesis of these neurotransmitters, may contribute to inter-individual variability in attentional function.

Previously, we evaluated the relationships between variations in cytokine genes and self-reported attentional function in a sample of oncology patients undergoing radiation therapy (RT) and their FCs (Merriman et al., 2013). Using growth mixture modeling (GMM), we found an association between a single nucleotide polymorphism (SNP) in IL6 (i.e., rs1800795) and attentional function latent class membership. No studies have evaluated for associations between neurotransmitter genes and subgroups of individuals who experience unique trajectories of self-reported attentional function during RT. Therefore, the purpose of this study, in the sample of 167 oncology patients and their 85 FCs, was to evaluate for associations between variations in candidate genes involved in catecholaminergic, GABAergic, and serotonergic mechanisms of neurotransmission and these attentional function latent classes.

Methods

This analysis is part of a larger study that evaluated multiple symptoms in patients who underwent primary or adjuvant RT for breast, prostate, lung, or brain cancer and in their FCs (Dunn et al., 2012; Merriman et al., 2013; Miaskowski et al., 2012). The methods, which are described in detail elsewhere (Merriman et al., 2013), are abbreviated below.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF) and by the institutional review board at the second site. Patients and their FCs were recruited during the patient's simulation visit at RT departments located in a Comprehensive Cancer Center and a community-based oncology program. Patients were eligible to participate if they were ≥ 18 years of age; were scheduled to receive primary or adjuvant RT; were able to read, write, and

understand English; and had a Karnofsky Performance Status (KPS) score of ≥ 60 .

Patients were excluded if they had metastatic disease, more than one cancer diagnosis, or a diagnosed sleep disorder. FCs were eligible to participate if they were ≥ 18 years of age; were able to read, write, and understand English; had a KPS score of ≥ 60 ; were living with the patient; and did not have a diagnosed sleep disorder.

After providing written informed consent, participants completed enrollment questionnaires. FCs who were not present were contacted by phone to determine their interest in participation. Interested FCs completed enrollment at home. Follow-up questionnaires were completed at 4 weeks after the initiation of RT; at the end of RT; and at 4, 8, 12, and 16 weeks after completion of RT (i.e., seven assessments over six months).

Participants completed a demographic questionnaire, the KPS scale (Karnofsky, 1977), and the Attentional Function Index (AFI). The 16-item AFI was designed to measure self-reported attentional function (i.e., ability to voluntarily direct and sustain attention; Cimprich et al., 2011). Higher mean scores on a 0 to 10 numeric rating scale indicate greater capacity to direct attention. Scores are grouped into categories of attentional function (i.e., <5.0 low, 5.0 to 7.5 moderate, >7.5 high; Cimprich, So, Ronis, & Trask, 2005). The AFI has established reliability, as well as construct and convergent validity (Cimprich et al., 2011). In this study, Cronbach's alpha was .95 for both patients and FCs.

Phenotypic Analyses

Phenotypic analyses were conducted as previously reported (Merriman et al., 2013) using SPSS 18 (IBM, Armonk, New York) and Mplus 6.11 (Muthén & Muthén, Los Angeles). In brief, GMM was used to identify latent classes (i.e., subgroups) of

participants with distinct trajectories of attentional function. Descriptive statistics and frequency distributions were generated for phenotypic characteristics and AFI scores for each latent class. Analyses of variance and Chi-square analyses were used to evaluate for differences in sample characteristics among these classes. Differences were considered statistically significant at $p < .050$. Post hoc contrasts used the Bonferroni correction to control overall family alpha. For any one of three possible pairwise contrasts, $p < .017$ was considered statistically significant.

Genotypic Analyses

Of 287 participants who completed the baseline assessment, DNA was recovered using the Puregene DNA Isolation System (Invitrogen, Carlsbad, CA) for 252 (i.e., 167 patients and 85 FCs). Genotyping was performed blinded to clinical status using the GoldenGate genotyping platform and GenomeStudio (Illumina, San Diego).

Gene and SNP selection. Genes involved in catecholaminergic neurotransmission that were evaluated included: adrenoceptor alpha 1D (ADRA1D); ADRA2A; adrenoceptor beta 2, surface (ADRB2); ADRB3; adrenergic, beta, receptor kinase 2 (ADRBK2); noradrenaline transporter (solute carrier family 6, member 2; SLC6A2); and DA transporter (SLC6A3). The gene that encodes for catechol-O-methyltransferase (COMT) is involved in the metabolism of catecholamines (Small et al., 2011). The gene that encodes for tyrosine hydroxylase (TH) is involved in the biosynthesis of dopamine (Bademci, Vance, & Wang, 2012).

The gene that encodes for the GABA transporter is SLC6A1. Genes that encode for serotonergic neurotransmission include: G-protein coupled 5-hydroxytryptamine receptor 1A (HTR1A), HTR1B, and HTR2A; ionotropic HTR3A; and serotonin

transporter SLC6A4. The gene that encodes for tryptophan hydroxylase 2 (TPH2) is involved in the biosynthesis of serotonin (Lesch, Araragi, Waider, van den Hove, & Gutknecht, 2012).

Tagging SNPs and literature-driven SNPs for these candidate genes were selected for analysis. Tagging SNPs were required to have minor allele frequencies (MAFs) $\geq 5\%$ in public databases. SNPs with call rates $< 95\%$ or Hardy-Weinberg expectations $p < .001$ were excluded. Potential functional roles of SNPs associated with attentional function were examined using PUPASuite 2.0 (Conde et al., 2006), a comprehensive search engine that tests a series of functional effects.

Statistical analyses. Allele and genotype frequencies were determined by gene counting. Measures of linkage disequilibrium (LD; i.e., D' and r^2) were computed from participants' genotypes with Haploview 4.2 (Broad Institute, Cambridge, Massachusetts). LD-based haplotype block definition was based on the D' confidence interval (CI) method (Gabriel et al., 2002). Haplotypes were constructed using PHASE 2.1 (Stephens, Smith, & Donnelly, 2001).

Multinomial logistic regression analyses were done with Stata 12 (StataCorp, College Station, Texas). A backwards stepwise approach was used to create a parsimonious phenotypic model. Self-reported race/ethnicity and three principal components derived from one hundred six ancestry informative markers (AIMs) were controlled for in these analyses to minimize confounding due to population stratification (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008). Only predictors with overall Wald Chi-square p-values of $< .050$ were retained in the phenotypic model.

Additive, dominant, and recessive genetic models were assessed for each SNP. Significant genetic variations identified in these bivariate analyses were evaluated further using multinomial logistic regression that controlled for predictors identified in the phenotypic model, potential confounding due to population stratification, and variations in other SNPs/haplotypes within each gene. Using a backwards stepwise approach, significant genetic variations in each gene were simultaneously evaluated until a parsimonious regression model was fit. Only genotypic predictors with overall Wald Chi-square p-values of $<.050$ were retained in the final multivariable model for each gene.

The final models were fit to determine covariate-adjusted odds ratios (ORs) and 95% CIs for the associations of each of the genotypes with attentional function latent class membership in pairwise comparisons (e.g., high versus moderate attentional function). Only genotype terms with Bonferroni-corrected p-values $<.017$ (i.e., $.050/3$) were considered statistically significant for pairwise class comparisons.

As was done in our previous studies (Dunn et al., 2012; Merriman et al., 2013; Miaskowski et al., 2012), based on recommendations in the literature (Hattersley & McCarthy, 2005; Rothman, 1990), the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. In addition, unadjusted associations are reported for all SNPs and haplotypes passing quality control criteria to allow for subsequent comparisons and meta-analyses (Table 1). Because significant genetic variations identified in the bivariate analyses were further evaluated in multivariable models that controlled for phenotypic differences among latent classes, population stratification, and other variations in the same gene, the significant

independent genetic associations reported are unlikely due solely to chance.

Results

As reported previously (Merriman et al., 2013), three distinct latent classes of attentional function trajectories were identified: moderate, moderate-to-high, and high attentional function (Figure 1).

Phenotypic Differences Among Latent Classes

Phenotypic differences among the classes at enrollment are described in detail elsewhere (Merriman et al., 2013). Significant differences among the classes are summarized in Table 2. In the multinomial logistic regression analyses, only age ($p=.019$), number of comorbidities ($p=.047$), and functional status (i.e., KPS score; $p=.013$) predicted latent class membership. Pairwise class comparisons revealed that these relationships were driven by the high versus moderate attentional function classes (Table 3).

