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Associations between catecholaminergic, GABAergic, and serotonergic genes and self-reported attentional function in oncology patients and their family caregivers

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Abstract

Purpose of the research—Evaluate for associations between variations in genes involved in catecholaminergic, gamma-aminobutyric acid (GABA)-ergic, and serotonergic mechanisms of neurotransmission and attentional function latent classes.

Patients and methods—This descriptive, longitudinal study was conducted at two radiation therapy departments. The sample included three latent classes of individuals with distinct trajectories of self-reported attentional function during radiation therapy, who were previously identified using growth mixture modeling among 167 oncology patients and 85 of their family caregivers. Multivariable models were used to evaluate for genotypic associations of neurotransmission genes with attentional function latent class membership, after controlling for covariates.

Results—Variations in catecholaminergic (i.e., ADRA1D rs4815675, SLC6A3 rs37022), GABAergic (i.e., SLC6A1 rs2697138), and serotonergic (i.e., HTR2A rs2296972, rs9534496)

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neurotransmission genes were significant predictors of latent class membership in multivariable models.

Conclusions—Findings suggest that variations in genes that encode for three distinct but related neurotransmission systems are involved in alterations in attentional function. Knowledge of both phenotypic and genetic markers associated with alterations in attentional function can be used by clinicians to identify patients and family caregivers who are at higher risk for this symptom. Increased understanding of the genetic markers associated with alterations in attentional function may provide insights into the underlying mechanisms for this significant clinical problem.

Keywords

cancer; serotonin; catecholamines; gamma-aminobutyric acid; neurotransmission; attentional function

Introduction

Optimal attentional function is important for maintaining meaningful activities (e.g., meeting personal goals, engaging in social interactions) during treatment for cancer (Cimprich et al., 2011). Findings from our research team (Merriman et al., 2013) suggest that both patients and their family caregivers (FCs) experience decrements in attentional function. This diminished attentional function has a negative impact on work ability, mood, and relationships (Boykoff et al., 2009; Cimprich et al., 2011; Merriman et al., 2011).

The attention system of the brain is comprised of multiple networks, including the alerting and executive attention networks (Posner, 2012). While these networks use different brain structures and neurotransmission systems, they operate collectively (Fan et al., 2002). The alerting attention network is associated with vigilance to tasks (Posner, 2012). The executive attention network is associated with planning, impulse control, and regulation of emotion (Posner, 2012).

The alerting attention network consists of the reticular activating system and multiple cortical brain structures (Petersen and Posner, 2012). While the tonic function of this network enables diurnal fluctuations in attention, its phasic function enables short spikes in attention (Petersen and Posner, 2012). Together, these two functions facilitate general alertness and vigilance to tasks (Petersen and Posner, 2012).

Norepinephrine (NE) is a catecholaminergic neurotransmitter that, together with epinephrine, regulates sympathetic nervous system function during homeostasis and during times of psychological or physical stress (Johnson and Liggett, 2011). NE, which is produced by the locus coeruleus, is the primary neurotransmitter used by adrenergic neurons in the alerting attention network (Fan et al., 2001). Adrenergic neurons project from the locus coeruleus to cortical structures throughout the brain (Aston-Jones and Cohen, 2005). Alertness appears to have an inverted U-shaped relationship with attention so that too much (i.e., hypervigilance) or too little alertness is problematic (Aston-Jones and Cohen, 2005). Therefore, NE production or function outside an optimal range may adversely affect the alerting attention network.

The gamma-aminobutyric acid (GABA) neurotransmission system moderates the functioning of the alerting attention network. GABA is the principal inhibitory neurotransmitter in the central nervous system (CNS) (Antonucci et al., 2012). GABAergic neurons are located in cortical and subcortical structures, including structures of the alerting attention network (Conti et al., 2004; McDonald et al., 2011). The inhibitory effects of GABA prevent over excitation of neurons (Antonucci et al., 2012). Therefore, GABA moderates the excitatory state of the network so that attention is maintained at an optimal level.

Dopamine (DA), which is produced in the ventral tegmental area, is a catecholaminergic neurotransmitter used by the executive attention network and the various reward systems that influence this network (Fernandez-Duque and Posner, 2001). The executive attention network consists of the anterior cingulate cortex, the anterior insula, and the dorsolateral prefrontal cortex (Posner, 2012). 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). These neurons also project into the reward systems (i.e., the striatum) that influence executive attentional control (Eriksen et al., 2010). Optimal DA levels are important for executive attention. For example, increases in DA levels improve working memory, which is closely related to attention (Cimprich et al., 2011; Gazzaley and Nobre, 2012), in people with poor performance but impair working memory in people with good performance (Frank and Fossella, 2011).

