## Title

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# 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 (167 oncology patients and 85 family caregivers) using the Attentional Function Index before radiation therapy and at 6 additional assessments over 6 months. Three latent classes of attentional function were identified using growth mixture modeling: moderate (36.5%), moderate-to-high (48.0%), and high (15.5%) attentional function. Participants in the moderate class were significantly younger, with more comorbidities and lower functional status, than those in the other 2 classes. However, only functional status remained significant in multivariable models. Included in the genetic association analyses were 92 single nucleotide polymorphisms (SNPs) among 15 candidate genes. Additive, dominant, and recessive genetic models were assessed for each SNP. Controlling for functional status, only IL6 rs1800795

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remained a significant genotypic predictor of class membership in multivariable models. Each additional copy of the rare “G” allele was associated with a 4-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

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 of these changes can be devastating (e.g., inability to work; Boykoff, Moieni, & Subramanian, 2009). 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.

Previous studies have found that subgroups of individuals are at greater risk for significant cognitive changes during periods of increased physical or psychological stress, such as diagnosis and treatment of cancer (Wefel, Vardy, Ahles, & Schagen, 2011). The colloquial term *chemo brain* implies that the changes in cognitive function cancer patients may experience 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, Visovatti, & Ronis, 2011). Effortful control in the face of these distractions can fatigue the attention system of the brain. In addition, both patients and FCs experience chronic stress (Schulz & Beach, 1999). The allostatic load model posits that stressors of any type 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 cognitive changes in both patients and FCs (Seruga, Zhang, Bernstein, & Tannock, 2008).

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, Vigues, 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 interindividual 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).

The purposes of the present study were to identify latent classes of individuals with distinct trajectories of attentional function in a sample of oncology patients and their FCs and to evaluate for differences among these subgroups in phenotypic and genotypic characteristics. For this evaluation, we used growth mixture modeling (GMM), 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).

## 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 in their FCs (Miaskowski et al., 2012). We provide an abbreviated version of the methods 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 providing written informed consent, participants completed baseline questionnaires. They completed follow-up questionnaires 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 6 months).

Questionnaires participants completed included a demographic questionnaire, the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977), and the Attentional Function Index (AFI; Cimprich et al., 2011). The AFI 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 surgery (Cimprich, 1992) 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). The AFI consists of 16 items (Cimprich et al., 2011). Higher mean scores on a 0–10 rating scale indicate greater capacity to direct attention. Scores are grouped into categories of attentional function (i.e., < 5.0 low function, 5.0–7.5 moderate function, > 7.5 high function; Cimprich et al., 2005). The AFI has well established reliability and validity (Cimprich et al., 2011). In the present study, Cronbach's alpha for the AFI was .95 for both patients and FCs.

## Phenotypic Analyses

We analyzed data using SPSS 19 (IBM, Armonk, NY) and Mplus 6.11 (Muthén & Muthén, Los Angeles, CA). We generated descriptive statistics and frequency distributions 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, we estimated models with dyad as a clustering variable to control for intra-dyadic dependency. The GMM methods are described in detail elsewhere (Dunn et al., 2012).

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

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

## Genotypic Analyses

We extracted genomic DNA from archived buffy coats using the Puregene DNA Isolation System (Invitrogen, Carlsbad, CA). Of 287 participants, we could recover DNA for 252 (i.e., 167 patients and 85 FCs). We found no differences in demographic and clinical characteristics between those participants from whom we could not recover DNA and those from whom we could.

We quantitated DNA using spectrophotometry and normalized it to a concentration of 50 ng/μL (diluted in 10 mM Tris/1 mM EDTA). Genotyping was performed blinded to clinical status using the GoldenGate genotyping platform and processed using GenomeStudio (Illumina, San Diego, CA). Two blinded reviewers visually inspected genotype calls for each single nucleotide polymorphism (SNP). A third reviewer adjudicated disagreements.

**SNP selection—**We selected a combination of tagging SNPs and SNPs suggested by the literature (i.e., associated with altered function, symptoms) for analysis. Tagging SNPs were

required to be common, defined as having minor allele frequencies (MAFs) ≥ 5% in public databases. We excluded SNPs with call rates < 95% or Hardy-Weinberg $p < .001$.