Genotypic Differences Among Latent Classes

Seventy-four SNPs among nine candidate genes in the catecholaminergic system, 18 SNPs in one candidate gene in the GABAergic system, and 47 SNPs among six candidate genes in the serotonergic system passed quality control filters. Genotype distributions differed among attentional function classes for six SNPs and two haplotypes in three catecholaminergic genes (i.e., ADRA1D, SLC6A2, SLC6A3), three SNPs in one GABAergic gene (i.e., SLC6A1), and seven SNPs and three haplotypes in one serotonergic gene (i.e., HTR2A; Table 1).

Catecholaminergic system. After controlling for age, number of comorbidities, and functional status, as well as population stratification and other significant variations

in the same gene, only models fit for ADRA1D rs4815675 ($p=.007$) and SLC6A3 rs37022 ($p=.037$) remained significant. See Figure 2 for allelic distributions of these SNPs.

Pairwise comparisons revealed that the relationship with ADRA1D genotype was driven by the moderate-to-high versus moderate attentional function classes (Table 4). Participants who were homozygous for the rare “C” allele had a 69% decrease in the odds of belonging to the moderate attentional function class (OR: 0.32; 95% CI: 0.137, 0.722; $p=.006$). Pairwise comparisons did not meet the Bonferroni-corrected threshold for significance for between-class differences by genotype for the high versus moderate (OR: 0.96; 95% CI: 0.281, 3.239; $p=.941$) and high versus moderate-to-high (OR: 3.03; 95% CI: 1.042, 8.829; $p=.042$) attentional function classes.

Pairwise comparisons revealed that the relationship with SLC6A3 genotype was driven by the high versus moderate-to-high attentional function classes (Table 4). Participants who were homozygous for the rare “A” allele had a 96% decrease in the odds of belonging to the moderate-to-high attentional function class (OR: 0.04; 95% CI: 0.003, 0.489; $p=.012$). Pairwise comparisons did not meet the threshold for significance for between-class differences by genotype for the high versus moderate (OR: 0.23; 95% CI: 0.037, 1.396; $p=.110$) and moderate-to-high versus moderate (OR: 5.67; 95% CI: 0.563, 56.996; $p=.141$) attentional function classes.

GABAergic system. In multivariable analyses, only the model fit for SLC6A1 rs2697138 ($p=.014$) remained significant. See Figure 3 for allelic distributions of this SNP.

Pairwise comparisons revealed that the relationship with SLC6A1 genotype was

driven by the high versus moderate-to-high attentional function classes (Table 4).

Participants who were heterozygous or homozygous for the rare “A” allele (i.e., CC versus CA+AA) had a 67% decrease in the odds of belonging to the moderate-to-high attentional function class (OR: 0.33; 95% CI: 0.141, 0.779; $p=.011$). Pairwise comparisons did not meet the threshold for significance for between-class differences by genotype for the high versus moderate (OR: 0.78; 95% CI: 0.314, 1.950; $p=.599$) and moderate-to-high versus moderate (OR: 2.36; 95% CI: 1.117, 4.979; $p=.024$) attentional function classes.

Serotonergic system. In multivariable analyses, only the model fit for HTR2A rs2296972 ($p=.033$) and rs9534496 ($p=.032$) remained significant. See Figure 4 for allelic distributions of these SNPs.

Pairwise comparisons revealed that for rs2296972 the relationship with HTR2A genotype was driven by the moderate-to-high versus moderate attentional function classes (Table 4). Participants who were homozygous for the rare “T” allele had a four-fold increase in the odds of belonging to the moderate attentional function class (OR: 4.07; 95% CI: 1.395, 11.867; $p=.010$). Pairwise comparisons did not meet the threshold for significance for between-class differences by genotype for the high versus moderate (OR: 1.31; 95% CI: 0.373, 4.631; $p=.671$) and high versus moderate-to-high (OR: 0.32; 95% CI: 0.083, 1.258; $p=.103$) attentional function classes.

Pairwise comparisons revealed that for rs9534496 the relationship with HTR2A genotype was driven by the high versus moderate-to-high attentional function classes (Table 4). Participants who were heterozygous or homozygous for the rare “C” allele (i.e., GG versus GC+CC) had a 67% decrease in the odds of belonging to the moderate-to-high

attentional function class (OR: 0.33; 95% CI: 0.145, 0.764; $p=.009$). Pairwise comparisons did not meet the threshold for significance for between-class differences by genotype for the high versus moderate (OR: 0.39; 95% CI: 0.160, 0.975; $p=.044$) and moderate-to-high versus moderate (OR: 1.19; 95% CI: 0.578, 2.429; $p=.644$) attentional function classes.

Discussion

This study is the first to evaluate for differences among subgroups of oncology patients and their FCs who reported distinct trajectories of attentional function prior to, during, and after RT in genes that encode for catecholaminergic, GABAergic, and serotonergic systems. Characteristics of the three GMM latent classes (i.e., high, moderate-to-high, and moderate attentional function) and phenotypic differences among the classes were previously discussed in detail (Merriman et al., 2013). The current study builds on our evaluation of associations among these attentional function classes with variations in cytokine genes (Merriman et al., 2013) to provide evidence that suggests that variations in a number of neurotransmission genes are associated with differences in self-reported attentional function.

Catecholaminergic System

Among the nine candidate genes evaluated as part of the catecholaminergic system, a SNP in the gene that encodes for adrenoceptor alpha 1D (i.e., ADRA1D rs4815675) and a SNP in the gene that encodes for the dopamine transporter (i.e., SLC6A3 rs37022) were associated with attentional function class membership.

For ADRA1D rs4815675, being homozygous for the rare C allele was associated with decreased odds of belonging to a poorer attentional function class. Alpha adrenergic

receptors are pervasive throughout the peripheral nervous system and CNS (Small, McGraw, & Liggett, 2003). These G protein-coupled receptors are needed for general alertness (Aston-Jones & Cohen, 2005), cognition (Perez & Doze, 2011), and sympathetic responses to stress (Johnson & Liggett, 2011). This SNP is located in an evolutionarily conserved region of the single intron for ADRA1D. No studies have identified an association between this SNP and cognitive function or clinical outcomes. However, this SNP occurs in a CpG island that is methylated in frontal cortex grey matter (Maunakea et al., 2010), suggesting that differential methylation at this SNP may impact cortical structure and function.

For SLC6A3 rs37022, being homozygous for the rare A allele was associated with decreased odds of belonging to a poorer attentional function class. The DA transporter (DAT) is a member of the sodium- and chloride-dependent neurotransmitter transporter family (SLC6; Eriksen et al., 2010). The DAT is involved in reuptake of DA from the synaptic cleft into the presynaptic terminal (Bamne, Talkowski, Chowdari, & Nimgaonkar, 2010). Additional evidence suggests that the DAT is involved in transporting DA back into the cleft (Leviell, 2011).

Attention-Deficit/Hyperactivity Disorder (ADHD) shares phenotypic similarities to the diminished attentional function reported by oncology patients and their FCs. Deficits in working memory performance and executive function exhibited in ADHD (Kebir & Joobar, 2011) may also be observed in patients with reduced attentional function after diagnosis of cancer (Cimprich et al., 2011). In addition, persons with ADHD exhibit deficits in response inhibition, which contributes to impulsive behavior (Kebir & Joobar, 2011). Patients with reduced attentional function similarly exhibit

increased impulsivity. For example, patients with breast cancer who received chemotherapy responded more quickly during attention tasks, which reduced their effectiveness on these tasks, compared to patients who did not receive chemotherapy (de Ruiter et al., 2011). A similar association between more impulsive responses and decreased levels of attentional function (Kesler, Bennett, Mahaffey, & Spiegel, 2009) and executive function (Kesler, Kent, & O'Hara, 2011) was found in other studies. Slower performance, decreased accuracy, and increased brain activation during a working memory task were found in patients after surgery for breast cancer but before chemotherapy (Scherling, Collins, Mackenzie, Bielajew, & Smith, 2011). These findings show deficits in response inhibition in oncology patients with diminished attentional function (Cimprich, 1992; Posner & Boies, 1971).

ADHD is a heterogeneous syndrome with multiple endophenotypes, which suggests that multiple etiologies contribute to observed phenotypes. Similarly, multiple etiologies may contribute to the diminished attentional function reported by oncology patients and their FCs. Numerous studies have examined the relationship of the DAT to ADHD. These studies suggest that the DAT moderates the severity of observed ADHD phenotypes, although it may not have a direct effect on cognitive function as measured by neuropsychological tests. (Kebir & Joobar, 2011).