The serotonergic neurotransmission system moderates the functioning of the executive attention network. Serotonergic neurons are located in cortical and subcortical structures, including structures of the executive attention network (Fineberg et al., 2010). Major psychosocial stressors can dysregulate serotonin neurotransmission, which results in impairments in the executive attention network (De Raedt and Koster, 2010). For example, decreased serotonergic function in the dorsolateral prefrontal cortex is associated with decreased executive regulation of emotion, increased impulsivity, and poorer mood (Carver et al., 2008; Posner, 2012).

Taken together, catecholaminergic, GABAergic, and serotonergic neurotransmission influence the alerting and executive attention networks. Poorer attentional function may be reported by individuals when the neurotransmission systems used by these networks are dysregulated (Ahles and Saykin, 2007). Therefore, inter-individual variability in self-reported attentional function may be due in part to variations in genes that encode for catecholaminergic, GABAergic, and serotonergic receptors and transporters, as well as in genes that encode for synthesis and metabolism of the neurotransmitters used in these systems.

Previously, we evaluated the relationships between variations in inflammatory cytokine genes and self-reported attentional function in a sample of 167 oncology patients undergoing radiation therapy (RT) and their 85 FCs (Merriman et al., 2013). In this study, we found an association between a single nucleotide polymorphism (SNP) in IL6 (i.e., rs1800795) and poorer attentional function in a subgroup of individuals. No studies have evaluated for associations between neurotransmitter genes and subgroups of individuals with different

levels of self-reported attentional function. Therefore, the purpose of this study, in the same sample of oncology patients and their FCs, was to evaluate for associations between variations in candidate genes involved in catecholaminergic, GABAergic, and serotonergic mechanisms of neurotransmission and attentional function latent class membership previously identified using growth mixture modeling (GMM).

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., 2013; 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 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).

Instrument To Evaluate Attentional Function

The 16-item Attentional Function Index (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 et al., 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 22 (IBM, New York) and Mplus 6.11 (Muthén & Muthén, California). 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 $p < .05$. Post hoc contrasts used the Bonferroni correction to control the overall family alpha. For any one of three possible pairwise contrasts, $p < .017$ (i.e., $.05/3$) was considered statistically significant.

Genotypic Analyses

Of 287 participants who completed the baseline assessment, deoxyribonucleic acid (DNA) was recovered using the Puregene DNA Isolation System (Invitrogen, California) for 252 (i.e., 167 patients and 85 FCs). Genotyping was performed using the GoldenGate genotyping platform and GenomeStudio (Illumina, California).

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 synthesis of DA (Bademci et al., 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 synthesis of serotonin (Lesch et al., 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 of $< 95\%$ or deviations from Hardy-Weinberg expectations of $p < .001$ were excluded. Rare alleles were defined as having MAF $< 50\%$ in the sample. Potential functional roles of SNPs associated with attentional function were examined using PupaSuite 3.1 (Conde et al., 2006).

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, 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 et al., 2001).

Multinomial logistic regression analyses were done with Stata 13 (StataCorp, 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 et al., 2008; Hoggart et al., 2003; Tian et al., 2008). Only predictors with overall Wald Chi-square p -values of $< .05$ were retained in the phenotypic model.

Additive, dominant, and recessive genetic models were assessed for each SNP. Significant genetic variations identified in the 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 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 $<.05$ 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 of $<.017$ (i.e., $.05/3$) were considered statistically significant in these pairwise class comparisons.

As was done in our previous studies (Dunn et al., 2013; Merriman et al., 2013; Miaskowski et al., 2012), based on recommendations in the literature (Hattersley and 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 (Supplemental Table). 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 (i.e., genomic and self-reported estimates of race and ethnicity), and other variations in the same gene, the significant independent genetic associations reported are unlikely to be due solely to chance.

Results

As reported previously (Merriman et al., 2013), three distinct latent classes of attentional function trajectories were identified: high ($n=39$), moderate-to-high ($n=121$), and moderate ($n=92$) attentional function (Figure 1).

Phenotypic Differences Among the Latent Classes

Phenotypic differences among the classes at enrollment are described in detail elsewhere (Merriman et al., 2013). Only significant differences among the classes are summarized in Table 1. In the multinomial logistic regression analyses, 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 due primarily to differences between the moderate attentional function class and each of the higher attentional function classes (Table 2).