**Statistical analyses—**We determined allele and genotype frequencies by gene counting and assessed Hardy-Weinberg equilibrium by the Chi-square or Fisher exact test. We computed measures of linkage disequilibrium (LD; i.e., *D'* and $r^2$) from the participants' genotypes with Haploview 4.2 (Broad Institute, Cambridge, MA). We based LD-based haplotype block definition on the *D'* confidence interval method (Gabriel et al., 2002). We constructed haplotypes using PHASE 2.1 (Stephens Lab, University of Chicago), as described previously (Miaskowski et al., 2012). We included 106 AIMs in the analysis to minimize confounding due to population stratification (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008), as described previously (Miaskowski et al., 2012).

We assessed additive, dominant, and recessive genetic models in association tests for each SNP. Barring trivial improvement (i.e., delta < 10%) from the additive model, we selected the model that best fit the data, by maximizing the significance of the *p*-value, 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, we fit logistic regression models that treated class as a discrete categorical variable. We estimated model fit and unadjusted/covariate-adjusted odds ratios using Stata 9 (StataCorp, College Station, TX). If the overall model included a statistically significant genotype term, we fit pairwise post hoc models (e.g., high versus moderate-to-high attentional function). We retained only post hoc models with Bonferroni-corrected statistical significance for genotype.

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, we did not make adjustments for multiple testing. In addition, we further evaluated significant SNPs identified in the bivariate analyses 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. We included only SNPs that remained significant in the final results. Therefore, the significant independent genetic association reported is unlikely to be due solely to chance. In addition, we report unadjusted (i.e., bivariate) associations for all SNPs passing quality control criteria (see online Supplemental Table) to allow for subsequent comparisons and meta-analyses.

## Results

### GMM Classes

We identified three distinct classes of attentional function trajectories (Figure 1). A three-class solution provided the best model fit because it had a significant Vuong-Lo-Mendell-Rubin likelihood ratio test (Table 1). 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 moderate attentional function ("moderate") class (36.5%) had estimated (i.e., model-predicted) AFI scores of 5.55 at enrollment that did not improve during the study (Table 2). Participants in the moderate-to-high attentional function ("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 high attentional function ("high") class (15.5%) had estimated AFI scores of 8.98 at enrollment that remained high throughout the study.

### Phenotypic Differences Among Classes

Participants in the moderate class were significantly younger and reported lower functional status than those in the other two classes (Table 3). 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 in the high class. We found no differences among the classes in years of education, gender, or race/ethnicity. Using a backwards stepwise approach, we found that only functional status (i.e., KPS score) significantly predicted class membership when controlling for population stratification due to race/ethnicity.

### Genotypic Differences Among Classes

A total of 92 SNPs among 15 candidate genes passed quality-control filters (see online Supplemental Table). Genotype distributions differed significantly among classes for six SNPs and two haplotypes (data not shown). 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, we retained the model fit for rs1800795 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 comparison ($p$ = .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 4-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

The present 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, with the moderate class reporting significantly lower functional status than the other classes. Clinically, this difference was a categorical change in KPS score 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” for the moderate class. Previous studies have not reported an association between functional status and self-reported attentional function. One possible explanation for the present finding 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 age was not a significant predictor of class membership after controlling for other covariates, the moderate class was significantly younger than the other two classes. 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 previously adjusted to some alterations in attentional function (Cimprich et al., 2011). For these reasons, we entered age as a covariate in the multivariable regression analysis in a post hoc evaluation, and the reported results for IL6 did not change.

Of the 167 patients participating, 12 were diagnosed with brain tumors. Although brain tumors and treatment for CNS disease can impact cognitive function (Correa, 2010), we found no differences 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). Only patients diagnosed with breast and prostate cancer differed from each other 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 increased odds of belonging to a lower attentional function class. Genotype uniquely explained 0.5% of variance in class membership.

High levels of IL6 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-α 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 rates of 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).

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 6 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.