SLC6A3 rs37022 is located in an evolutionarily conserved region of the gene in intron seven. No associations were found in studies that evaluated relationships between this SNP and the effects of amphetamines (Hamidovic, Dlugos, Palmer, & de Wit, 2010), attitudes about novelty seeking and harm avoidance (Roe et al., 2009), schizophrenia (Pal et al., 2009), bipolar disorder (Shi et al., 2008), and alcohol and tobacco consumption

(Preuss, Zill, Koller, Bondy, & Sokya, 2007). In these studies, the effects being evaluated were thought to be associated with dysregulation of the DAT. Our finding of an association between this SNP and improved attentional function suggests that being homozygous for the A allele may be associated with improved production or function of the DAT.

GABAergic System

A SNP in the gene that encodes for GABA transporter 1 (i.e., SLC6A1 rs2697138) was associated with attentional function class membership. Being heterozygous or homozygous for the rare A allele was associated with decreased odds of belonging to a poorer attentional function class. GABA transporters (GATs), particularly the most common one (i.e., GAT-1), remove GABA from the synaptic cleft into the presynaptic terminal (Conti et al., 2004). Therefore, increased production or function of GAT-1 reduces the amount of GABA in the synaptic cleft. This reduction in GABA contributes to increased excitability of the CNS (Antonucci et al., 2012), which manifests behaviorally as increased anxiety and hypervigilance to environmental stimuli (i.e., severely increased alerting; Thoeringer et al., 2009). This SNP is located in intron 15. No studies have identified an association between this SNP and cognitive function or clinical outcomes.

Serotonergic System

Among the six candidate genes evaluated as part of the serotonergic system, two SNPs in HTR2A (rs2296972 and rs9534496) were associated with attentional function class membership. Being homozygous for the rare T allele for rs2296972 was associated with increased odds of belonging to a poorer attentional function class. In contrast, being

heterozygous or homozygous for the rare C allele for rs9534496 was associated with reduced odds of belonging to a poorer attentional function class. In the HTR2A multivariable model (Table 4), both SNPs maintained a significant association with attentional function latent class membership. Furthermore, the LD between the two SNPs was minimal ($D'=0.042$, $r^2=0.001$), suggesting that these SNPs are independent predictors.

The G protein-coupled serotonin receptor 2A is involved with mood regulation and cognition. The efficiency of serotonergic neurons is dependent on the density of serotonin receptors. Dysregulated serotonin 2A receptor density is associated with poor outcomes such as suicidality and mood disorders. (Brezo et al., 2010)

Both SNPs are located in the second intron of the gene. In one study, being homozygous for the “G” allele for HTR2A rs2296972 was associated with less childhood social withdrawal compared to children who carried the T allele (Broekman et al., 2011). In another study, each additional dose of the T allele was associated with more severe panic disorder (Unschuld et al., 2007). These findings are consistent with our finding that the T allele was associated with increased odds of poorer attentional function. Moreover, these relationships are consistent with the mechanistic link of the executive attention network to mood through prefrontal-cortex and ACC control of the amygdala (Posner, 2012).

HTR2A rs9534496 has no known function. In one study of healthy, university-age participants, carriers of the C allele performed worse at delayed recall tasks (Sigmund, Vogler, Huynh, de Quervain, & Papassotiropoulos, 2008). This finding of decreased working memory performance contrasts with our finding that the C allele was associated

with reduced odds of poorer attentional function. These conflicting findings may be due to the different compositions of the samples or to random sample variation. This SNP occurs in a CpG island that is methylated in frontal cortex grey matter (Maunakea et al., 2010), suggesting that differential methylation at this SNP may impact cortical structure and function. Therefore, it is possible that differential methylation in the two samples, which was not measured, may contribute to these phenotypic differences.

Conclusions

The present study provides preliminary evidence of associations between SNPs in catecholaminergic genes (i.e., ADRA1D rs4815675, SLC6A3 rs37022), a GABAergic gene (i.e., SLC6A1 rs2697138), and a serotonergic gene (i.e., HTR2A rs2296972, rs9534496) and self-reported attentional function. The fact that these relationships were found in a heterogeneous sample suggests that these SNPs influence attentional function regardless of etiology of reduced attentional function. Specifically, these associations suggest that variations in genes that encode for catecholaminergic and serotonergic receptors, as well as catecholaminergic and GABAergic transporters, influence attentional function trajectories for both oncology patients and FCs.

All SNPs identified in the multivariable analyses are intronic, and both catecholaminergic SNPs are located in evolutionarily conserved gene regions. While the function of these polymorphisms is unknown, they may be surrogates for unmeasured functional polymorphisms that are in LD. Therefore, it is not entirely clear mechanistically how these SNPs impact attentional function.

In addition to the limitations previously acknowledged regarding sample size and composition (Merriman et al., 2013), this study did not evaluate for variations in all

candidate genes for attentional function. In particular genes that encode for the cholinergic system, which is thought to be involved in the orienting attention network, were not evaluated. The orienting attention network enables disengagement from attended stimuli to focus on other stimuli. Individuals with diminished attentional function are less able to shift focus from negative to positive internal stimuli. These individuals may ruminate on stimuli with negative emotional connotations, which predisposes them to prolongation of negative affect and risk for depressive symptoms (De Raedt & Koster, 2010; Nolen-Hoeksema, 2000; Nolen-Hoeksema, Morrow, & Fredrickson, 1993).

Before clinical implications are evaluated, future studies in independent samples are needed to determine whether and how the SNPs identified in this study are associated with attentional function. Studies of genes that encode for other physiological pathways that impact neurotransmission and neuronal health (e.g., nitric oxide synthase, brain-derived neurotrophic factor) may further enhance understanding of the genetic factors associated with attentional function trajectories.

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Figure Legends

Figure 1. Observed and estimated (i.e., model predicted) Attentional Function Index (AFI) score trajectories for participants in each latent class, as well as mean AFI scores for the total sample. This figure was previously published in Merriman, J. D., Aouizerat, B. E., Langford, D. J., Cooper, B. A., Baggott, C. R., Cataldo, J. K., . . . Miaskowski, C. (2013). Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. *Biological Research for Nursing*. doi: 10.1177/1099800413479441.

Figure 2a. Catecholaminergic system: Differences among the attentional function (AF) latent classes in the percentages of patients who were homozygous or heterozygous for the common “T” allele versus homozygous for the rare “C” allele for rs4815675 in adrenergic, alpha-1D receptor (ADRA1D). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 2b. Catecholaminergic system: Differences among the AF latent classes in the percentages of patients who were homozygous or heterozygous for the common “T” allele versus homozygous for the rare “A” allele for rs37022 in solute carrier family 6, member 3 (SLC6A3; transporter for the neurotransmitter dopamine). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 3. GABAergic system: Differences among the AF latent classes in the percentages of patients who were homozygous for the common “C” allele versus heterozygous or homozygous for the rare “A” allele for rs2697138 in solute carrier family 6, member 1 (SLC6A1; transporter for the neurotransmitter gamma-aminobutyric acid). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 4a. Serotonergic system: Differences among the AF latent classes in the percentages of patients who were homozygous or heterozygous for the common “G” allele versus homozygous for the rare “T” allele for rs2296972 in the G protein-coupled 5-hydroxytryptamine receptor 2A (HTR2A). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 4b. Serotonergic system: Differences among the AF latent classes in the percentages of patients who were homozygous for the common “G” allele versus heterozygous or homozygous for the rare “C” allele for rs9534496 in the G protein-coupled 5-hydroxytryptamine receptor 2A (HTR2A). Values are plotted as unadjusted proportions with corresponding p-value.