Genotypic Differences Among the 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 latent classes for six SNPs and two haplotypes in three catecholaminergic genes (i.e., ADRA1D, SLC6A2, SLC6A3), three SNPs in the GABAergic gene (i.e., SLC6A1), and seven SNPs and three haplotypes in one serotonergic gene (i.e., HTR2A) (Supplemental Table).

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, models fit for ADRA1D rs4815675 ($p=.007$) and SLC6A3 rs37022 ($p=.037$) remained significant. The allelic distributions of these SNPs are depicted in Figure 2.

Pairwise comparisons revealed that the relationship between latent class membership and the ADRA1D genotype was due to the difference in genotype frequencies between the moderate-to-high versus moderate attentional function classes (Table 3). Participants who were homozygous for the rare “C” allele had a 68% 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; $p=.941$) or 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 due to the difference in genotype frequencies in the high versus moderate-to-high attentional function classes (Table 3). 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; $p=.110$) or moderate-to-high versus moderate (OR: 5.67; 95% CI: 0.563, 56.996; $p=.141$) attentional function classes.

GABAergic System—In multivariable analyses, the model fit for SLC6A1 rs2697138 ($p=.014$) remained significant. The allelic distributions of this SNP are depicted in Figure 3.

Pairwise comparisons revealed that the relationship with SLC6A1 genotype was due to the difference in genotype frequencies between the high versus moderate-to-high attentional function classes (Table 3). Participants who were heterozygous or homozygous for the rare “A” allele (i.e., 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; $p=.599$) or moderate-to-high versus moderate (OR: 2.36; 95% CI: 1.117, 4.979; $p=.024$) attentional function classes.

Serotonergic System—In multivariable analyses, the model fit for HTR2A rs2296972 ($p=.033$) and rs9534496 ($p=.032$) remained significant. The LD between these SNPs was

weak (i.e., $r^2=0.001$, $D'=0.042$). The allelic distributions of these SNPs are depicted in Figure 4.

Pairwise comparisons revealed that for rs2296972, the relationship with HTR2A genotype was due to the difference in genotype frequencies between the moderate-to-high versus moderate attentional function classes (Table 3). 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; $p=.671$) or 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 due to the difference in genotype frequencies between the high versus moderate-to-high attentional function classes (Table 3). Participants who were heterozygous or homozygous for the rare “C” allele (i.e., 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; $p=.044$) or 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 in genes that encode for catecholaminergic, GABAergic, and serotonergic neurotransmission among subgroups of oncology patients and their FCs who reported distinct trajectories of attentional function prior to, during, and after RT. Characteristics of the three latent classes of attentional function (i.e., high, moderate-to-high, moderate) identified using GMM and phenotypic differences among the classes were discussed previously (Merriman et al., 2013). The current study extends our findings on associations among these attentional function latent classes and variations in cytokine genes and provides preliminary evidence that variations in several 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 DA transporter (i.e., SLC6A3 rs37022) were associated with latent class membership.

For ADRA1D rs4815675, being homozygous for the rare C allele was associated with a decreased odds of belonging to a poorer attentional function class. Alpha adrenergic receptors are pervasive throughout the peripheral nervous system and CNS (Small et al., 2003). These G protein-coupled receptors are involved in general alertness (Aston-Jones and Cohen, 2005), cognition (Perez and Doze, 2011), and sympathetic responses to stress (Johnson and Liggett, 2011). This SNP is located in an evolutionarily conserved region of

the single intron for ADRA1D. The C allele can become methylated, which may influence gene expression. In fact, this allele was found to be methylated in genomic DNA collected from nucleated cells in the human frontal cortex (Maunakea et al., 2010; Meyer et al., 2013). The effects of DNA methylation of this SNP on attentional function warrant evaluation.

For SLC6A3 rs37022, being homozygous for the rare A allele was associated with a 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). DAT is involved in both the reuptake of DA from the synaptic cleft into the presynaptic terminal (Bamne et al., 2010) and in the transport of DA back into this cleft (Leviel, 2011). Therefore, DAT is essential for the regulation of DA levels. SLC6A3 rs37022 is located in an evolutionarily conserved region of the gene in intron seven. Being homozygous for the rare A allele of rs37022 may be associated with more optimal functioning of DAT.