The present study provides preliminary evidence for a relationship between IL6 rs1800795 and distinct trajectories of self-reported attentional function. The fact that we found a significant relationship 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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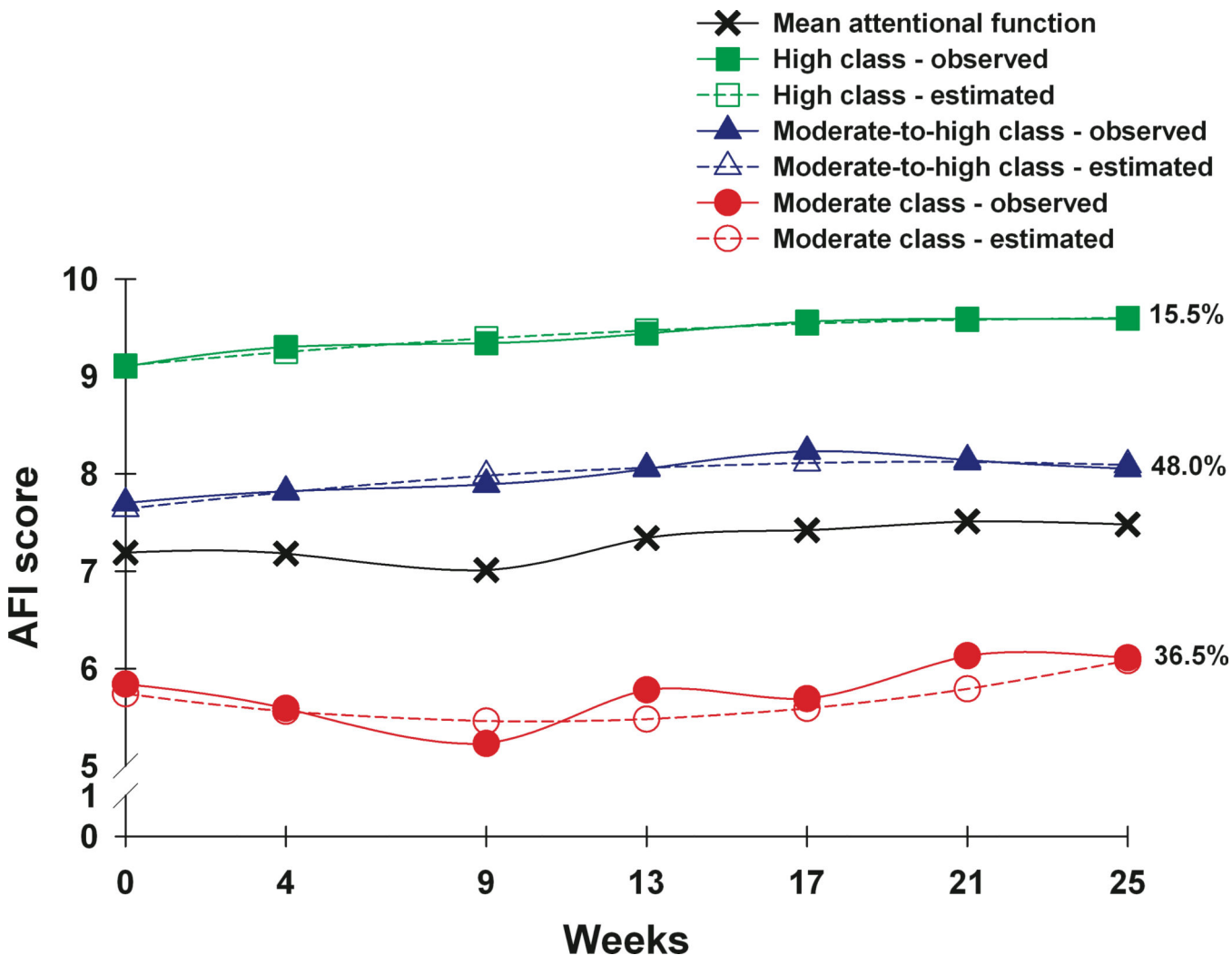


**Figure 1.**

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.