Table 1. Differences in Single Nucleotide Polymorphisms in Neurotransmitter Candidate Genes and Haplotypes Among the Three Attentional Function Classes

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
CATECHOLAMINERGIC NEUROTRANSMISSION								
Receptors								
ADRA1D	rs3787441	4153060	20	.254	T>C	3.494	.479	A
ADRA1D	rs6084664	4155930	20	.149	T>C	1.351	.853	A
ADRA1D	rs2326478	4156247	20	.337	C>T	1.746	.782	A
ADRA1D	rs835880	4156895	20	.219	A>G	4.696	.320	A
ADRA1D	rs8183794	4158448	20	.207	C>T	2.206	.698	A
ADRA1D	rs6116268	4159440	20	.492	C>T	5.500	.240	A
ADRA1D	rs946188	4163316	20	.232	A>G	2.347	.672	A
ADRA1D	rs1556832	4163557	20	.430	C>T	7.054	.133	A
ADRA1D	rs8118409	4164663	20	.207	G>A	9.204	.010	D
ADRA1D	rs4815670	4164864	20	.492	A>G	11.800	.003	D
ADRA1D	rs6076639	4167258	20	.188	C>T	7.137	.129	A
ADRA1D	rs4815675	4171454	20	.461	T>C	10.277	.006	R
ADRA1D	HapA1					1.746	.782	
ADRA1D	HapA3					4.696	.320	
ADRA1D	HapB1					5.500	.240	
ADRA1D	HapB2					2.160	.706	
ADRA1D	HapB3					2.435	.656	
ADRA1D	HapC1					6.582	.160	
ADRA1D	HapC2					13.022	.011	
ADRA1D	HapC3					7.777	.100	
ADRA1D	HapD1					2.945	.567	
ADRA1D	HapD2					10.335	.035	
ADRA2A	rs521674	112825580	10	.378	A>T	3.354	.500	A
ADRA2A	rs3750625	112829591	10	.076	C>A	5.354	.253	A
ADRB2	rs2400707	148185245	5	.413	G>A	6.607	.158	A
ADRB2	rs11168070	148186120	5	.365	C>G	5.625	.229	A
ADRB2	rs1042718	148187110	5	.242	C>A	4.292	.368	A
ADRB2	rs1042719	148187640	5	.318	G>C	3.454	.485	A
ADRB2	HapA1					2.399	.663	
ADRB2	HapA2					4.292	.368	
ADRB2	HapA4					5.727	.220	
ADRB3	rs4994	37942955	8	.076	T>C	1.270	.866	A
ADRBK2	rs1008673	24324013	22	.219	A>G	1.659	.798	A
ADRBK2	rs3817819	24405188	22	.409	C>T	2.307	.680	A
ADRBK2	rs5761159	24432308	22	.395	G>T	n/a	n/a	n/a
ADRBK2	rs9608416	24441018	22	.436	A>G	1.404	.844	A
Transporters								
SLC6A2	rs2242446	54247926	16	.293	T>C	0.924	.921	A
SLC6A2	rs17841327	54251754	16	.368	C>A	3.760	.439	A
SLC6A2	rs3785143	54252607	16	.091	C>T	4.540	.338	A
SLC6A2	rs192303	54257725	16	.285	G>C	4.460	.347	A
SLC6A2	rs6499771	54258172	16	.153	A>G	1.302	.861	A
SLC6A2	rs36027	54260281	16	.399	A>G	1.956	.744	A
SLC6A2	rs36024	54263892	16	.440	C>T	0.592	.964	A
SLC6A2	rs36021	54269451	16	.430	T>A	3.129	.536	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
SLC6A2	rs40147	54274341	16	.293	C>T	2.720	.606	A
SLC6A2	rs1814270	54274578	16	.355	T>C	2.129	.712	A
SLC6A2	rs36017	54276319	16	.415	C>G	6.696	.153	A
SLC6A2	rs3785155	54279891	16	.126	G>A	5.120	.275	A
SLC6A2	rs47958	54283963	16	.421	C>A	5.841	.211	A
SLC6A2	rs5568	54287625	16	.285	A>C	6.622	.036	D
SLC6A2	rs1566652	54289076	16	.310	G>T	5.139	.273	A
SLC6A2	rs5569	54289336	16	.316	C>T	3.574	.467	A
SLC6A2	rs998424	54289447	16	.314	C>T	4.663	.324	A
SLC6A2	HapA2					3.857	.426	
SLC6A2	HapB1					2.410	.661	
SLC6A2	HapB2					0.467	.977	
SLC6A2	HapC3					4.593	.332	
SLC6A2	HapC8					2.189	.701	
SLC6A2	HapD1					3.626	.459	
SLC6A2	HapD4					4.618	.329	
SLC6A3	rs3863145	1445711	5	.233	C>T	0.755	.944	A
SLC6A3	rs40184	1448077	5	.436	G>A	0.694	.952	A
SLC6A3	rs11564773	1449813	5	.107	A>G	2.858	.582	A
SLC6A3	rs6876225	1459036	5	.081	C>A	4.014	.404	A
SLC6A3	rs6347	1464412	5	.295	A>G	2.815	.589	A
SLC6A3	rs37022	1468629	5	.219	T>A	8.079	.018	R
SLC6A3	rs2975292	1472932	5	.469	C>G	4.773	.311	A
SLC6A3	rs11564758	1473588	5	.293	G>C	5.618	.230	A
SLC6A3	rs464049	1476905	5	.465	T>C	3.909	.418	A
SLC6A3	rs10053602	1481135	5	.202	T>C	3.712	.446	A
SLC6A3	rs463379	1484164	5	.256	C>G	2.626	.622	A
SLC6A3	rs403636	1491354	5	.225	G>T	2.084	.720	A
SLC6A3	rs6350	1496199	5	.064	C>T	1.192	.879	A
SLC6A3	rs2937639	1496728	5	.457	G>A	6.158	.046	R
SLC6A3	HapA1					2.998	.558	
SLC6A3	HapB1					5.822	.213	
SLC6A3	HapB5					2.327	.676	
SLC6A3	HapB7					2.696	.610	
Synthesis								
TH	rs2070762	2142911	11	.459	T>C	3.010	.556	A
TH	rs6357	2144814	11	.258	G>A	2.447	.654	A
TH	rs6356	2147527	11	.369	G>A	1.982	.739	A
TH	HapA1					2.620	.623	
TH	HapA2					1.903	.754	
TH	HapA3					2.447	.654	
Metabolism								
COMT	rs5748489	18307146	22	.430	C>A	2.499	.645	A
COMT	rs2020917	18308884	22	.262	C>T	5.479	.242	A
COMT	rs737866	18310109	22	.273	A>G	4.258	.372	A
COMT	rs1544325	18311668	22	.428	G>A	2.738	.603	A
COMT	rs5993882	18317533	22	.221	T>G	1.279	.865	A
COMT	rs5993883	18317638	22	.483	T>G	4.327	.364	A
COMT	rs740603	18325177	22	.488	A>G	2.794	.593	A
COMT	rs4646312	18328337	22	.360	T>C	3.444	.486	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
COMT	rs165656	18328863	22	.486	C>G	5.476	.242	A
COMT	rs6269	18329952	22	.395	A>G	1.233	.873	A
COMT	rs4633	18330235	22	.498	C>T	4.823	.306	A
COMT	rs6267	18330263	22	.000	G>T	100% homozygous for G allele		
COMT	rs740601	18330763	22	.409	A>C	1.274	.866	A
COMT	rs5031015	18331103	22	.000	G>A	100% homozygous for G allele		
COMT	rs4818	18331207	22	.376	C>G	1.676	.795	A
COMT	rs4680	18331271	22	.496	G>A	5.441	.245	A
COMT	rs165774	18332561	22	.302	G>A	4.069	.397	A
COMT	rs174699	18334458	22	.068	T>C	4.419	.352	A
COMT	rs9332377	18335692	22	.165	T>C	3.458	.484	A
COMT	rs165599	18336781	22	.365	A>G	1.462	.833	A
COMT	HapA1					5.752	.218	
COMT	HapA7					1.247	.870	
COMT	HapA11					3.378	.497	
COMT	HapB10					4.125	.389	
COMT	HapB13					2.162	.706	
COMT	HapC2					1.462	.833	
COMT	PAIN LPS					2.354	.671	
COMT	PAIN APS					4.846	.303	
COMT	PAIN HPS					1.134	.889	
COMT	PAIN DIPLO					7.315	.695	
COMT	PAIN RECODE A					1.162	.559	
GABAERGIC NEUROTRANSMISSION								
GABA Transporter								
SLC6A1	rs2697149	11011480	3	.236	T>G	2.623	.623	A
SLC6A1	rs2601126	11011624	3	.413	C>T	2.402	.662	A
SLC6A1	rs1710885	11013807	3	.180	T>C	2.011	.734	A
SLC6A1	rs1710886	11014655	3	.322	G>C	5.997	.050	R
SLC6A1	rs1710887	11014960	3	.341	G>T	6.179	.186	A
SLC6A1	rs9990174	11015439	3	.320	G>T	1.951	.745	A
SLC6A1	rs1568072	11016606	3	.198	C>T	0.915	.922	A
SLC6A1	rs1728811	11016870	3	.448	C>T	2.185	.702	A
SLC6A1	rs11718132	11020020	3	.153	G>T	3.280	.512	A
SLC6A1	rs2697144	11026099	3	.242	A>G	3.209	.523	A
SLC6A1	rs2928079	11030114	3	.428	A>T	3.457	.485	A
SLC6A1	rs1170695	11030338	3	.335	T>C	1.534	.821	A
SLC6A1	rs2933308	11030624	3	.357	G>A	3.964	.411	A
SLC6A1	rs10510403	11041670	3	.149	A>G	1.178	.882	A
SLC6A1	rs2675163	11050014	3	.211	T>C	1.549	.818	A
SLC6A1	rs10514669	11050912	3	.229	C>T	7.607	.022	D
SLC6A1	rs2697138	11051907	3	.154	C>A	8.635	.013	D
SLC6A1	rs1062246	11055169	3	.428	A>G	10.936	.027	A
SLC6A1	HapA1					2.402	.662	
SLC6A1	HapA2					1.745	.783	
SLC6A1	HapA3					2.623	.623	
SLC6A1	HapB1					2.185	.702	
SLC6A1	HapB2					4.254	.373	
SLC6A1	HapC1					0.855	.931	