Attention-deficit/hyperactivity disorder (ADHD) shares some phenotypic similarities with the diminished attentional function reported by oncology patients and their FCs. For example, deficits in working memory performance found in individuals with ADHD (Kebir and Jooper, 2011) are reported by oncology patients (Cimprich et al., 2011). In addition, individuals with ADHD exhibit deficits in response inhibition, which contributes to impulsive behavior (Kebir and Jooper, 2011). Similar deficits in response inhibition were found in studies of oncology patients following chemotherapy (de Ruiter et al., 2011; Kesler et al., 2009). While the diminished attentional function reported by patients and FCs during treatment for cancer is not ADHD, some of the changes in attentional function associated with both conditions may provide insights into the mechanisms that underlie these changes.

For example, in a review (Kebir and Jooper, 2011), the role of DAT polymorphisms in ADHD was described. Of note, none of the studies included in the review evaluated SLC6A3 rs37022. However, findings from this review suggest that DAT moderates the severity of various ADHD phenotypes. The relationships found between polymorphisms in DAT and attentional function in persons with ADHD suggest that variability in DAT production and function contribute to changes in cognitive function.

GABAergic System

An intronic 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 a 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). An optimal level of GABA in the cleft maintains optimal excitability of the alerting attention network (Antonucci et al., 2012; Thoeringer et al., 2009). While the function of rs2697138 is unknown, it may be a surrogate for an unmeasured functional polymorphism that is in LD.

While no clinical studies have evaluated SLC6A1 rs2697138, a pre-clinical study using GAT-1 overexpressing mice found cognitive deficits in learning and novel object

recognition compared to wild type mice (Hu et al., 2004). These deficits were reversed with administration of a GAT-1 inhibitor (Hu et al., 2004). The same group found better learning and memory, as well as reduced anxiety, in GAT-1 heterozygous mice compared to wild type and knockout mice (Shi et al., 2012). These findings suggest that optimal levels of GAT-1 are associated with better cognitive function and mood.

Serotonergic System

Among the six candidate genes evaluated as part of the serotonergic system, two SNPs in HTR2A (i.e., rs2296972, rs9534496) were associated with attentional function class membership. Being homozygous for the rare T allele for rs2296972 was associated with an 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 a decreased odds of belonging to a poorer attentional function class. In the HTR2A multivariable model (Table 3), both SNPs maintained a significant association with attentional function latent class membership. Furthermore, the LD between the two SNPs was weak, which suggests that these SNPs are independent predictors.

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

Both SNPs are located in the second intron of the gene. It is interesting to note that HTR2A rs2296972 has demonstrated associations in several clinical conditions. The rare T allele was associated with more severe panic disorder (Unschuld et al., 2007), while the “G” allele was associated with less social withdrawal (Broekman et al., 2011). These findings are consistent with our finding that the T allele is associated with worse outcomes. In contrast, a recent study found that the rare allele was associated with less severe bulimia nervosa (Koren et al., 2014). While the function of rs2296972 is unknown, this SNP may be a surrogate for an unmeasured functional polymorphism that is in LD.

In terms of the second SNP, in a study of university students, carriers of the C allele in HTR2A rs9534496 performed worse at delayed recall tasks (Sigmund et al., 2008). This finding of poorer working memory performance contrasts with our finding that the C allele was associated with a decreased odds of poorer attentional function. These inconsistent findings may be related to variations in sample characteristics (e.g., age) or differences in the measures of cognitive function used in the studies. For example, the cognitive constructs measured for working memory and self-reported attentional function may be affected differently by the C allele. Of note, the “G” allele for this SNP has the potential to become methylated, which can influence gene expression. This allele was methylated in genomic DNA collected from nucleated cells in the human frontal cortex (Maunakea et al., 2010; Meyer et al., 2013). Therefore, the effect of DNA methylation of this SNP on attentional function warrants evaluation.

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

genes for all of the mechanistic pathways involved in attentional function. For example, genes involved in the cholinergic system that is used by the orienting attention network were not evaluated. The orienting attention network enables disengagement from attended stimuli to focus on other stimuli (Petersen and Posner, 2012). 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 mood disorders (De Raedt and Koster, 2010; Nolen-Hoeksema, 2000; Nolen-Hoeksema et al., 1993). Future work should evaluate these relationships.

In summary, 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 sample of patients and FCs suggests that these SNPs influence attentional function regardless of the etiology of diminished attentional function.