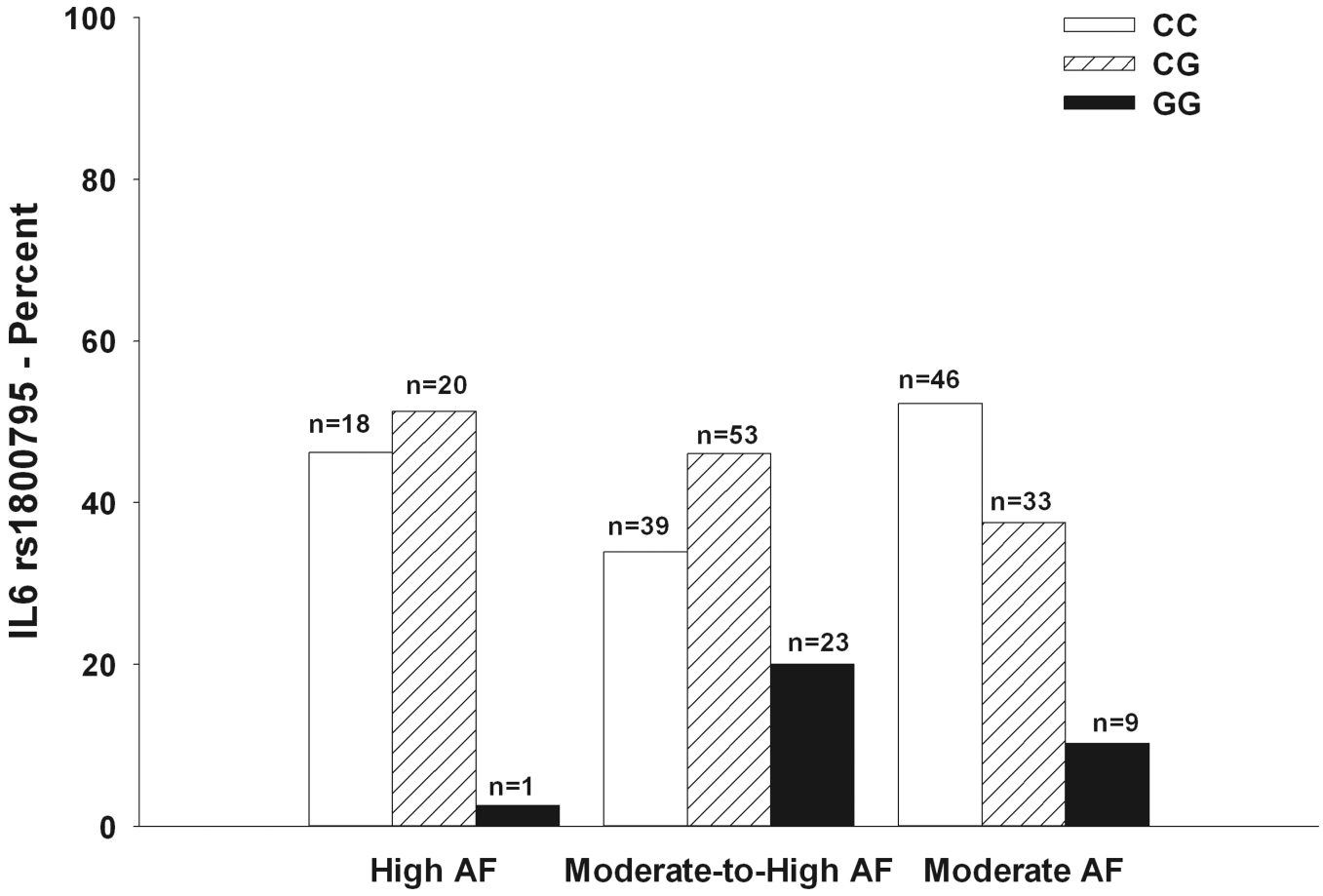


**Figure 2.**

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**

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 |

*Notes*. LL = log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test.

[a]Random 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.

[b]A 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.

[c]This 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 2

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) |

*Notes*. SE = standard error.

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

[b] Trajectory class sizes are for classification of individuals based on most likely latent class membership.

[c] Fixed at 0 to improve estimation.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

## Table 3

Differences in Demographic and Clinical Characteristics at Enrollment.

| Characteristic | (1) High Attentional Function *n* = 39 (15.5%) | (2) Moderate-to-High Attentional Function *n* = 121 (48.0%) | (3) Moderate Attentional Function *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) | $F(2,113) = 6.5$, $p = .002$; 3 < 1,2 |
| 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) | $F(2,249) = 3.6$, $p = .030$; 3 > 1 |
| 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) | $F(2,108) = 9.0$, $p < .001$; 3 < 1,2 |
| | *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) | $\chi^2 = 9.160$, $p = .010$; 3 < 1 |
| 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) | $\chi^2 = 9.518$, $p = .009$; 3 > 1 |

*Notes*. SD = standard deviation; NS = not significant; KPS = Karnofsky Performance Status; FC = family caregiver.