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
SLC6A1	HapC2					3.964	.411	
SLC6A1	HapC3					1.534	.821	
SLC6A1	HapD1					2.690	.611	
SLC6A1	HapD2					7.960	.093	
SEROTONERGIC NEUROTRANSMISSION								
Receptors								
HTR1A	rs6449693	63291774	5	.444	A>G	3.763	.439	A
HTR1B	rs6296	78228979	6	.244	G>C	2.137	.711	A
HTR2A	rs6314	46307035	13	.083	C>T	2.159	.340	A
HTR2A	rs7322347	46308104	13	.440	T>A	3.231	.520	A
HTR2A	rs1923882	46309662	13	.236	C>T	2.168	.705	A
HTR2A	rs7997012	46309986	13	.363	G>A	2.320	.677	A
HTR2A	rs3742278	46317578	13	.190	A>G	0.574	.966	A
HTR2A	rs1923884	46319837	13	.165	C>T	0.975	.914	A
HTR2A	rs1923886	46321292	13	.405	T>C	5.183	.269	A
HTR2A	rs7330636	46321593	13	.353	C>T	4.128	.389	A
HTR2A	rs9567739	46322945	13	.368	G>C	4.431	.351	A
HTR2A	rs2296972	46326472	13	.306	G>T	8.583	.014	R
HTR2A	rs9534495	46327229	13	.118	A>G	0.741	.691	A
HTR2A	rs9534496	46329109	13	.182	G>C	9.304	.010	D
HTR2A	rs4942578	46330611	13	.242	G>T	2.148	.709	A
HTR2A	rs2770292	46333107	13	.134	C>G	3.098	.542	A
HTR2A	rs1928042	46335217	13	.196	A>C	1.511	.825	A
HTR2A	rs2770293	46336975	13	.380	C>T	4.373	.358	A
HTR2A	rs1328674	46339708	13	.048	G>A	n/a	n/a	n/a
HTR2A	rs2770298	46344848	13	.291	T>C	5.374	.251	A
HTR2A	rs1928040	46345237	13	.477	T>C	5.324	.256	A
HTR2A	rs972979	46347165	13	.403	G>A	7.976	.019	R
HTR2A	rs731779	46350039	13	.210	T>G	5.637	.228	A
HTR2A	rs2770304	46353366	13	.364	A>G	8.080	.089	A
HTR2A	rs927544	46354052	13	.298	T>C	9.689	.046	A
HTR2A	rs594242	46356053	13	.145	C>G	3.677	.451	A
HTR2A	rs4941573	46362858	13	.430	A>G	7.371	.118	A
HTR2A	rs1328684	46364231	13	.264	T>C	1.451	.835	A
HTR2A	rs6304	46364550	13	.010	A>G	n/a	n/a	n/a
HTR2A	rs2296973	46364782	13	.304	G>T	9.324	.009	R
HTR2A	rs2070037	46365071	13	.252	T>C	6.424	.040	D
HTR2A	rs9534511	46366581	13	.448	C>T	5.172	.270	A
HTR2A	rs6313	46367941	13	.448	C>T	6.432	.040	D
HTR2A	HapA1					3.231	.520	
HTR2A	HapA2					2.589	.629	
HTR2A	HapB1					5.183	.269	
HTR2A	HapB2					3.442	.487	
HTR2A	HapC1					4.113	.391	
HTR2A	HapC5					10.245	.036	
HTR2A	HapD3					1.511	.825	
HTR2A	HapE2					5.997	.199	
HTR2A	HapE3					4.554	.336	
HTR2A	HapF1					10.204	.037	
HTR2A	HapF4					4.999	.287	

Gene	SNP	Position	Chr	MAF	Alleles	Chi-Square	p-value	Model
HTR2A	HapG4					6.906	.141	
HTR2A	HapG5					9.689	.046	
HTR2A	HapH4					7.475	.113	
HTR2A	HapH7					7.377	.117	
HTR3A	rs1985242	113353483	11	.357	T>A	2.047	.727	A
HTR3A	rs11214796	113359889	11	.275	T>C	2.904	.574	A
HTR3A	rs10160548	113361891	11	.393	T>G	1.962	.743	A
HTR3A	HapA1					2.016	.733	
HTR3A	HapA4					2.673	.614	
Transporter								
SLC6A4	rs3813034	25548930	17	.473	A>C	1.837	.766	A
SLC6A4	rs1042173	25549137	17	.475	T>G	2.313	.678	A
SLC6A4	rs4325622	25550601	17	.459	T>C	2.105	.716	A
SLC6A4	rs3794808	25555919	17	.473	G>A	0.812	.937	A
SLC6A4	rs140701	25562658	17	.465	G>A	0.907	.924	A
SLC6A4	rs140700	25567515	17	.070	G>A	0.828	.661	A
SLC6A4	rs2020942	25571040	17	.322	G>A	0.497	.974	A
SLC6A4	rs8076005	25571336	17	.236	A>G	2.158	.707	A
SLC6A4	rs6354	25574024	17	.184	A>C	0.211	.995	A
SLC6A4	rs2066713	25575791	17	.326	C>T	0.717	.949	A
SLC6A4	HapA1					2.313	.678	
SLC6A4	HapA4					2.105	.716	
SLC6A4	HapB1					0.497	.974	
SLC6A4	HapB2					0.751	.945	
SLC6A4	5HTTLPR					3.981	.409	A
SLC6A4	5HTTLPR + rs25531					2.754	.600	A
Synthesis								
TPH2	rs11179000	70624895	12	.254	A>T	4.370	.358	A
TPH2	rs7955501	70636293	12	.407	A>T	2.001	.735	A
TPH2	rs1487275	70696559	12	.258	T>G	4.372	.358	A

Abbreviations: A = additive model, ADRA1D = adrenoceptor alpha 1D, ADRA2A = adrenoceptor alpha 2A, ADRB2 = surface adrenoceptor beta 2, ADRB3 = adrenoceptor beta 3, ADRBK2 = adrenergic, beta, receptor kinase 2, Chr = chromosome, COMT = catechol-O-methyltransferase, D = dominant model, GABA = gamma-aminobutyric acid, Hap = haplotype, HTR1A = G protein-coupled 5-hydroxytryptamine receptor 1A, HTR1B = G protein-coupled 5-hydroxytryptamine receptor 1B, HTR2A = G protein-coupled 5-hydroxytryptamine receptor 2A, HTR3A = ionotropic 5-hydroxytryptamine receptor 3A, MAF = minor allele frequency, n/a = not assayed because SNP violated Hardy-Weinberg expectations ($p < .001$) or because MAF was $< .05$, SLC6A1 = solute carrier family 6, member 1 (transporter for GABA), SLC6A2 = solute carrier family 6, member 2 (transporter for noradrenaline), SLC6A3 = solute carrier family 6, member 3 (transporter for dopamine), SLC6A4 = solute carrier family 6, member 4 (transporter for serotonin), SNP = single nucleotide polymorphism, TH = tyrosine hydroxylase, TPH2 = tryptophan hydroxylase 2.