Before clinical implications are evaluated, these findings need to be confirmed in independent samples. When confirmed, knowledge of both phenotypic and genetic markers associated with alterations in attentional function could be used by clinicians to identify patients and family caregivers who are at higher risk for this symptom. Moreover, increased understanding of these genetic markers may provide insights into the underlying mechanisms for this significant clinical problem. Studies of genes that encode for other physiologic pathways that impact neurotransmission and neuronal health (e.g., nitric oxide synthase, brain-derived neurotrophic factor) may provide additional insights into the genetic factors that influence attentional function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Decreases in attentional function occur in both patients and their family caregivers.

Findings from this study suggest that variations in genes that encode for three distinct but related neurotransmission systems are involved in alterations in attentional function.

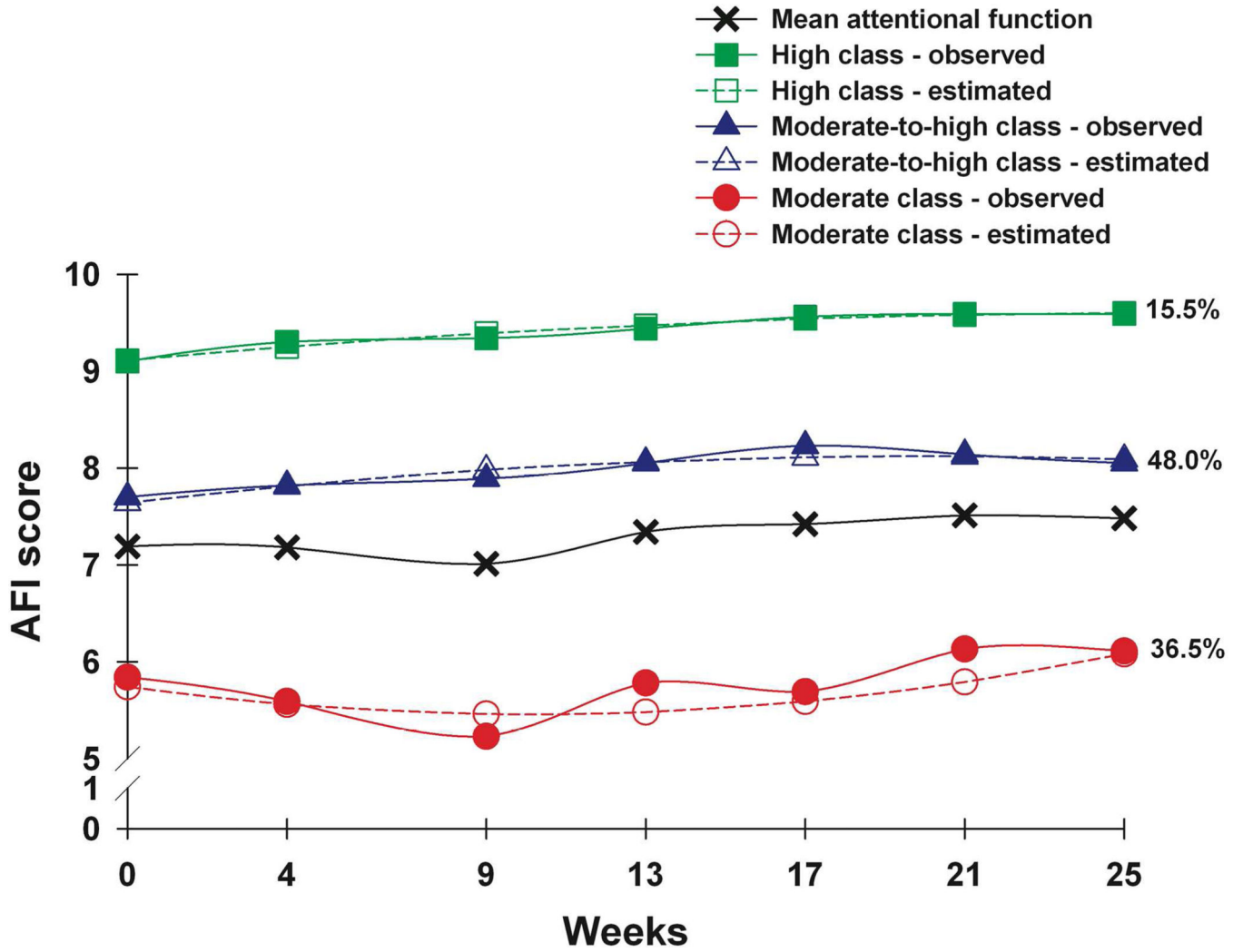


Figure 1. Observed and estimated (i.e., model predicted) Attentional Function Index (AFI) score trajectories for participants in each latent class, as well as mean AFI scores for the total sample. [Merriman et al. 2013, used with permission from Sage Publications]

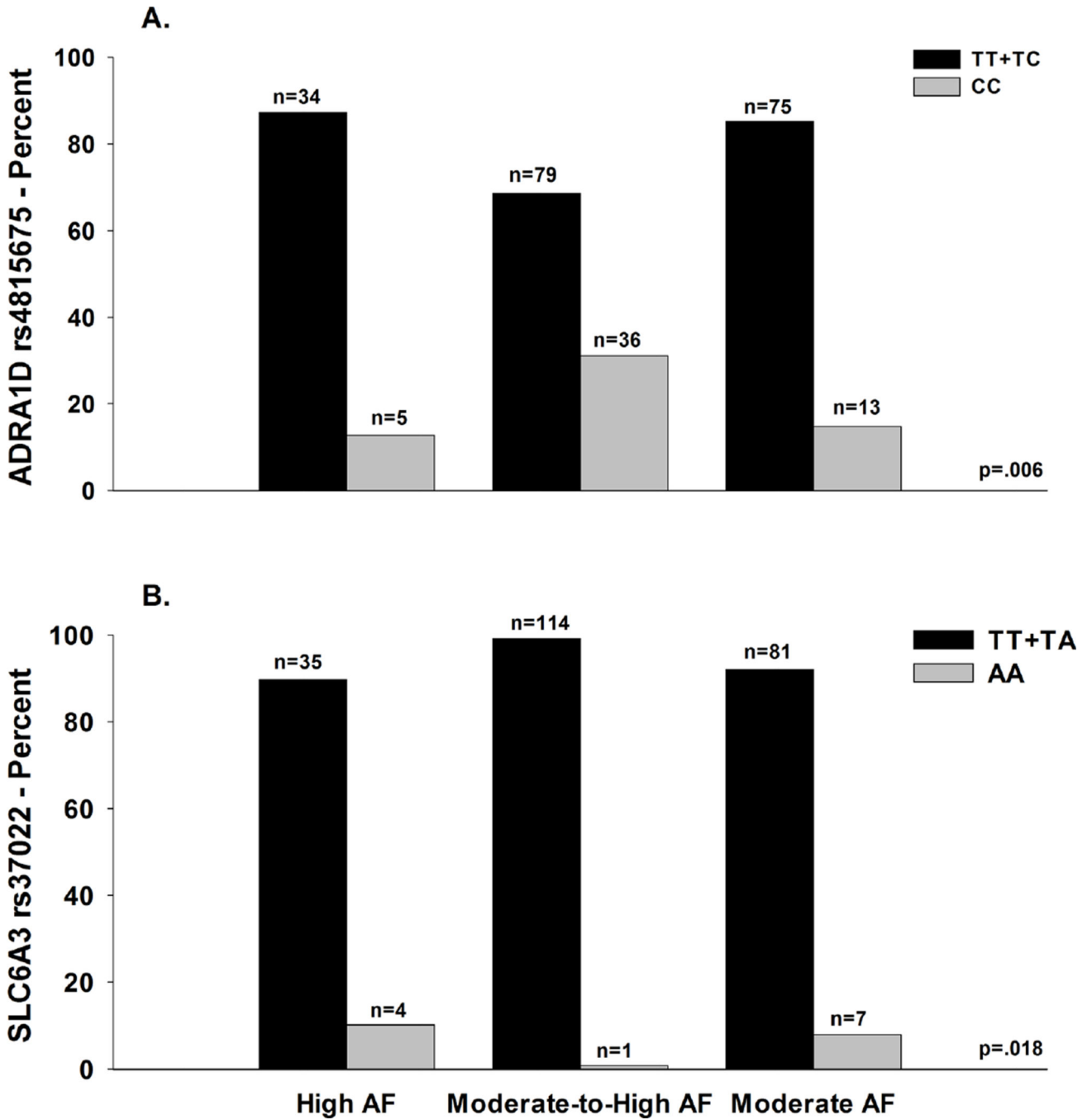


Figure 2.
 a – Catecholaminergic system: Differences among the attentional function (AF) latent classes in the percentages of patients who were homozygous or heterozygous for the common “T” allele versus homozygous for the rare “C” allele for rs4815675 in adrenergic, alpha 1D receptor (ADRA1D). Values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