Table 2. Significant Differences in Demographic and Clinical Characteristics Among the Attentional Function Classes at Enrollment*

Characteristic	High Attentional Function (0) n = 39 (15.5%)	Moderate-to- High Attentional Function (1) n = 121 (48.0%)	Moderate Attentional Function (2) n = 92 (36.5%)	Statistics and Post Hoc Comparisons
	Mean (SD)			
Age (years)	65.3 (8.7)	62.6 (10.3)	58.4 (12.7)	F(2,113) = 6.5, p=.002; 2<0,1
Number of comorbidities	3.8 (2.4)	4.5 (2.7)	5.1 (2.7)	F(2,249) = 3.6, p=.030; 2>0
KPS score	96.2 (8.8)	93.6 (9.5)	87.9 (13.7)	F(2,108) = 9.0, p<.001; 2<0,1
	n (%)			
Married or partnered (yes)	33 (84.6)	87 (72.5)	54 (59.3)	$\chi^2 = 9.160$, p=.010; 2<0
Patient/FC (patient)	19 (48.7)	78 (64.5)	70 (76.1)	$\chi^2 = 9.518$, p=.009; 2>0

Abbreviations: SD = standard deviation; KPS = Karnofsky Performance Status; FC = family caregiver.

*modified from Merriman, J. D., Aouizerat, B. E., Langford, D. J., Cooper, B. A., Baggott, C. R., Cataldo, J. K., . . . Miaskowski, C. (2013). Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. *Biological Research for Nursing*. doi: 10.1177/1099800413479441

Table 3. Multinomial Logistic Regression Model for Phenotypic Predictors of Attentional Function Class Membership

GMM class comparison	Predictor ^a	Odds Ratio	Standard Error	95% CI	z	p-value
High versus moderate-to-high AF	Age	0.88	0.094	0.716, 1.087	-1.17	.240
	Number of comorbidities	1.13	0.091	0.959, 1.319	1.45	.148
	KPS score	0.77	0.194	0.474, 1.265	-1.02	.307
High versus moderate AF	Age	0.75	0.085	0.600, 0.935	-2.56	.011
	Number of comorbidities	1.23	0.107	1.041, 1.464	2.43	.015
	KPS score	0.55	0.138	0.339, 0.903	-2.37	.018
Moderate-to-high versus moderate AF	Age	0.85	0.065	0.731, 0.985	-2.16	.031
	Number of comorbidities	1.10	0.067	0.973, 1.238	1.51	.131
	KPS score	0.71	0.101	0.541, 0.944	-2.37	.018
Overall model fit (n=235): $\chi^2 = 54.54$, $p < .001$, pseudo $R^2 = 0.114$						

Abbreviations: GMM = growth mixture model, 95% CI = 95% confidence interval, AF = attentional function, KPS = Karnofsky Performance Status.

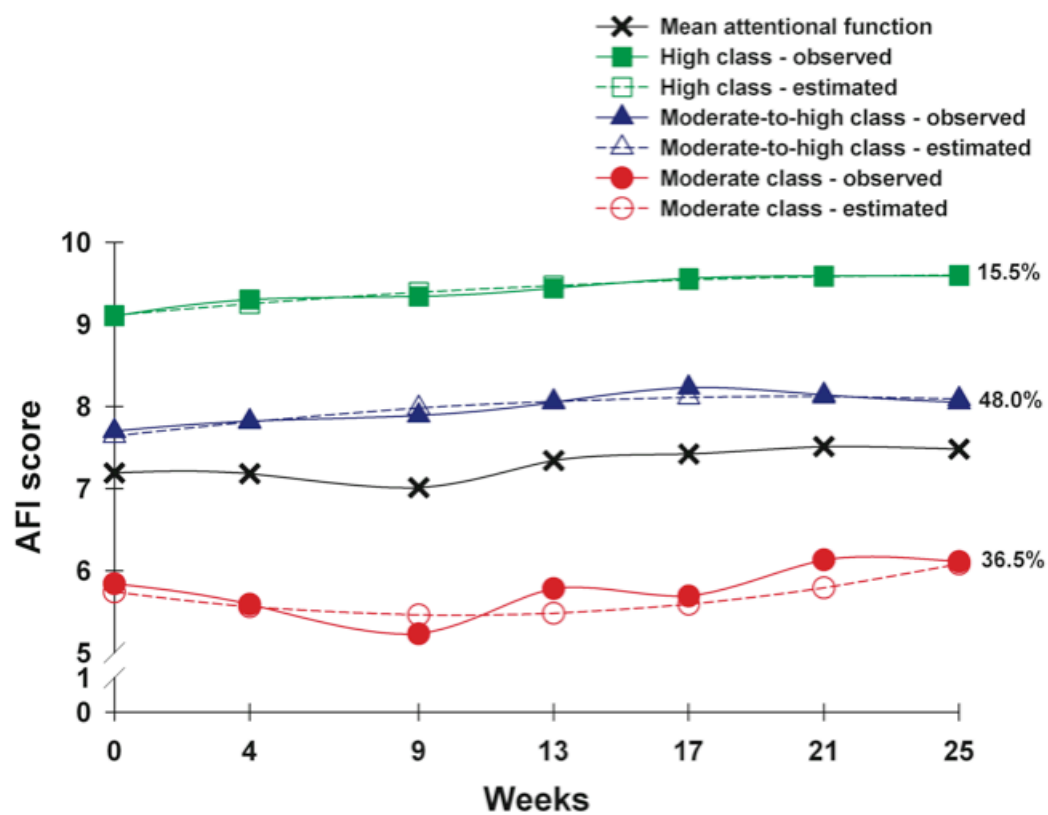
^aSelf-reported race/ethnicity and the first three principle components identified in the analysis of ancestry informative markers were retained in the model to adjust for potential confounding due to population stratification (data not shown). Age is in five-year increments. KPS score is in ten-point increments.

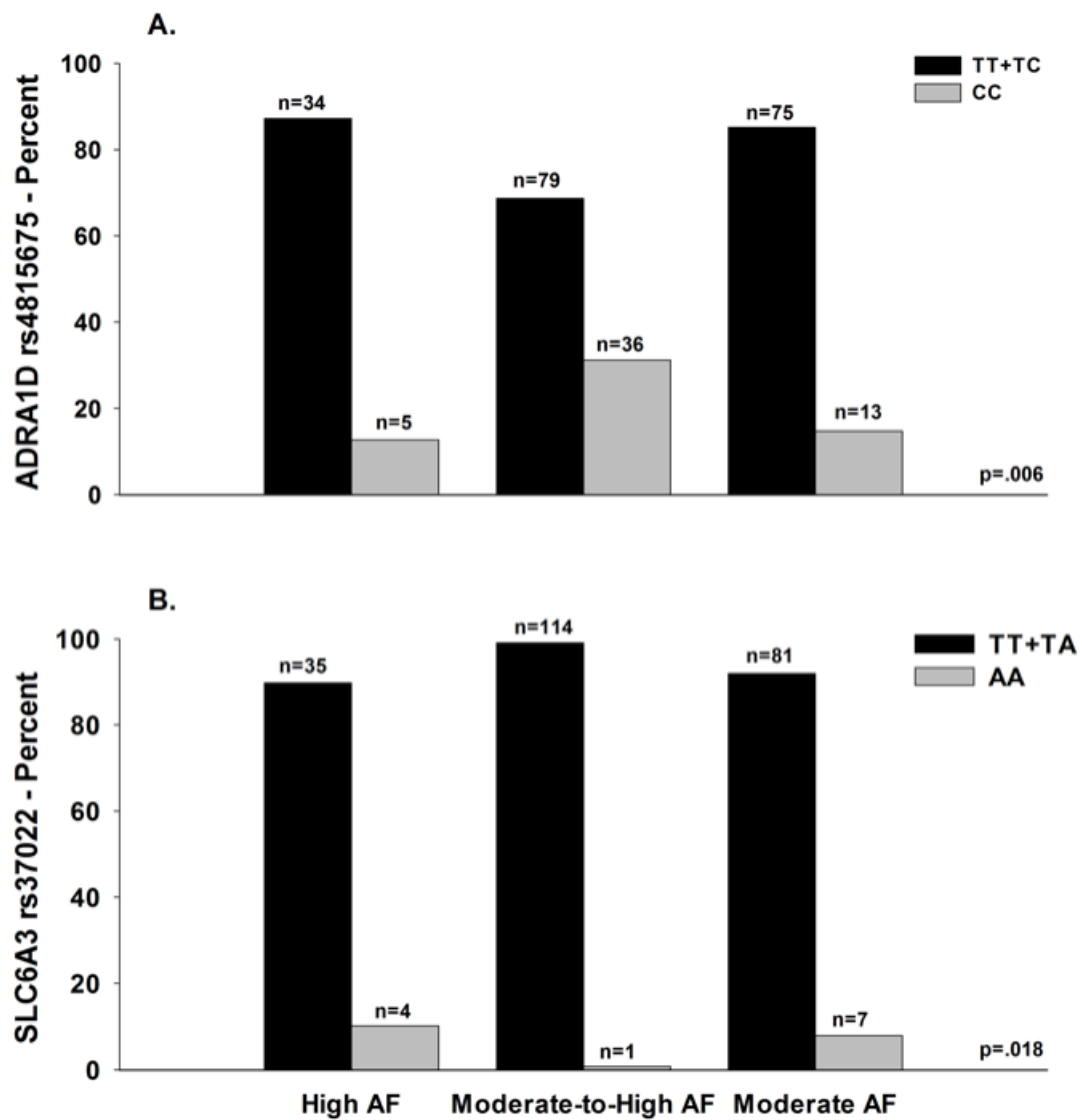
Table 4. Multinomial Logistic Regression Models for Genotypic Predictors of Attentional Function Class Membership by Candidate Gene