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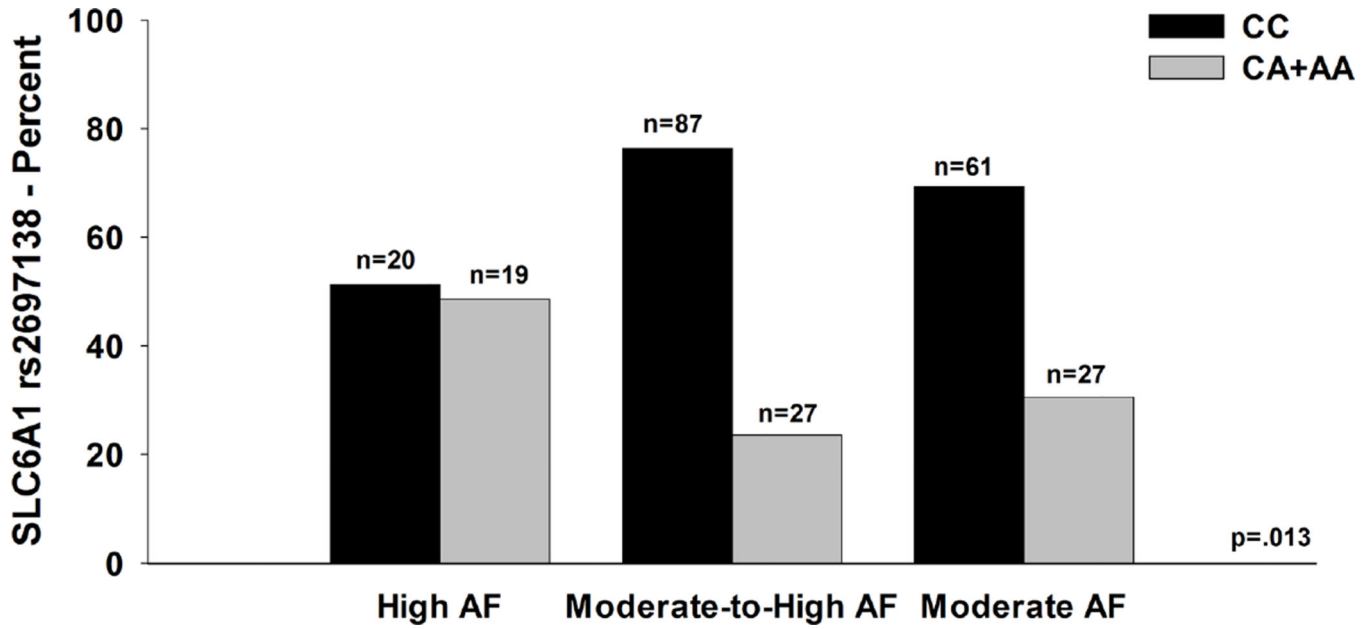


Figure 3. GABAergic system: Differences among the AF latent classes in the percentages of patients who were homozygous for the common “C” allele versus heterozygous or homozygous for the rare “A” allele for rs2697138 in solute carrier family 6, member 1 (SLC6A1; transporter for the neurotransmitter gamma-aminobutyric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

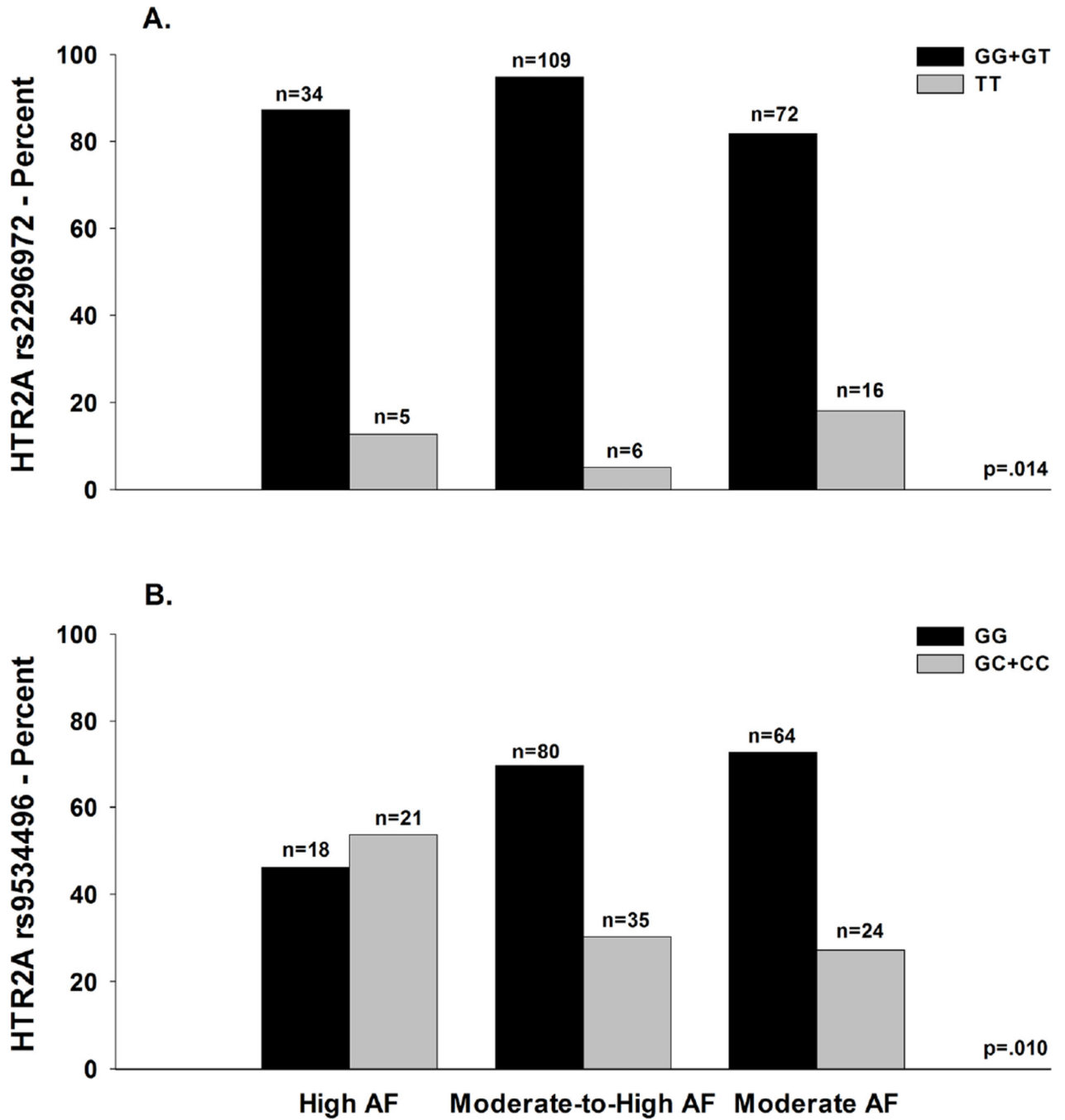


Figure 4.
 a – Serotonergic system: Differences among the AF latent classes in the percentages of patients who were homozygous or heterozygous for the common “G” allele versus homozygous for the rare “T” allele for rs2296972 in the G protein-coupled 5-hydroxytryptamine receptor 2A (HTR2A). Values are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

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Table 1

Significant differences in demographic and clinical characteristics among the attentional function classes at enrollment.^a

Characteristic	High Attentional Function (0) <i>n</i> = 39 (15.5%)	Moderate-to-High Attentional Function (1) <i>n</i> = 121 (48.0%)	Moderate Attentional Function (2) <i>n</i> = 92 (36.5%)	Statistics and post hoc comparisons
	Mean (SD)	Mean (SD)	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)	$F(2,108) = 9.0, p < .001; 2 < 0,1$
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
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.

^aModified from Merriman et al. 2013.

Multinomial logistic regression model for phenotypic predictors of attentional function class membership.

Table 2

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; CI = confidence interval; AF = attentional function; KPS = Karnofsky Performance Status.

^a Self-reported race/ethnicity and genomic estimates of race/ethnicity (i.e., 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 3

Multinomial logistic regression models for genotypic predictors of attentional function class membership by candidate gene.

Neurotransmission system	GMM class comparison	Predictor ^a	Odds ratio	Standard error	95% CI	z	p-value
Catecholaminergic	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 $R^2 = 0.136$							
GABAergic	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	High versus moderate-to-high AF	SLC6A1 rs2697138	0.33	0.145	0.141, 0.779	-2.53	.011
		Age	0.90	0.723, 1.109	-1.01	.311	
		Number of comorbidities	1.10	0.930, 1.289	1.09	.277	
		KPS score	0.82	0.497, 1.344	-0.80	.426	
Overall model fit (n=234): $\chi^2 = 62.65, p < .001$, pseudo $R^2 = 0.131$							
Serotonergic	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
Serotonergic	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; CI = confidence interval; AF = attentional function; KPS = Karnofsky Performance Status; GABA = gamma-aminobutyric acid.

^dSelf-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).

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