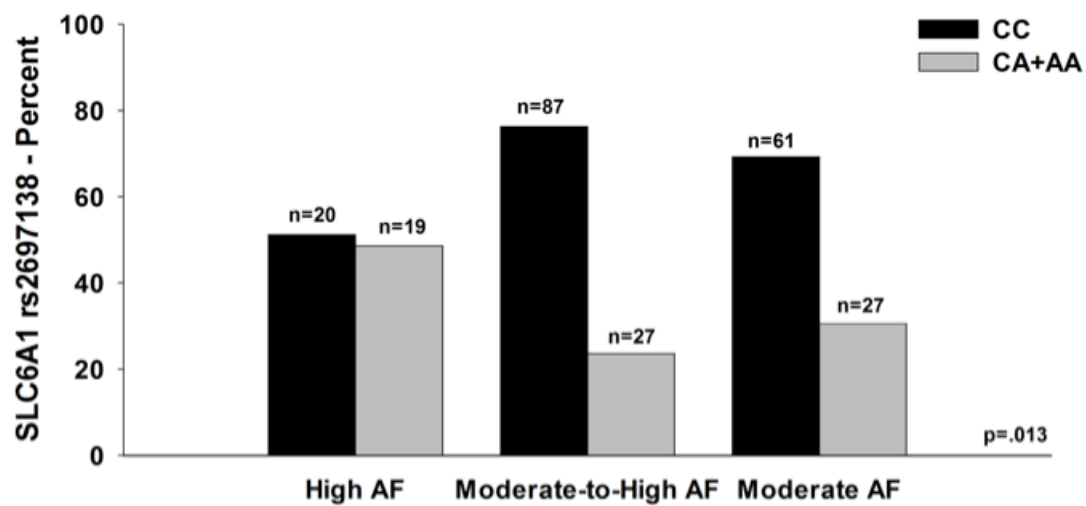
GMM class comparison	Predictor ^a	Odds Ratio	Standard Error	95% CI	z	p-value
Catecholaminergic System						
Moderate-to-high versus moderate AF	ADRA1D rs4815675	0.32	0.133	0.137, 0.722	-2.73	.006
	Age	0.83	0.065	0.708, 0.964	-2.42	.016
	Number of comorbidities	1.12	0.070	0.985, 1.262	1.72	.085
	KPS score	0.73	0.104	0.553, 0.967	-2.19	.028
Overall model fit (n=235): $\chi^2 = 65.01$, $p < .001$, pseudo $R^2 = 0.136$						
High versus moderate-to-high AF	SLC6A3 rs37022	0.04	0.051	0.003, 0.489	-2.52	.012
	Age	0.88	0.096	0.706, 1.086	-1.21	.225
	Number of comorbidities	1.16	0.098	0.980, 1.366	1.72	.086
	KPS score	0.81	0.204	0.497, 1.329	-0.83	.409
Overall model fit (n=235): $\chi^2 = 63.07$, $p < .001$, pseudo $R^2 = 0.132$						
GABAergic System						
High versus moderate-to-high AF	SLC6A1 rs2697138	0.33	0.145	0.141, 0.779	-2.53	.011
	Age	0.90	0.098	0.723, 1.109	-1.01	.311
	Number of comorbidities	1.10	0.091	0.930, 1.289	1.09	.277
	KPS score	0.82	0.207	0.497, 1.344	-0.80	.426
Overall model fit (n=234): $\chi^2 = 62.65$, $p < .001$, pseudo $R^2 = 0.131$						
Serotonergic System						
Moderate-to-high versus moderate AF	HTR2A rs2296972	4.07	2.222	1.395, 11.867	2.57	.010
	Age	0.84	0.065	0.717, 0.972	-2.32	.020
	Number of comorbidities	1.11	0.070	0.979, 1.253	1.63	.104
	KPS score	0.73	0.105	0.549, 0.966	-2.20	.028
High versus moderate-to-high AF	HTR2A rs9534496	0.33	0.141	0.145, 0.764	-2.60	.009
	Age	0.91	0.101	0.731, 1.129	-0.87	.386
	Number of comorbidities	1.11	0.094	0.944, 1.315	1.28	.200
	KPS score	0.73	0.187	0.443, 1.206	-1.23	.220
Overall model fit (n=235): $\chi^2 = 69.47$, $p < .001$, pseudo $R^2 = 0.145$						

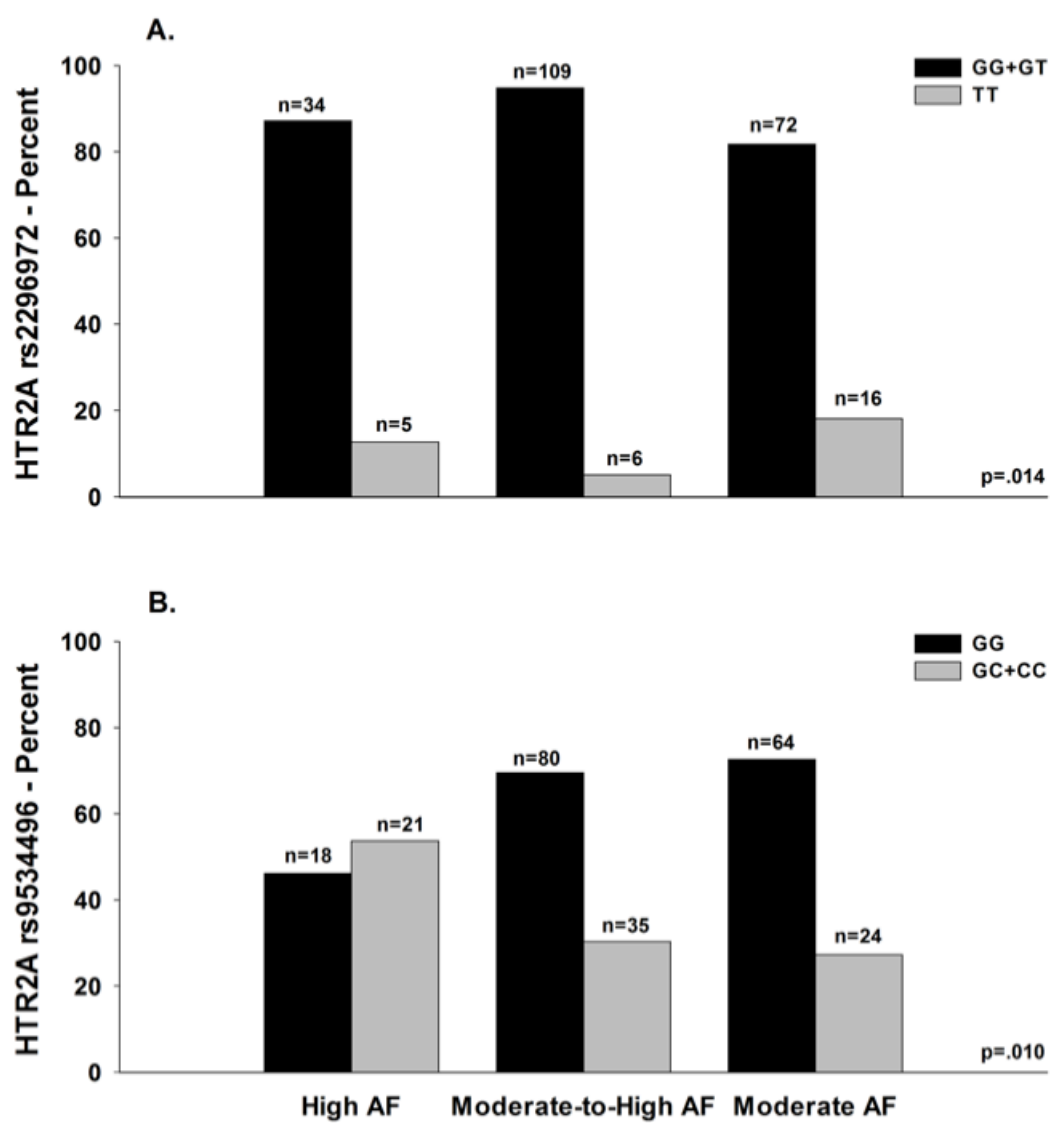
Abbreviations: GMM = growth mixture model, 95% CI = 95% confidence interval, AF = attentional function, KPS = Karnofsky Performance Status, GABA = gamma-aminobutyric acid.

^aSelf-reported race/ethnicity and the first three principle components identified in the analysis of ancestry informative markers were retained in the models to adjust for potential confounding due to population stratification (data not shown). Age is in five-year increments. KPS score is in ten-point increments. The genotypic predictors evaluated in the models were ADRA1D rs4815675 (TT+TC versus CC), SLC6A3 rs37022 (TT+TA versus AA), SLC6A1 rs2697138 (CC versus CA+AA), HTR2A rs2296972 (GG+GT versus TT), and HTR2A rs9534496 (GG versus GC+CC).









Conclusions for Dissertation

The purposes of this dissertation research were to identify subgroups of individuals with distinct trajectories of attentional function and to evaluate for phenotypic and genotypic (i.e., cytokine and neurotransmission gene polymorphisms) differences among these subgroups.

In chapter one, the potential mechanisms that underlie diminished attentional function were reviewed. Cancer- and treatment-related cognitive changes may be mediated through inflammatory cytokine dysregulation and hormonal changes (Ahles & Saykin, 2007). The biology of cancer (Allavena & Mantovani, 2012), stress (Juster, McEwen, & Lupien, 2010), and attentional fatigue (Cimprich, 1992) may contribute to cognitive changes. Genetic variations (Ahles & Saykin, 2007) and co-occurring symptoms (De Raedt & Koster, 2010) may explain some of the inter-individual variability. The severity of cognitive changes may be moderated by age (Ahles, Root, & Ryan, 2012). In summary, multiple mechanisms may contribute to diminished attentional function in patients with non-CNS cancers, as well as in their FCs. Of particular relevance to the studies in this dissertation, cognitive changes may be mediated through genetic predisposition to dysregulation of cytokine and/or neurotransmission systems (Ahles & Saykin, 2007).

In chapter two, evidence is provided for an association between IL6 rs1800795 and distinct trajectories of self-reported attentional function. This association suggests that cytokine dysregulation negatively impacts attentional function for both oncology patients and FCs at a time when the capacity to direct attention is important for successfully navigating the cancer treatment experience.

In chapter three, evidence is provided for an association between IL1R1 rs949963 and distinct trajectories of self-reported attentional function. This association suggests that cytokine dysregulation negatively impacts attentional function in women with breast cancer at a time when the capacity to direct and sustain attention is important for quality of life during treatment for breast cancer.

In chapter four, evidence is provided for associations between SNPs in catecholaminergic genes (i.e., ADRA1D rs4815675, SLC6A3 rs37022), a GABAergic gene (i.e., SLC6A1 rs2697138), and a serotonergic gene (i.e., HTR2A rs2296972, rs9534496) and self-reported attentional function. These findings build on the evaluation of associations among these attentional function classes with inflammatory cytokine gene variations to provide evidence that suggests that neurotransmission gene variations are associated with differences in self-reported attentional function.

Implications for Clinical Practice

Phenotypic predictors of poorer attentional function class membership included younger age, higher comorbidity scores, and decreased functional status. Younger patients may notice changes in their attentional function in response to the diagnosis and treatment of cancer more than do older adults, who may have adjusted to previous age-related alterations in attentional function (Cimprich, Visovatti, & Ronis, 2011). Managing multiple comorbidities may decrease a patient's capacity to direct and sustain attention (Merriman et al., 2011), or cognitive changes may be associated with specific comorbidities (Bauer, Johnson, & Pozehl, 2011; Wefel, Vardy, Ahles, & Schagen, 2011). The higher comorbidity scores reported by the poorer attentional function classes may mediate the relationship between functional status and subgroup membership. Clinicians

could use these consistent findings across two independent samples to identify patients at higher risk for poorer attentional function. However, clinicians cannot accurately predict the severity of cognitive changes that patients will experience.

Progress is being made in understanding mechanisms of cancer and treatment-related cognitive changes. However, the genotypic predictors of attentional function identified in these dissertation studies warrant replication before clinical implications are evaluated. For now, clinicians need to understand how cytokine and/or neurotransmission system dysregulation may contribute to cognitive changes so that they can explain to patients possible reasons for these changes.

The Attentional Function Index (AFI) has minimal respondent burden, as it is estimated to require less than five minutes to complete (Cimprich et al., 2011). However, the AFI is not an appropriate screening tool for diminished attentional function in clinical settings. A practical brief cognitive screening would employ quick objective measures and self report of select cognitive domains (e.g., attention, working memory, processing speed). Time constraints in clinical interactions must be considered. Until a validated clinical screening tool is available, it is important to ask patients whether they have difficulty concentrating (i.e., diminished attentional function).

Recommendations for Future Research

Important areas for future research include elucidation of mechanisms of diminished attentional function, determination of factors that increase susceptibility to these cognitive changes, and interventions to prevent or reduce these changes.

It is unknown whether the variations in cytokine and neurotransmission genes identified in these dissertation studies have functional effects that could explain their

associations with attentional function. Measuring serum cytokine levels could support hypothesized relationships between cytokine levels and cognitive function (e.g., Ahles & Saykin, 2007; Banks & Erickson, 2010; Capuron & Miller, 2011; Raison et al., 2010; Tong, Balazs, Soiampornkul, Thangnipon, & Cotman, 2008). An alternative approach would be the measurement of messenger ribonucleic acid (mRNA; Conley et al., 2013) to determine functional effects of genetic variations.

Epigenetics is the study of potentially heritable changes outside the genome that impact gene expression (Feero, Guttmacher, & Collins, 2010). Epigenetic changes such as DNA methylation at cytosines and histone acetylation (Stephens, Miaskowski, Levine, Pullinger, & Aouizerat, 2012) may contribute to variation in attentional function. Evidence suggests that their mechanism of action includes reduction in binding of transcription factors to promoter regions of affected genes, reducing the expression of protein products (Stephens et al., 2012). DNA methylation is more easily measured than histone acetylation (Stephens et al., 2012). Therefore, it is the more likely candidate for initial studies of the effects of epigenetic mechanisms on attentional function.

AFI scores for the patients with breast cancer in each of the latent classes were lower than in the previous study of patients and family caregivers (Merriman et al., 2013). These differences in AFI scores may be due to the inclusion of male patients and family caregivers in the previous sample. Future studies of patients with cancer diagnoses that affect both men and women (e.g., colorectal cancer) may provide insights into these relationships. Studies of patients with additional cancer diagnoses and different treatments may clarify the associations of attentional function with cytokine and neurotransmission genes. Larger samples could uncover additional latent classes and

genetic associations.

Inclusion of objective tests in future studies may improve understanding of the phenotype of diminished attentional function. It is possible that subjective and objective instruments measure different aspects of the same phenomenon or different phenomena entirely. Current neuropsychological tests may not be sensitive to the attentional demands that patients and FCs report when completing instrumental activities of daily living. Thus, they may have limited ecological validity (Bender et al., 2008; Chaytor & Schmitter-Edgecombe, 2003; Dijkstra & Jolles, 2002). Also, patients may have difficulty rating their cognitive function.

A potential bridge between subjective and objective measurement is functional and structural brain imaging, which may reveal how a patient can perform normally on objective tests and yet report important cognitive changes (Ferguson, McDonald, Saykin, & Ahles, 2007). In addition, imaging may identify brain markers associated both with diminished attentional function and affective symptoms. Such studies may clarify relationships between attentional function and mood identified in the preliminary studies to this dissertation.

While a perfect method for measuring such intricate phenomena may never be developed, understanding their complexities and designing studies that compensate as much as possible will advance the science of cancer- and treatment-related cognitive changes. The emerging synergy in combining the disciplines of symptom research, immunology, genetics, neuropsychology, and imaging may provide strong evidence for the hypothesized mechanisms of changes in attentional function reported by oncology patients and FCs. While additional research on underlying mechanisms and risk factors is

warranted, the information available today can be used to develop and test interventions to improve this important clinical problem.

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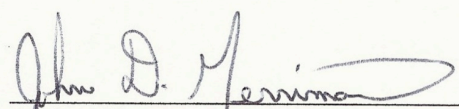
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